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Relationship between serum selenium deficiency and preeclampsia among pregnant women at the Rivers State university teaching hospital, Port Harcourt, Nigeria

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Abstract

Background: Preeclampsia is a multi-system disorder of pregnancy. It is associated with a significantly increased risk of maternal and fetal morbidity and mortality. Oxidative stress has been implicated. Selenium is a very important trace element in the synthesis of endogenous antioxidants which help to balance the effects of oxidative free radicals. This study sought to determine the relationship between serum selenium deficiency and preeclampsia among pregnant women.

Method: A prospective case-control study was carried out on consenting preeclamptic (135) and normotensive (135) pregnant women in their second half of pregnancy. Blood samples were taken for serum selenium estimation and analyzed using Atomic Absorption Spectrophotometry (AAS). Their Socio-demographic information was collected through a structured proforma. Data were analyzed using SPSS version 20. A P-value of < 0.05 was considered to be statistically significant.

Results: There was no significant difference in characteristics between the two groups. The mean selenium level of the preeclamptic women (0.52 ± 0.31µmol/l) was significantly (*P*=0.001) lower than that of the normotensive women (0.73 ± 0.24µmol/l). Bivariate analysis showed that preeclamptic women were 3.6 times more likely to have a deficiency in selenium compared to normotensive women (OR=3.61; *P*=0.001; 95%CI: 2.13-6.10). No significant difference was noted in the serum level of selenium in patients with mild versus severe preeclampsia.

Conclusion: This study showed that pregnant women with selenium deficiency were 3.6 times more likely to develop preeclampsia compared to healthy normotensive pregnant women. However, there was no significant difference between levels in mild compared to severe preeclamptic women.

Keywords: Preeclampsia; Selenium deficiency; Trace elements; Antioxidants

1. Introduction

The National Heart Lung and Blood Institute (NHLBI) working group on research on hypertension during pregnancy defines preeclampsia as a clinical syndrome that occurs after the 20th week of pregnancy which is characterized by de novo appearance of systolic blood pressure ≥ 140mmhg and diastolic blood pressure of ≥ 90mmhg, accompanied by new-onset proteinuria, defined as ≥ 300mg per 24 hours [1]. Preeclampsia is a progressive condition that could be mild

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or severe. The severe form if untreated can progress to eclampsia, which is characterized by seizures, and other complications such as renal or hepatic damage and even death [2]. It is polymorphic in nature since it can affect virtually all body systems and organs [3].

Preeclampsia affects 2% - 10% of all pregnant women globally [3]. It is a significant public health threat in both developing and developed countries, with the impact felt more in the former where the prevalence of preeclampsia is 1.8 -16.7% [4,5]. Preeclampsia accounts for 20 – 80% of maternal mortality in developing countries unlike in developed countries with good health care delivery systems [6]. The impact is seen more in the fetuses who are usually delivered prematurely [6]. Preeclampsia /eclampsia is the leading cause of maternal mortality in Nigeria accounting for 28.2% of all national maternal deaths [2].

Preeclampsia is a pregnancy-specific complex multi-systemic condition that is associated with a significant increase in the risk of maternal as well as perinatal morbidity and mortality [6]. It is associated with an increased rate of caesarean section and preterm delivery [2], has been linked to several risk factors and the prevention of this condition is quite challenging [7]. Despite being a common obstetric condition it is still regarded as a disease of theories, although considerable progress has been made in unraveling the pathophysiology and management of the disease [8]. The exact cause of preeclampsia is still largely unknown, although oxidative stress generated predominantly by the placenta, with little contributions from maternal leukocytes and endothelin has been implicated in its pathogenesis [9].

A biochemical imbalance between the production of endogenous antioxidants and the production of free radicals is thought to occur in pregnant women with preeclampsia. This imbalance will lead to an increase in oxidative stress, lipid lipoperoxidation, superoxide anion radicals, and a deficiency of anti-oxidants [10]. If this generated oxidative stress overwhelms the natural protective antioxidant mechanism in the body, there will be an increase in trophoblastic turnover and subsequent release of harmful trophoblastic debris into the maternal circulation [11,12]. This will trigger an exacerbated immune response in the mother that will culminate in endothelial damage, the most important pathologic characteristic of preeclampsia responsible for symptom manifestation [13,14].

