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Requests of laboratory tests for the diagnosis and management of calcium-phosphate disorders in Spain

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ABSTRACT

***Background**: Knowledge about the variability in the request of calcium-phosphate metabolism laboratory tests in primary care is important to design strategies to improve health system efficiency. **Aim**: To compare the inter-practice variability in calcium-phosphate metabolism laboratory tests requested by general practitioners from diverse regions across Spain. **Material and Methods**: One hundred and forty one clinical laboratories were invited to participate in an observational cross-sectional study. They informed the number of serum calcium, phosphate, parathyroid hormone and 25-hydroxyvitamin D requested by general practitioners. Appropriateness indicators were calculated as number of test requests per 1,000 inhabitants and ratio of related tests requests. The differences according to hospital setting, region and type of management were analyzed. **Results:** We recruited 76 laboratories (17,679,195 inhabitants). General practitioners requested 3,260,894 calcium-phosphate metabolism tests. The rate of request ranged from 2.97 per 1,000 inhabitants for 25-hydroxyvitamin D to 98.89 per 1,000 inhabitants for calcium. The rates of request for calcium, phosphate, parathyroid hormone in some areas were 30, 100 and 340 times higher than in other areas. Parathyroid hormone and 25-hydroxyvitamin D were highly requested in private management areas. There were also differences in phosphate, parathyroid hormone and 25-hydroxyvitamin D requesting between regions across Spain. **Conclusions**: The high variability observed is difficult to explain by differences in patient case mix between regions. Depending on the area, calcium could be under requested to detect primary hyperparathyroidism.*

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***Key words:** Calcium Metabolism Disorders; Clinical Laboratory Services; Practice Patterns, Physicians)*

Solicitud de pruebas de laboratorio para el diagnóstico y manejo de los desórdenes del metabolismo fosfocálcico en España

Objetivo:** Conocer la variabilidad en la solicitud de pruebas de laboratorio en atención primaria es importante para diseñar estrategias que mejoren la eficiencia del sistema de salud. La propuesta de este estudio fue comparar la variabilidad en la solicitud de pruebas para la evaluación del metabolismo fosfocálcico por médicos de atención primaria de diversas regiones de España. **Material y

Método: *Se invitó a participar a 141 laboratorios clínicos de diversas regiones españolas. Completaron una encuesta con el número de determinaciones de calcio, fósforo, hormona paratiroidea y 25-hidroxivitamina D solicitadas por médicos de atención primaria de sus áreas. Se calcularon las tasas en relación a la población y se construyeron indicadores de adecuación. Los resultados se compararon por características del hospital, región y tipo de gestión.* ***Resultados:*** *Obtuvimos los datos de 76 laboratorios (17.679.195 habitantes). Los médicos de atención primaria solicitaron 3.260.894 pruebas de metabolismo fosfocálcico. La tasa de solicitud varió de 2,97 por 1.000 habitantes de 25-hidroxivitamin D a 98,89 por 1.000 habitantes de calcio. Las tasas de calcio, fósforo, hormona paratiroidea en algunas áreas fue 30, 100 y 340 veces más alta respecto a otras. Hormona paratiroidea y 25-hidroxivitamina D fueron más solicitadas significativamente en hospitales con gestión privada. También hubo diferencias en fósforo, hormona paratiroidea y 25-hidroxivitamina D solicitas entre distintas regiones de España.* ***Discusión:*** *La alta variabilidad observada es difícil de explicar por las diferencias de las características de los pacientes. Dependiendo de la región podría haber una infra solicitud para la detección del hiperparatiroidismo primario.*

Hypercalcemia can be caused by many disorders, but is most commonly due to neoplastic disease in inpatients and to primary hyperparathyroidism (PHPT) in outpatients[1,2]. PHPT is the third most common endocrine disease after diabetes and thyroid diseases[3]. Due to its mild symptoms, the disorder can be detected in primary care, through an unexpected hypercalcaemia. It is crucial to diagnose this highly prevalent disorder early in its clinical course, as timely treatment delays progression and prevents its devastating complications, thus improving prognosis[4-6].

Test requesting inappropriateness is a major issue for a healthcare system[7,8]; test under requesting results in misdiagnosis, on the other hand, over requesting produces unnecessary expenses, but even physical and psychological patient adverse effects[8-11].

There is high variability in the request of calcium (S-calcium) and phosphate (S-phosphate), between different regions, and referring physicians[12-16]. In certain areas, S-calcium is under-requested to detect asymptomatic PHPT[14,15]. Currently, through studies investigating regional and geographical differences in test request[12,13,17,18], we can detect requesting inappropriateness, and deduce the root causes of such potential problem.

