State Of Kuwait
Ministry Of Health
Office of Under Secretary

دولة الكويت
وزارة الصحة
مكتب وكيل الوزارة

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تعميم رقم ١٦٣ لسنة 2014
بشأن بروتوكول فحص فيتامين (د)

السادة/ مدراء المناطق الصحية	**المحترمين**
السادة/ مدراء الإدارات الفنية المركزية	**المحترمين**
السادة/ مدراء المستشفيات	**المحترمين**
السادة/ رؤساء المراكز الصحية	**المحترمين**
السادة/ الأطباء	**المحترمين**

نظراً لما يمثله فيتامين (د) من أهمية بالغة لصحة الإنسان وسلامته، ونظراً للطلب المتزايد على فحص فيتامين (د) وتباين الآراء حول أهمية ودقة الفحص المستخدم حالياً في المختبرات لتشخيص حالات النقص والزيادة في نسبة الفيتامين المذكور في الدم.

ورغبة من الوزارة في تطبيق الطريقة المثلى لفحص فيتامين(د) لتحقيق نتائج مهمة في التشخيص والعلاج، فقد تم تشكيل لجنة مشتركة من اختصاصي الغدد الصماء والكيمياء الإكلينيكية لدراسة أهمية ودقة الفحص في التشخيص والعلاج، مع اقتراح الفحص الأمثل لإدخاله في المختبرات.

هذا وقد انتهت اللجنة المذكورة من أعمالها باقتراح البروتوكول المرفق لفحص فيتامين (د) وأهميته مع قائمة بالمصادر العلمية المستند عليها.

وحيث أنه قد تمت الموافقة على هذا البروتوكول المقترح واعتماده وكذا الموافقة على طرق الفحص الواردة به كفحص أمثل لفيتامين (د) في الدم.

لذا يرجى تعميم ذلك واعتماد ما ورد بالبروتوكول المرفق عند فحص نسبة الفيتامين المذكور في الدم.

مع أطيب التمنيات ...

وكيل وزارة الصحة

د. خالد السهلاوي
وكيل وزارة الصحة

مرفق:
- بروتوكول فحص فيتامين (د) عدد (5 صفحات).

Guideline and Protocols

Advisory Committee

Vitamin D Testing Protocol

(Pediatric <18)

Scope

This laboratory protocol explains the guidelines for the appropriate use of vitamin D testing within the general pediatric (pediatric <18 years) population in Kuwait. Patients with malabsorption syndromes, renal failure, unexplained bone pain, unusual fractures, chronic medical disorders and other evidence of metabolic bone disorder are included in this protocol.

Guidelines for vitamin D testing

- **Routine serum vitamin D testing or screening for vitamin D deficiency is NOT recommended**
- **Routine serum vitamin D testing during vitamin D supplementation is NOT recommended**
- **Screening for vitamin D deficiency is recommended for population who are at risk but a follow up test is not required except for patients with bone deformities, non-complaints and patients with recurrent symptoms.**
- **Measurement of $1,25(OH)_2D$ should NOT be requested for vitamin D deficiency.**

Indication for population at risk

Patients with secondary osteoporosis, malabsorption syndromes, renal failure, unexplained bone pain, unusual fractures, medications (chronic use of steroids, anticonvulsants), morbid obesity, chronic medical disorders and other evidence of metabolic bone disorder, screening for vitamin D deficiency is recommended but a follow up test is not required except for patients with bone deformities, non-complaints and patients with recurrent symptoms.

Physiology

Vitamin D is a fat-soluble vitamin that is naturally present in very few foods. It stimulates intestinal calcium and phosphate absorption and is important in maintaining adequate calcium

There is good evidence that oral supplementation with at least 400-800 international units (IU) of vitamin D3 per day (with no calcium except in certain cases) is required to reduce risk of fracture, therefor 400-800 IU daily is recommended from day 1 to age 18 years.

