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The Worth of Total Calcium Levels Adjusted By Various Formulae in the Diagnosis of Hypocalcemia

Çeşitli Formüllerle Hesaplanan Düzeltilmiş Total Kalsiyum Düzeylerinin Hipokalsemi Tanısındaki Değeri

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ÖZ

Amaç: Farklı formüllerle hesaplanan düzeltilmiş kalsiyum düzeylerinin hipokalsemi açısından tanısal doğruluğunun araştırılması amaçlandı.
Araçlar ve Yöntem: 410 bireye ait tam kan serbest kalsiyum ve serum total kalsiyum düzeyi değerlendirildi. Düzeltilmiş kalsiyum düzeyleri Modifiye Orrell, Orrell, Payne, Berry ve James metoduyla hesaplandı. Hipoalbuminemi ve normoalbuminemi grupları oluşturularak herbir grupta ölçülen ve hesaplanan total kalsiyum düzeyleri için tanısal performans parametreleri incelendi. Hipokalsemi tanısında serbest kalsiyum düzeyleri referans alındı. Gruplar arasındaki farklar Mann-Whitney U testiyle incelendi. Serbest kalsiyum ile ölçülen ve hesaplanan total kalsiyum düzeyleri arasındaki ilişki Spearman korelasyon analizi ile incelendi.
Bulgular: Hipoalbuminemi grubunda en yüksek sensitiviteye sahip test %80.3 oranıyla total kalsiyum testiydi. Tüm düzeltilmiş kalsiyum düzeylerinin sensitivitesi <%60' tı. Normoalbuminemi grubunda ise ölçülen ve hesaplanan bütün düzeltilmiş kalsiyum düzeyleri için <%40'tı. Hipoalbüminemi grubunda, Modifiye Orrell, Payne, Orrell, Berry ve James yöntemi ile hesaplanan her bir kalsiyum düzeyi ile serbest kalsiyum arasında düşük düzeyde bir korelasyon gözlendi ($p<0.001$, $r=0.240$; 0.258; 0.230; 0.247; 0.193).
Sonuç: Düzeltilmiş kalsiyum konsantrasyonunun hesaplanmasında kullanılan formüllerin geliştirilmeye ihtiyacı vardır. Düzeltilmiş kalsiyum düzeyleri serbest kalsiyumun yerini alamadığı gibi, ölçülen total kalsiyum düzeylerinden daha iyi performans sergileyemedi. Düzeltilmiş kalsiyum düzeyleriyle serbest kalsiyum konsantrasyonu konusunda yorum yapmanın güvenilir olmadığı kanaatindeyiz.

Anahtar Kelimeler: düzeltilmiş kalsiyum; hipokalsemi; serbest kalsiyum; tanısal performans

ABSTRACT

Purpose: The aim was to evaluate the diagnostic accuracy of the corrected total calcium (cCa) calculated with different formulas in the diagnosis of hypocalcemia.
Materials and Methods: Whole blood free calcium and serum total calcium levels of a total of 410 individuals were evaluated.cCa levels were calculated using the Modified Orrell, Orrell, Payne, Berry, and James methods. In each of the hypoalbuminemia and normoalbuminemia groups, the diagnostic performance parameters of measured total calcium and cCa in the diagnosis of hypocalcemia were calculated. Hypocalcemia was diagnosed by measuring free calcium levels. The difference between the groups was analyzed using the Mann-Whitney.U test.A Spearman correlation analysis was performed to determine the correlation between free calcium and total Ca levels.
Results: In the diagnosis of hypocalcemia, the test with the highest sensitivity in the hypoalbuminemia group was the total calcium test, measured at a rate of 80.3%. The sensitivity was <60% in all cCa levels calculated with the five different formulas. Sensitivity rates were <40% for measured and all cCa concentrations in the normoalbuminemia group.In the hypoalbuminemia group, a low level of correlation was observed between free calcium and each calcium level calculated by the Modified Orrell, Payne, Orrell, Berry, and James method ($p<0.001$, $r=0.240$;0.258;0.230;0.247;0.193).
Conclusion: The formulas used to calculate the cCa concentration need improvement. cCa did not replace free calcium,and cCa did not outperform the total calcium level in the diagnosis of hypocalcemia.We are of the opinion that it is not reliable to comment on the free calcium levels by cCa concentration.

