Research Article

Gülsen Yılmaz*, Nurullah Aydoğan, Sevilay Sezer, Sezen Tutar, Andaç Uzdoğan, Özcan Erel and Fatma Meriç Yılmaz

Assessment of regulation on vitamin D test requesting in terms of the rational laboratory use

[VİTAMİN D TEST İSTEMİ İLE İLGİLİ DÜZENLEMENİN AKILCI LABORATUVAR KULLANIMI AÇISINDAN DEĞERLENDİRİLMESİ]

https://doi.org/10.1515/tjb-2020-0175
Received April 10, 2020; accepted October 1, 2020;
published online October 29, 2020

Abstract

Objectives: The aim of this study is to identify the possible effects of the Ministry of Health regulation on Vitamin D testing and vitamin D deficiency detection and to investigate the effect of the reflex test algorithm implementation.
Materials and methods: A total of requested 78,919 25(OH)D and 5,653 1,25(OH)2D test results were examined. Test requests were classified in 3 groups according to the Regulation; Group 1: Requests from inpatients and intensive care units, Group 2: Requests from outpatients of non-restricted departments, Group 3: Requests from outpatients of restricted departments. In addition, the reflex test algorithm was simulated and the name of the 1,25-dihydroxyvitamin D test request was changed to 1,25-dihydroxycholecalciferol.
Results: Changing the test name as 1,25 dihydroxycholecalciferol reduced the number of monthly test requests (–71.7%). The hypovitaminous detection rate was similar in Group 1, 2, and 3 in the 25(OH)D requests and was higher in the reflex test algorithm. In 1,25(OH)2D requests, the rate of hypovitaminous detection was higher in Group 1 than in Group 2 and 3.
Discussion: With simple acts like using structured test ordering forms, reflex test algorithms applied in the clinic-laboratory-interface involving Medical Biochemistry Specialists, bigger impact with less underdiagnosis might be possible in test demand management.

Keywords: 1,25(OH)2D; 25(OH)D; clinic-laboratory-interface; pre-preanalytical phase; rational laboratory use; reflex test algorithms; vitamin D.

Öz

Amaç: Bu çalışmanın amacı, Sağlık Bakanlığı tarafından yapılan düzenlemenin VitaminD test istemi ve eksiklik tespiti üzerine olası etkilerini belirlemek ve refleks test algoritma uygulamasının etkisini araştırmaktır.
Gereç ve Yöntem: Bir yıl boyunca yapılan 78.919 25-hidroksivitaminD [25(OH)D] ve 5.653 1,25-dihidroksivitaminD [1,25(OH)2D] test sonucu analiz edilmiştir. Bu test istemleri yapılan düzenlemeye göre 3 gruba ayrılmıştır; Grup 1: Servis ve yoğun bakımlardan gelen istemler, Grup 2: Polikliniklerden ve istem kısıtlaması olmayan bölümlerden gelen istemler, Grup 3: Polikliniklerden ve istem kısıtlaması olan bölümlerden gelen istemler. Ayrıca, refleks test algoritması oluşturulmuş ve

*Corresponding author: Gülsen Yilmaz, Ministry of Health Ankara City Hospital, Medical Biochemistry Laboratory, Ankara, Turkey; and Ankara Yıldırım Beyazıt University, Faculty of Medicine, Medical Biochemistry Department, Ankara, Turkey,
E-mail: dr.gulsenyilmaz@gmail.com
Nurullah Aydoğan, Sevilay Sezer, Sezen Tutar and Andaç Uzdoğan, Ministry of Health Ankara City Hospital, Medical Biochemistry Laboratory, Ankara, Turkey. https://orcid.org/0000-0002-0926-3793 (S. Sezer). https://orcid.org/0000-0003-2950-2680 (A. Uzdoğan)
Özcan Erel and Fatma Meriç Yılmaz, Ministry of Health Ankara City Hospital, Medical Biochemistry Laboratory, Ankara, Turkey; Ankara Yıldırım Beyazıt University, Faculty of Medicine, Medical Biochemistry Department, Ankara, Turkey

Open Access. © 2021 Gülsen Yılmaz et al., published by De Gruyter. This work is licensed under the Creative Commons Attribution 4.0 International License.

çalışmanın son ayında 1,25-dihidroksi VitaminD test isteminin adı 1,25-dihidroksikolekalsiferol olarak değiştirilmiştir.
Bulgular: 1,25-dihidroksikolekalsiferol olarak test isminin değiştirilmesi aylık test istem sayısını (–%71.7) düşürdü. Hipovitaminöz saptanma oranı, 25(OH)D istemlerinde Grup 1, 2 ve 3'de benzer iken refleks test algoritmasında daha yüksekti. 1,25(OH)2D istemlerinde Grup 1'de Grup 2 ve 3'e göre hipovitaminöz saptanma oranı fazlaydı.
Sonuçlar: Bu kısıtlama ile birlikte klinik-laboratuvar arayüzünde refleks test, yapılandırılmış test istem formları gibi basit uygulamalarla Tıbbi Biyokimya Uzmanlarının dahil edilmesi, test istem yönetiminde daha az yetersiz tanı ile birlikte daha büyük etki sağlanması mümkün olabilir.

Anahtar Kelimeler: 1,25(OH)2D; 25(OH)D; akılcı laboratuvar kullanımı; klinik-laboratuvar-arayüzü; pre-preanalitik faz; refleks test algoritmaları; vitamin D.

