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Research Paper

Comparative Analysis of Adjusted Calcium and Free Ionized Calcium in Patients with Calcium Derangement in Clinical Setting

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ABSTRACT

Background*: Calcium derangements, including hypocalcaemia and hypercalcemia, are significant clinical conditions that affect multiple physiological processes. While adjusted calcium and free ionized calcium are both used to assess calcium status, their comparative utility remains a topic of investigation. This study evaluates the demographic patterns, prevalence, and biochemical characteristics of these conditions, focusing on the relationship between adjusted and free ionized calcium levels.*

Method*: This cross-sectional study included 166 patients diagnosed with either hypocalcaemia or hypercalcemia based on hospital laboratory reference values. Venous blood samples were analysed for free ionized calcium using an ion-selective electrode method and O-cresolphthalin complexone method for Total calcium. Adjusted calcium was derived with a formular. Demographic data, including age and gender, were recorded.*

Results*: Among the 166 patients studied, hypocalcaemia was observed in 45% of the participants, while 55% were diagnosed with hypercalcemia, reflecting a slightly higher prevalence of the latter. Gender distribution showed no significant difference between the groups (p = 0.898), with hypocalcaemia affecting 40% males and 60% females, and hypercalcemia affecting 39.6% males and 60.4% females. The highest prevalence was observed in individuals aged 60 and above, comprising 40% of hypocalcaemia and 49.5% of hypercalcemia cases, with no significant differences in age distribution between groups (p = 0.455). The mean ionized calcium in hypocalcaemia was 0.9 ± 0.6 mmol/L, significantly lower than the 1.9 ± 0.9 mmol/L observed in hypercalcemia. Adjusted calcium levels were also significantly lower in the hypocalcaemia group (1.1 ± 0.9 mmol/L) compared to the hypercalcemia group (3.1 ± 1.1 mmol/L).*

Conclusion*: This study demonstrates that free ionized calcium is a reliable indicator of calcium disorders, so also adjusted total calcium particularly in diagnosing hypocalcemia and hypercalcemia. The findings show strong correlation between adjusted calcium and ionized calcium in both groups*

Keywords*: Hypocalcaemia, Hypercalcemia, Ionized Calcium, Adjusted Calcium, Calcium Derangements, Clinical Practice*

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I. INTRODUCTION

Calcium is essential for numerous physiological functions, existing in two key forms in the bloodstream: total calcium (both bound and unbound) and free ionized calcium (the biologically active form). While total calcium is commonly measured in clinical settings, free ionized calcium is assumed to offer a more precise reflection of calcium homeostasis [1, 2].

Total calcium measurement, though standard practice, may not fully capture a patient's calcium status, as it includes calcium bound to proteins like albumin, which can distort the true physiological picture[3]. Free ionized calcium, being the metabolically active form, provides a more accurate measure of calcium imbalance but it is often overlooked due to technical or logistical challenges[2, 4]. Calcium plays a critical role in numerous physiological processes, including bone health, neuromuscular function, enzymatic activity, and blood coagulation[5]. Maintaining calcium homeostasis is essential for overall health, and its derangement—manifesting as hypocalcaemia or hypercalcemia—can have significant clinical implications[6, 7]. Accurate

assessment of calcium levels is pivotal in diagnosing and managing conditions associated with calcium imbalances, such as parathyroid disorders, chronic kidney disease, and malignancies[8].

Traditionally, total serum calcium, often adjusted for albumin levels, has been used as a surrogate marker for assessing calcium status. However, it is well-recognized that total calcium may not always reflect the biologically active fraction of calcium, which is the free ionized calcium[9, 10]. Ionized calcium represents the unbound, physiologically active form of calcium in circulation and is directly involved in cellular processes. Discrepancies between adjusted total calcium and ionized calcium measurements can lead to misclassification of calcium status and inappropriate clinical decisions.

