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Serum Cortisol, Lipid Profile and Microalbumin Levels in Newly Diagnosed Adult Hypertensive with and without Malaria Infection in Nnewi, Nigeria

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Abstract

Malaria and Hypertension are among the important public health challenges in sub-Saharan Africa including Nigeria. Microalbuminuria and dyslipidemia have been regarded as two predictors of cardiovascular and renal dysfunction. This study is a hospital-based cross-sectional study designed to evaluate the serum cortisol, lipid profile, and microalbumin levels in adults hypertensive with and without malaria attending Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State, Nigeria. One hundred and fifty adult volunteers were randomly recruited from the nephrology clinic for the study. 50 of them were newly hypertensive individuals (20 males and 30 females), 50 were newly hypertensive with malaria infection (25 males and 25 females), and 50 were normotensive participants (26 males and 24 females) within the age range of 30-90 years. Methods: A blood sample was collected from each of the participants for assaying lipid profiles (total cholesterol, triglycerides, low-density lipoprotein (LDLc) and high-density lipoprotein cholesterol (HDLc), cortisol, and microalbumin) using enzymatic methods. Peripheral malaria was determined using rapid detection and Giemsa stain techniques. Results: The mean serum cortisol, TC, LDL-C, triglycerides, and microalbumin levels were significantly higher, while HDL-C was lower in hypertensive individuals with or without malaria parasite infection than normotensive individuals ($p \leq .05$, respectively), though higher in malaria-infected individuals. Body mass index (BMI), waist-to-hip ratio (WHR), systolic blood pressure (SBP), and diastolic blood pressure

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(DBP) were significantly higher in hypertensive individuals with or without malaria infection than in normotensive individuals (p≤.05). Conclusions: There is established evidence of risk factors for cardiovascular diseases and renal dysfunction, which were more severe in hypertensive patients with malaria infection. Hence, monitoring hypertensive patients for malaria infection is very necessary and should be a routine check to curb complications and disease progression in this population.

Keywords*: hypertension, malaria, cortisol, lipid profile, microalbumin, Nigeria.*

Introduction

Hypertension is currently defined as a sustained elevation of blood pressure with systolic and diastolic blood pressure values of >130/80 mmHg.[1] The combined effect of hypertension and malaria would pose a greater disease burden with resultant adverse cardiovascular and renal effects, which may lead to increased morbidity and mortality, especially in developing countries, Nigeria included.[2-4] The prevalence of hypertension is higher among blacks than whites, and it increases with advancing age in all groups.[5-6] Malaria is very common and endemic in about 32 countries in Sub-Saharan Africa, with about 93% of malaria deaths globally. Nigeria has the highest burden of P. falciparum malaria infection, with a mortality rate of about 31.9 percent compared with other African countries.[7] Currently, some interventions, programs, and strategies have before now introduced to help eliminate malaria worldwide, this include, Roll Back Malaria (RBM) initiative which was designed for quick malaria detection, treatment, and prevention[8], the WHO Global Technical Strategy for eradication of Malaria within 2016–2030[9], E−2025 initiative; another WHO initiative to reduce the spread of malaria in twenty-five countries[10] and locally, in Nigeria and some African countries; the National Malaria Control Program (NMCP), the National Malaria Elimination Program (NMEP), the National Malaria Strategic Plan[11], and Nigeria End Malaria Council program.1[2] All these plans, if run effectively, would go a long way in ameliorating the spread of malaria and its adverse health conditions, especially in the endemic countries.

Microalbuminuria is a multifactorial condition that has some cardiovascular and renal implications from malaria infection as well as hypertensive disorders.[13] It is a powerful indicator of endothelial and glomerular dysfunction associated with various diseases in which the albumin excretion in the urine is above the clinically detectable limit of 20–200 mg/min or 30-300 mg/day.[13-14] Microalbuminuria has been reported in nondiabetic hypertensive populations, with some prognostic implications that have been associated with increased cardiovascular morbidity and mortality.[15-17] Reducing albuminuria is a useful therapeutic goal to minimize end-organ damage.[18] The albumin molecule is relatively small and is often the first protein to enter the urine after the kidney is damaged. Glomerular hyperfiltration has also been linked to higher levels of albumin excretion, causing hypertension and a reduction in nephrons by increasing the activity of the renin-angiotensin system, which predisposes the individual to a higher risk of cardiovascular events.[19] Microalbuminuria not only predicts cardiovascular risk but also seems to be a sensitive marker for detecting the onset of other cardiovascular events.[20]

