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Original Research Article

Correlation between corrected serum calcium and serum albumin in children with idiopathic nephrotic syndrome in North central, Nigeria

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ABSTRACT

Background: Nephrotic syndrome is a clinical condition caused by alteration of glomerular membrane permeability resulting in a net loss of protein, and vitamin D binding proteins in urine leading to hypoalbuminaemia and hypocalcaemia. A positive correlation between serum albumin and ionized calcium in childhood nephrotic syndrome has been described but the correlation between total serum calcium or corrected serum calcium and serum albumin has not been extensively described.

Methods: This study was carried out at Dalhatu Araf Specialist Hospital, Lafia Nigeria. Fifteen children with idiopathic nephrotic syndrome were recruited consecutively as the cases, 15 age and gender matched healthy children were recruited as the controls. Total serum calcium and albumin was assayed in all these children. Corrected serum calcium was calculated for the cases. Tests of correlation was carried out to see if there was any relationship between corrected or total serum calcium and serum albumin.

Results: The mean total serum calcium and serum corrected calcium levels in the cases was 2.04±0.34 mmol/l and 2.5 mmol/l respectively. The mean total serum calcium was 2.12±0.32 mmol/l for the controls. The mean serum albumin level was 14.7±4.1 g/l and 34.6±2.7 mmol/l for the cases and controls respectively. A negative and weak correlation was found between serum albumin and corrected serum calcium and a similar negative correlation between serum albumin and total serum calcium.

Conclusions: The common reports of a positive correlation between serum ionized calcium and serum albumin cannot be applied to total or corrected serum calcium and serum albumin.

Keywords: Albumin, Calcium, Corrected, Correlation, Serum

INTRODUCTION

One percent of total body calcium is found in body fluids. The remaining 99% of total body calcium is stored in bone and teeth. The tightly regulated concentration of serum total calcium between 2.1 to 2.6 mmol/l is the result of the balance or interplay between gastrointestinal (GI) calcium absorption, urinary calcium loss and the movement of calcium out of bone.[1] This balance is hormonally controlled. The mobilization of calcium from bone occurs via the effect of low serum calcium on calcium sensing receptors located on parathyroid cells, bone cells and the nephron.[1] The hormone Parathyroid hormone (PTH) promotes renal tubular re-absorption of calcium, resorption of calcium from bone and increases phosphate loss in urine. Calcitriol formed from 1 α hydroxylation of 25OHD3 to 1,25-dihdroxycalciferol (calcitriol) in the kidney tubules promotes GI dietary calcium absorption.[1] The interplay between these hormones maintains calcium homeostasis.[2,3] Approximately 40% of plasma calcium is protein (mainly albumin)- bound, 10% are complexed to anions (complexed calcium) and the remaining 50% is the physiologically active and free (ionized calcium). Any change in the level of ionized calcium will affect cellular integrity, cellular division and function, blood coagulation process, hormone secretion, myocardial function, neural conduction, enzymatic processes and neuromuscular transmission.[1,4]

Some laboratories measure only the total serum calcium due to the analytical challenges, cost and equipment maintenance required to assay ionized calcium levels.[5] Total calcium concentration should reflect ionized calcium activity except in settings of hypoalbuminaemia and acid-base disturbances.[6] Total calcium levels can be corrected to mitigate the effect of hypoalbuminaemia using various formulae.[7,8,9] Corrected calcium therefore reflects total calcium level if serum albumin was normal.[7,8] The commonly used Payne correction formula assumes a constant relationship between albumin concentration and the fraction of calcium bound to albumin although the derivation of this formulae did not make allowances for different populations or laboratory methodologies. Furthermore, this formula was not validated.[6] Corrected calcium is also not very reliable in conditions that affect calcium binding like hyperparathyroidism, critical illnesses and kidney failure.[10]

Some researchers have reported that only in instances of severe and prolonged hypoalbuminaemia would serum ionized calcium also be reduced.[7,11] Amballi and colleagues stated in their study that only total calcium not the ionized fraction was affected in nephrotic syndrome and that a duration of hypoalbuminaemia of > 2months is required for serum ionized calcium to be reduced.[12]