Despite its clinical relevance, ionized calcium is not routinely measured in many settings due to the specialized equipment and stringent pre-analytical conditions required for accurate determination. This limitation often necessitates reliance on adjusted calcium, which incorporates albumin correction to approximate ionized calcium levels. While this approach is convenient, it may lack precision in certain clinical scenarios, such as in critically ill patients or those with altered albumin concentrations.

This study aims to conduct a comparative analysis of adjusted calcium and free ionized calcium in patients with calcium derangement, evaluating their concordance and clinical implications. By examining the potential discrepancies between these two measures, this research seeks to provide evidence-based insights into their reliability and utility in clinical practice. The findings will help guide clinicians in making more informed decisions regarding the assessment and management of calcium-related disorders.

II. METHODS

2.1 Ethical Considerations

Ethical approval to carry out the study was obtained from the Research and Ethics Committee of Rivers state University Teaching Hospital, Rivers State, Nigeria. A written informed consent was obtained from the persons involved in the study prior to their inclusion into the study

2.2 Study Population

This cross-sectional study involved 166 patients presenting with clinical signs and symptoms of calcium derangement (hypocalcemia or hypercalcemia).

2.3 Analysis of Serum Calcium

Serum levels of albumin were determined by bromocresol green method, total calcium was estimated using O-cresolphthalincomplexone method, free ionized calcium and bicarbonate were measured using ion selective electrode as previously described[11, 12].

Throughout the study period, serum ionized calcium levels were measured using the ion-selective electrode method. Venous blood samples were collected in serum separating tubes or serum gel tubes, and ionized calcium levels were adjusted to a pH of 7.40 to compensate for potential pH changes during sample transport. The normal reference range for serum ionized calcium, based on our hospital laboratory standards, was defined as 1.15–1.35 mmol/L. Hypocalcaemia was classified as serum ionized calcium levels below 1.15 mmol/L, while hypercalcemia was identified as levels exceeding 1.35 mmol/L during the patient's visit to the hospital[2, 13].In clinical practise free ionized calcium is best option with a normal reference range of 1.1 to 1.3mmol/L while the normal reference range of adjusted calcium is 2.2 to 2.6mmol/L[4].

2.4 Data Analysis

Descriptive statistics, including the mean and standard deviation of calcium levels, were calculated for the entire cohort. Subgroup analyses based on age, gender, and comorbidities. Statistical significance was determined using appropriate tests, with p-values < 0.05 considered significant.

III. RESULTS

Of the 166 participants, 60.2% were female and 39.8% were male. The mean age of the participants was 52.1 years, with a standard deviation of 18.1 years. Regarding age groups, 17.5% were between 30 and 39 years old, 37.3% were between 40 and 59 years old, and 45.2% were 60 years old or older.

Table 1: *Demographic Data of Participants*

Variable	Frequency (n = 166)	Percent (%)
Gender		
Male	66	39.8%
Female	100	60.2%
Age Groups (years)		
30 – 39	29	17.5%

40 – 59	62	37.3%
60 and above	75	45.2%
Mean age ±SD	***52.1 ± 18.1***	

Figure 1 shows that off 166 patients, 45% were diagnosed with hypocalcemia, while 55% had hypercalcemia.