For high risk group (such as secondary osteoporosis, malabsorption syndromes, renal failure, unexplained bone pain, unusual fractures, chronic medical disorders, medications), the patient should be started with a dose of 1000-2000 IU/day as long as the risk is persisting. In the case of severe deficiency with rickets (diagnosed clinically, biochemically and radiologically), the patient should be started with a dose of 2000-4000 IU/day for 6-8 weeks with calcium for 2 weeks. Then the patient should be switched to maintenance dose as described above. Injected vitamin D supplement is not preferable in pediatrics age group and should be reserved for non-adherent patient.

1 alpha-hydroxylated vitamin D analog should never be prescribed as a treatment of vitamin D deficiency.

Vitamin D supplementation without testing

Because vitamin D supplementation in the general population is safe, it is reasonable to advise supplementation without testing. Routine testing of vitamin D levels [25(OH)D] is not medically necessary prior to or after starting vitamin D supplementation.

Vitamin D toxicity

Vitamin D toxicity is uncommon. Any harm that would occur from excessive vitamin D ingestion is mediated by hypercalcemia and/or hypercalciuria. Therefore, if there is a strong clinical suspicion of vitamin D over-use, then recommended test is serum calcium (albumin- corrected total calcium or ionized calcium), urinary calcium and calcium to creatinine ratio. Vitamin D measurement is indicated only if serum calcium or urine calcium or calcium to creatinine ratio level is elevated.

Method

The gold standard for measuring 25(OH) D is LC-MS/MS (HPLC is also a gold standard) but it is costly and time consuming. The currently widely used is enzymatic immunoassay which may demonstrate some difficulties with low concentrations of vitamin D but this disadvantage has limited impact on treatment decisions. The enzymatic immunoassay is available from Liaison, Architect and Roche which can be used in the Ministry of Health Laboratory for measuring vitamin D. The following are some important consideration that should be taken into account before measuring vitamin D:

levels for bone mineralization, bone growth and remodeling. Vitamin D deficiency has been linked to a wide variety of common disease including cancer, diabetes and cardiovascular disease. Vitamin D is reported to be involved in the regulation of cell growth and metabolism, modulation of immune function and reduction of inflammation. For human there are two sources of vitamin D: Vitamin D2 (erogocalciferol) is derived from plants and D3 (cholecalciferol) is produced in the skin by action of UV light on 7-dehydrocholesterol. Vitamin D2 is only one –third as effective as vitamin D3 in raising levels of 25-hydroxyvitamin D (25(OH)D). Both D2 and D3 are hydroxylated in the liver to 25(OH)D, the major circulating form of vitamin D. it undergoes further hydroxylation in the kidney to the active metabolite, 1,25-dihydroxyvitamin D (1,25$(OH)_2$ D) or calcitriol. Calcitiol stimulates intestinal calcium absorption, enables parathyroid hormone mediated mineral absorption within the kidney, stimulates osteoclastic bone resorption and osteoblasts, decreases production of collagen, influences muscle function, stimulates cell differentiation and modules the immune system. Aging brings with it a reduction in the efficiency with which the skin synthesizes vitamin D and reduction in the kidney's ability to convert vitamin D to its active form. Increased pigmentation and use of high efficiency sun blockers also reduce skin synthesis of vitamin D. Consensus has been reached that a 25(OH)D level that is less than 50 nmol/liter indicates vitamin D deficiency. 50-75 nmol/L indicates insufficiency. The optimum level of serum vitamin D is 125-175 nmol/L.

Sun exposure and vitamin D synthesis by skin

The amount of vitamin D produced by the skin is dependent on the surface area exposed, skin pigmentation, age, season, latitude and use of sun block. Adequate vitamin D can be made in the body during carful exposure of the arms and legs to sunlight for 5-15 minutes per day between 10 am to 3 pm, preferably 12 noon. However, the risk of the skin cancer due to exposure and tanning beds must be considered.