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The lipid profile, additionally, is a panel of blood tests that serve as an initial screening tool for abnormalities in lipids, such as cholesterol. It is an index for determining the susceptibility of an individual to hypertension. The profile is used to determine the risk of coronary heart disease. The concentration and relative ratio of lipids to one another are among the best indicators of whether an individual is susceptible to heart attack or stroke resulting from atherosclerosis or blockage of the blood vessels.[21-23] Many believe that a sharper prediction of risk is provided by the measurement of serum TC and HDL-C levels. It has also been documented that the presence of hyperlipidemia substantially worsens the prognosis in hypertensive patients.[24] The increased cardiovascular morbidity and mortality associated with microalbuminuria in nondiabetic hypertensive patients may partly be related to their serum lipid abnormalities, particularly reductions in high-density lipoprotein cholesterol and elevations in low-density lipoprotein cholesterol and lipoprotein (a). Thus, adverse lipid profiles may contribute not only to the development of microalbuminuria in hypertension and malaria but also correlate with cardiovascular morbidity and mortality.[25] Acute kidney injury (AKI) has been reported in adult patients in malaria-endemic areas due to acute tubular necrosis and maldistribution of microvascular blood flow, with a higher mortality rate if immediate renal replacement therapy (RRT) is not initiated.[26-27]

Elevated serum cortisol, on the other hand, has been associated with increased secretion of microalbumin in urine, even in the normal range, leading to kidney dysfunction and other cardiovascular diseases.[28-30] Cortisol is a kind of glucocorticoid hormone whose elevation can alter many metabolic processes through disturbances of its regulatory and effector pathways.[31] The alterations can result from both environmental factors (stress) and the presence of non-communicable diseases leading to obesity, hypertension, dyslipidemia, osteoporosis, arteriosclerosis, and other cardiovascular diseases.[32] Stress has been associated with the imbalances of the hypothalamic-pituitary-adrenal (HPA) axis, causing the secretion of corticotrophin-releasing hormone (CRH) and adrenocorticotrophic hormone (ACTH), which in turn stimulates the adrenal cortex to secrete cortisol hormone and, through the feedback mechanisms, can alter immune function.[33] Raised serum cortisol levels have been shown to correlate with hyperfiltration in hypertensive patients with increased malaria susceptibility.[34-35] However, the actual mechanism behind the possible changes in serum cortisol, lipids, and microalbumin levels in hypertensive subjects in malaria-endemic regions, including Nigeria, remains elusive, hence the present study.

Materials And Methods

Study design

This is a hospital-based cross-sectional study designed to assess serum cortisol, microalbumin, and serum lipid profile levels in adult hypertensive individuals with malaria infection attending Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State, Nigeria. A total of one hundred newly diagnosed adult hypertensive participants (hypertensive only, n = 50 (20 males and

30 females) and (hypertensive with malaria infection, n = 50 (20 males and 30 females) and 50 normotensive participants without malaria infection (26 males and 24 females) within the age range of 30-90 years were recruited for this study. All subjects were screened for malaria parasitemia (asymptomatic).

Study area

The participants for this study were recruited from the nephrology clinic nephrology clinic of Nnamdi Azikiwe University Teaching Hospital, Nnewi, between June and October 2022. Only the participants who voluntarily agreed to participate were subsequently enrolled in the study.

Data collection

Sociodemographic data and history were obtained, a physical examination was carried out, and anthropometric measurements were taken during the subjects' visit to the hospital. Blood pressure was taken from the left arm after 5 minutes of relaxation in a sitting position using a standard mercury sphygmomanometer with an appropriate cuff size; systolic (SBP) and diastolic (DBP) blood pressure readings were taken. Height and body weight were measured, and body mass index (BMI) was calculated as weight divided by height squared (kg/m2). Hip and waist were measured to the nearest 1 cm, and waist-to-hip ratio (WHR) was calculated as waist circumference divided by hip circumference.