Keywords: corrected calcium; diagnostic performance; free calcium; hypocalcemia

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INTRODUCTION

Ranking fifth among the elements that make up organisms, calcium (Ca) is the cation found in the highest amount within the human body. Approximately 99% of the calcium element is found within the bone and tooth structure in the form of hydroxyapatite crystals.[1] Calcium plays a role in many physiological processes, such as neuromuscular activity, bone mineralization, hormone secretion, coagulation cascade, and cell division.[2,3] Calcium balance is regulated mainly by the parathyroid hormone (PTH), vitamin D, and the calcitonin hormone in the intestines, kidneys, and bones.[2]

Calcium is found in plasma at a concentration of approximately 9.5 mg/dl (2.38 mmol/l). A total of 45% of the calcium in this concentration is free (ionized), 45% is bound to plasma proteins, and 10% is chelated with anions.[1,4] Free calcium, which is a biologically active form of calcium, is recommended as a reference test for the evaluation of calcium levels.[1,5]

In the event that the protein concentration changes with a change in posture, venous stasis, or various underlying diseases, the total calcium level may change, although there is no change in the biologically active free calcium level.[6] In this case, the corrected total calcium level is calculated.

In this study, the aim was to evaluate the diagnostic accuracy of the corrected calcium level calculated with five different formulas in the diagnosis of hypocalcemia based on the free calcium level.

MATERIALS and METHODS

This retrospectively designed study was approved by the Van Yüzüncü Yıl University Faculty of Medicine Ethics Committee for Pharmaceutical and Non-Medical Device Research (10.12.2021-2021/13-16). Whole blood free calcium and venous serum total calcium levels of a total of 410 individuals (aged 0–92 years) analyzed from concurrent samples between January and December 2017, were evaluated. The results of all individuals who applied to any clinic of the hospital for any reason were evaluated. Only arterial blood gas samples with pH values in the 7.35–7.45 range were included in the study. The free calcium level was measured in heparinized whole blood samples with the ABL 90 (Radiometer Medical ApS, Denmark) blood gas analyzer and the ion-selective electrode method within 15 minutes. The serum total calcium level was measured with Architect C8000 (Abbott Diagnostics, CA, USA) systems and Arsenazo (III) method. The serum albumin level was measured with Architect C8000 (Abbott Diagnostics, CA, USA) systems and the bromine cresol green (BCG) method.

Corrected calcium levels were calculated using the Modified Orrell,[7] Orrell,[8] Payne,[9] Berry[10] and James [11] methods (Table 1). Individuals were divided into groups according to reference intervals[12,] determined by age [Ionized calcium (mmol/l); 0-5 months:1.22-1.40, 6-12 months: 1.20-1.40, 1-5 years:1.22-1.32, 6-12 years:1.15-1.32, 13-17 years: 1.12-1.30, 18-60 years: 1.15-1.27, 60-90 years: 1.16-1.29, >90 years: 1.12-1.32; Albumin (mg/dl); 0-4 days: 2.8-4.4, 5 days-14 years: 3.8-5.4, 15-59 years: 3.5-5.2, 60-90 years: 3.2-4.6, >90 years: 2.9-4.5] . The hyperalbuminemic group contained only one individual, and this meant that the group could not be included in the study. In each of the hypoalbuminemia and normoalbuminemia groups, the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), positive likelihood ratio [LHR(+)], and negative likelihood ratio [LHR] of measured total calcium and corrected total calcium concentration in the diagnosis of hypocalcemia were calculated. The area under the curve (AUC) was evaluated using receiver operating curve (ROC) analysis. Hypocalcemia was diagnosed by measuring free calcium levels. In order to compare measured and calculated parameters, the difference between the groups was analyzed using the Mann-Whitney U test. A Spearman correlation analysis was performed to determine the correlation between free calcium and measured or corrected total calcium levels. Statistical analysis was performed using the Microsoft Excel v.2019 and IBM SPSS Statistics 22 programs. The $p<0.05$ level was considered statistically significant.

Table 1. Overview of the different formulas used to calculate the corrected total calcium concentration.