The predominant anti-oxidant enzyme systems whose deficiencies are linked to the occurrence of preeclampsia include Glutathione peroxidase and catalase [15]. Other anti-oxidants include superoxide dismutase and reduced glutathione which is not an enzyme. Selenium is an essential trace metal whose role in the synthesis of endogenous anti-oxidants has been well documented [16]. Reduction in the activities of specific anti-oxidant especially glutathione peroxidase and catalase which are associated with low micronutrients like selenium and zinc, can result in adverse pregnancy outcomes like preeclampsia and intrauterine growth restriction (IUGR) [17]. These micronutrients function essentially as co-factors to anti-oxidant systems which act to balance the harmful effects of oxidative stress [17].

Preeclampsia occurs more commonly in developing countries with predominantly poor populations and this may be due to the consumption of diets low in essential minerals and vitamins including selenium [18]. Nutritional deficiencies are common during pregnancy and pregnant women in developing countries have been reported to consume diets that are low in minerals and vitamins including selenium [19]. The main source of selenium in the body is diet. Dietary sources include brown rice, wheat, meat, seafood, fish, and eggs [20,21]. Since the diet consumed by pregnant women, especially in developing countries, is largely deficient in micronutrients, selenium supplementation preconception and during the early antenatal period may help in the prevention of preeclampsia [21].

Selenium is an essential trace element with well-documented health benefits in humans due to its antioxidant properties [22]. Several studies have linked low serum selenium levels with an increased risk of cancer and other problems including preeclampsia [23-25]. This is because selenium and other selenoproteins act as co-factors for both enzymatic and non-enzymatic antioxidants. According to a report, the recommended dietary allowance for selenium is 60mcg per day [26]. Many authors are of the opinion that the requirement for selenium in pregnant and lactating mothers increases due to the transfer of selenium from the mother to her fetus [21]. Normal serum selenium is 60 –150 ng/ml (0.76 – 1.91µmol/L).

Several investigators have documented a link between selenium deficiency and the occurrence of preeclampsia [27]. A few studies however showed no statistical difference. Whether this deficiency is a "cause or effect" of preeclampsia is not clear. Ikechukwu et al in a study in Enugu, Nigeria showed significantly lower levels of selenium, zinc, and copper in preeclampsia [27]. A case-control study in Owerri, Nigeria, also showed a significantly reduced level of selenium in preeclamptic women when compared with normotensive women. However, a case-control study in Brazil involving normotensive, hypertensive (pregnancy-induced and chronic hypertension), and preeclamptic women showed no statistically significant difference in the level of selenium in all 3 groups [28]. However, a systematic review and meta-analysis showed an inverse association between blood selenium level and risk of preeclampsia [29].

The mechanism by which selenium deficiency is suspected to cause preeclampsia is not fully understood but has been linked by several authors to its effect on the activities of antioxidants [25,30-32]. A retrospective case-control study in St John's College Hospital in India concluded that serum selenium level in itself may not be an independent predictor of preeclampsia [22]. Its effect on the occurrence of preeclampsia may require other complementary elements/factors.

Majority of the studies on Selenium deficiency have been done in developed countries, with a paucity of data in our environment, despite the poverty and nutritional deficiency that plague the developing world. This study was designed to determine the relationship between serum selenium deficiency and the occurrence and severity of preeclampsia. The findings of this study will add to the body of knowledge on the subject.

Aim/objective

To compare the serum selenium levels in preeclamptic and normotensive pregnant women and determine if low serum selenium is associated with the incidence and severity of preeclampsia.

1.1. Study hypothesis

Null Hypothesis: There is no significant reduction in the level of serum selenium among preeclamptic compared to normotensive pregnant women.

Alternate Hypothesis: There is significant difference in the level of serum selenium among preeclamptic and normotensive pregnant women.

2. Methodology

2.1. Study area

This study was conducted at the Rivers State University Teaching Hospital (RSUTH), Port Harcourt. Rivers State, Nigeria. The hospital serves as a referral hospital for the primary and secondary health facilities in the state and other neighboring states in the South-South and South-East Regions of Nigeria. The hospital has several departments including the Department of Obstetrics and Gynaecology where the study was conducted. There is an average annual delivery of over 2000. Ethical approval was obtained from the Research and Ethics Committee of the hospital before the commencement of the study.