Inclusion and exclusion criteria

Newly diagnosed adult hypertensive subjects with an age range of 30-90 years were recruited for the study. Hypertensive subjects who were already on antihypertensive medications were not recruited for this study. Other exclusion criteria include prior diagnosis of diabetes mellitus, pregnancy, obesity, patients with overt proteinuria or congestive heart failure, current or recent intake of drugs such as statins, beta blockers, etc. that affect lipid metabolism, and corticosteroids.

Sample collection

Five milliliters (5 ml) of venous blood were collected from each of the subjects and dispensed into a well-labeled plain container and an EDTA container. The plain sample was allowed to clot, and centrifugation was performed at 1500 rpm for 5 minutes using a bench centrifuge, and the serum was separated. The sample was stored at -20 degrees centigrade (-20°C) until the analyses for fasting lipid profile and serum cortisol. Microalbumin was done on first morning urine samples of both patients and controls. A well-structured questionnaire was administered to each participant to obtain their biodata. Other medical histories were obtained from their records.

Laboratory analysis

The participants were screened for malaria using an Abbot Malaria Rapid Test (RTD) kit as described by Abbot Laboratories and the Giemsa staining technique for antigens detection. The test qualitatively detects Plasmodium antigen in human whole blood samples. This test applies lateral flow immunochromatography, which is a tool in the diagnosis of malaria. The determination of total cholesterol (TC), HDL, and LDLc was done using the enzymatic method.36 The triglycerides were determined after enzymatic hydrolysis with lipases. Cortisol was also determined using the enzyme-linked immunosorbent assay (ELISA) kit method as described by Abbott Laboratories. Microalbuminuria was determined using the URIT 13G urine test strips and the URIT 50 Urine Stripe Reader.

Ethical approval

The ethical approval of this study was obtained from the board of ethics committee of Nnamdi Azikiwe University Teaching Hospital, Nnewi, Anambra State, Nigeria. Informed consent from the subject was sought and obtained before the study.

Statistical analysis

Statistical Package for Social Sciences (SPSS) version 22 was used for the statistical analysis. The data generated was analyzed using an analysis of variance (ANOVA) to compare more than two independent variables and a student's t-test for two independent variables. Pearson correlation was used to correlate different parameters. Values were considered statistically significant if the p-value was ≤ 0.05.

Results

Anthropometric characteristics of hypertensive, hypertensive with malaria, and control participants

The mean age of the hypertensive participants (60.46+ 12.93) and hypertensive with malaria infection (58.05±14.93) were significantly higher when compared with control participants (41.27± 12.71) ($p<0.05$, respectively). The mean SBP and DBP in hypertensive participants (151.38±32.67, 108.60±24.78) and hypertensive participants with malaria infection (168.93±34.26, 116.11±26.06) were significantly higher when compared with control (111.35±8.67, 88.00±10.05) participants ($p<0.05$, respectively). The blood pressure was significantly higher in hypertensive with malaria parasite infection compared with their counterparts without malaria infection ($p<0.05$). Furthermore, the mean values of BMI and WHR were significantly higher in hypertensive (31.21±9.27, 1.24±0.36) and hypertensive with malaria infection (29.54±11.03, 1.18±0.05) when compared with control participants (24.12±5.04, 0.92±0.13) ($P<0.05$ respectively) though, BMI was significantly higher in hypertensive compared with those with malaria infection ($p<0.05$) (table 1).

