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Original Research

Serum Prolactin Levels and Clinical Features of Hyperprolactinaemia in Obese and Non- Obese Infertile Women in Kano, Northwest Nigeria: A Comparative Study

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Abstract

Background: Hyperprolactinaemia can cause infertility. Serum prolactin and clinical features of hyperprolactinaemia may vary between obese and non-obese infertile women. Identifying the differences may inform changes in the management of obese women with hyperprolactinaemia. This study aimed to compare the serum prolactin levels and the clinical features of hyperprolactinaemia in obese and non-obese infertile women in Kano.

Methodology: This was a comparative cross-sectional study comprising 160 obese infertile women (study group) and another 160 non-obese infertile women (control group). Participants were recruited in the gynaecology clinics of Aminu Kano Teaching Hospital (AKTH) and Murtala Muhammed specialist Hospital (MMSH). Serum prolactin and clinical features of those with hyperprolactinaemia were analysed using SPSS 23. P-values ≤ 0.05 were considered significant. Odd ratios at 95% confidence were calculated.

Results: The mean serum prolactin levels were 28.18 ± 10.53ng/ml and 17.50 ±8.00 ng/ml in the obese and non-obese women respectively (P=0.0001). All categories of hyperprolactinaemia were more common (P=0.001) amongst the obese infertile women. The prevalence of hyperprolactinaemia was 37.5% and 18.1% in the obese and non-obese arms respectively (P=0.0001). However, 23.1% obese hyperprolactinaemic infertile women presented with galactorrhoea compared to 64.0% of the non-obese counterparts (P= 0.0001). Abnormal menstrual flow and galactorrhoea were observed more in moderate-markedly elevated serum prolactin level as seen in 65.2% and 69.6% respectively compared to those with mildly elevated serum prolactin level.

Conclusion: Obese infertile women have higher baseline and prevalence of hyperprolactinaemia than their non-obese counterparts. However, non-obese hyperprolactinaemic infertile women presented more with galactorrhoea.

Key words: Clinical Features**;** Hyperprolactinaemia; Infertility; Obesity; Serum Prolactin Level.

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Introduction

Infertility is defined as the inability to conceive after one to two years of unprotected intercourse.[1] Infertility could be caused by male, female or both factors and in some instance the aetiology may be unexplained.[1] Female factor infertility commonly results from tubal factors in developing countries.[2] Other less common factors include cervical and uterine factors as well as anovulatory infertility.[1] Male infertility on the other hand may be due to pre-testicular, testicular and post –testicular causes.[3]

Hyperprolactinaemia, one of the causes of anovulation is defined as serum prolactin level greater than or equals to 25ng/ml in a woman who has not been pregnant nor breastfed for a period of one year or less.[1,4] Its prevalence varies from country to country, amongst studies and population studied. It is said to be on the rise in Sudan,[5] Algeria [6] and in the Northwestern [7-8] part of Nigeria. Globally, it accounts for 5-10% of all anovulatory infertility.[1] In America, the prevalence is reported at 1% and 5 to 14% for the general population and patients presenting with secondary amenorrhoea respectively.[9] In Brazil, the prevalence is 52.9% [3] and 37.9% [10] among infertile patients with pituitary adenoma and other causes of hyperprolactinaemia respectively while in Europe the prevalence is reported at 55.1%.[11] The prevalence of 39.0%,[12] 89.0%,[13] 36.7%[14] as well as 4.9%[15] were reported in Pakistani studies, while in Algeria the prevalence was reported to be 98.9%.[6] In Nigeria, the prevalence ranges between 5.2% to 41.9% [7-8,16-18] amongst infertile women.