Methods	Formulas
Modified Orrell method[7]	cCa= tCa+0.8 × (4-Alb)
Orrell method[8]	cCa= tCa-0.707 × (Alb-3.4)
Payne method[9]	cCa= tCa-(0.989 × Alb)+4
Berry method[10]	cCa= tCa-0.91 × (Alb-4.6)
James method[11]	cCa= tCa + 0.12 × (3.99-Alb)

cCa: Corrected total calcium (mg/dL), tCa: Measured total calcium (mg/dL), Alb: Albumin (mg/dL)

RESULTS

Of the individuals, 54% were male and 46% were female. The results of the individuals and *p* values for comparisons of groups are summarized in the table (Table 2). When categorizing according to albumin results, 46.3% of the results were in the hypoalbuminemia group and 53.7% in the normoalbuminemia group. All of the total calcium levels (measured total calcium, calcium corrected by Modified Orrell, Payne, Orrell, Berry, and James methods) were higher in normocalcemia group than the hypocalcemia group (p<0.001). In the diagnosis of hypocalcemia (with reference to the free calcium level), the test with the highest sensitivity in the hypoalbuminemia group was the total calcium test, measured at a rate of 80.3%. The sensitivity was <60% in all corrected total calcium levels calculated with the five different formulas. The specificity rate was 100% for all corrected calcium levels. The specificity for the measured total calcium level was calculated at 40.0%. PPV was calculated as 96.0% for measured total calcium; for all other corrected values, it was calculated as 100.0%. The NPV rate was evaluated as low (5.4%-10.9%) for all calcium levels (Table 3). Sensitivity rates were <40% for all measured and all corrected calcium concentrations in the normoalbuminemia group. Specificity and PPV were evaluated at a rate of >95%. The NPV rate was low (9.7-14.3%) for all levels (Table 4). The AUCs of measured and calculated total calcium levels were in the range of 0.68-0.80 in the hypoalbuminemia and normoalbuminemia groups (Tables 3, 4).

In the hypoalbuminemia group, a significant correlation was observed between free calcium and each calcium level calculated by the Modified Orrell, Payne, Orrell, Berry, and James method (p<0.001). However, this correlation was low. (r=0.240; 0.258; 0.230; 0.247; 0.193). No correlation was observed between free calcium and total calcium level in the hypoalbuminemia group (p>0.05, r=0.124). In the normoalbuminemia group, none of the calcium levels (measured total calcium, calcium corrected by Modified Orrell, Payne, Orrell, Berry, and James methods) were correlated with free calcium (p>0.05; r=0.002; 0.061; 0.071; 0.051; 0.068; 0.033).

Table 2. Results of measured and calculated parameters in different groups.

Variables	All (n=410)	Hypoalbuminemia (n=189)	Normoalbuminea (n=220)	p^* value	Hypocalcemia (n=377)	Normocalcemia (n=32)	p^{**} value
Age (Year)	53.0 (0.0-92.0)	58.0 (0.0-92.0)	43.5 (0.0-91.0)	<0.001	18.0 (0.0-59.0)	37 (0.0-91.0)	0.01
Albumin (mg/dl)	3.4 (1.4-5.2)	2.6 (1.4-3.7)	3.9 (3.2-5.1)	<0.001	2.1 (1.4-3.7)	4.0 (1.8-5.1)	0.034
Ionized Calcium (mmol/l)	0.87 (0.28-1.47)	0.87 (0.25-1.26)	0.87 (0.4-1.47)	0.114	0.78 (0.38-1.11)	1.17 (1.12-1.39)	<0.001
Total Calcium (mg/dl)	8.8 (6.0-13.6)	8.1 (6.0-13.6)	9.2 (7.5-11.8)	<0.001	7.9 (6.6-10.3)	9.7 (6.9-13.6)	<0.001
Modified Orrell Method[7] (mg/dl)	9.2 (7.6-14.5)	9.2 (7.6-14.5)	9.3 (7.8-12.4)	0.048	9.3 (8.4-11.1)	9.6 (7.8-14.5)	<0.001
Payne Method[8] (mg/dl)	9.3 (7.9-14.7)	9.4 (8.0-14.7)	9.3 (7.9-12.5)	0.022	9.6 (8.6-11.3)	9.8 (8.0-14.7)	<0.001
Orrell Method[9] (mg/dl)	8.7 (7.0-14.0)	8.6 (7.0-14.0)	8.9 (7.4-11.9)	<0.001	8.7 (7.8-10.6)	9.2 (7.3-14.0)	<0.001
Berry Method[10] (mg/dl)	9.8 (8.4-15.1)	9.9 (8.4-15.1)	9.8 (8.4-13.0)	0.699	10.0 (9.1-11.8)	10.3 (8.4-15.1)	<0.001
James Method[11] (mg/dl)	9.0 (7.0-14.0)	8.7 (7.0-14.1)	9.2 (7.7-12.1)	<0.001	8.8 (7.7-10.8)	9.6 (7.4-14.1)	<0.001

Since the number of hypercalcemia and hyperalbuminemia cases is small (n=1, n=1), they are not listed in the table. All values are mentioned as median (min-max). *:p value for comparison of hypoalbuminemia and normoalbuminemia groups, **: p value for comparison of hypocalcemia and normocalcemia groups.