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Table 1. Anthropometric characteristics of Hypertensive, Hypertensive with malaria, and control participants

Groups	Age (years)	SBP HHmg	DBP HHmg	BMIKg/m2	WHR (cm)
Hypertensive (A) (n -50)	60.46±12.93	151.38±32.67	108.60±24.78	31.21±9.27	1.24±0.36
Hypertensive with mal (B) (n -50)	58.05±14.93	168.93±34.26	116.11±26.06	29.54±11.03	1.18±0.05
Control (C) (n -50)	41.27±12.71	111.35±8.67	88.00±10.05	24.12±5.04	0.92±0.13
F- value	4.890	41.538	8.704	7.597	19.002
P- value	0.000	0.000	0.000	0.000	0.000
A vs B	0.331	0.016	0.010	0.431	0.618
A vs C	0.000	0.000	0.001	0.000	0.000
B vs C	0.000	0.000	0.000	0.000	0.000

Key: SBP (systolic blood pressure), DBP(diastolic blood pressure), BMI(body mass index), WHR(waist-hip-ratio), MA (microalbumin), TC(total cholesterol), TG (triglycerides), HDL-C(high-density lipoprotein cholesterol), LDL-C(low-density lipoprotein cholesterol), VLDL-C (very low-density lipoprotein cholesterol).

Levels of cortisol (ng/ml), Microalbumin (mg/l), and lipid profile (mg/dl) in Hypertensive, Hypertensive with malaria, and control participants

The mean TC, TG, LDL VLDL were significantly higher in hypertensive (212.24 ± 44.61, 128.14 ± 56.20; 145.22 ± 42.68; 20. 40+10.90), hypertensive with malaria (248.01±46.43, 167.31±59.01, 152.64±47.09, 26.12±8.71) when compared with control participants (174.07 ± 18.72, 104.03 ± 34.05, 108.17 ± 18.03, 20.80 ± 6.86) ($p<0.05$ respectively). However, the mean serum HDL was significantly lower in hypertensive and hypertensive with malaria infection (39.96 ± 9.98, 33.87±6.47) when compared with control participants (45.00 ± 8.49) ($p<0.05$, respectively). The abnormal lipid profile was significantly higher in hypertensive patients with malaria infection when compared with their hypertensive counterparts ($p<0.05$). The mean microalbumin level in hypertensive participants with malaria infection (86.43±39.31) was significantly higher when compared with the value in control participants (71.33±20.59) ($p<0.05$). Furthermore, the mean cortisol level was significantly higher in hypertensive (101.17±32.19) and hypertensive with malaria infection (138.37±33.46) participants when compared with control participants (81.64±29.62) ($p<0.05$, respectively). Similarly, the mean cortisol level was significantly higher in hypertensives with malaria infection (138.37±33.46) when compared with hypertensives without malaria infection (101.17±32.19) ($p<0.05$) (table 2).

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Table 2. Levels of cortisol (ng/ml), Microalbumin (mg/l), and lipid profile (mg/dl) in Hypertensive, Hypertensive with malaria, and control participants

Groups	TC	TG	HDL	LDL	VLDL	MA	Cortisol
Hypertensive (A) (n -50)	212.24±44.61	128.14±56.20	39.96±9.98	145.22±42.68	25.40±10.90	77.26±36.21	101.17±32.19
Hypertensive with mal (B) (n -50)	248.01±46.43	167.31±59.01	33.87±6.47	152.64±47.09	26.12±8.71	86.43±39.31	138.37±33.46
Control (C) (n -50)	174.07±18.72	104.03±34.05	45.00±8.49	108.17±18.03	20.80±6.86	71.33±20.59	81.64±29.62
F- value	7.838	7.038	4.294	8.028	6.701	6.625	7.402
P- value	0.000	0.000	0.014	0.000	0.011	0.022	0.000
A vs B	0.000	0.000	0.021	0.035	0.659	0.032	0.006
A vs C	0.000	0.000	0.006	0.000	0.003	0.423	0.001
B vs C	0.000	0.000	0.000	0.000	0.001	0.010	0.000

Key: TC (total cholesterol), TG (triglycerides), HDL-C (high-density lipoprotein cholesterol), LDL-C (low-density lipoprotein cholesterol), VLDL-C (very low-density lipoprotein cholesterol).

Correlation of parameters in hypertensive patients with and without malaria infection.

The results show the correlation of some parameters in newly hypertensive patients with and without malaria infection. Age, SBP, DBP, and BMI were inversely correlated with HDL and microalbumin ($p<0.05$, respectively). Microalbumin was positively correlated with LDL and TC ($p<0.05$, respectively) in both hypertensive patients with and without malaria infection. BMI was positively correlated with age and SBP ($p<0.05$, respectively). Age was also positively correlated with SBP and DBP ($P<0.05$) (table 3).