Prolactin is a polypeptide hormone with 198 amino acids secreted in pulsatile manner and the stimulus may be physiological or pathological including sleep, stress, pregnancy, chest wall stimulation and trauma.[9,19-20] Other conditions that can cause elevated prolactin level include pituitary adenoma, drugs like antipsychotics, some antidepressants, some antiemetic and some antiulcer drugs.[19-20] Conditions like polycystic ovarian syndrome and primary hypothyroidism have also been documented to cause elevated prolactin levels.[19-20] Occasionally a rise in prolactin levels may be seen for unknown reasons and termed idiopathic hyperprolactinaemia.[19-20]

Recently, evidence for the relationship between obesity and hyperprolactinaemia has increased in literature.[21-25] Obesity refers to a body mass index equal to or greater than 30 kg/m^2.[9,26] Prolactin is reported to affect fat accrual particularly visceral fats.[23] It also affects energy balance and fat metabolism and may enhance lipogenesis.[21-23] Other authors report reduced dopamine (D_2) receptors in the brains of obese individuals.[23] As such, obesity is a possible risk or causal factor for hyperprolactinaemia. Malini and Kumari [24] and Jawad et al [25] noted that serum prolactin level is higher in the obese. However, Kopelman in his study [21] reported a decrease in the serum level of prolactin in the obese while Salo and Das [27] found no relationship between obesity and serum prolactin levels. Different clinical features of hyperprolactinaemia like galactorrhoea, headaches and menstrual irregularities for example, hypomenorrhoea and amenorrhoea have also been documented amongst obese and non-obese and their presentation may be related to serum levels of prolactin in an individual. [21-22]
The relationship between infertility and obesity has since been established. Obesity is associated with menstrual irregularities and chronic anovulation.[28] If pregnancy occurs in the obese, it could lead to miscarriages and poor outcomes in the case of assisted reproduction.[28]

As there is inconsistency in the relationship between obesity and hyperprolactinaemia, studies exploring their relationship are necessary. The findings may help in early diagnosis as well as reducing the overall cost of infertility. The aim of this study was to compare the serum prolactin levels and the clinical features of hyperprolactinaemia in obese and non-obese women managed for infertility in Kano, Northwest Nigeria.

Methods

Study design: This was a comparative cross-sectional study.

Study setting: It was conducted in two hospitals, comprising the Departments of Obstetrics and Gynaecology of Aminu Kano Teaching Hospital (AKTH) Kano and that of Murtala Mohammed Specialist Hospital (MMSH), Kano, Nigeria. The two hospitals are situated in Kano metropolis, which is the urban, central part of the Kano state.

Study population: Obese and non-obese infertile women, attending gynaecologic clinics in the study sites constituted the study population.

Study procedure: The records of patients who presented to infertility clinics with history suggestive of infertility were reviewed in the gynaecology record department of AKTH and MMSH. Infertile women were women who had not conceived within one year of regular and unprotected sexual intercourse.

The case folders of those that met the inclusion criteria were identified, and they were seen in the clinic. They were counselled on the study protocol and a written consent was obtained in the clinic from them as soon as they gave their permission to participate in the study. A proforma was used to record social and reproductive characteristics (excluding names) as well as clinical symptoms from each woman recruited during the study period. The serum prolactin levels of all the respondents and clinical features of those found to have hyperprolactinaemia were recorded and added to the proforma for the final statistical analysis.

Their body weight (kg) and height (m) were measured to the nearest 0.5kg and 0.1 m in light clothing and barefoot using Hospitex® scale made in Italy (Model 210, year 2015, sensitivity 1kg=1kg- 0.1) and a Hospitex® stadiometer also made in Italy (Model 210, year 2015, sensitivity 1m=1m-0.1) respectively. The body mass index (BMI) was calculated in kg/m^2. Those with BMI $\geq 30kg/m^2$ were classified as obese (study group) and those with BMI less than $30kg/ m^2$ were classified as non-obese.[26]

Obese Participants (Study group) were selected via simple random sampling technique from the above population until the sample size was met. The next non obese patient who presented immediately after a recruited patient and who was matched for age (±3 years) and parity (±2) was recruited as control group. They fasted overnight for about eight hours and abstained from sexual contact via nipple and chest wall stimulation for about 24 hours prior to the 2^{nd} or 3^{rd} day of their menstruation, since these acts would alter serum prolactin levels.

The specimen of all the participants was collected on the 2^{nd} or 3^{rd} day of their menstrual flow in the gynaecological ward of AKTH. The onset of their menstruation either spontaneously or following a withdrawal bleed was ascertained via phone call. Withdrawal bleed was achieved using combined oral contraceptive pills (COCP) after excluding pregnancy in those who presented with oligomenorrhoea.