Nephrotic syndrome is a combination of heavy proteinuria (urine protein/creatinine ratio of >2g/g, hypoalbuminaemia <25g/l, oedema and hyperlipidaemia. In Nephrotic syndrome, the urinary losses includes the loss of albumin, 25OHD3 and its carrier protein predisposing to the development of hypoalbuminaemia and hypocalcaemia.[2] The use of steroids in the treatment of nephrotic syndrome also stimulates bone resorption, reduces GI absorption and increases renal excretion of calcium.[13,14] Previous researchers have reported a positive correlation between serum albumin and ionized calcium in children with idiopathic nephrotic syndrome.[15,16]

Despite the fact that total calcium is still more conventionally measured, several of the research carried out has focused on the correlation between ionized calcium and albumin and not on the relationship between total or corrected serum calcium and albumin.[11,16,17] These previous studies reported positive correlations between serum ionized calcium and serum albumin. Only in the Garniasih et al study was the relationship between serum albumin and total serum calcium investigated.[18] They also found a positive and very significant correlation (r +0.547) (P value 0.000), with the equation Y = 5.59+ 1.12 X.

This study aims first to determine the total and corrected serum calcium levels in children with idiopathic nephrotic syndrome seen at Dalhatu Araf Specialist Hospital, Lafia. This study also aimed to determine whether the previous reports of a positive relationship between serum albumin and serum ionized calcium is reproducible and applicable to total or corrected serum calcium and serum albumin.

METHODS

This cross sectional analytical study was conducted between the months of February 2019 to October 2020 at the Dalhatu Araf Specialist Hospital, Lafia. Dalhatu Araf Specialist Hospital is a tertiary hospital located in North central Nigeria. This hospital is one of the two tertiary hospitals in the state and serves the state and some neighboring states. Ionizied calcium is currently not carried out in our hospital laboratory or in nearby private laboratories. A total of 19 children with idiopathic nephrotic syndrome were seen during the study period.

Inclusion criteria

All children with idiopathic nephrotic syndrome seen during the study period, children whose parents gave consent, children who were able to give assent were included in the study. Age and gender matched healthy children were recruited as the controls.

Exclusion criteria

Children with kidney failure, who had received albumin infusions or blood transfusions, who had taken calcium supplementation within last 12 hours, children with liver disease, children with severe malnutrition, children with acid base imbalances, children who were critically ill were excluded from the study.

For the purpose of this study the Payne formula was used to correct total calcium in children with hypoalbuminaemia.[9]

{Corrected calcium(mmol/l) = measured total serum calcium(mmol/l) + 0.02(40 - serum albumin(g/l))}.[1,9]

Four children with nephrotic syndrome were excluded from partaking in this study. Two had kidney failure and were critically ill, another child was excluded on account of taking calcium supplementation and the last child was excluded because he had absconded from the hospital before consent to participate in the study was obtained and before samples for calcium and albumin were collected. The two children with kidney failure had estimated glomerular filtration rates of 7 ml/min/1.73m^2 and 3.9 ml/min/1.73m^2 respectively using the 2009 bedside Schwartz formula. Fifteen children with nephrotic syndrome and 15 age and gender matched healthy children recruited as controls into the study. Sampling was done consecutively for the cases.

For each child, a pre-formed proforma was labeled using unique identification numbers. Blood samples were taken after due explanation to the child and care giver of how the sampling will be carried out. Confidentiality was assured. Maintaining all standard precautions, five milliliters (mls) of blood sample was collected from both cases and control into plain bottles and centrifuged. The serum was subsequently used to determine the concentrations of bicarbonate, creatinine, calcium and albumin.