Table 3. Correlation of parameters in hypertensive with and without malaria infection

Group	Hypertensive (n=50)		Hypertensive with mal (n=50)	
Parameter	R	P- value	R	P -value
Age vs BMI	0.480	0.032	0.495	0.049
Age vs SBP	0.419	0.001	0.491	0.010
Age vs DBP	0.348	0.042	0.336	0.049

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BMIvs SBP	0.540	0.021	0.560	0.018
SBP vs MA	-0.485	0.038	-0.521	0.043
Age vs MA	-0394	0.045	-0.587	0.001
BMI vs MA	-0.577	0.009	-0.592	0.000
HDL vs MA	-0.505	0.010	-0.569	0.006
LDL vs MA	0.587	0.002	0.602	0.000
TC vs MA	0.487	0.026	0.527	0.040

Key: SBP (systolic blood pressure), DBP (diastolic blood pressure), BMI (body mass index), MA (microalbumin), TC (total cholesterol), TG (triglycerides), HDL-C (high-density lipoprotein cholesterol), LDL-C (low-density lipoprotein cholesterol)

Discussion

Malaria and Hypertension are among the important public health challenges in sub-Saharan Africa, including Nigeria. Microalbuminuria and dyslipidemia are also important predictors of cardiovascular and renal dysfunction. The study was designed to assess the impact of malaria infection on serum cortisol, lipid profile, and microalbumin in newly hypertensive adult individuals. The results revealed that the mean serum levels of TC, TG, LDL, VLDLc were significantly higher, while the high density of lipoprotein cholesterol was significantly lower in hypertensive participants with and without malaria infection when compared with control participants. This indicates a significant degree of hyperlipidemia, which is more severe in those with malaria parasite infections. Previous findings in hypertensive individuals have shown similar observations.[37-38] Some authors have also observed abnormal changes in lipid profile in malaria infection.[39-40] Higher levels of these lipids may be attributed to physical inactivity, stress, increased age, alcohol consumption, high consumption of dietary fat, and others. This study was done on newly diagnosed hypertensive patients with asymptomatic malaria, and an increased lipid profile has been reported previously both in untreated hypertension and uncomplicated malaria elsewhere.[41] Although the rationales for the alterations in lipid profile during hypertension and malaria infection have not been clearly understood, the acute phase response has been implicated.[42] Serum TG levels are increased due to increased very-low-density lipoprotein cholesterol secretion as a consequence of fat tissue lipolysis.[43] Also, the exact mechanism by which a low HDL-C increases CVD risk is still not well understood, though studies have documented the possible impact of HDL-C in promoting cholesterol transport from foam cells to biliary excretion.[44] Hypertension and malaria pose a major health and economic burden globally, leading to an overall increase in abnormal lipids and predisposing individuals to the risk of developing cardiovascular diseases.[45-47] Malaria, on the other hand, can upset the blood pressure control system as well as the vascular pathways that cause inflammation leading to hypertension, which may result in fibrosis, heart failure, and other adverse cardiovascular injuries.[48]

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Hyperlipidemia has also been shown to exacerbate hypertension, causing ischemic stroke, arteriosclerosis, and heart attacks.[49] The overall negative effects of these disease conditions may worsen the health burden of the affected individuals, especially in Nigeria, which is endemic for malaria infection with a high prevalence rate of hypertension.[50] Some reports have noted that hypertension is more common in high malaria-endemic regions, thereby implicating malaria as the main cause of hypertension.[51-52] However, reports have shown that polymorphisms in the angiotensin-converting enzyme (ACE) gene that increase the levels of angiotensin II (Ang II) could have some impact on hypertension as well as protection against malaria.[53-54] Malaria and hypertension have previously been associated with adverse pregnancy disorders, including gestational hypertension and preeclampsia.[55-56] It has been documented that children who were born to women with this type of disorder may have increased incidences of hypertension during their adult lives.[57-58] A previous report shows that children born by mothers who had malaria episodes during pregnancy experience blood pressure elevation during their first year.[59] This may have contributed to increased occurrences of adult hypertension seen in malaria-endemic regions.[60-61] Malaria and hypertension can synergistically cause arterial stiffness and serious inflammatory reactions, which can progressively linger through adult life (Etyang et al., 2016). Reports have shown that since blood pressure levels run through adulthood, the variations can enhance the occurrence of adult hypertension in children of hypertensive mothers who had some episodes of malaria attack during pregnancy periods.[62-63] This intermingled relationship between pregnancy-induced hypertensive disorders and malaria infection may have increased the risk of essential hypertension in women even after pregnancy.[64]