Introduction

The use of clinical laboratory test results in diagnostic decision making is an integral part of clinical medicine and up to 70% of the clinical decisions are substantially based on results of diagnostic tests [1]. Laboratory testing and its associated costs have increased substantially due to increased use. Like other sectors of the health economy, laboratory medicine is under increasing pressure to remove inefficiencies and reduce costs, while maintaining or indeed improving standards [2]. As a result for providing qualified medicine cost effectively, reduction in the ordering of unnecessary laboratory tests has become a favorite target of these efforts. The recent emphasis on reducing health care costs and the emergence of managed care organizations led to efforts to reduce the abuse (overordering) and misuse (e.g., ordering the right test for the wrong purpose or vice versa) of these tests [3]. It has been tried to reduce such unnecessary tests by interventions targeting the ordering of tests. The easiest and preferred way of controlling laboratory test requesting is to pick the test causes to big load to the budget. Vitamin D is one of the high demand test with more commonly ordered tests [e.g., complete blood count (CBC), electrolytes (sodium, potassium, chloride), thyroid stimulating hormone (TSH), glucose, etc.] routinely performed on site by most hospital-based clinical laboratories.

Vitamin D is critical for bone and mineral metabolism and is effective in the prevention and treatment of rickets and osteomalacia [4, 5]. Classification of vitamin D status is based on serum 25-hydroxyvitamin D [25(OH)D] that is mainly derived from hydroxylation of vitamin D in the liver. Compared to vitamin D, 25(OH)D has a much higher serum concentration and a longer half-life (about 3 weeks vs. 1 day) and is therefore considered the best parameter to indicate vitamin D supply from all different sources. 1,25-dihydroxyvitamin D [1,25(OH)2D] is the active vitamin D hormone that has the highest affinity to the almost ubiquitously expressed vitamin D Receptor. Serum concentrations of 1,25(OH)2D are not accepted as a good indicator of vitamin D supply due to its short half-life and dependence on substrate availability of 25(OH)D [6, 7]. Epidemiological studies showing low 25(OH)D concentrations are associated with various acute and chronic diseases have risen a high interest in vitamin D testing [8, 9]. United States data indicate that testing for 25(OH)D has increased by 80–90% annually, yet there are no reports that investigate the cost of either 25(OH)D or 1,25(OH)2D testing in Turkey [10]. However, data in Ministry of Health strongly indicate that 25OHD testing is consuming a large amount of the annual health budget. Due to this increased cost, Ministry of Health has been released the regulation on vitamin D testing to prevent unnecessary and excessive request of some tests, including vitamin D invoiced to the Social Security Institution (SGK) beginning on January 2020. Although there are private health maintenance organizations, the main agency, all citizens covered by, is government-sponsored agency (SGK). According to this regulation, vitamin D testing reimbursement in primary health care facilities by SGK has been stopped. In secondary and tertiary health care facilities, vitamin D testing reimbursement has been limited for patients at emergency units and outpatients based on specialties. These medical specialty areas are pediatrics and its subspecialties, internal medicine and its subspecialties, gynecology and obstetrics, physical therapy and rehabilitation, orthopedia and traumatology and neurologia. There is no limitation for patients at intensive care units and inpatients [11].

The Ankara City Hospital, where the study was conducted in, is the tertiary and biggest hospital in Turkey having a total of 3,704 hospital beds. Currently, the hospital serves approximately 20.000 outpatient patients per day and this number is expected and planned to further more increased numbers under normal circumstances. Medical Biochemistry Laboratory is carried out approximately 150,000 tests daily. The analysis performed in the laboratory includes general and specific clinical chemistry, haematology and coagulation, cardiac markers, urinalysis, blood gas testing, immunochemistry, HbA1c, electrophoresis and flow cytometry. 25(OH)D testing has risen above the general trend of other common medical biochemistry tests.

In this study, it was aimed to show the possible effects of vitamin D testing restriction based on medical specialty

put into practice by the Ministry of Health on hypovitaminosis D detection and testing costs by evaluating the 1-year Ankara City Hospital vitamin D test requests retrospectively as a tertiary hospital with a high capacity hospital based laboratory. In addition, it has been investigated whether medical biochemistry specialists, as a medical specialty not included in this new regulation, can have a role in detecting hypovitaminosis D and improving test cost-effectiveness by using reflex test, reflective test or other applications involved in the rational laboratory project of the Ministry of Health.

Material and methods

Vitamin D test results from subjects who admitted to Ankara City Hospital for health examination were included in the present study. A total of 84,572 vitamin D test results, 78,919 25(OH)D and 5,653 1,25(OH)2D result, were examined and analyzed. Due to total number of vitamin D tests requested by emergency unit was too low to analyze, these requests were neglected and excluded from the study (n=24). 25(OH)D and 1,25(OH)2D were analyzed seperately and the results were divided into 3 groups according to the Act of Ministry of Health such as:

Group 1: Non-restriction group in vitamin D test requests based on patient type; it covers all vitamin D tests requested from non-restricted patient groups (vitamin D requested from inpatients and intensive care units)

Group 2: Non-restriction group in vitamin D test requests based on medical specialist field; it covers all vitamin D tests requested by non-restricted specialists (vitamin D requested from outpatients by pediatricians, internal medicine specialists, obstetrician and gynecologists, physical therapy and rehabilitation specialists, orthopedics and traumatology specialists and neurologists);

Group 3: Restricted group in vitamin D test requests based on medical specialist field; it covers all vitamin D tests requested by restricted specialists (vitamin D requested from outpatients by specialists other than involved in Group 2).