Total serum calcium was analyzed in the laboratory using the Stern and Lewis colorimetric method and serum albumin was assayed using the Doumas et al bromocresol green method. Serum bicarbonate was analysed using the Albert et al direct acidimetric titration method and creatinine using the IDMS traceable (Max-Jaffe) method. The serum total calcium was then corrected by the investigator using the above Payne formula and cross checked by the second investigator to prevent any errors of calculation. The results of serum albumin, total serum calcium and the corrected serum calcium were then entered by the investigators into the labeled pre-structured proforma. The estimated glomerular filtration rate (eGFR) was calculated for all participants. The data obtained was transferred into and analyzed using the Statistical Package for Social Service SPSS version 16.0. Unpaired t-test, Chi-square test were done to compare the mean differences in serum calcium between the cases and control. Pearsons correlation test was used to test for the association between serum corrected calcium and serum albumin levels.

RESULTS

A total of 30 children were recruited into this study. The characteristics of the study participants are shown in Table 1.

All the children with idiopathic nephrotic syndrome had presented within two days to two weeks of developing symptoms. All the cases had presented with symptomatic hypoalbuminaemia.

The mean albumin levels in the cases (14.7±4.1)g/l was lower than that in the control group (34.6±2.7)g/l (P value<0.001) Table 2. The mean total serum calcium in the cases (2.04±0.34) was lower than that in the control group (2.12±0.32)mmol/l (P value 0.516) Table 2.

The mean corrected serum calcium in the cases was 2.5mmol/l. Serum bicarbonate was lower in the cases (27.2±1.6) than in the control group (28.1±2.2)mmol/l (p value 0.227) and the calculated eGFR was lower in the cases (97.9±42.9) µmol/l than in the control group (107.9±27.8) µmol/l (p value.0.455) Table 2.

Table 1: Characteristics of study participants.

Variable	Study group		Total	X^2	P value
	Cases	**Control**			
Age (in years)					
0-6	6 (40.0)	6 (40.0)	12 (40.0)	0.000	1.000
7-12	8 (53.3)	8 (53.3)	16 (53.3)	0.000	1.000
>12	1 (6.7)	1 (6.7)	2 (6.7)	0.144	0.705
Mean±SD	7.6±2.9	7.6±2.9	7.6±2.9		
Sex					
Male	6 (40.0)	5 (33.3)	11 (36.7)		
Female	9 (60.0)	10 (66.7)	19 (63.3)		
	Mean±SD	**Mean±SD**	**Mean±SD**		
Height	118.8±16.5	120.5±11.31		0.329	0.744
Weight	25.4±9.6	25.9±11.3		0.140	0.890

X^2= Chi square

Table 2: Difference between mean values of the laboratory parameters between the cases and control.

Parameter (Mean)	Cases	Control	T-test	P value
Total calcium	2.04±0.34	2.12±0.32	0.658	0.516
Albumin	14.7±4.1	34.6±2.7	15.690	<0.001
HCO_3	27.2±1.6	28.1±2.2	1.235	0.227
eGFR	97.9±42.9	107.9±27.8	0.757	0.455

T test= Student T test

Some (20%) of the cases were found to have severe hypercalcaemia (serum calcium >3.00mmol/L) after correcting for hypoalbuminaemia. All the 15 controls had normal serum albumin and a correction of serum calcium was not carried out.

When total (not corrected) calcium was looked at, hypocalcaemia was found in 8(53.3%) of the cases and in 7 (43.7%) of the control group. This was however not statistically significant P value 0.715 Table 3. None of the cases had hypocalcaemia after the correction was done.

Table 3: Hypocalcaemia in the cases and control groups.

Hypocalcaemia	Group		Total	X^2	P value
	Cases f (%)	Control f (%)	f (%)		
Yes	8 (53.3)	7 (43.7)	15 (50.0)		
No	7 (46.7)	8 (53.3)	15 (50.0)		
Total	15 (50.0)	15 (50.0)	30 (100.0)	0.133	0.715

X^2= Chi-square

There was a weak negative correlation between corrected calcium and albumin levels in the cases r= -0.360 (P value 0.188) and a very weak negative correlation between total serum calcium and albumin levels in the cases r= -0.107 (p value 0.705) Table 4.

Table 4: Correlation between serum albumin and total serum calcium and corrected serum calcium in the cases.

Variable	R	P value
Albumin and total calcium	-0.107	0.705
Albumin and corrected calcium	-0.360	0.188

r=Pearson correlation coefficient.