Dietary sources of vitamin D

Vitamin D can be obtained from dietary sources (e.g. salmon, tuna, egg yolk), fortified milk (e.g. cow, soy or rice milk) and supplements. There are not plant sources that provide a sufficient amount of vitamin D naturally.

Vitamin D supplementation

Due to limited sun exposure, the pediatric population is unlikely to achieve adequate vitamin D levels through diet and sunlight only. Consideration should be given to supplementation. The two major forms of vitamin D supplements are available as D2 (erogocalciferol) or D3 (cholecalciferol). Vitamin D3 has been shown to be three times more effective than vitamin D2 at increasing serum 25(OH)D levels and maintain these levels over a longer period of time. As a result, Vitamin D2 dosage should be tripled to achieve the same benefit.

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Vitamin D Guidelines and Protocols

Vitamin D2 (Ergocalciferol) ingested from food or supplements
Vitamin D3 (Cholecalciferol) ingested from supplements

Vitamin D3 (Cholecalciferol) synthesized in the body, exposure to sunlight.
5 - 15 minutes daily between 10 am to 3 pm, preferably 12 noon

→ 25-hydroxyvitamin D [25(OH)D] Inactive precursor → 1,25-dihydroxyvitamin D [1,15(OH)2D] Active hormone

Measured by lab test as total 25(OH)D (D2 and D3 may be differentiated)

Calcium hemostasis
Muscle health
Bone health
Cardiovascular health
Immunomodulation
Prevention of autoimmune disease
Regulation of cell growth

Food sources of Vitamin D

Salmon 3.5 oz.	360 IU
Tuna, Canned 3 oz.	200 IU
Sardines 3.5 oz.	250 IU
Milk (fortified) 8 oz.	98 IU
Egg 1 whole	20 IU
Liver 3.5 oz.	15 IU
Cheese 1 oz.	12 IU

Vitamin D supplement intake recommendation

	Loading dose (Deficiency)		Requirement (Maintenance)	
1 day – 18 yr				
	Oral	Injection	Oral	Injection
Normal population			400-800 IU	
High Risk group	2000-4000 IU/ day for 6-8 weeks with Calcium for 2 weeks		1000-2000 IU	
>18 yr				
	50,000 IU weekly for 8-12 weeks	200,000-300,000 IU/IM monthly for 2 months	800-2000 IU daily OR 10,000 IU weekly OR 30,000-50,000 monthly	200,000-300,000 IU/IM every 6 months
Pregnancy and Lactation				
			800-2000 IU daily OR 10,000 IU weekly OR 30,000-50,000 monthly	200,000-300,000 IU/IM every 6 months

Vitamin D Ranges

Unit	Deficient	Insufficient	Sufficient	Ideal	Toxic
nmol/L	<50	50-75	75-125	125-175	>375
ng/ml	<20	20-30	30-50	50-70	>150

- Sample for 25-OHD is stable at ambient temperature but collection tubes must be carefully selected to avoid potential interferences. Blood for 25-(OH) D measurement is probably best collected into plain tubes or separating gels and should be protected from direct sunlight.
- Follow-up test should be performed using the same method used previously
- Reference ranges should be based on published data and until the goal of standardization is achieved, must be appropriate to the method used
- Maintaining good performance of 25-(OH) D assays requires rigorous internal quality control procedures and participation in an external quality control program.

The measurement of $1,25(OH)_2D$ is not done routinely and seldom requested except in very severe renal disease, rare conditions such as vitamin D resistant rickets and granulomatous diseases such as tuberculosis, psoriasis and sarcoidosis. Therefore, measuring $1,25(OH)_2D$ should be requested by a specialist (Endocrinologist or Nephrologist) and to be done in a reference laboratory outside Kuwait.

Vitamin D Ranges

Unit	Deficient	Insufficient	Sufficient	Ideal	Toxic
nmol/L	<50	50-75	75-125	125-175	>375
ng/ml	<20	20-30	30-50	50-70	>150