Reflex testing algorithm based on Srivastava et al.study was used for the diagnosis of low vitamin D [12]. Of the 78,919 patients who has 25(OH)D test request, patients over 55 years of age with serum albumin-adjusted calcium ≤2.1 mmol/L and serum alkaline phosphatase >150 U/L were selected. In these patients, hypovitaminosis D was examined by accepting the 25(OH)D level under the replacement cut-off [<20 ng/mL (50 nmol/L)].

All results were examined on seasonal basis. Additionally, due to most of 1,25(OH)2D testing was requested with 25(OH)D simultaneusly, the name of the 1,25-diydroxyvitamin D was changed as 1,25-dihydroxycholecalciferol (the main source of 1,25(OH)2D) at the beginning of the last month of the study. To evaluate the effects of this intervention on hypovitaminosis detection, patients with 1,25(OH)2D results were classified into 2 groups as before intervention and after intervention. Patients are categorized as normal and deficient. Deficiency is described as 1,25(OH)2D results below cut-off (<26.1 pg/mL). Categorical data comparisons between groups were conducted by the chi squared (χ^2) test.

Vitamin D measurements were performed by immunoassay. All devices in this study: Atellica Immunoassay Analyzer (Siemens Healtineers, Germany) for for 25(OH)D and IDS-iSYS auto analyzer (Immunodiagnostic Systems Holding, United Kingdom) 1,25(OH)2D were used under standardized Westgard's quality control rules with approved reagents. Manufacturers' instructions were followed while performing all measurements. The allowable total analytical error (TEa) was calculated using internal and external quality control results according to Ricos C. et al. study [13] for 25(OH)D and 1,25(OH)2D and the obtained 7.34 and 10.72% value was under the TEa limit ±15% according to Royal College of Pathologists of Australasia (RCPA) [14]. The study was approved by the Institutional Ethical Committee.

Results

The numbers of the participants with normal and low vitamin D levels included into the study has been shown in Table 1. At first, all of the 25(OH)D and 1,25(OH)2D results were examined. The percentage of requested tests classified in the Group 1, the Group 2 and Group 3 for 25(OH)D were 7.2, 77.2, and 15.6; 14.6, 60.7, and 24.7% for 1,25(OH)2D, respectively. Most of the 25(OH)D and 1,25(OH)2D test requests were classified in Group 2 (77.2%, n=60,911; 60.7%, n=3,430). Secondly, the 25(OH)D and 1,25(OH)2D results below cut-off (<20 ng/mL, <26,1 pg/mL, respectively) (50 nmol/L) were examined and 44.5% of all requests for 25(OH)D and 10.8% of all requests for 1,25(OH)2D were below cut-off. The percentage of requested tests found cut-off classified in Group 1, Group 2, and Group 3 for 25(OH)D were 7.0, 78.5, and 14.5; 34.4, 48.4, and 17.3% for 1,25(OH)2D, respectively Most of the 25(OH)D and 1,25(OH)2D test requests with low vitamin D levels were classified in Group 2 (78.5 %, n=27,565; 48.4%, n=294). Thirdly, prevalance of hypovitaminosis in 25(OH)D and 1,25(OH)2D results were examined. The percentage of prevalance of hypovitaminosis found by requested tests for Group 1, Group 2 and Group 3 for 25(OH)D were 43.6%, 45.3%, and 41.3; 25.3, 8.6, and 7.5% for 1,25(OH)2D, respectively.

The requested tests with normal and low 25(OH)D levels included in the study were analyzed as whole year and on seasonal basis and were shown in Figure 1. Compared to hypovitaminosis diagnosis throughout the whole year, hypovitaminosis vitamin D diagnosis in summer was lower than the whole year (26.3% vs. 44.5%) and hypovitaminosis vitamin D diagnosis in winter was higher than the whole year (59.2% vs. 44.5%). Compared to hypovitaminosis diagnosis throughout the whole year, hypovitaminosis vitamin D diagnosis in fall and spring was similar to the whole year (46.4%, 45.5; for fall and spring, respectively vs. 44.5%). The percentage of hypovitaminosis D diagnosis showed similar distribution based on groups for

Table 1: The numbers of the participants with normal and low Vitamin D levels included into the study.

	25-hydroxyvitamin D				1,25-dihydroxyvitamin D			
	Total	Group1	Group2	Group3	Total	Group1	Group2	Group3
Total test request (n)	78,919	5,665	60,911	12,343	5,653	825	3,430	1,398
% of requested test	100	7.2	77.2	15.6	100	14.6	60.7	24.7
Normal results (n)	32,551	2,407	24,695	5,449	5,045	616	3,136	1,293
% of requested test above cut-off*	100	7.4	75.9	16.7	100	12.2	62.2	25.6
Hypovitaminosis (n)	46,368	3,258	36,216	6,894	608	209	294	105
% of requested test below cut-off*	100	7.0	78.1	14.9	100	34.4	48.4	17.3
Prevalance of hypovitaminosis	58.8	57.5	59.5	55.9	10.8	25.3	8.6	7.5

*Cut-off for 25(OH)D <20 ng/mL; for 1,25(OH)2D <26.1 pg/mL.

each season and throughout the year (48.5, 46.9, 43.3% for fall; 57.2, 59.3, 59.6% for winter; 45.8, 46.0, 42.6% for spring; 22.9, 27.9, 21.2% for summer and 43.6, 45.3, 41.3% for whole year of Group 1, Group 2, and Group 3, respectively (Figure 1).