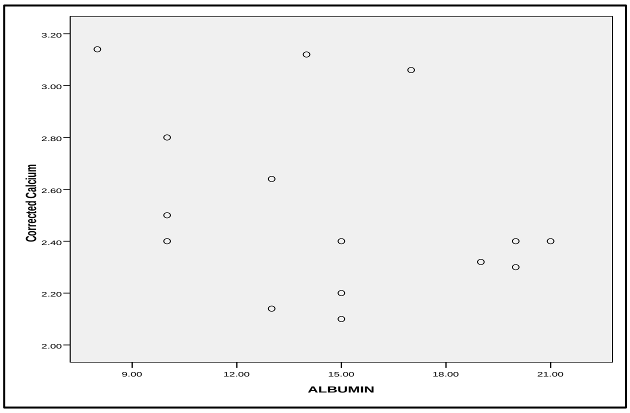

Figure 1: Correlation between serum corrected calcium and serum albumin.

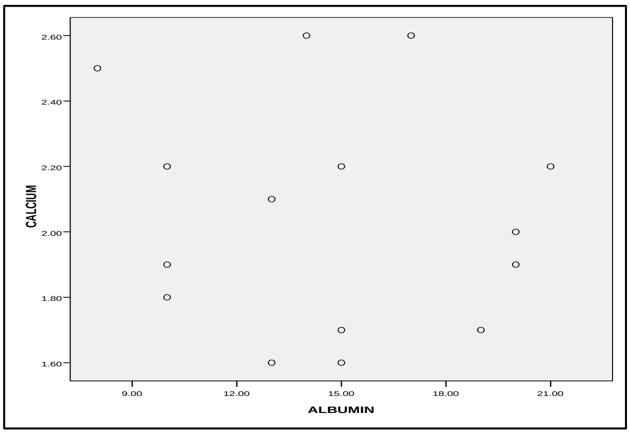

Figure 2: Correlation between serum total calcium and serum albumin.

DISCUSSION

In our study, a significantly lower level of serum albumin was found in the cases than the controls P value <0.001 (Table 2). This significant difference in serum albumin levels is not unexpected as the increased glomerular permeability seen in children with nephrotic syndrome causes a massive proteinuria and hence hypoalbuminaemia.[2] The mean total serum calcium was also lower in the cases than in the control group. This difference in total serum calcium was however not statistically significant (Table 2). Our finding of lower serum albumin and serum calcium in the cases compared to healthy controls is the trend in reports of previous researchers who reported on the serum albumin and calcium in patients with nephrotic syndrome.[12,15,16] Abnormalities of calcium metabolism resulting in hypocalcaemia are well documented in nephrotic syndrome.[14-18] Although there are several causes of hypocalcaemia in nephrotic syndrome, the foremost cause is hypoalbuminaemia. This is based on the important hypothesis that a decrease in albumin leads to a decrease in the albumin-bound calcium fraction which leads to a decrease in total calcium while ionized calcium levels remain normal and such patients remain asymptomatic.[11,20]

After correction for hypoalbuminaemia in our study, the cases had normal to increased serum corrected calcium levels. The finding of normal serum corrected calcium in some of the cases is in consonance to the report by Hooft et al who had reported that children with nephrotic syndrome would have had proteinuria for more than 2 months before a decrease in ionized calcium level is found.[21] Viola et al had also reported in their study that although the ionized calcium levels in the cases were lower than that found in the healthy controls, some of the cases in their study also had normal ionized calcium.[15] The duration of proteinuria in their cases ranged from 7 days to 2 months and they attributed the normal ionized calcium levels to the shorter duration of proteiniuria in those cases. In our study, the duration of hypoalbuminaemia in all the cases was not long as they had all presented to the hospital within two days to two weeks of developing symptoms.

