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Vitamin D, Asthma Prevalence and Asthma exacerbations:

A large adult population-based study

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Contributorship statement

1. Ronit Confino-Cohen : Substantial contributions to conception and design, acquisition of data and analysis and interpretation of data. Drafting the article and revising it critically for important intellectual content. Final approval of the version to be published.

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Abstract

Background : The impact of low vitamin D status on asthma, asthma morbidity and control is unclear. We aimed to investigate in adults the associations between serum 25-hydroxyvitamin D level and prevalent asthma as well as asthma exacerbations.

Methods: A cohort of Israeli adults aged 22-50 years with documented vitamin D status were extracted from Clalit Health Services (HMO) between July 1, 2008 and July 1, 2012. Among this population those with physician diagnosed asthma and asthma exacerbations were identified. Asthma exacerbations were defined as any of the following: prescription for oral corticosteroids, > 5 prescriptions for short acting beta agonists and more than 4 visits to a physician for asthma. Logistic regression models assessed the associations between vitamin D and both asthma and asthma exacerbations.

Results: Approximately 308,000 members with at least one vitamin D measurement were included in the cohort. Among them, 6.9% (21,237), had physician diagnosed asthma versus 5.7% in the general population. Serum 25OHD levels across both groups were similar. However, among those with vitamin D deficiency, the odds of having an exacerbation were 25% greater compared to those with levels in the normal range. This association remained significant after controlling for known confounders.

Conclusions: While there was no significant association between vitamin D status and physician diagnosed asthma, there was a strong association with asthma exacerbations. The presented evidence supports vitamin D screening in the subgroup of asthmatics that are uncontrolled and experience recurrent exacerbations.

Key words: Asthma; Asthma exacerbation; Asthma control; Vitamin D; Vitamin D deficiency

Introduction

Asthma is a major public health problem worldwide with an increasing prevalence in the past 30 years(1). Different factors have been implicated including obesity, a sedentary lifestyle, and certain ethnic traits. There is preliminary evidence that vitamin D deficiency is a risk factor for asthma and it is suggested that increased levels are protective.(2). Women, the elderly, those that spend less time outdoors, and the obese may be at risk for vitamin D deficiency.(3).

Vitamin D may play a role in the primary prevention of asthma due to its significant immune-modulatory effects on innate and adaptive immunity (4-6) which might influence asthma pathogenesis. However, the current evidence on this association is inconsistent, mainly comes from studies with limited sample size, and does not point to causal associations. Keet et al. recently found that serum vitamin D levels were inversely associated with both current wheeze and asthma (7), as did a study among inner-city youth which demonstrated that those with asthma also had had vitamin D deficiency or insufficiency.(8).However, several studies found no association.(9,10).

Also of interest is the association between vitamin D and asthma-related morbidity.(11-15), where evidence comes mainly from the pediatric population. While these data suggest that adequate vitamin D blood levels are protective against asthma exacerbations, the evidence among adults is limited and inconclusive. (16-17).

In addition, there is little consensus on the definition of vitamin D insufficiency in the literature.(18). Recently, the Institute of Medicine panel concluded that circulating levels of >20 ng/ml are sufficient regarding skeletal health though the debate is unresolved regarding optimal levels for non-musculoskeletal health.(19).

The present population-based study examined the association between vitamin D status and asthma prevalence and a nested cohort study assessed the association with asthma exacerbations. We utilized the electronic health records of 307,893 adult members of a large managed care organization between 2008-2012.

Methods

Data Source

Data for all Clalit Health Services (CHS) members were accessed for this study from CHS' integrated data warehouse. CHS is both an insurer and provider and is the largest of Israel's four Health Maintenance Organizations covering close to 4 million patients. CHS provides community-based medical services laboratory tests, and hospitalizations. Starting in 1998, CHS created a centralized electronic warehouse where primary care, specialist, hospital, pharmacy and laboratory records, in addition to demographic and socio-economic

information , are stored. The data are comprehensive as members receive the majority of their care within CHS.

Use of data from the electronic medical records (EMRs) in this study was made accessible upon approval from the Clalit Ethics Committee.

Study Cohort

Inclusion criteria: All CHS members aged 21 to 50 that had at least one recorded 25(OH) D test result during the study period June .2008-June 2012. In 2008 testing became more generalized across the CHS population and, while testing is indicated in patients with parathyroid disease, bone diseases and post-menopausal women, there are no other guidelines for testing.