During the same period, reflex test algorithm on vitamin D requests was performed in 66 patients over 55 years of age with serum albumin-adjusted calcium ≤2.1 mmol/L and serum alkaline phosphatase >150 U/L. The 25(OH)D results <20 ng/mL (50 nmol/L) were accepted as hypovitaminosis D. The prevalance of hypovitaminosis D diagnosis during the same period based on reflex testing algorithm was 68%. The prevalance of hypovitaminosis D diagnosis based on reflex testing algorithm was higher than the prevalance of hypovitaminosis D diagnosis detected in each group (57.5, 59.5, and 55.9 for Group 1, 2, and 3, respectively).

The requested tests with normal and low 1,25(OH)2D levels included in the study were analyzed as whole year and on seasonal basis and were shown in Figure 2. Compared to low 1,25(OH)2D levels throughout the whole year, low 1,25(OH)2D levels in each season similar to the whole year except winter (11,8%, 1.7%, 17.0%, 14.2, and 10.8% for fall, winter, spring, summer and whole year, respectively. The prevalance of low 1,25(OH)2D levels were higher in Group 1 compared to prevalance of low 1,25(OH)2D levels detected in other groups for each season and throughout the year (22.8%, 11.0% , 8.4% for fall; 7.0%, 0.9% , 0.4% for winter; 35.1%, 12.7% , 11.4% for spring; 41.7, 10.5, 7.5% for summer and 25.3, 8.6, 7.5% for the whole year in Group 1, Group 2 and Group 3, respectively. The difference in prevalance of low 1,25(OH)2D levels was high between groups (14.4, 6.6, 23.7, 34.2 and 17.8% for fall, winter, spring, summer and whole year, respectively.

The numbers of the total test requests, 25(OH)D and 1,25(OH)2D were presented in Figure 3. The highest number of 25(OH)D test was requested in January 2020 (max: 12,769; min: 3,224). The highest number of 1,25 Hydroxy vitamin D test was requested in December 2019 (max: 1,153; min: 263). Because most of the 1,25(OH)2D test result were normal and the ratio of 25(OH)D to 1,25(OH)2D test requests remained high up to the beginning of the last month of the

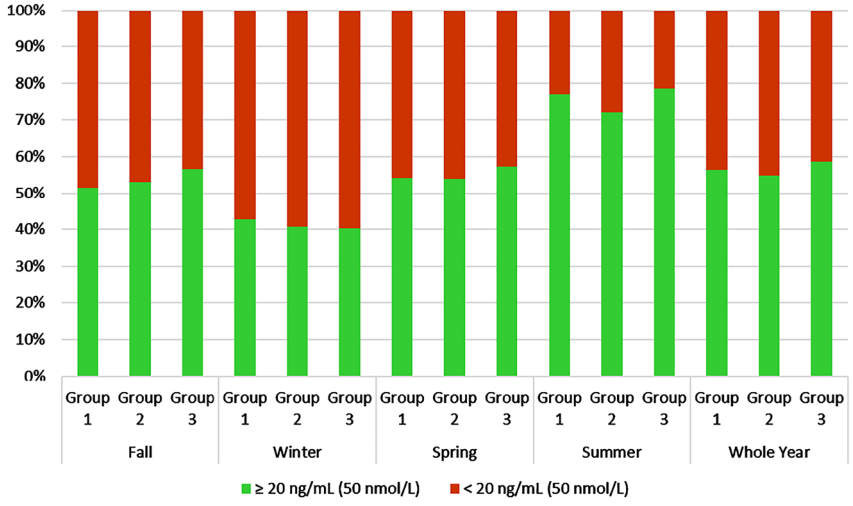

Figure 1: Distribution and percentage of 25(OH)D requests analyzed on seasonal basis and throughout the whole year.

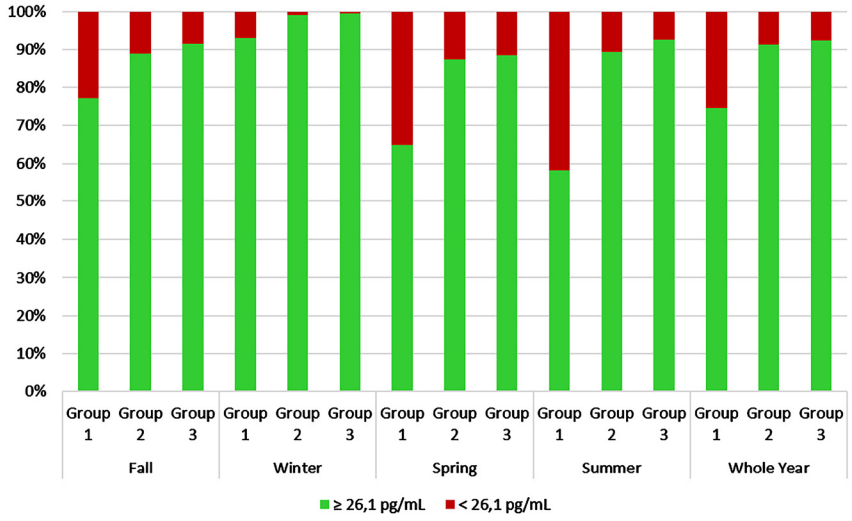

Figure 2: Distribution and percentage of 1,25(OH)2D requests analyzed on seasonal basis and throughout the whole year.

study, we have considered about a change in test name. The name of the 1,25(OH)2D was changed as 1,25-dihydroxycholecalciferol in test request panel. With the name change 1,25 cholechalsiferol requests were dropped dramatically from 1153 test requests to 296 test requests (–71.7%) without any complaint from physicians. There was no statistically difference in detecting deficiency after the intervention of changing the name of the 1,25-dihydroxyvitamin D as 1,25-dihydroxycholecalciferol (p=0.659).