2.2. Study design & period

This was a prospective case-control study. The study period was from 10th June 2020 to 17th May 2021.

2.3. Study population

A total of 270 women were recruited into the study, 135 preeclamptic women and 135 normotensive women as controls.

2.3.1. Inclusion criteria

Consenting preeclamptic and normotensive pregnant women in the second half of pregnancy.

2.3.2. Exclusion criteria

Smokers, HIV positive pregnant women, Women with multiple pregnancy; Pregnant women with diabetes mellitus, sickle cell disease, and chronic renal failure; Pregnant women on micronutrients/selenium supplementation; Chronic alcoholics; Ultrasound scan showing abnormal foetus; Pregnant women on anti-thyroid drugs; Hepatitis B or C positive pregnant women and those that failed to give informed consent.

2.3.3. Sample size

The sample size was calculated based on the formula for proportions as stated by Araoye [33] and a previously reported 8.8% prevalence of preeclampsia by Musa et al [1].

$$n = Z2pq/d2$$

Where;

n = sample size for case and control

Z = 95% confidence interval = 1.96

p = proportion of the target population used = 8.8% = 0.088

q = 1.0 – 0.088 = 0.912

d = degree of accuracy desired (usually set at 0.05)

$$n = \{(1.96)2(0.088)\ (1.0 - 0.088)\} \div 0.052$$

$$= (3.841 \times 0.088 \times 0.912) \div 0.0025$$

n = 123.32, approx. 123

Using a 10% non-response rate (10% of 123 = 12.3), the final sample size was 123 +12 = 135 for each group giving a total of 270 subjects.

2.4. Sampling technique

All **c**onsecutive consenting and eligible Preeclamptic women were enrolled from the antenatal clinic and labour ward following diagnosis of Preeclampsia. After selecting a study participant, a consenting and eligible healthy normotensive pregnant woman who matched for gestational age was enrolled to serve as the control. The recruitment was done until the desired sample size (135 in each group) was achieved.

2.5. Data collection

After obtaining informed consent from each eligible participant, their socio-demographic characteristics were obtained and documented in a structured proforma. The proforma contained information on age, parity, and gestational age at recruitment. The folder of each participant was tagged for easy identification.

2.6. Study procedure

An average of 6 preeclamptic women, and an equal number of normotensive mothers, were expected to be recruited weekly but it took eleven months to recruit the desired sample size. Five milliliters (5mls) of venous blood were collected from the antecubital vein using a sterile disposable syringe and transferred to a sterile plain bottle. The blood sample was then allowed to stand for 30 minutes to clot and then centrifuged by a medical laboratory Technician to separate serum from cells. Serum obtained was stored at a temperature of -200C. Analysis of the serum samples was done at the chemistry laboratory of the Rivers State University (RSU) by a medical laboratory scientist, using Atomic Absorption Spectrophotometry (Buck Scientific, AAS/AES Model 205) after acid digestion.

AAS is an analytical technique that is used to measure the concentration of elements in blood or urine samples. The technique is based on the principle that atoms generated by the spectrophotometer from the elements absorb light waves. The concentration of the element is derived from the degree of absorption [34].

2.7. Data analysis

Data was entered into an Excel sheet and analyzed using the IBM SPSS® software version 20. The data were presented as tables and figures. Categorical measurements were given as numbers and percentages, and numerical measurements as mean and standard deviation. The Chi-square test, Mann-Whitney or Fisher exact test, and ANOVA tests were used for statistical analysis of non-continuous and continuous variables as appropriate. Multivariate logistic regression analysis was used to determine the significant association between selenium levels and incidence and severity of preeclampsia, and statistical significance was set at $P<0.05$ with a confidence interval of 95%.

3. Results

Table 1 shows the maternal demographic characteristics of respondents. Most of the respondents were within the age range of 21-30 years, 92(68.15%) in the preeclamptic group, and 86(48.31%) in the normotensive group. No

statistically significant difference was observed (*P*=0.637) in the age distribution. The mean age was 28.59 ± 4.54 years in the preeclamptic group and 29.19 ± 4.20 in the normotensive group (t =1.13; *P*=0.261).