Exclusion criteria: Patients with a COPD diagnosis from 2003 on were excluded.

Variables

Main predictor: The first laboratory 25-OHD test (index test) recorded during the study period was extracted with the test month. The levels were divided into four 25-OHD subgroups (nmol/L): 0-25 (deficiency), 25.1-50 (insufficiency), 50.1-90 (normal), 90.1+ (high).(19).

Independent variables: The following demographic baseline variables were included in the analysis, taking the record closest to the index vitamin D test: age (22-30, 31-40,41-50), sex, population sector (general, ultra-orthodox Jews, and Arabs), Clalit's geographic districts,

Ethiopian origin (born in Ethiopia or not), BMI (<18.5, 18.5-24.9, 25-29.9 and >30), smoking status (ever/never), and season of vitamin D test (winter: December–February ; spring: March- May; summer: June–August; fall: September–November). The following co-morbidities were also examined: chronic renal failure, malignancy, hyperparathyroidism, inflammatory bowel disease, and the Johns Hopkins Adjusted Clinical Groups (ACG) Resource Utilization Bands (RUBs), a that adjusts for case mix differences in the analysis of co-morbidities, as well as ambulatory, laboratory, pharmacy, and health care utilization.

Dependent variables:

The first phase of the study examined *physician diagnosed asthma* recorded between January, 2003- July, 2012. The second phase of the study examined *asthma exacerbations* during the year before the first vitamin D test in the study period which was assumed to be a period free of vitamin D supplementation and a more accurate assessment of patients' baseline vitamin D levels. Any of the following events during this period were considered an exacerbation as recently defined by the National Institutes of Health and other federal agency expert groups (20).

1. Prescription for oral corticosteroids for less than 21 days
2. More than 4 visits per year to a family physician for asthma
3. More than 5 prescriptions per year for short acting beta agonists (SABA)

Laboratory tests

25OHD assay: Biochemical analysis of blood was performed on fresh serum samples at CHS laboratories. 25-OHD was measured using the LIAISON R 25-OH vitamin D TOTAL

assay (DiaSorine), a competitive two-step chemiluminescence assay, measuring both the D2 and D3 25-OHD metabolites. The measuring range is 10-375 nmol/L (4-150 ng/mL) (detailed in online supplement 1).

Statistical Analysis

Association between vitamin D and asthma prevalence: Descriptive statistics assessed the distribution of characteristics across the study population with vitamin D tests compared to the general population of CHS members age 22-50. Among the study population we examined the distribution of characteristics across those with physician-diagnosed asthma compared to non-asthmatics including their 25-OHD levels. Univariate logistic regression was then performed to assess for significant independent predictors of asthma. A logistic multivariate regression model assessed the association between vitamin D levels and asthma prevalence, controlling for the significant demographic and clinical variables. In the descriptive statistics we included all the above mentioned variables to characterize the study population. In the adjusted analyses we just included the ACG RUBs.

Association between vitamin D and asthma exacerbations among the asthmatic population: The distribution of exacerbations was assessed across asthmatic members' vitamin D levels and evidence of a trend was examined using univariate linear regression. We dichotomized members into those who had at least one of the exacerbation criteria and those who did not and examined the identified demographic and clinical variables across them. . The multivariate logistic regression assessed the association between vitamin D levels and having an asthma exacerbation controlling for the significant covariates. The robustness of the main results of this model was tested through three sensitivity analyses using multivariable analyses. First, the exacerbation outcome was disaggregated into two to examine whether oral corticosteroids medications, indicated for acute exacerbations, had a

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differential association with vitamin D compared to the joint outcome of frequency of doctor visits or SABA use. Second, asthma exacerbations was assessed as an outcome the year following the vitamin D test to minimize the possibility that the vitamin D levels were influenced by the frequency of asthma exacerbations in the previous year. Third, because low vitamin D could be highly correlated with obesity due to a sedentary lifestyle, and the obesity status could be the causal factor influencing asthma exacerbations, the association between vitamin D and exacerbations was stratified by BMI groups. All analyses were performed using IBM SPSS version 20.0.

Results

Association between Vitamin D and Asthma prevalence

A total of 1,783,334 CHS members between age 22- 50 were identified and among them, 307,900 (17.26%) had at least one vitamin D measurement during the study period and were included in the study cohort.