Additionally, we analyzed the effect of the act cost effectivity according to SUT (Healthcare Implementation Communique) released by SGK. Group 3 is the only groups which have restriction on vitamin D testing. Assuming the regulation was valid last year, only the tests classified in Group 3 [15.6% of 25(OH)D tests and 24.7% of 1,25(OH)2D tests] would be ordered or unpaid by SGK if it would be allowed to be ordered. The restriction in vitamin D test ordering would provide 44,137 $ benefit for 25(OH)D and 4,720 $ benefit for 1,25(OH)2D per year. Totally, there would be a 2.69% benefit of total medical biochemistry laboratory budget if the regulation was valid during the past year. However, with the regulation 14.9% of 25(OH)D tests under cutoff 17.3% of 1,25(OH)2D tests under cutoff would not be detected due to the restriction of test ordering. By switching the name of the 1,25(OH)2D test to

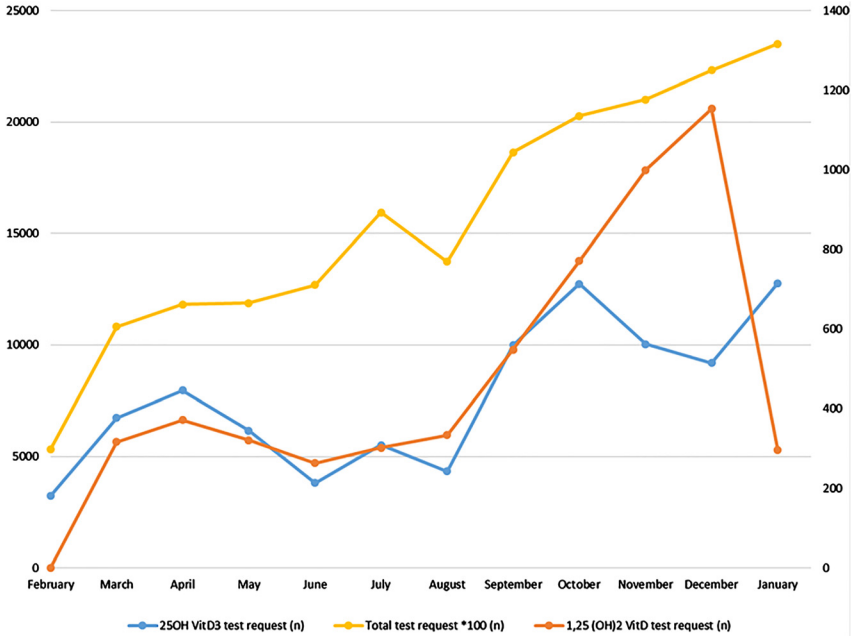

Figure 3: The numbers of the total test requests, 25(OH)D and 1,25(OH)2D.

1,25-dihydroxycholecalciferol in test request panel provides 2,622 $ benefit in one month compared to the previous month cost.

Discussion

Avoiding screening for patients at low risk of vitamin D deficiency has been recommended by initiatives and guidelines worldwide [15–19]. Hovewer, in specific patient populations, including patients with calcium or parathyroid disorders, malnutrition syndromes, chronic kidney disease, osteoporosis, and those who are on specific medications, especially steroids, specific antiepileptics, or certain HIV medications, screening for and treating vitamin D deficiency is recommended [15, 20, 21]. In the light of these guidelines and studies, we investigated whether implementing the Regulation of Ministry of Health regarding with vitamin D testing is effective on controlling test demand and affect the hypovitaminosis D diagnosis by analyzing the database of Ankara City Hospital Medical Biochemistry Laboratory, a tertiary hospital laboratory with a high workload. Prior to regulation, the Rational Laboratory Use Project has been launched by Ministry of Health in Turkey. Rational test ordering is one of the crucial parts of the project. According to this project, vitamin D ordering interval has established for only 25(OH)D as 90 days and it is obligatory to send reminder messages for reminding the interval via Hospital Information System (HIS). Also, the manager of medical biochemistry laboratory has the responsibility and authority to audit the feeding back individual doctors' test ordering patterns to the hospital management and Ministry of Health at a push. Department of inspection and diagnosis services. Because increasingly busy physicians just skip the message, enough decrease in the number of unnecessary test repetitions via alert messages to the requesting physician could not be provided. At the beginning of 2020, the Regulation regarding with vitamin D testing has been launched. With the act, even though the ordering for vitamin D tests is free for inpatients and patients in intensive care unit, the ordering for vitamin D tests has only allowed in some specialties of medicine for outpatients and patients at emergy unit. These specialists are pediatricians, internal medicine specialists, obstetrician and gynecologists, physical therapy and rehabilitation specialists, orthopedics and traumatology specialists and neurologists. Our results have shown that main demand for vitamin D testing comes from Group 2 which covers all vitamin D tests requested by non-restricted specialists (requests from outpatients) and 77.2 and 60.7% for 25(OH)D and 1,25(OH)2D, respectively. with the regulation, only 15.6% for 25(OH)D and 24.7% 1,25(OH)2D would be limited in our hospital. This probable rate is less than the achieved rate found in Felcher et al. study (30% approximately), in which clinical decision support (CDS) tools were used without test ordering restriction. They evaluated the impact of CDS tools on rates of vitamin D testing and how rates of vitamin D screening changed after the implementation of CDS tools such as an alert that requires clinician acknowledgment of current guidelines to continue ordering the test (a "hard stop"), and a modification of laboratory ordering preference lists that eliminates shortcuts with a new vitamin D screening guideline [22].