The study also observed significantly higher levels of urine microalbumin in hypertensive participants with or without malaria infection compared with control participants. This is consistent with previous studies.[65-66] The authors reported that microalbuminuria is a common finding in adults with hypertension, including malaria infection, which is a common coronary risk factor that occurs as a result of increased lipid abnormalities. As in our study, BMI as well as dyslipidemia were associated with microalbuminuria and may add to the increased cardiovascular risk in hypertensive individuals.[67] The reason for the association between microalbuminuria and serum lipid profile has not been fully established, though microalbumin has been well-recognized as a marker for endothelial dysfunction and inflammation in high blood pressure.[68] Abnormal serum lipid may enhance the occurrence of severe microalbumin due to lower HDLc and higher LDLc levels, leading to the development of kidney diseases.[69] While microalbumin, on the other hand, may indicate or precede the development of high blood pressure and can be the cause of dyslipidemia.[70] These further explain the observed association of age with hypertension as well as malaria infection, which is consistent with previous reports by Schwartz *et al*. [71] and Checkley *et al.* [72]. Furthermore, it has been noted that the inflammatory pathways activated by malaria infection could contribute to the burden of hypertension and malaria.[73-74] The inflammatory responses caused by the compound effects of stress, abnormal lipids, malaria, and hypertension could have a very severe impact on the kidneys and may have contributed to the microalbuminuria observed. This may have a progressive adverse effect on the cardiovascular health of the affected individuals. As in our study, the authors reported increased serum cortisol levels in asymptomatic malaria-

infected individuals with hypertension. Previous studies noted that in healthy individuals, cortisol shields the body from stress by controlling the blood pressure and immune function through a negative feedback loop mechanism, even though stress could break the feedback mechanism, thereby increasing the cortisol and corticosteroid-releasing hormone (CRH) levels with resultant inflammatory responses that may lead to adverse health conditions.[75] Some authors reported increased cortisol levels in malaria-infected individuals[76], while others reported higher serum cortisol levels in malaria individuals with hypotension.[77] This may be the reason for not using corticosteroids in malaria therapy.[78] The variations in these studies may be attributed to the level of stress induced by different diseases.[79] However, it has been suggested that serum cortisol levels should be elevated during stress to reduce the crisis.[80] The combined burden of malaria and hypertension can induce enough stress on the body, which may have caused the observed increase in this study. Additionally, our study was done on newly diagnosed hypertensive patients with asymptomatic malaria infection, which may indicate the presence of an acute stress condition. The hypertensive patients had significantly higher BMI and WHR than the controls. This observation may be due to common risk factors for hypertension, obesity, and dyslipidemia, as well as cardiovascular diseases. Obesity is known to play a major role in the causation of microalbuminuria in hypertension and the sustenance of metabolic syndrome.[81-82] However, the significant association between hypertension and microalbuminuria in our study has been attributed to enhanced systemic arterial blood pressure, which increases the pressure in the glomerular capillaries.[83]

Conclusion

In conclusion, the study has demonstrated significant elevation in lipids profile, cortisiol and microalbumin in all the hypertensive participant which is more in those with malaria infection. This suggest increase dyslipidaemia with microalbuminura which may be as a result of combined effects of hypertension and malaria infection and can subsequently lead to disease severity. Timely assessment of lipid profile, microalbumin levels, and malaria screening are strictly recommended in all hypertensive cases to stop further aggravation and the risks of cardiovascular comorbidity and mortality. This would help ameliorate the CVD risk and improve the cost-effectiveness of therapy for the affected patients.

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