The aim of this research was to study the inter-practice variability in calcium-phosphate metabolism laboratory tests requested by General Practitioners (GPs) in Spain to investigate the degree in requesting appropriateness and deduce its potential causes.

Materials and Methods

Data collection

Encouraged by the previous pilot studies in the Valencian Community[12] and all around Spain[13-18] a call for data was posted via email. Spanish laboratories willing to participate in the study were invited to fill out an enrollment form and submit their results online. A total of 141 laboratories were invited to participate. We obtained production statistics (number of tests requested by GPs for the year 2012 from laboratories at different hospitals from diverse regions across Spain. Every patient seen in any primary care center (PCC) of any of these health departments, regardless of the reason for consultation, gender or age, was included in the study. Each participating laboratory was required to be able to obtain patient data from local databases and to provide organizational data (i.e. population served, public/private management, location). S-calcium, S-phosphate, albumin, parathyroid hormone (PTH) and 25-hydroxyvitamin D [25(OH)D] test requesting were examined in a cross-sectional study.

Data processing

After collecting the data, two types of appropriateness indicators were calculated: every test request per 1,000 inhabitants and ratio of related

tests requests (S-phosphate/S-calcium; 25(OH)D/PTH). In order to explore the inter-practice variability, another indicator, the "index of variability", was calculated as follows: top decile divided by bottom decile (90th percentile/10th percentile).

We calculated if the rate of test requests was different according to the setting (rural, urban, or rural-urban) of the hospital and whether the institution had a public or private management.

Finally, the indicators results obtained in the laboratories in the three regions with the highest number of departments participating in the study were compared between them and to the pooled results of the remaining regions in order to establish whether there were regional differences in the requesting patterns.

Statistical methods

The statistical treatment of the calculated data included: the distribution, the mean, 95% confidence level for the mean, standard deviation, median and interquartile range. The analysis of the distribution of the number of indicators results was conducted by way of the Kolmogorov-Smirnov test.

The differences in indicators results according to the hospital characteristics and per region were calculated by way of the Mann-Whitney U or Kruskal-Wallis test analysis, as appropriate.

A two-sided $p \leq 0.05$ rule was utilized as the criterion for rejecting the null hypothesis of no difference.

Results

We obtained production statistics from 76 laboratories at different hospitals from diverse regions across Spain. 17,679,195 patients (37.8% of the Spanish population) were included in the study, from 13 Communities (Valencian Community, 23 laboratories and 4,848,900 patients (96.9% of the Valencian Community population); Andalucía, 12 laboratories and 3,849,485 patients (37.8% of Andalucía population); Castilla y León, 9 laboratories and 1,695,916 patients (67.1% of Castilla y León population) and other region, 32 laboratories and 7,284,889 patients). GPs requested 3,260,894 calcium-phosphate metabolism laboratory tests. A summary of the organizational data of the different laboratories that participated in the study is showed in Table 1.

Table 2 shows the descriptive statistical analysis and the variability index for the indicator results. The rates of request for S-calcium, S-phosphate and PTH in some areas were 30, 100 and 340 times higher than in other areas respectively.

GPs requested albumin to the 76 laboratories. However, only 17 laboratories additionally provided calcium corrected per albumin.

Table 3 compares the appropriateness indica-

Table 1. Descriptive characteristics of the hospitals/health care departments that participated in the study

Descriptive characteristics		Data
Areas (n)		76
Subjects (n)		17,679,195
Population/area [mean (CI95%)]		232,621 (200,099.8-265,142.2)
Location [n (%)]	Valencian Community	23 (30.3%)
	Andalucía	12 (15.8%)
	Castilla y León	9 (11.8%)
	Other región	(42.1%)
Type of Management [n (%)]	Public	70 (92.1%)
	Private	6 (7.9%)
Setting [n (%)]	Urban	15 (19.7%)
	Rural	3 (3.9%)
	Urban-rural	58 (76.3%)

CI: Confidence interval of the mean.

tors results obtained at the different laboratories according to their setting and type of management. PTH and 25(OH)D that were higher requested in areas with private management.

Table 4 compares the number of requests per 1,000 inhabitants in the different regions. There were no differences in S-calcium requesting, however S-phosphate was higher requested in Castilla y León when compared to Andalucía. PTH and 25(OH)D were over requested in Valencian Community when compared to Castilla y León, Andalucía and the remaining regions.