In Ankara City hospital, not only vitamin D testing but also all tests of medical biochemistry laboratory has been rising progressively. This exponential growth in requests for laboratory tests is common throughout the world due to the progressive automation of laboratories, the aging population and the limited physician time availability for patient care [23–25]. In Whiting et al. study, they identified 38 studies that discussed factors that may influence test ordering and revealed that five key factors emerged as reasons for test ordering: diagnostic factors, therapeutic and prognostic factors, patient-related factors, doctor-related factors, and policy and organization-related factors [26]. It has also shown that general practitioners with more clinical experience, confidence in their clinical judgment, pride in their work, and who do not fear risk taking or uncertainty tend to request fewer tests than those who dislike uncertainty and have less experience [27–29]. Most factors identified as influencing test ordering are doctor-related factors but the type of testing should also take into count. Vitamin D is not a kind of test physicians who fear risk taking other than vitamin D intoxication. Because of the popularity of vitamin D, patients feel desire for testing and want to be tested. With the regulation, vitamin D is excluded from test panel for primary care facilities. Vitamin D is one of the tests used for national health and nutrition examination surveys and using data from primary care units with standardization is one of easiest way getting data for this kind of aim. With the regulation, vitamin D results from primary care facilities cannot be provided and used for determining vitamin D status which has a high worldwide prevalence of deficiency that may require public health actions such as vitamin D food fortification.

With the rational laboratory use project, the practice of adding on laboratory tests as reflex and reflective tests to existing requests is common in medical biochemistry of Turkey. In the project, reflex and reflective testing were defined in accordance with the literature [30, 31]. The

definitions are "According to the first results in the patient sample, the automatic addition of new test (s) within the scope of certain algorithms is the reflex test application. Reflex test is applied within the knowledge of the relevant institution/organization management." for reflex testing and "According to the results in the patient sample and evaluating the other clinical and laboratory information of the patient, the process of studying new tests in the same patient sample within the knowledge of the clinician, is reflective testing." for reflective testing. In the present study, we used the same algorithm in Srivastava et al. study which has revealed the diagnosis of hypovitaminosis D based on hypocalcaemia and elevated alkaline phosphatase activity in patients over 55 years [12]. We examined the patients aged over 55 years with serum albumin-adjusted calcium ≤2.1 mmol/L and serum alkaline phosphatase >150 U/L. And we have found that, 68% of these patients have decreased levels 25(OH)D (<50 nmol/L: the target concentration for replacement in Turkey). This percentage is higher than the ratio of hypovitaminosis D found in Group 2 (45.3% for whole year). Besides the ratios of hypovitaminosis D are found similar for Group 1, 2, and 3. (43.6, 45.3, 41.3%, respectively). Due to clinical findings depend on the degree and duration of vitamin D deficiency, most patients are asymptomatic and serum calcium, phosphorus and alkaline phosphatase levels are normal in these patients. Increased serum PTH levels were reported in 40–51% of patients with 25 (OH) D levels below <20 and 10 ng/mL, respectively [19, 32]. So, the addition of vitamin D test within the scope of certain algorithms via reflex or reflective testing would be beneficial in detecting hypovitaminosis D especially in a situation which vitamin D test requesting are removed from primary health care facilities and limited for patients admitted to the hospitals except patients at intensive care units and inpatients. Additionally, for the follow-up of the patients with high risk of hypovitaminosis D admitted to primary care facilities and hospitals, test restriction based on patient hypovitaminosis D risk would be more beneficial compared to test restriction based on medical specialty.

Various methods are available for measuring circulating concentrations of 25(OH)D. Current methods include HPLC, RIA with low throughput to high throughput, automated chemiluminescence immunoassays, and liquid chromatography-tandem mass spectrometry (LC-MS/MS). Correlation and agreement studies between immunoassays and LC-MS/MS methods for 25(OH)D have been reported. These studies report reasonable correlations but with significant differences which confounds the diagnosis od hypovitaminosis D [33–35]. Since LC/MS/MS measures 25(OH)D2 and 25(OH)D3 separately, it provides results for both of these, in addition to total 25(OH)D. This differs from immunoassays which only report a single total number for 25(OH)D. The additional information can be helpful to a physician, to assess compliance by someone on vitamin D supplementation such as bariatric surgery [36]. Measuring 25(OH)D by high performance liquid chromatography (HPLC), liquid chromatography/tandem mass spectrometry (LC/MSMS) methods are accepted as reliable [19].