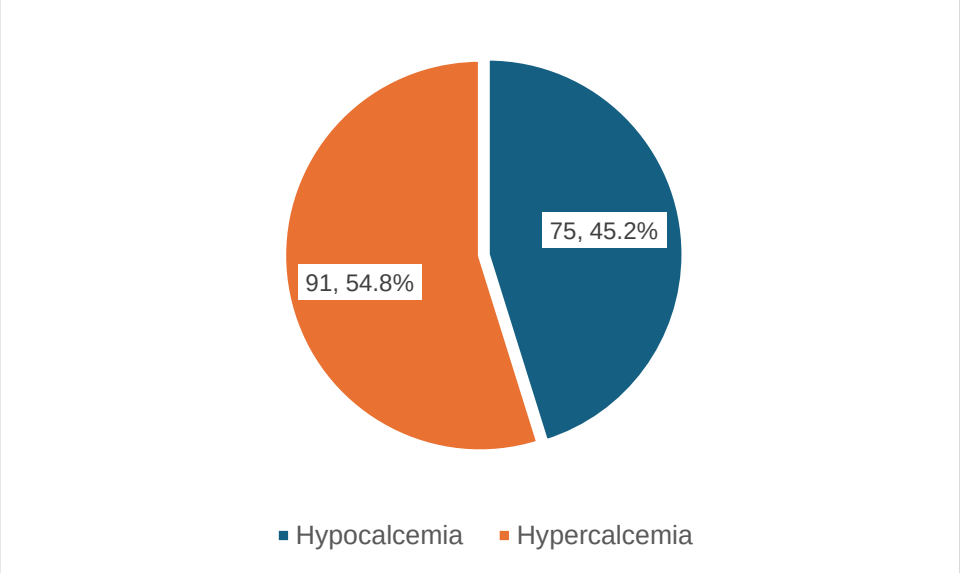

Figure 1: Distribution of calcium derangement

Table 2 shows the distribution of calcium derangement by demographic information of the patients. Of the 75 individuals with hypocalcemia, 40% were male and 60% were female, while of the 91 individuals with hypercalcemia, 39.6% were male and 60.4% were female. There was no significant difference in gender distribution between the two groups (p = 0.898).

Regarding age groups, 20% of hypocalcemia cases and 15.4% of hypercalcemia cases were in the 30-39 age group. Similarly, 40% of both groups were in the 40-59 age group. However, 40% of hypocalcemia cases and 49.5% of hypercalcemia cases were in the 60 and above age group. Similarly, there were no significant differences in age group distribution between the two groups (p = 0.455).

Table 2: Distribution of Calcium Derangement by Demography

Variable	**Hypocalcaemia n=75, (%)**	**Hypercalcemia n=91, (%)**	**Chi-square (p-value)**
Gender			
Male	30(40.0)	36(39.6)	0.02 (0.898)
Female	45(60.0)	55(60.4)	
Age Groups (years)			
30 – 39	15(20.0)	14(15.4)	1.57 (0.455)
40 – 59	30(40.0)	32(35.2)	
60 and above	30(40.0)	45(49.5)	

Albumin levels were within the normal range for all patients. In the hypocalcemic group, the mean free ionized calcium level (0.9 ± 0.6 mmol/L) was significantly lower than that of patients with hypercalcemia (1.9 ± 0.9 mmol/L). The average adjusted calcium levels were 1.1 ± 0.9 mmol/L in the hypocalcemic group, below the normal reference range, and 3.1 ± 1.1 mmol/L in the hypercalcemic group as shown in Table 3.

Table 3: Comparison of Ionized Calcium and Adjusted Calcium by Calcium Derangement

Calcium Measure	**Hypocalcaemia**	**Hypercalcemia**	**t-test (p-value)**
Free ionized Calcium (mmol/l)	0.9 ± 0.6	1.9 ± 0.9	-12.8 (<0.0001)
Adjusted Calcium (mmol/l)	1.1 ± 0.9	3.1 ± 1.1	-8.5 (<0.0001)

**Statistically significant (p<0.05)*

IV. DISCUSSION

This study highlights significant findings in the prevalence, demographic patterns, and biochemical characteristics of calcium derangements, with a particular focus on hypocalcemia and hypercalcemia. The

results provide insights into the clinical presentation and potential implications for diagnosis and management in routine practice.