The finding of increased levels of corrected serum calcium in some of the cases is similar to reports by other researchers who had reported that the use of the Payne formula tends to overestimate or report normal levels of calcium in patients with hypoalbuminaemia.[22,23] Based on this fact we also conclude that the corrected calcium levels in our study may have been overestimated as found with previous reports where correction formulas were used. Furthermore, current research has shown that unlike the previous hypothesis where a decrease in albumin led to a decrease in the albumin-bound calcium the calcium affinity for albumin has been found to increase significantly when there is hypoalbuminaemia negating the initial hypothesis.[11,20] This may explain the finding of overestimated levels of corrected calcium when correction formulaes are used.[20] Other researchers in an attempt to get the perfect formulae have proposed using PH adjusted formulaes, anion-gap adjusted formulaes, while others concluded that locally derived formulaes or focusing on the mathematical conception of the regression equations as a means of getting a more accurate correction formula.[20,24,25] Payne had also reminded the academic and research world that the Payne formula was not intended for universal use.[26] In actual fact, most of these formulas have not performed better than uncorrected total serum calcium levels. Lian et al in their study had found that uncorrected calcium performed significantly better than the best calcium-adjusted formula and that uncorrected total calcium had correctly categorized 70-80% of patients.[25,27] Several researchers have also reported that the more severe the hypoalbuminaemia, the poorer the performance of the formula.[28,29] In our study, the hypoalbuminaemia found in the children with nephrotic syndrome in our study was severe in 66.7% of the children. This severity may also explain the poor performance and overestimation of calcium in our cohort of cases. In this study, all the control had normal albumin levels. There was no acid base imbalance or renal failure in the controls therefore no correction of total calcium was carried out in them. Total calcium was found to be reduced in as much as 7 (46.7%) of the healthy controls.

If the short duration of hypoalbuminaemia, the poor performance of the correction formula is considered and total serum calcium is uncorrected. Then as much as eight (53.3%) of the 15 cases had hypocalcaemia. Table 3 The hypocalcaemia found in this study may therefore not be a result of hypoalbuminaemia but may be a reflection of some other confounder generalizable to both the cases and control. Perhaps a reflection of a low calcium intake in the food consumed among children in our environment. We are however unable to confirm this in our study.

In this study, we found a weak negative relationship between corrected calcium levels and albumin and an even weaker negative relationship between total calcium levels and albumin in the children with nephrotic syndrome. This means that when serum albumin reduces, there is a low likelihood of there being a corresponding rise in serum corrected calcium and an even lower likelihood of a corresponding rise in the total calcium levels. Our finding is similar to the findings of Choi et al who found a negative and weak correlation between serum albumin and ionized calcium levels but differs from the findings of Garniasih et al, Winata et al, Hossain et al and Butler et al who all reported positive correlations between serum albumin and ionized calcium.[11,15-18] The disparity between our findings and those of previous researchers who reported positive correlations may be due to the fact that the duration of hypoalbuminaemia in the children in our study was not prolonged that is (i.e.) not >2 months therefore the hypoalbuminaemia could not have had any effect on calcium as was reported by Amballi et al and Hooft et al. Winata et al had reported that the children in her study had hypoalbuminaemia lasting 7 days to 2 months before being treated.[12,16,21] Secondly, the poor performance of the correction formula may also explain the weak negative relationship between hypoalbuminaemia and corrected calcium. This is because with the overestimation of corrected calcium using the payne formula it is therefore not unexpected to find a negative correlation rather than a positive one. Thirdly, the difference between our findings and previous findings may be because they all except Garnaisih et al had compared serum albumin to ionized calcium rather than to total or corrected calcium as we have done in our study.[18]

Limitations

We had a limited sample size. There is a scarcity of research on relationship between total or corrected serum calcium and serum albumin in childhood nephrotic syndrome to compare with the findings in our study. No further samples for serum calcium and albumin were taken in the cases to determine the effect of duration of disease on the relationship between serum calcium and total serum albumin.

CONCLUSION

We found a negative and very weak relationship between total serum calcium and serum albumin as well as a negative and weak relationship between corrected serum calcium and serum albumin.

Recommendations

More studies need to be undertaken with a focus on the duration of the nephrotic syndrome and performance of albumin-adjusted calcium in children with nephrotic syndrome. For settings like ours where the ionized calcium assay is still unavailable, total serum calcium may be more reliable than corrected calcium if hypoalbuminaemia has not persisted for 2 months or longer.

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