One of the ways of reducing inappropriate testing is using the structured test ordering form. The introduction of a structured test ordering form has been found to reduce test ordering and increases the complexity of laboratory test selection by increasingly busy physicians [37, 38]. This kind of structured test ordering form was not in use in our hospital. For ordering vitamin D test in our hospital, physicians were searching for vitamin D term and two of the tests were appeared in the test ordering list at LIS system. We have realized that 25(OH)D and 1,25(OH)2D were requested simultaneously and changed the name 1,25(OH)2D as 1,25-dihydroxycholecalciferol. We have achieved %75 decrease in 1,25(OH)2D test ordering per one month compared with the previous month. The ratio of decreased in 1,25(OH)2D test ordering was much higher than the effect of implementation of the act because only 1,25(OH)2D test requests in Group 3 would be limited (24.7 vs. 75%). Additionally, only 10.8% of all patients with 1,25(OH)2D test request have 1,25(OH)2D levels lower than cut-off (<26.1 pg/mL). And the percentage of hypovitaminosis detection is highest in Group 1 compared to other groups (25.3, 8.6, and 7.5% for Group 1, 2, and 3, respectively). Serum concentrations of 1,25(OH)2D are mainly derived from renal hydroxylation of 25(OH)D and are rather dependent on regulators of mineral metabolism (e.g., parathyroid hormone (PTH), phosphate or fibroblast growth factor-23 (FGF-23) or kidney function, than on substrate availability of 25(OH)D, so that they do not well reflect vitamin D supply [8]. 1,25 (OH)D vitamin measures the bioactive form of vitamin D. It is used in the differential diagnosis of hypocalcemia and to monitor patients with renal osteodystrophy or chronic renal failure. This test is not suitable for diagnosis of vitamin D deficiency and monitoring supplementation in most patients. The 25(OH) D Vitamin test is the recommended test for those purposes. So, it is a correct action not to restrict 1,25(OH)2D test requests for inpatients and patients in intensive care units. However, rectriction based on diagnosis in addition to medical specialty basis restriction would be more effective considering the data that revealed about 90% of 1,25(OH) 2D test results were above cut-off.

In the present study, we could not get the information of patients' medications including vitamin D. Although we did

not evaluate the appropriate use of vitamin D testing, the effect of restriction on hypovitaminosis D detection and testing costs might be affected by the number of patients with vitamin D deficiency undertreatment. Future studies evaluating appropriate use of vitamin D testing by means of risk factors for vitamin D deficiency such as hypo- or hypercalcemia, hypo- or hyper-parathyroidism, malnutrition, inflammatory bowel disease, celiac disease, chronic kidney disease, osteoporosis, or long-term steroid, antiepileptic, or specific HIV medication use after eliminating patients under vitamin D treatments would be beneficial.

At the present time, attention has focused on laboratory medicine as a potential source of savings, because their costs are perceived as being easily identifiable and quantifiable. If the aim of the regulation of Ministry of Health is managing demand for laboratory tests, medical biochemistry specialists should be considered in the regulation on vitamin D testing. Although laboratory tests play a central role throughout the clinical decision making and managed care, the medical specialty is "laboratory medicine", which is limited to a few theoretical courses spread across the entire curriculum in most medical faculties as mentioned by Michael Laposata [39]. This statement is valid for our country, and an urgent change in this direction should be encouraged in curricula at the medical school. In addition, approaches to rational laboratory use should be a compulsory and inseparable part in the curriculum of Medical Biochemitry Specialty education and training. So, the goal of training medical biochemistry specialitists who play a central role in contemporary diagnostic medicine would be achieved in the short run.

Research funding: None declared.

Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission.

Competing interests: None.

Çıkar Çatışması: Yoktur.tr.

Informed consent: Informed consent was obtained from all individuals included in this study.

Ethical approval: The study was approved by the Institutional Ethical Committee.

References

1. Rohr UP, Binder C, Dieterle T, Giusti F, Messina CG, Toerian, et al. The value of in vitro diagnostic testing in medical practice: a status report. PloS One 2016;11:e0149856.
2. Fryer AA, Smellie WS. Managing demand for laboratory tests: a laboratory toolkit. J Clin Pathol 2013;66:62–72.
3. Wians FH. Clinical laboratory tests: which, why, and what do the results mean?. Lab Med 2009;40:105–13.
4. Christakos S, Dhawan P, Verstuyf A, Verlinden L, Carmeliet G. Vitamin D: metabolism, molecular mechanism of action, and pleiotropic effects. Physiol Rev 2016;96:365–408.
5. Uday S, Högler W. Nutritional rickets and osteomalacia in the twenty-first century: revised concepts, public health, and prevention strategies. Curr Osteoporos Rep 2017;15:293–302.
6. Bouillon R. Genetic and racial differences in the vitamin D endocrine system. Endocrinol Metab Clin N Am 2017;46: 1119–35.
7. Pilz S, Zittermann A, Trummer C, Theiler-Schwetz V, Lerchbaum E, Keppel MH, et al. Vitamin D testing and treatment: a narrative review of current evidence. Endocr Connect 2019;8:R27–43.
8. Chowdhury R, Kunutsor S, Vitezova A, Oliver-Williams C, Chowdhury S, Kiefte-de-Jong JC, et al. Vitamin D and risk of cause specific death: systematic review and meta-analysis of observational cohort and randomised intervention studies. BMJ 2014;348:g1903.
9. Gaksch M, Jorde R, Grimnes G, Joakimsen R, Schirmer H, Wilsgaard T, et al. Vitamin D and mortality: individual participant data meta-analysis of standardized 25-hydroxyvitamin D in 26916 individuals from a European consortium. PloS One 2017; 16:e0170791.
10. Singh RJ. Are clinical laboratories prepared for accurate testing of 25-hydroxy vitamin D? [Letter]. Clin Chem 2008;54:221–3.
11. http://e-belge.saglik.gov.tr.to.9cc97462-9267-4d22-a052-e77f812a7ee4 [Last accessed: May 2020].
12. Srivastava R, Bartlett WA, Kennedy IM, Hiney A, Fletcher C. Reflex and reflective testing: efficiency and effectiveness of adding on laboratory tests. Ann Clin Biochem 2010;47:223–7.
13. Ricos C, Ramon F, Salas A. Minimum analytical quality specifications of inter-laboratory comparisons: agreement among Spanish EQAP organizers. Clin Chem Lab Med 2012;50:455–61.
14. www.westgard.com/rcpa-biochemistry.htm#vitamins [Last accessed: April 2020].
15. Holick MF, Binkley NC, Bischoff-Ferrari HA. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96: 1911–30.
16. LeFevre ML. Screening for vitamin D deficiency in adults: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2015;162:133–40.
17. LeBlanc ES, Zakher B, Daeges M, Pappas M, Chou R. Screening for vitamin D deficiency: a systematic review for the U.S. Preventive services task force. Ann Intern Med 2015;162:109–22.
18. American Board of Internal Medicine. Choosing wisely; 2020. http://www.choosingwisely.org [Accessed 26 July 2020].
19. http://temd.org.tr/admin/uploads/tbl_kilavuz/20190506164125-2019tbl_kilavuz0f7419cd64.pdf [Accessed 26 July 2020].
20. Health Quality Ontario. Clinical utility of vitamin D testing: an evidence based analysis. Ont Health Technol Assess Ser 2010;10: 1–93. 22.
21. Kennel KA, Drake MT, Hurley DL. Vitamin D deficiency in adults: when to test and how to treat. Mayo Clin Proc 2010;85:752–7.
22. Felcher AH, Gold R, Mosen DM, Stoneburner AB. Decrease in unnecessary vitamin D testing using clinical decision support tools: making it harder to do the wrong thing. J Am Med Inf Assoc 2017;24:776–80.