Table 1 Comparison of Maternal characteristics of preeclamptic and normotensive women

Variables	Maternal Status		χ2/t-test/ Mann-Whitney	*p*-value
	Preeclamptic n=135 (%)	Normotensive n=135 (%)		
Age group (years)				
≤20	1 (0.74)	2 (1.48)		0.637 γ
21-30	92 (68.15)	86 (48.31)		
31-40	42 (31.11)	47 (34.81)		
Mean (SD)	28.59 ± 4.54	29.19 ± 4.20	1.13μ	0.261
Median (Range)	28.0 (19-38)	29.0 (19-40)	1.85 α	0.173
Marital Status				
Married	126 (93.33)	129 (95.56)	0.28	0.595
Single	9 (6.67)	6 (4.44)		
Parity category				
0	78 (57.78)	81 (60.0)	0.83	0.659
1	33 (24.44)	27 (20.0)		
2+	24 (17.78)	27 (20.0)		
Mean (SD)	0.70 ± 1.01	0.70 ± 1.02	0.00μ	1.000
Mode	0	0		
Gestational Age				
Preterm (<37 weeks)	84 (62.22)	84 (62.22)	0.02	0.900
Term (37-41 weeks)	51 (37.78)	51 (37.78)		
Mean (SD)	34.92 ± 3.95	34.92 ± 3.95	0.00μ	1.000

*Statistically significant (p<0.05); χ2=Chi-Square (compares proportional differences); μ=Student t-test (compares mean differences), γ=Fisher's Exact, α=Mann-Whitney (compares median differences)

Most of the respondents were married in both groups, 126(93.33%) for the preeclamptic group and 129(95.56%) for the normotensive group (*P*=0.595). Nulliparous women were higher in both the preeclamptic group, 78(57.78%), and the normotensive group, 81(60.0%). No statistically significant difference was observed in the parity distribution (*P*=0.659). Additionally, the mean parity was 0.70 ± 1.01 in the preeclamptic group and 0.70 ± 1.02 in the normotensive group (t =0.00; *P*=1.00). Also, the mean gestational age was 34.92 ± 3.95 in the preeclamptic group and 34.92 ± 3.95 in the normotensive group (t =0.00; *P*=1.00).

Table 2 shows a comparison of serum levels of selenium in preeclamptic and normotensive pregnant women. There was a significant difference between serum levels of selenium in preeclamptic and normotensive pregnant women. The preeclamptic group showed a reduced mean serum level of selenium (0.52 ± 0.31) compared to the normotensive pregnant women (0.73 ± 0.24) (t=6.13; *P*=0.001).

Table 3 Compared the serum level of selenium in preeclamptic and normotensive pregnant women using bi-variate logistics regression. A significant association between serum levels of selenium in preeclamptic and normotensive pregnant women was seen. Preeclamptic pregnant women showed a more considerable proportion of serum selenium deficiency than normotensive pregnant women (77.04% vs.22.96% *P*=0.003). The bi-variate logistic regression analysis

showed that preeclamptic pregnant women were 3.6 times more likely to have a deficiency in serum levels of selenium compared to normotensive pregnant women (OR=3.61; *P*=0.001; 95%CI: 2.13-6.10).

Table 2 Comparison of serum level of selenium in preeclamptic and normotensive women

Variables	**Maternal Status**		**Student t-test/ Mann-Whitney**	***p*-value**
	Preeclamptic n=135 (%)	Normotensive n=135 (%)		
Serum selenium level				
0.012-0.40	52 (38.52)	14 (10.37)		
0.41-0.76	52 (38.52)	51 (37.78)		
0.77-1.0	19 (14.07)	57 (42.22)		
1.01-1.46	12 (8.89)	13 (9.63)		
Mean (SD)	0.52 ± 0.31	0.73 ± 0.24	6.13 μ	0.001*
Median (Range)	0.41 (0.01-1.46)	0.76 (0.17-1.25)	38.99 α	0.001*

*Statistically significant (p<0.05); μ=Student t-test (compares mean differences), α=Mann-Whitney (compares median differences)

Table 3 Comparison of serum level of selenium in preeclamptic and normotensive women using bi-variate logistics regression