Members with a vitamin D test included fewer smokers but included more 41-50 year olds, more women and ultra-Orthodox Jews, more obese, and the ACG resource utilization band indicated that the study population was sicker and utilized more health care services during the baseline period

(Table 1).

Among the vitamin D tested population, 6.9% (21,237), had physician diagnosed asthma versus 5.7% in the non-tested CHS population.

The asthmatic group was more obese (21.7% vs. 16.6%), included more ever-smokers (27.8% vs. 24.4%), had a greater proportion of patients of Ethiopian origin (3.1% vs. 1.5%), and had a smaller proportion of ultra-orthodox Jews (4.8% vs. 6.1%) and Arabs (17.9% vs. 25.1%) (Table 1). Vitamin D levels across the two groups were similar.

The multivariate analysis further confirmed the lack of a significant association between vitamin D deficiency and asthma prevalence (OR =1.04; CI: 0.99-1.09) while controlling for the multiple covariates (Table 2).

Association between Vitamin D and Asthma Exacerbations

The effect of vitamin D levels on asthma exacerbations among the asthma patients was evaluated during the year previous to the vitamin D test.

Asthmatics with exacerbations were more likely to be older, Arab, have other chronic diseases, and more likely to have vitamin D deficiency when compared to asthmatics with no exacerbations (Table 3).

Furthermore, there was an inverse linear association between the proportion of asthmatics with exacerbations and vitamin D levels ($p<.0001$). Nearly 15% of asthmatics with vitamin D deficiency (0-25 nmol/L) had at least one exacerbation, while 12% in the 25.1-50 nmol/L group had at least one, and only 9% of those in the 90+ nmol/L group had one or more exacerbations. An inverse relation was also found when investigating the exacerbation categories separately (Figure 1).

The multivariate analysis controlling for the established confounders, further confirmed this trend. The odds of an exacerbation were 22% greater for those with vitamin D deficiency (OR =1.22; CI = 1.07-1.39) while those with vitamin D insufficiency (25-50nmol/L) had similar odds (OR=1.07; CI=0.99-1.19) compared to those with vitamin D in the normal range. The other confounders in the model confirmed what was seen in the descriptive analysis.(Table 4).

The multivariable sensitivity analyses that disaggregated the exacerbation outcome yielded comparable results. The first found that those with vitamin D deficiency had an elevated risk of being on oral corticosteroids for less than 21 days (OR = 1.16; CI: 1.01-1.33) and also had an elevated risk of going to the family physician for asthma more than 4 times per year *or* receiving more than 5 prescriptions per year for SABA (OR: 1.30; CI: 1.07-1.58). The second sensitivity analysis assessed asthma exacerbations in the year following the vitamin D test rather than the year prior to, and demonstrated attenuated but significant results (OR = 1.15; CI: 1.01-1.32). Lastly, when the analysis was stratified by the four BMI groups the associations held; vitamin D deficiency remained associated with exacerbations across the groups, and it was most strongly associated with exacerbations in the obese group (OR= 1.30; CI: 1.01-1.68) (results not shown).

Discussion

Our study is one of the few large-scale studies evaluating the association between serum vitamin D levels and prevalence of asthma and asthma morbidity in adults. Among the 307,900 members tested for vitamin D, we observed no significant association between

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serum vitamin D levels and physician diagnosed asthma. This is in contrast to the significant association found between asthma exacerbations and vitamin D deficiency among the 21,237 asthmatic patients. The probability of having an asthma exacerbation was inversely correlated with vitamin D levels and remained significant after confounding factors such as BMI and smoking were taken into consideration. These results corroborate the few previous studies which found an association between vitamin D and asthma control among adults.

The prevalence of asthma has increased over the last four decades (1). Vitamin D deficiency and asthma share risk factors such as obesity, African American ethnicity, and a sedentary life style further suggesting a link between these two conditions. Moreover, considering the immunomodulatory effects of vitamin D, especially the development of immune system tolerance and of the integrity of the epithelial barrier, vitamin D may play a role in the primary prevention of asthma and a deficiency in vitamin D may explain asthma pathophysiology. (4-6).