The blood sample was obtained via venepuncture, observing aseptic techniques and after application of tourniquet within the minimum possible time, a 5ml syringe was used by the research assistant to obtain 5ml of venous blood and transfer into gel activator tubes. The specimen bottles were labelled serially with a code made up of the hospital where the owner of the specimen was recruited from and the position at recruitment, for example $\mathbf{M_1}$and $\mathbf{A_1}$denoting number 1 positions and hospitals at recruitment for MMSH and AKTH respectively. The samples collected were taken to the chemical pathology department of AKTH within one hour of collection for centrifugation, storage, and further analysis.

In the chemical pathology department of AKTH, the clotted specimens were centrifuged at 3000rpm for 10minutes to obtain clear, transparent serum without losing proteins other than the clotting factors. The sera were distributed into serum containers with tight screw cap using different Pasteur pipettes for different sample to avoid contamination and they were stored in aliquots of 100µl at -20^{0}C until ready for analysis. Analysis was done in batches at two weeks interval until sample size was achieved. This prevented prolonged storage and deterioration of samples.

All analyses were done with 10µl of stored serum using ELECSYS 2010 auto analyser manufactured by Roche, Germany employing electrochemiluminescence immunoassay (ECLIA) technique which has very high sensitivity and specificity. Both the principal researcher and the chemical pathologist were blinded to the patient's body mass index groups. This technique uses the sandwich principle, with the total duration of assay lasting for 18 minutes.

The results were reported in the conventional chemical pathology forms, and it was subsequently transferred to the proforma bearing the same code and BMI from where it was entered into a computer. The normal serum prolactin level was taken as serum prolactin levels less than 25ng/ml,[29] while Mild, moderate, and marked hyperprolactinaemia were taken as 25 to 50ng/ml, 51 to 100ng/ml and >100 ng/ml respectively.[4]

The prevalence of hyperprolactinaemia for the obese and non-obese was gotten by dividing the total number of women with hyperprolactinaemia in each group by the total number of all the respondents in each group and then multiplied by 100.

All analytical tests were done according to the standard operating procedures. It involved the use of inter and intra-run of control sera along with the samples. Pre-analytical, analytical, and post-analytical precautions were observed.

Ethical approval and consent to participate: Ethical clearance was obtained from the research and ethics committee of AKTH (NHREC/21/08/2008/AKTH/EC/2769) and MMSH (MOH/Off/797/T.I/779). Written informed consent was obtained from each participant after the study had been thoroughly explained to them. They retained their right to withdraw at any time during the study, without any loss of benefit or reduction in their quality of care. Codes were substituted for patient's names as a means of identification. This study adhered strictly to the standard protocol in the management of infertility and respected the Helsinki declaration (1964).

Statistical Analysis

Data obtained on a proforma were recorded in excel spread sheet and transferred for analysis using the statistical package for social science SPSS version 23 Inc. (SPSS inc, Chicago, IL USA, 2015). Quantitative variables were reported using either measures of central tendencies or measures of dispersion as appropriate. Qualitative variables were reported in frequencies and percentages. Continuous variables were compared using student t-test while either Chi-square test or fishers exact test (where applicable) were used to compare categorical variables. P value less than 0.05 was taken as statistically significant. Odd ratios (OR) with 95% CI were calculated for strength of association. Results were presented in tables and in text forms.

Results

Over the 20-week study period from February 2019 to June 2019, 1238, infertile women attended the infertility clinics of both the Aminu Kano Teaching Hospital (AKTH) and the Murtala Mohammed Specialist Hospital (MMSH) Kano. Of these, 756 met the inclusion criteria (334 and 422 at AKTH and

MMSH respectively) from which 126 and 194 were randomly selected to participate. These subjects were classified into two groups of 160 non-obese and obese subjects.

In all 126 and 194 (39.4% and 60.6%) from AKTH and MMSH respectively participated in the study. All the 320 participants had their serum prolactin levels assayed. Eighty-nine (28.0%) of the study subjects had hyperprolactinaemia, with obese infertile women accounting for most 60(67.4%). The prevalence of hyperprolactinemia was therefore (60) 37.5% amongst obese infertile women, while the prevalence amongst non-obese infertile women was (29) 18.1%. This was statistically significant with a p=0.0001.