Variables	**Preeclamptic (n=135)%**	**Normotensive (n=135)%**	**χ2**	**OR (95% CI)**	***P*-value**
Serum selenium level					
Deficiency (≤0.76 μmol/L)	104 (77.04)	65 (48.15)	22.84	3.61 (2.13-6.10)	0.001*
Normal (0.762-1.91 μmol/L)	31 (22.96)	70 (51.85)			

*Statistically significant (p<0.05); χ2=Chi-Square; Bi-variate logistic regression, OR=Odds Ratio

Table 4 Comparison of mean serum level of selenium in preeclamptic and normotensive women using bi-variate logistics regression

Variables	**Maternal Status**		**Mean Δ in SLS (Difference)**	**Student t-test**	**p-value**
	Preeclamptic (n=135)	**Normotensive (n=135)**			
	Mean ± SD	Mean ± SD			
Serum level of selenium					
Mean (SD)	0.52 ± 0.31	0.73 ± 0.24	-0.207	6.13	0.001*

*Statistically significant (p<0.05)

Table 4 shows the relationship between low serum selenium levels and the incidence of Preeclampsia. Low serum selenium level was significantly associated with the incidence of Preeclampsia, as preeclamptic women showed a 0.207 decrease in serum level of selenium compared to normotensive pregnant women, and this difference was statistically significant (t=6.13; *P*=0.001).

Regarding the number of preeclamptic women with mild and severe preeclampsia, most of the patients had severe preeclampsia, 126(93.33%), and the rest, 9(6.67%) had mild preeclampsia. There was no significant difference in the serum level of selenium in patients with mild or severe preeclampsia, even with a reduced serum level of selenium seen in severe preeclampsia (0.51 ± 0.32) compared to mild preeclampsia (0.66 ± 0.28) (t=1.50; *P*=0.136).

Table 5 compares the serum level of selenium in mild versus severe preeclamptic pregnant women using bi-variate logistics regression. There was no significant association between serum levels of selenium in preeclampsia status (*P*=0.722).

Table 5 Comparison of serum level of selenium in mild and severe preeclampsia using bi-variate logistics regression

Variables	**Preeclampsia status**		**χ2**	**OR (95% CI)**	***P*-value**
	Severe (n=126)%	**Mild (n=9)%**			
Serum selenium level					
Deficiency (≤0.76 µmol/L)	98 (77.78)	6 (66.67)	0.13	1.75 (0.41-7.45)	0.722
Normal (0.762-1.91 µmol/L)	28 (22.22)	3 (33.33)			

*Statistically significant (p<0.05); χ2=Chi-Square; OR=Odds Ratio

4. Discussion

The results obtained from this study showed no significant difference in socio-demographic characteristics in both groups. The groups' similarity supports the assumption that any differences observed in the serum selenium parameter is most likely attributable to the preeclampsia status and not due to any extraneous variables.

This study shows that most of the participants were in the age range 21-30 years in both groups and there was no significant difference in the mean age. This is similar to the findings in a recent study in Nigeria where the participants were aged 25-29 years [35]. A nested case-controlled study in Iran also showed no significant difference in age between the preeclamptic and normotensive groups [36]. However, a registry-based study in Finland concluded that preeclampsia was more likely to occur at advanced maternal ages than in younger women [37]. Preeclampsia occurred more commonly in younger women in this study and other studies in Nigeria and the reason may be because the median age at first childbirth in women aged 25-49 years in Nigeria is 20.2 years [38]. This means that most pregnant women in Nigeria will be younger women in their twenties and as such will form the bulk of participants in studies involving pregnant women.

This study shows that there was no significant difference in parity in both groups, as most of the participants in both groups were nulliparous. A similar finding was seen in a study in Brazil [28]. This further strengthens the theory that preeclampsia is a disease of primigravida. In this study, the participants were matched for gestational age. The mean gestational age was 34.92 ± 3.95 weeks. This was not an unexpected finding since greater than 90% of preeclampsia occurs after 34 weeks gestation (late-onset preeclampsia) [39]. A study in 2017 showed preeclampsia occurred more in the early third trimester, the mean gestational age at occurrence of preeclampsia in that study was 36.93 ± 0.46 weeks [40]. This is like findings in this study. Early-onset preeclampsia (when it occurs before 34 weeks) is uncommon.