The relationship between asthma and vitamin D has been the subject of several studies and, while most of these studies support a protective effect of adequate vitamin D levels, most of them are observational in nature, focus mainly on the pediatric population, and do not test for causality (21-23). Furthermore, asthma outcomes have often been identified via self-reported surveys as opposed to physician diagnosis (1), as was done in the present study. Furthermore, we did not include adults older than 50, to minimize the possibility of disease miss-classification. Lastly, the current study population is unique as it includes patients who are all living in a narrow latitude band (30–33°N) and vitamin D levels do not substantially vary on average by season (24). Previous research by Brehm (11) suggests that time spent outside is not the only factor influencing vitamin D levels and factors such as skin color as well as dress code also influence vitamin D production and need to be taken into account.

Our study controlled for these factors, and still could not establish an association between asthma diagnosis and vitamin D.

One of the major goals of asthma treatment includes preventing morbidity and recurrent exacerbations (25). Our results clearly suggest that asthma exacerbations occur more frequently among patients with vitamin D deficiency. Moreover, as vitamin D levels increase the probability of having an exacerbation steadily decreases even, after controlling for several key confounding factors.

Our results corroborate findings from previous studies which were primarily among children (10-12) as well as the few studies among adults that suggest that low serum vitamin D is associated with reduced lung function (26), increased medication usage, and severe disease (25). A recent publication by Castro et.al.(27) aimed to evaluate, prospectively, the effect of vitamin D supplementation in symptomatic, Vitamin D deficient asthmatics. They defined decline in lung function, increase use of β -agonists, use of systemic corticosteroids, and health care as a combined outcome indicating asthma treatment failure. Vitamin D supplementation did not affect the rate of asthma treatment failure as compared to the placebo supplemented asthmatics. These results do not support recommendation for vitamin D supplementation in symptomatic asthmatics. However, 28 weeks of follow-up might be a too short period for evaluation of the effect of supplementation and the definition of exacerbation was different than in the other studies. There are several limitations to this study. Part one presents a snapshot of the characteristics of the study population but cannot reveal pathophysiologic mechanisms or causality. Moreover, the cohort comprised only those tested for vitamin D. If physicians were more likely to check vitamin D status among those who were sicker or had asthma then the associations found would be attenuated. To evaluate whether vitamin D has a direct effect on asthma onset would require a long-term

prospective study, with comprehensive vitamin D and supplementation data taken prior to asthma diagnosis. The association between vitamin D levels and asthma exacerbations in this study provides strong evidence that vitamin D deficiency is a risk factor for asthma exacerbations. While we do not have data on supplementation, we tried to minimize the likelihood of supplementing by extracting exacerbation data the year previous to the first ever vitamin D measurement with the assumption that vitamin D levels in any given year are reflective of levels during the previous one. However, if members were in fact partially supplementing with vitamin D, which may also be associated with other health –promoting behaviors, we would have an underestimation of the association between vitamin D and asthma exacerbations, and also would be introducing a bias by not accounting for an important confounding factor.

In conclusion, the present findings add more evidence to the link between vitamin D and asthma. They suggest beneficial effects of vitamin D on asthma morbidity. Given the known limitations of observational studies, however, a recommendation for or against vitamin D supplementation as preventive or adjuvant therapy, and how much, for all asthma patients cannot be made until further insights from additional clinical trials are known. However, the presented evidence is compelling enough to support a recommendation for screening for vitamin D level in the subgroup of asthma patients that are uncontrolled and experience recurrent exacerbations. In those with vitamin D deficiency, supplementation may be warranted.

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Table 1: Socio-demographic and clinical factors of the study population and the general Clalit member population

	General Clalit population		Study population*		
	N	%	Non-asthmatics	Asthmatics	Total
			%	%	%
Number	1,475,441	100	286,656	21,237	307,893
Sex					
Male	727,336	49.3	31.8	30.8	31.7
Female	748,103	50.7	68.2	69.2	68.3
Age Group					

21-30	615,777	41.7	32.9	32.0	32.8
31-40	464,167	31.5	32.8	31.2	32.6
41-50	395,497	26.8	34.4	36.7	34.5

Vitamin D levels (nmol/L)

0-25					
25.1-50			22.8	21.9	22.7
50.1-90	N/A		39.0	38.9	38.9
90.1+			33.8	34.7	33.9
			4.4	4.6	4.4

BMI Group

<18.5	46,119	3.1	4.6	4.0	4.6
18.5-24.9	524,395	35.5	44.4	41.2	44.2
25-29.9	347,729	23.6	25.9	26.2	25.9
30+	206,505	14.0	16.6	21.7	17.0
No Measurement	350,693	23.8	8.4	6.9	8.3