Table 3. Data on the diagnostic performance of measured and corrected total Ca levels in the hypoalbuminemia group in hypocalcemia.

Variables	Sensitivity(%) %95 Cl	Spesifity(%) %95 Cl	PPV (%) %95 Cl	NPV (%) %95 Cl	LHR (+) %95 Cl	LHR (-) %95 Cl	AUC %95 Cl
Total Calcium	80.3	40.0	96.0	10.3	1.34	0.49	0.684
	74.7-85.9	12.2-67.8	94.5-97.5	4.8-15.8	0.80-1.88	0.22-0.76	0.530-0.839
Modified Orrell Method[7]	16.9	100.0	100.0	6.3	-	0.83	0.756
	11.7-22.1			5.9-6.7		0.78-0.88	0.599-0.913
Payne Method[8]	6.2	100.0	100.0	5.6	-	0.94	0.760
	3.1-9.3			5.5-5.9		0.90-0.97	0.602-0.918
Orrell Method[9]	53.9	100.0	100.0	10.9	-	0.46	0.757
	46.3-61.4			9.4-12.5		0.39-0.53	0.600-0.914
Berry Method[10]	1.1	100.0	100.0	5.4	-	0.99	0.756
	0.1-4.0			5.3-5.5		0.97-1.00	0.598-0.914
James Method[11]	44.4	100.0	100.0	9.2	-	0.56	0.737
	37.0-51.0			8.1-10.3		0.49-0.63	0.578-0.896

PPV: positive predictive value, NPV: negative predictive value, LHR (+): positive likelihood ratio, LHR (-): negative likelihood ratio, AUC:area under the curce Cl: confidence ınterval.

Table 4. Data on the diagnostic performance of measured and corrected total Ca levels in the normoalbuminemia group in hypocalcemia.

Variables	Sensitivity %95 Cl	Spesifity %95 Cl	PPV %95 Cl	NPV %95 Cl	LHR (+) %95 Cl	LHR (-) %95 Cl	AUC %95 Cl
Total Calcium	18.3	95.2	97.3	11.0	3.84	0.86	0.803
	13.1-23.5	90.5-99.9	95.0-99.6	10.0-12.0	0.55-7.13	0.76-0.96	0.707-0.898
Modified Orrell Method[7]	10.2	100.0	100.0	10.6	-	0.90	0.741
	6.3-14.1			10.2-11.1		0.86-0.94	0.639-0.843
Payne Method[8]	7.6	100.0	100.0	10.3	-	0.92	0.722
	4.6-10.6			10.0-10.7		0.89-0.96	0.610.828
Orrell Method[9]	39.1	95.2	98.7	14.3	8.21	0.64	0.758
	32.2-46.0	90.5-99.9	97.6-99.8	12.6-16.0	1.20-15.22	0.55-0.73	0.658-0.857
Berry Method[10]	0.5	100.0	100.0	9.7	-	0.99	0.739
	0.0-2.8			9.6-9.8		0.98-1.00	0.635-0.844
James Method[11]	15.2	95.2	96.8	10.7	3.20	0.89	0.782
	10.5-21.0	90.5-99.9	94.1-99.5	9.7-11.7	0.46-5.94	0.79-0.99	0.685-0.878

All values are mentioned as percentages (%). PPV: positive predictive value, NPV: negative predictive value, LHR (+): positive likelihood ratio , LHR (-): negative likelihood ratio, AUC:area under the curce Cl: confidence ınterval.

DISCUSSION

In this study, we evaluated the performance of corrected total calcium levels, particularly those calculated using the five different formulas for the diagnosis of hypocalcemia. cCa did not replace free calcium, and cCa did not outperform the total calcium level in the diagnosis of hypocalcemia.