Most of the participants in this study were married with no statistically significant difference in terms of marital status between the two groups. A case-control study conducted in Thailand showed no evidence of associations of preeclampsia with maternal characteristics such as maternal marital status, level of education, or employment status during pregnancy [41].

Selenium levels can be compared reliably in both the preeclamptic and normotensive groups in this study since there was no significant difference in terms of socio-demographic characteristics between both groups. Selenium deficiency has severally been linked to the occurrence of disease entities like preeclampsia and cancers [23-25]. This study showed

that there was a significant difference in the level of serum selenium between the preeclamptic and normotensive groups. The selenium levels were significantly lower in the preeclamptic group than in the normotensive group.

Several researchers have given conflicting reports on the level of serum selenium in preeclamptic women compared to healthy pregnant women. Ikechukwu et al in a study in Enugu, Nigeria also showed significantly lower levels of selenium and other trace metals in women with preeclampsia compared to healthy pregnant women [27]. A recent study in Nigeria showed a significantly reduced level of serum selenium among preeclamptic compared to normotensive women [35]. Also a case-control study in Iran published in 2011 showed that the mean plasma level of selenium was significantly decreased in preeclamptic compared to healthy pregnant women, a finding similar to this study [42]. Moreover, a more robust systematic review and meta-analysis is also in agreement with the findings of this study [29]. The researchers also concluded that selenium supplementation significantly reduced the incidence of preeclampsia.

Some other researchers have found no significant difference in the level of serum selenium in both preeclamptic women and healthy normotensive controls. A cross-sectional survey in a city close to the RSUTH showed no statistically significant difference in the level of selenium, zinc, and copper in both preeclamptic and normotensive groups [43]. Also a case-control study in Brazil involving only 32 normotensives, 20 hypertensives (pregnancy-induced and chronic hypertension), and 38 Preeclamptic women showed no statistically significant difference in the level of selenium in all 3 groups [28]. Another study done in 1996 in the United Kingdom (UK) did not show any difference in the level of serum selenium in healthy pregnant women [44]. One study in the United States of America even reported a higher level of selenium in preeclamptic compared to normotensive women [45]. Findings from all these studies can not be disregarded, however other factors which may influence selenium levels like nutrition, geographical location and ethnicity should be considered.

Findings from this study showed that preeclamptic pregnant women were 3.6 times more likely to have a deficiency in serum levels of selenium compared to normotensive pregnant women. This clearly shows that pregnant women with selenium deficiency are at risk of having preeclampsia. This may mean that selenium supplementation may be beneficial. A study in Nigeria had a similar finding [35]. However, this study found no statistically significant difference in the level of selenium in those with severe preeclampsia and mild preeclampsia, which means that the level of selenium is not a key determinant of the severity of preeclampsia, as there may be other factors that influence severity. However, the small proportion of mild preeclamptic women of 6.67% in this study, might have influenced this finding. A study in Nigeria has shown that serum selenium levels were significantly lower in those with severe disease than in those with mild disease [35].

Limitations

The limitation of this study is the fact that it was an institutional and a single-center study hence the findings can not be generalized. Also, the sampling technique used in this study to enroll participants should have been randomized to eliminate all possible biases.

5. Conclusion

This study showed that pregnant women with selenium deficiency were 3.6 times more likely to develop preeclampsia compared to healthy normotensive pregnant women. The study, however, did not find a significant difference between levels in mild compared to severe preeclamptic women and therefore does not support selenium levels as prognostication for the severity of the disease.

It is recommended that a multi-center randomized study on the relationship between serum selenium deficiency and preeclampsia be carried out. Further studies should explore the possibility of selenium supplementation in pregnant women as a randomized control trial to see the benefit in the prevention of preeclampsia in high-risk patients.

Compliance with ethical standards

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Disclosure of conflict of interest

No conflict of interest statement.

Statement of ethical approval

Before the sample and data collection, the proposal was submitted to the RSUTH Research and Ethics Committee, as the study involved human subjects. An ethical clearance letter (RSUTH/REC/2020020) was obtained.

Statement of informed consent

Informed written consent was obtained from all participants included in the study.

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