Table 2. Descriptive statistical analysis and the variability index

		Range	Mean	CI95%	Median	IQR	Variability Index
Tests/1,000 inhabitants	S-calcium	11.37-334.10	98.89	82.55-115.23	88.38	80.96	7.63
	S-phosphate	2.29-230.66	61.29	49.15-73.43	45.17	65.29	16.82
	PTH	0.05-17.77	3.01	2.07-3.94	1.55	1.89	23.15
	25OHD	0.03-21.19	2.97	1.93-4	1.11	1.79	51.65
	Albumin	0.25-231.84	55.38	41.73-69.02	31.20	56.93	31.89
Related test requested ratios	25OHD/PTH	0.015-9.004	1.336	0.937-1.735	0.861	0.987	14.85
	S-phosphate/ S-calcium	0.046-0.993	0.621	0.558-0.685	0.659	0.492	4.62

Legend: Serum calcium (S-calcium); phosphate (S-phosphate); parathyroid hormone (PTH) and 25-hydroxyvitamin D [25(OH)D].

Table 3. Differences of appropriateness indicators results obtained at the laboratories of the different locations and according to the type of management

S-calcium		Test per 1,000 inhabitants (mean±SD)			Ratios of related tests (mean±SD)		
		S-phosphate	PTH	25(OH)D	S-phosphate/ S-calcium	25(OH)D/PTH	
Location	U	131.95 ± 81.30	87.62 ± 48.62	4.37 ± 5.08	5.10 ± 6.53	0.757 ± 0.235	1.014 ± 0.597
	R	64.29 ± 25.70	24.57 ± 2.20	1.66 ± 0.82	0.80 ± 0.40	0.428 ± 0.187	0.483 ± 0.096
	U-R	92.13 ± 68.42	56.38 ± 53.44	2.72 ± 3.85	2.51 ± 3.75	0.596 ± 0.282	1.469 ± 1.939
Management	P	98.51 ± 72.22	59.51 ± 54.44	2.37 ± 3.03†	2.54 ± 4.03†	0.608 ± 0.282	1.395 ± 1.783
	PV	103.31 ± 25.12	81.98 ± 29.92	10.42 ± 7.11	7.75 ± 6.76	0.781 ± 0.166	0.669 ± 0.356

* Kruskal-Wallis test significative ($p < 0.05$); †U-Mann-Whitney test significative ($p<0.05$).

Table 4. Differences of appropriateness indicators results obtained at the laboratories of the different regions of Spain

	Tests/1,000 inhabitants (mean ± SD)				Ratio of related tests (mean ± SD)	
	S-calcium	S-phosphate	PTH	25(OH)D	S-phosphate/ S-calcium	25(OH)D/PTH
V	91.93 ± 76.01	52.70 ± 48.50	5.71 ± 5.97*	6.11 ± 6.26*	0.604 ± 0.250	0.852 ± 0.303
A	117.08 ± 106.75	39.87 ± 41.36	2.41 ± 3.44	1.48 ± 2.41	0.415 ± 0.292	0.898 ± 0.626
CL	119.83 ± 51.91	109.34 ± 56.66*	1.07 ± 0.64	0.78 ± 0.50	0.886 ± 0.090*	1.528 ± 2.180
OR	91.18 ± 56.35	61.98 ± 53.12	1.83 ± 1.57	1.79 ± 2.62	0.637 ± 0.271	1.481 ± 1.705

*Kruskal-Wallis test (p value < 0.05); Legend: VC: Valencian Community; A: Andalucía; CL: Castilla y León; OR: Other regions. Serum calcium (S-calcium); phosphate (S-phosphate); parathyroid hormone (PTH) and 25-hydroxyvitamin D [25(OH)D]. S-phosphate request in CL was significantly higher than in A; PTH and 25(OH)D in V were significantly higher than A, CL and OR; S-phosphate/ S-calcium in CL significantly higher than A, V and OR.

Discussion

There were significant differences in the request of calcium-phosphate metabolism laboratory tests, as seen in prior investigations[12,13]. The variability observed for S-calcium in the study was from 11.37 to 334.10 tests per 1,000 inhabitants. This variability could be explained in the different areas by case mix variations, or the possible variability in the patient demographic. However the differences observed between areas are so high that it was probably caused by additional reasons.

Hypercalcaemia is a highly prevalent condition[19], up to of 3.9% of the general population[20]. Eleven requests of S-calcium tests per 1,000 inhabitants, as in certain areas, indicate that, on average, every patient would get a test ordered every 100 years. In this scenario, S-calcium may be under requested for two main reasons. First, S-calcium is crucial to detect asymptomatic PHPT[14]. Second S-calcium testing does not usually yield false positive results with a proper sampling technique[21]. At least 88% of patients with hypercalcaemia will turn out to have an underlying disorder during a 10-year follow-up period, which makes necessary careful investigation of such subjects[22].