Table 1: Social and Reproductive Characteristics of Respondents

Variables	**Non-Obese n= 160(%)**	**Obese n= 160(%)**	**Chi-square**	**P-value**
Age(years)				
20-29	74(46.3)	80(50.0)	**0.49**	**0.78**
30-39	55(34.4)	50(31.3)		
≥40	31(19.3)	30(18.7)		
Ethnicity				
Hausa	111(69.4)	104(65.0)	**4.40**	**0.36**
Fulani	32(20.0)	27(16.9)		
Igbo	7(4.4)	10(6.2)		
Yoruba	5(3.1)	12(7.5)		
Others	5(3.1)	7(4.4)		
Highest educational level				
None	7(4.4)	18(11.2)	**22.72**	**0.0001****
Quranic	14(8.8)	8(5.0)		
Primary	21(13.1)	47(29.4)		
Secondary	49(30.6)	44(27.5)		
Tertiary	69(43.1)	43(26.9)		
Occupation				
Unemployed	94(58.8)	125(78.1)	**14.03**	**0.001****
Informal employment	29(18.1)	14(8.8)		
Formal employment	37(23.1)	21(13.1)		
Parity				

Nulliparity	113(70.6)	96(60.0)	**5.03**	**0.081**
Primiparity	31(19.4)	36(22.5)		
Multi +grandmultiparity	16(10.0)	28(17.5)		
Duration of infertility (Years)				
<5	57(35.6)	30(18.8)	**11.71**	**0.003****
5 to10	71(44.4)	86(53.8)		
>10	32(20.0)	44(27.4)		
Type of infertility				
Primary	98(61.3)	79(49.4)	**4.56**	**0.03****
Secondary	62 (38.7)	81(50.6)		
Time spent since presentation(months)				
<6	64(40.0)	38(23.8)	**10.97**	**0.004****
6 to12	41(25.6)	43(26.9)		
>12	55(34.4)	79(49.3)		
Menstrual cycle				
Normal cycle	135(84.4)	114(71.2)	**7.98**	**0.005****
Oligomenorrhoea	25(15.6)	46(28.8)		
Pattern of menstrual flow				
Hypomenorrhea	4(2.5)	15(9.3)	**22.18**	**0.0001****
Normal flow	144(90.0)	110(68.8)		
Menorrhagia	12(7.5)	35(21.9)		

Keys: ** = Statistically significant, Ethnicity (others) = Kanuri, Ibibo, Ebira, Akoko-edo and Urhobo

As can be seen from table 1, the obese group compared to non- obese group, had a longer duration of infertility (81.2%, P=0.003), spent more time in the hospital from the time of presentation (49.3%, P =0.004), were more unemployed (78.1%, P=0.001) and only a few attained tertiary levels of education (26.9%), P=0.0001. Other sociodemographic and reproductive characteristics are also represented on table I.

Table 2: Comparison of Baseline Serum Prolactin Levels of Study Subjects

Serum prolactin level(ng/ml)	Non-Obese n =160 (%)	Obese n=160 (%)	Test statistic (χ2/t-test)	P-value	Odds ratio (95% CI)
Normal (<25)	131(81.9)	100(62.5	**17.01 †**	**0.001****	**Reference**
Mildly elevated (25-50)	21(13.1)	39(24.4)			**2.43 (1.35-4.39)**
Moderately elevated (>50 to100)	3(1.9)	14(8.7)			**6.11(1.71-21.85)**
Markedly elevated (>100)	5(3.1)	7(4.4)			**1.83 (0.57-5.95)**
Mean ± SD	17.50±8.00 ng/ml	28.18 ± 10.53 ng/ml	**4.72 ††**	**0.0001**	

Keys

**** = Statistically significant**

Test statistic- †= chi-square, ††=t-test

The comparison of base-line serum prolactin levels amongst study subjects is depicted in table 2. The mean serum prolactin level of obese infertile women is 28.18 ± 10.53 ng/ml, while that of non-obese infertile women is 17.50 ± 8.00ng/ml (P = 0.0001) All categories of hyperprolactinaemia was commoner in the obese group and this was statistically significant (p = 0.001).