The nearly balanced distribution of hypocalcemia (45%) and hypercalcemia (55%) among the 166 patients studied is consistent with reports from similar studies examining hospitalized populations. Such findings underline the need for vigilance in identifying both extremes of calcium imbalance, as their underlying causes and clinical consequences differ significantly. Although hypercalcemia was slightly more prevalent, the gender distribution showed no significant difference ($p = 0.898$). The observed female predominance in both hypocalcemia (60%) and hypercalcemia (60.4%) aligns with other research that attributes this pattern to higher rates of postmenopausal osteoporosis and endocrine disorders in women (e.g., hyperparathyroidism). Comparable studies, such as that by Wongdee et al. found similar patterns, emphasizing the importance of gender-specific health interventions in managing calcium derangements in women[14]. However, the lack of significant differences in gender distribution suggests that both genders require equal clinical attention in screening and treatment.

The study's age-related findings indicate a higher prevalence of calcium derangements in middle-aged and elderly individuals, with 40% of cases in the 40-59 age group and an even higher prevalence (49.5% for hypercalcemia) in those aged 60 years and above. This age-related trend is consistent with findings in other studies, which associate advancing age with increased risk of conditions such as renal dysfunction, malignancies, and parathyroid abnormalities that alter calcium homeostasis[1, 14, 15]. The absence of significant differences in age group distribution ($p = 0.455$) implies that both hypocalcemia and hypercalcemia are equally likely across these groups, albeit with different etiological factors. Proactive screening and early management of conditions associated with calcium imbalances in these age groups are crucial to prevent complications such as fractures or cardiovascular issues[10].The distinct biochemical profiles observed in the study further reinforce the utility of ionized calcium in assessing calcium status. The significantly lower mean free ionized calcium in hypocalcemia (0.9 ± 0.6 mmol/L) compared to hypercalcemia (1.9 ± 0.9 mmol/L) underscores the diagnostic value of ionized calcium measurements. This finding is consistent with literature advocating for the use of ionized calcium as a reliable marker in critically ill or hypoalbuminemic patients, where total calcium or adjusted calcium may be misleading[16, 17].

Adjusted calcium levels also differed significantly between groups, with hypocalcemia cases showing mean levels (1.1 ± 0.9 mmol/L) below the reference range and hypercalcemia cases exhibiting elevated levels (3.1 ± 1.1 mmol/L). These findings highlight the limitations of adjusted calcium in accurately reflecting ionized calcium, as previously noted[14]. While adjusted calcium remains useful in resource-limited settings, its limitations in conditions affecting albumin levels warrant greater reliance on ionized calcium in clinical practice.Routine measurement of ionized calcium should be prioritized, especially in critically ill or elderly patients, to improve diagnostic accuracy. This approach aligns with current recommendations advocating for ionized calcium as the gold standard in assessing calcium homeostasis. The higher prevalence in women and older adults suggests the need for targeted interventions, including bone health monitoring and management of age-related conditions such as osteoporosis and secondary hyperparathyroidism.The findings of this study are consistent with those of similar investigations, such as those by Kotepui et al. [16], which emphasize the clinical challenges of accurately diagnosing calcium imbalances using adjusted calcium alone. Moreover, studies on the gender and age distribution of calcium disorders corroborate the patterns observed here, suggesting a broader applicability of these results.

V. CONCLUSION

The study demonstrates that free ionized calcium is a reliable indicator of calcium disorders than adjusted total calcium, particularly in diagnosing hypocalcemia and hypercalcemia. The findings show a strong correlation between adjusted calcium and ionized calcium in both groups, though discrepancies were more pronounced in older patients. In the hypocalcemic group, free ionized calcium levels were significantly lower than those in the hypercalcemic group, and adjusted calcium levels were below the normal range in patients with hypocalcemia. Moreover, patients with hypercalcemia had significantly reduced bicarbonate levels, suggesting a link between calcium imbalance and acid-base disturbances. These results highlight the need to incorporate free ionized calcium measurements in clinical practice for more accurate diagnosis and management of calcium disorders, especially in elderly populations, and chronically ill patient to prevent misdiagnosis and improve patient care outcomes. This study suggests that adjusted calcium can be used as a replacement for free ionized calcium if plasma albumin is normal.

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