Smoking

Never	973,673	66.0	75.1	72.0	74.9
Ever	463,621	31.4	24.4	27.8	24.7
Unknown	38,147	2.6	0.5	0.2	0.5

Population group

Haredi	46,109	3.1	6.1	4.8	6.0
Arab	374,015	25.3	25.1	17.9	24.7
General	1,055,317	71.5	68.8	77.3	69.4
Ethiopian origin	34,924	2.4	1.5	3.1	1.6

Asthma	84,620	5.7	0	6.9	6.9
Chronic renal failure	4,104	0.3	0.5	0.5	0.5
Malignancy	23,580	1.6	1.9	2.1	1.9
Hyperparathyroidism	7,663	0.5	0.7	0.8	0.7
Inflammatory bowel disease	4,664	0.3	0.6	0.6	0.6
JH-ACG Resource Utilization Band					
0	99,506	6.7	0.7	0.2	0.6
1	265,439	18.0	10.2	6.2	9.9
2	334,071	22.6	19.7	13.7	19.3
3	614,981	41.7	59.2	63.8	59.5
4	93,542	6.3	9.2	14.6	9.6
5	6,711	0.5	0.6	1.1	0.6
Not recorded	61,191	4.1	0.4	0.3	0.4

* Study population includes Clalit members with a recorded vitamin D level between 6.2008-6.2012

Table 2: Multivariate association between asthma diagnosis and vitamin D level, socio-demographic, and clinical characteristics**

	Odds ratio	95% CI
Vitamin D levels (nmol/L)	1.04	
0-25	0.99	0.99-1.09
25.1-50	Ref	0.96-1.02
50.1-90	1.03	

90.1+		0.96-1.11
Sex		
Male	Ref	
female	0.99	0.96-1.03
Age		
21-30	Ref	
31-40	0.92	0.89-0.96*
41-50	0.96	0.93-0.99*
BMI		
<18.5	0.67	0.62-0.73*
18.5-24.9	0.77	0.74-0.79*
25-29.9	0.88	0.84-0.91*
30+	Ref	
JH-ACG Resource Utilization Band		
0-2		
3-5	Ref	
	1.75	1.69-1.82*
Smoking		
Never	Ref	
Ever	1.14	1.11-1.18*
Population group		
Hardee	0.71	0.66-0.76*

Arab	0.66	0.63-0.69*
General	Ref	
Ethiopian origin		
No	Ref	
Yes	1.95	1.79-2.13*

*OR significant at 0.05 level of significance

**The model also includes the 9 districts of Israel and the season of the vitamin D test

Table 3: Distribution of socio-demographic, vitamin D, and clinical characteristics by asthmatics with one or more exacerbation (12 months prior to their vitamin D test) vs. those with no exacerbations

	No exacerbations		1 or more exacerbation	
Number (%)	18465	87.7	2584	12.3
Vitamin D levels nmol/L				
0-25	3914	21.2	702	27.2
25.1-50	7162	38.8	1006	38.9
50.1-90	6519	35.3	786	30.4
90.1+	870	4.7	90	3.5
Sex				
Male	5766	31.2	706	27.3

Female	12699	68.8	1878	72.7
Age Group				
21-30	6173	33.4	539	20.9
31-40	5768	31.2	807	31.2
41-50	6524	35.3	1238	47.9
BMI Group				
<18.5	755	4.1	87	3.4
18.5-24.9	7760	42.0	911	35.3
25-29.9	4755	25.8	758	29.3
30+	3878	21.0	694	26.9
No Measurement	1317	7.1	134	5.2
Smoking				
Never	13340	73.0	1815	70.3
Ever	5084	26.8	768	29.7
Unknown	41	0.2	1	0.0
Population group				
Haredi	909	4.9	98	3.8
Arab	3129	16.9	633	24.5
General	14427	78.1	1853	71.7
Ethiopian origin	554	3.0	96	3.7
Chronic renal failure	74	0.4	23	0.9
Malignancy	347	1.9	96	3.7
Hyperparathyroidism	137	0.7	34	1.3

IBD	93	0.5	39	1.5
JH-ACG Resource Utilization Band				
0	41	0.0	0	0.0
1	1254	5.2	65	2.5
2	2713	13.0	182	7.0
3	11804	65.9	1666	64.5
4	2476	14.8	615	23.8
5	171	1.1	55	2.1
NA	6	0.0	1	0