Table 3: Clinical Features amongst Women with Hyperprolactinaemia

Clinical presentations	Non-obese n=25 (%)	Obese n= 52 (%)	Chi-square (χ^2)	P-value	Odds ratio (95% CI)
Age (Years)					
20-29	13(52.0)	22(42.3)	**1.78**	**0.41**	
30-39	9(36.0)	17(32.7)			
≥40	3(12.0)	13(25.0)			
Menstrual cycle	16(64.0)	40(76.9)	**1.42**	**0.23**	**0.53 (0.19-1.51)**
Normal cycle	9(36.0)	12(23.1)			
Oligomenorrhoea					

Pattern of menstrual flow	5(20.0)	18(34.6)	**1.72**	**0.19**	**2.12 (0.68-6.58)**
Abnormal flow	20(80.0)	34(65.4)			
Normal flow					
Galactorrhoea	16(64.0)	12(23.1)	**12.22**	**0.0001****	**0.17 (0.00-0.48)**
Present	9(36.0)	40(76.9)			
Absent					

Keys: **= Statistically significant, Abnormal flow = hypomenorrhoea and menorrhagia

Clinical presentation amongst hyperprolactinaemic obese and non-obese infertile women is as shown in table 3. It was observed that 23.1% obese hyperprolactinaemic infertile women presented with galactorrhoea compared to 64% of the non-obese counterparts that presented with galactorrhoea. P= 0.0001. It was also observed that abnormal flow was more common in obese (34.6%) than non-obese (20.0%) hyperprolactinaemic infertile women, though this finding was not statistically significant. In all 28 (36.4%) and 23 (29.9%) of all the respondents with hyperprolactinaemia irrespective of the BMI group presented with galactorrhoea and abnormal menstrual flow, respectively. Other clinical presentations were as represented in table 3.

Table 4: Relationship between Clinical Features and Baseline Serum Prolactin Level Amongst all Hyperprolactinaemic Infertile Women

Clinical presentations	**Mildly elevated n=54 (%)**	**Moderate-markedly elevated n= 23 (%)**	**Chi square (χ^2/Fishers)**	**P-value**	**Odds ratio (95% CI)**
Duration of infertility (Years)					
≤5	25(46.3)	0(0.0)	†††	**0.0001****	
>5	29(53.7)	23(100)			
Menstrual cycle					
Normal cycle	40(74.1)	16(69.6)	**0.165** †	**0.68**	**1.25 (0.43-3.67)**
Oligomenorrhoea	14(25.9)	7(30.4)			
Pattern of menstrual flow					
Abnormal flow	8(14.8)	15(65.2)	**19.56** †	**0.0001****	**10.78 (3.45-33.72)**

Normal flow	46(85.2)	8(34.8)				
Galactorrhoea						
Present	12(22.2)	16(69.6)	**15.62†**	**0.0001****	**8.00**	**(2.66-23.93)**
Absent	42(77.8)	7(30.4)				

Keys: **= tatistically significant Test statistic- †= chi -square, †† = t-test, †††= fishers

Abnormal flow= hypomenorrhoea and menorrhagia

Table 4 shows the relationship between clinical features and levels of serum prolactin amongst all the hyperprolactinaemic infertile women. It shows that abnormal menstrual flow and galactorrhoea were more likely in moderate-markedly elevated serum prolactin level as seen in 65.2% and 69.6% respectively and both were statistically significant.

Discussion

The study examined relationships between serum prolactin levels and obesity in infertile women and found that serum prolactin level was significantly higher in obese infertile women. It also investigated the clinical features of hyperprolactinaemia in obese and its relationship to serum levels of prolactin and found that galactorrhoea was more in non-obese and clinical features were more when the serum prolactin levels were moderate-markedly elevated.

The mean serum prolactin level observed was significantly higher in obese compared to non-obese infertile women. Also, all classes of hyperprolactinaemia were significantly more common in obese compared to non-obese.

Obese women are thought to have ineffective tonic negative dopamine inhibition of prolactin, related to the reduced brain dopamine receptors (D_2).[23] This finding of higher serum prolactin level in obese compared to non-obese in this study is similar to the finding in a study by Pereira-Lima et al[10] in South America, an Iraqi[25] and a Sudanese study.[30]

In the Iraqi study however, the mean prolactin levels amongst obese women were 25.81±14 ng/ml and 24.296 ± 17.310ng/ml for obese and non-obese infertile women respectively lower than the value reported in this study. Radioimmune assay technique used to assay the level of the serum prolactin which is not as sensitive and specific in detecting protein sequence as electrochemiluminescence immunoassay used in the present study may also be contributory to lower value of serum level observed in the above study.