Asymptomatic PHPT is usually detected in health screenings. With the introduction of automated S-calcium measurement with multichannel continuous-flow analyzers in the 1970s, this silent disease began to be detected[23]. At that time, unexpected high S-calcium values on serum biochemical screening contributed to the diagnosis of 250 new cases of PHPT per million inhabitants per year[24]. Then, the disappearance of the multichannel analyzers and simultaneous introduction of random access analyzers, that in general would benefit the appropriate laboratory test requesting by demanding and measuring only those tests related to a certain diagnosis, resulted in S-calcium under requesting and, hence, a decreased detection of asymptomatic PHPT[25, 26]. PHPT became a not so infrequent disease that was often overlooked by physicians[27]. In fact, with the disappearance of multichannel continuous-flow analyzers S-calcium is at risk of being the "forgotten test", and strategies must be encouraged to increase its request for a correct PHPT detection[14].

The prevalence of PHPT in Spain varies between 1 and 4/1,000 in the general population[28]. Lately, thanks to the establishment of PHPT screening strategies, it is even increasing[14]. Depending on the criteria used to define PHPT, the prevalence of the disorder in older women ranges from 3.6% to 13.9%, making it really important to define hypercalcemia as a first step to detect the disorder[29]. Total calcium (S-calcium) occurs in plasma in free form, "ionized calcium", and in complex bound form, especially with albumin[30]. It is only ionized calcium which is physiologically relevant, and this would be the fraction to be measured. Methods are available, but they require specially analyzers and rapid anaerobic handling of the sample. So, in most clinical situations disturbances in calcium metabolism have to be assessed from changes in the S-calcium concentration. As ionized calcium, the biologically active, is unstable in PCCs samples, it is crucial the calculation of total calcium corrected per albumin. It is true that calcium binding to albumin is influenced by pH and hence by stasis, but within the range found in current clinical practice the proportion of S-calcium which is bound varies little[31]. However, as showed in our study results, only 22% of laboratories reported albumin-corrected calcium.

The interest of measuring S-phosphate is always related to S-calcium. The request of S-phosphate ranged from a one to one ratio when compared to S-calcium request, to almost zero. S-phosphate should be probably only requested based on algorithms after abnormal values of S-calcium, as performed with aminotransferases[32] or thyroid hormones[33].

The variability in PTH and 25(OH)D requesting was even higher than that for S-calcium and S-phosphate and is very difficult to interpret, mainly for two reasons. First, we do not know if the different request patterns could be explained by the different implication of GPs in the management of calcium-phosphate metabolism disorders in the different areas. Second, there are no prior studies regarding PTH and 25(OH)D request in primary care to compare with. Both tests were over requested in areas with private management. This could be explained by the fact that this type of management is new, and physicians working in such areas may be more prone to manage calcium-phosphate metabolism disorders. The fact that these areas with private management are located in Valencian Community could explain or at least could contribute to the over

request of such tests in Valencian Community, when compared to other regions. Additionally, it seems plausible that centers that are interested in hyperparathyroid disorders request more of all these markers. There was a high variability in the ratio 25(OH)D/PTH between the different areas, which ranged from 0.015 to 9. More studies are necessary to explain those striking results. Along the last years, hypovitaminosis D has been associated with many clinical condition (immunology and oncology disorders) there was a spread of 25(OH) D test requests among different centers other than those specialized in metabolic bone disease and also among general practitioners[34].

The strength of this study includes the national representation of the studied population; this allows us to provide accurate estimates of indicator calculation. Nonetheless, the study had certain limitations. First, the differences in calcium-phosphate metabolism laboratory tests request between health care regions in Spain could be partly explained by case mix variations in the different areas, or the possible variability in the patient population. Second, we did not take into account the differences in blood sampling techniques and the distribution of age, gender, medication and body mass index of the subjects at the different participating laboratories. Third, we did not evaluate the request of ionized calcium, because we did not get those data, and another potential indicators as S-calcium/PTH Also, the variability showed in our study could be explained by regional different degrees of awareness in the management of calcium-phosphate disorders in primary care. Finally, it is difficult to know whether there is over or under request without clinical patient data.

In all, there was high variability in the request of calcium-phosphate tests in almost half of the Spanish population, difficult to explain by differences in patient case mix between regions. S-calcium was probably under requested in some areas to detect silent diseases such as PHPT. Great efforts must be done from every stakeholder that intervenes in calcium-phosphate metabolism disorders, mainly S-calcium and PTH requests should be homogeneous, as they are basic for PHPT diagnosis.

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