Table 4: Multivariate association between asthma exacerbations and vitamin D level, socio-economic, and clinical characteristics **

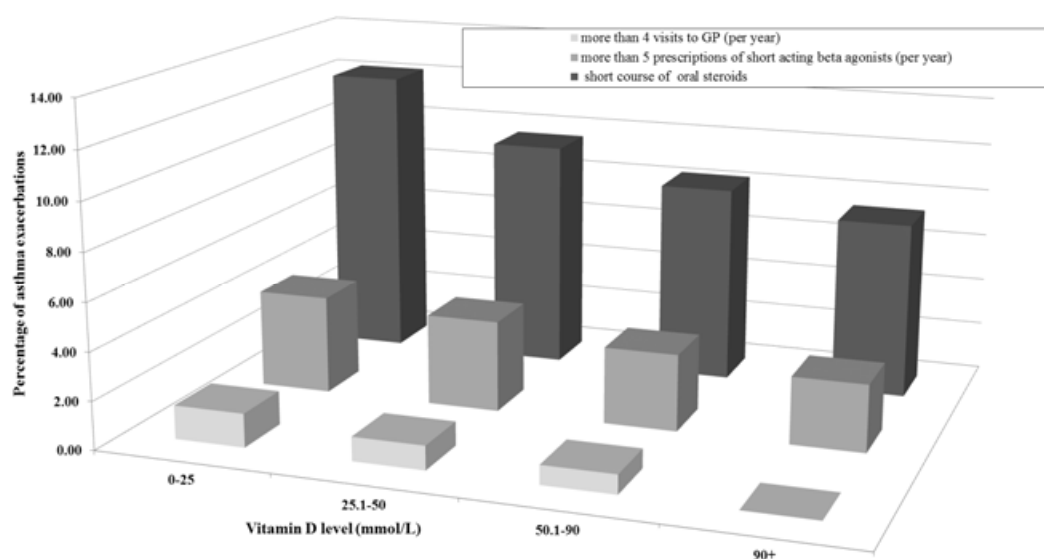
	Odds ratio	95% CI*
Vitamin D levels (nmol/L)		
0-25	1.22	1.07-1.39*
25.1-50	1.07	0.99-1.19
50.1-90	Ref	
90.1+	0.94	0.74-1.20
Sex		
Male	Ref	
female	0.99	0.90-1.10
Age		

21-30	Ref	
31-40	1.45	1.29-1.64*
41-50	1.84	1.64-2.07*
BMI		
<18.5	0.96	0.76-1.22
18.5-24.9	1.10	0.87-1.41
25-29.9	1.07	0.84-1.37
30+	Ref	
JH-ACG Resource Utilization Band		
0-2		
3-5	Ref	
	2.33	2.02-2.69*
Smoking		
Never	Ref	
Ever	1.17	1.06-1.29*
Population group		
Haredi	0.98	0.78-1.24
Arab	1.49	1.32-1.69*
General	Ref	
Ethiopian origin		
No	Ref	
Yes	1.12	0.89-1.43

*OR significant at 0.05 level of significance

**The model also includes the 9 districts of Israel and the season of the vitamin D test

Figure 1: Percentage of asthma exacerbations (by type) occurring in the year previous to vitamin D test by vitamin D level group (mmol/L)



Vitamin D – 25OHD assay – online only supplement 1

The CHS laboratories are authorized to perform tests according to the international quality standard ISO-9001. Periodic assessment of quality control is performed on a regular basis. The accuracy of the measurements in the individual laboratory is confirmed by in-house daily QC monitoring (OLIMPUS and BIO-RAD) and by monthly external QC program (NEQAS).

The measuring range is 10-375 nmol/L (4-150 ng/mL); the analytical sensitivity <2.5 nmol/L (<1.0 ng/mL), and the functional sensitivity <10.0 nmol/L (<4.0 ng/mL). The intra-assay coefficient variations (CVs) for low (18 nmol/L) and high (320 nmol/L) 25-OHD concentrations were 5.5% and 4.8%. The inter-assay CVs were 12.7% and 7.9% for low and high 25-OHD concentrations, respectively. Performance characteristics of the vitamin D assay were evaluated by the CHS laboratory and were comparable to the manufacturers' specifications