Converse to Iraqi study, the Sudanese study [30] reported a higher value of mean serum prolactin level in contrast to the index study. This discrepancy may be due to differences in study sample size as the sample size in the present study was more than twice the sample size of the Sudanese study. Also, different stress levels in the two countries where the studies were conducted may have a role as prolactin can be stress induced. [9,31] Sudan was a war ridden country at the time the study was being conducted.

The prevalence of hyperprolactinaemia in obese and non-obese infertile women was found to be 37.5% and 18.1%, respectively. Malini et al [24] and Nallusammy et al [32] in their studies also noted higher prevalence in obese compared to non-obese infertile women although the prevalence reported by them were higher than that reported in the present study. Both studies included those with BMI ≥ 25kg/m^2 as

obese group thereby causing a summation increase. In converse, to this study, Nwagha et al [18] reported a prevalence of 41.9% in the non- obese arm. This high prevalence may be due to inclusion of patients with BMI of 30kg/m^2 as non-obese in their study which may be associated with high prolactin level.

The overall prevalence of hyperprolactinaemia was 28.0%. This was similar to findings from studies done in Iraq,[33] and Sudan.[34] Higher prevalence was observed in Europe (55.1%),[11] Jigawa (36.7%),[8] and in Kano (33.7%).[7] In Jigawa[8] and Kano[7] states of Nigeria respectively, prevalence reported was higher than the present study since the study was conducted on only those symptomatic of hyperprolactinaemia; and those found with subclinical hypothyroidism. Hypothyroidism causes elevation of thyroid stimulating hormone which inhibits dopamine (D_2-receptor), the most effective suppressor of prolactin and thus causing elevation of serum prolactin. It might have also shown a trend towards decreasing prevalence of hyperprolactinaemia over the years as the previous study was done about nine years ago. Exclusion of patients with hypothyroidism in the present study may have also contributed to the lower prevalence recorded in the present study. In America,[35] exclusion of patients with features suggestive of hyperprolactinemia may be responsible for the lower prevalence recorded.

In this study 23.1% of obese hyperprolactinaemic infertile women presented with galactorrhoea compared to 64.0% observed in the non- obese counterparts. This finding may be related to higher oestrogen level in obese women which inhibit milk let down thus, making it more difficult for galactorrhoea to occur in them.[36] Galactorrhoea was observed in 36.4% of all the patient with hyperprolactinaemia, similar to the findings by Ugwa et al [8] who reported galactorrhoea in 36.7% of hyperprolactinaemic patients. This was in converse to study by Isah et al [37] who reported that hyperprolactinaemic infertile women present with galactorrhoea in 27.4%. Serum prolactin level less than 25ng/ml regarded as hyperprolactinaemia may be contributory to this finding, as galactorrhoea is more likely a feature of moderate to severe hyperprolactinaemia as seen in this study.

The findings of the present study also shows that abnormal menstrual flow and galactorrhoea occurred more when serum prolactin level was moderately to markedly elevated. This was not surprising as the alterations leading to these symptoms rely on abnormal serum prolactin level to occur. The higher the serum prolactin level, the more the alterations (ineffective D_2- receptor and disordered gonadotrophin pulsatility) and more pronounced the symptoms.

Conclusion

Obese infertile women have higher serum prolactin levels and prevalence of hyperprolactinaemia than non-obese infertile women. Galactorrhoea is not a common clinical presentation in obese infertile women and clinical presentations known to herald hyperprolactinaemia are more evident if the serum prolactin level is moderate to markedly high. However, all degrees/ forms of hyperprolactinaemia can lead to infertility. It is recommended that routine serum prolactin level assay in obese and non-obese infertile women especially in those with unknown causes of infertility is advocated. This is despite presentation with galactorrhoea or not. In addition, obese infertile women should be evaluated, and treatment should be commenced immediately to prevent untoward effects of being in the hospital for a long time as they have been found to spend more time in the hospital than their non- obese counterparts.

Competing interests

The authors declare that they have no competing interests.

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