Although direct measurement of free calcium is recommended to determine the calcium level, it is commonly evaluated by measuring the total calcium level. The total calcium level can be misleading in cases such as protein concentration change, acid-base imbalance, citrate blood transfusion, and citrate anticoagulation. Therefore, many methods are recommended to calculate the corrected calcium level.[13,14]

Although various corrected calcium formulae have been proposed to estimate free calcium in the previous studies,[7-11] many studies have shown that the corrected calcium level does not reflect the free calcium level.[15-20] In a study with 254 samples, Mir et al.[15] calculated the corrected Ca levels using various methods (Orrell, Berry, and Payne methods), and they subsequently obtained the calculated free calcium levels by taking half of the values. They compared the ionized calcium levels measured directly by the ion-selective electrode method and the calcium levels corrected with various formulas, and a significant difference was seen. They concluded that the corrected calcium formulas were inconsistent with ionized calcium measurements.[15] In another study, Smith et al. analyzed total calcium and corrected calcium levels calculated by the modified Payne method, and it was reported that, in the case of hypoalbuminemia, the corrected calcium was calculated higher than it should be; normocalcemic patients can in fact be considered hypercalcemic and hypocalcemic patients as normocalcemic, and it would be more appropriate to use total calcium instead of corrected calcium when albumin is <3.[16] In a study on hemodialysis patients, Gorransson et al. reported that albumin-corrected total calcium did not replace ionized calcium in the classification of hypocalcemia, normocalcemia, and hypercalcemia. In this study, it has been found that errors potentially leading to incorrect treatment practices may be caused if the decision is made with only corrected calcium.[17] Similar results have been shown in many studies.[18-20] In the present study, all of the measured and corrected total calcium levels were higher in the normocalcemia group than the hypocalcemia group (p<0.001), (Table 2). AUCs of measured and calculated total calcium levels were in the range of 0.68-0.80 in the hypoalbuminemia and normoalbuminemia groups. However, the diagnostic sensitivity of corrected calcium was rather low (Tables 3, 4). The data we obtained in this study showed that the corrected total calcium level was not more beneficial than the measured total calcium level, and this was consistent with the aforementioned studies.

The studies were both different among themselves and different from this study. Measuring calcium levels with bromine cresol purple or bromine cresol green can lead to different results. In this study, serum albumin level was measured by the bromine cresol green (BCG) method. In this study, only samples with physiological pH were evaluated. The fact that pH is ignored in some studies and whether it is included in correction formulas should be kept in mind as a factor that may cause results to vary. Total calcium had a surprisingly higher sensitivity in the hypoalbuminemic group. However, when albumin decreases, the binding status of serum total calcium changes, and it is insufficient to evaluate the blood calcium level. For this reason, the use of corrected formulas is recommended. However, these results could have been obtained because the current study included a quite diverse patient population. At the same time, the albumin cut-off value used may cause different results, since there may be differences in albumin measurement according to measurement techniques. It is a known issue that calcium levels are measured lower in analyses made with samples taken in heparinized tubes.[21] In the present study, ionized calcium was measured in blood that was collected into a heparinized tube. The proportion of hypocalcemic samples was high (%91.9), confirming the effect mentioned above. For this reason, it is important to consider the tubes in which the blood is collected and the type of sample the analysis is performed on when performing the ionized calcium analysis. As a separate discussion topic, these issues may lead to different results.

The formulas used to calculate the corrected calcium concentration need improvement. Corrected total calcium did not replace free calcium, and corrected calcium did not outperform the total calcium level in the diagnosis of hypocalcemia. We are of the opinion that it is not reliable to comment on the free calcium levels by corrected calcium concentration.

Due to the retrospective screening of the cases, the inaccessibility of additional disease information that may affect the results, and the fact that it is difficult to master the preanalytical phase of blood gas analysis were among the limitations of the present study.

Conflict of Interest

The authors declare that there is not any conflict of interest regarding the publication of this manuscript.

Ethics Committee Permission

Approval for this study was obtained from Van Yüzüncü Yıl University Faculty of Medicine Pharmaceutical and Non-Medical Device Research Ethics Committee (10.12.2021 dated and 2021/13-16 numbered).

Authors' Contributions

Concept/Design: TB, HİA, EÇ. Data Collection and/or Processing: TB, EÇ. Data analysis and interpretation: TB, HİA. Literature Search: TB, HİA. Drafting manuscript: TB, HİA, EÇ. Critical revision of the manuscript: TB, HİA, EÇ.

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