23. Armbruster DA, Overcash DR, Reyes J. Clinical chemistry laboratory automation in the 21st century – Amat Victoria Curam (Victory loves careful preparation). Clin Biochem Rev 2014;35: 143–53.
24. Pefoyo AJK, Bronskill SE, Gruneir A, Calzavara A, Thavorn K, Petrosyan Y, et al. The increasing burden and complexity of multimorbidity. BMC Publ Health 2015;15:415.
25. Green ME, Hogg W, Savage C, Johnston S, Russell G, Jaakkimainen LR, et al. Assessing methods for measurement of clinical outcomes and quality of care in primary care practices. BMC Health Serv Res 2012;12:214.
26. Whiting P, Toerien M, de Salis I, Sterne JA, Dieppe P, Egger M, et al. A review identifies and classifies reasons for ordering diagnostic tests. J Clin Epidemiol 2007;60:981–9.
27. Bugter-Maessen AM, Winkens RA, Grol RP, Knottnerus JA, Kester AD, Beusmanset GH, et al. Factors predicting differences among general practitioners in test ordering behaviour and in the response to feedback on test requests. Fam Pract 1996;13: 254 e8.
28. Bunting PS, van Walraven C. Effect of a controlled feedback intervention on laboratory test ordering by community physicians. Clin Chem 2004;50:321 e6.
29. Zaat JO, van Eijk JT. General practitioners' uncertainty, risk preference, and use of laboratory tests. Med Care 1992;30:846 e54.
30. Paterson JR, Paterson R. Reflective testing: how useful is the practice of adding on tests by laboratory clinicians? J Clin Pathol 2004;57:273–5.
31. Murphy MJ, McMahon MJ, Paterson JR. Reflective testing: the practice of adding on tests by laboratory staff. Ann Clin Biochem 2005;42:1–2.
32. Valcour A, Blocki F, Hawkins DM, Rao SD. Effects of age and serum 25-OH-vitamin D on serum parathyroid hormone levels. J Clin Endocrinol Metab 2012;97:3989–95.
33. Carter GD, Carter R, Jones J, Berry J. How accurate are assays for 25-hydroxyvitamin D? Data from the international vitamin D external quality assessment scheme. Clin Chem 2004;50: 2195–73.
34. Binkley N, Krueger D, Cowgill CS, Plum L, Lake E, Hansen KE, et al. Assay variation confounds the diagnosis of hypovitaminosis D: a call for standardization. J Clin Endocrinol Metab 2004;89:152–74.
35. Souberbielle JC, Fayol V, Sault C, Lawson-Body E, Kahan A, Cormier C. Assay-specific decision limits for two new automated parathyroid hormone and 25-hydroxyvitamin D assays. Clin Chem 2005;51:395–400.
36. Chen H, McCoy LF, Schleicher RL, Pfeiffer CM. Measurement of 25-hydroxyvitamin D3 (25OHD3) and 25-hydroxyvitamin D2 (25OHD2) in human serum using liquid chromatography-tandem mass spectrometry and its comparison to a radioimmunoassay method. Clin Chem Acta 2008;391:6–12.
37. Eccles M, Steen N, Grimshaw J, Thomas L, McNamee P, Soutter J, et al. Effect of audit and feedback, and reminder messages on primary-care radiology referrals: a randomised trial. Lancet 2001; 357:1406 e9.
38. Verstappen WH, ter Riet G, Dubois WI, Winkens R, Grol RP, van Der Weijden T. Variation in test ordering behaviour of GPs: professional or context-related factors? Fam Pract 2004;21:387 e95.
39. Laposata M. Insufficient teaching of laboratory medicine in US medical schools. Acad Pathol 2016;3. https://doi.org/10.1177/2374289516634108.