Abstract
This comprehensive review addresses the issue of Vitamin D deficiency and its management in adults. Briefly describing the history of Vitamin D development and its role in human physiology, it discusses D deficiency in adults. Pragmatic suggestions for diagnosis, choice of therapy, and monitoring are presented from a patient-centred viewpoint, keeping socioeconomic realities in perspective. The review adds to current medical literature by collating evidence in a format that will be useful to practicing clinicians.

Keywords: Bone health, musculoskeletal health, osteomalacia, osteoporosis, rickets, Pakistan, South Asia.

History
The fourth vitamin to be identified, Vitamin D was discovered by McCollum and his co-workers in 1922. The Nobel Prize has been awarded to other Vitamin D related discoveries as well: Niels Bohr made the Medicine Prize in 1903 for his work in heliotherapy in lupus vulgaris, and H Weill was awarded the 1927 Chemistry Prize for unraveling the structure of this vitamin.

Definition
Vitamin D levels are usually assessed by measuring levels of 25-hydroxy Vitamin D (25 OHD), which can be expressed in units of ng/ml or nmol/l. In Pakistan and India, ng/ml units are used. The conversion factor is: 1 ng/ml = 2.5 nmol/l. By definition, normal Vitamin D levels are 30-100 ng/ml, with 20-29 ng/ml being classified as Vitamin D insufficiency, and < 20 ng/ml being listed as Vitamin D deficiency. These cut-offs are based upon correspondence levels of parathyroid hormone (PTH). Low Vitamin D levels kickstart a feedback mechanism which stimulates PTH to rise. The mean levels of Vitamin D at which secondary hyperparathyroidism occurs are used to differentiate between normal and insufficient Vitamin D. Recent studies have shown that PTH levels continue to be suppressed as Vitamin D levels rise to levels of > 60ng/ml.

Natural Vitamin D
Humans source D from sunlight (ultraviolet light B) (wave length 290-315 mm), maximal absorption occurring between 10 am and 3 pm, in spring and summer. Exposure of nearly complete body to one minimal erythema dose of UV radiation (slight pinkness to the skin after 24 hours of exposure) produces Vitamin D equivalent to an oral dose of 10000-25000IU. In northern latitudes (330 or more) (i.e., north of Islamabad or Damascus), there is minimal vitamin D synthesis in winter.

Vitamin D is also available in some natural foods, eg, cod liver oil, and wild (as opposed to farmed) oily sea - fish, e.g, salmon, foods fortified with vitamin D: mushrooms, margarine, hydrogenated fat (dalda ghee), orange juice and breakfast cereals. Fortification of milk with vitamin D is being proposed as a public health intervention in India.

Exposure of 15% body surface area (face, neck and hands) for 20-30 minutes between 10 am and 3 pm allows synthesis of 1000 IU of Vitamin D daily.

The Current Situation
Though almost a century has passed since the discovery of vitamin D, our understanding of this molecule has grown only in recent decades. There are still many lacunae in our knowledge, and these gaps tend to magnify when assessed from a clinical practice perspective. Some of the factors which tend to create confusion amongst health care professionals, as well as
lay public, include: Incomplete understanding of contribution of Vitamin D deficiency to symptoms of various musculoskeletal and rheumatological diseases; lack of simple, economical surrogate markers of vitamin D deficiency; different approaches towards management of skeletal and extra-skeletal manifestations of vitamin D deficiency; lack of clarity regarding doses for ‘cure’ and presentation of vitamin D deficiency, or achievement and ‘maintenance’ of vitamin D health; lack of uniformity in international guidelines; lack of indigenous guidelines on Vitamin D diagnosis and dosage; and the multidisciplinary nature of vitamin D biology which makes teamwork a challenge.

Such issues have created a vitamin D paradox in many countries: we have under-diagnosis of vitamin D deficiency, coupled with over-enthusiastic over-treatment of the condition. Thus, clinicians encounter a full spectrum (vitamin D levels in practice, ranging from undetectable, to deficient, insufficient and normal, as well as to intoxicating levels.

Assessment
Vitamin D status can be assessed clinically, biochemically and radiologically. Some of the symptoms asked for, and signs elicited, are listed in Table-2. However, these clinical markers will not be present in every person with vitamin D deficiency. It is noteworthy here that severity of clinical symptoms or signs does not correlate with vitamin D levels; rather their correlation with PTH levels is much stronger.

The gold standard for assessment of vitamin D status is serum 25 OHD. This active metabolite is produced by activation of vitamin D in the liver, has a long life (2-3 weeks) is a stable molecule, and provides an accurate idea of circulating vitamin D.6 Ideally, it should be estimated

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**Table-1**: Factors associated with vitamin d deficiency.

<table>
<thead>
<tr>
<th>Decreased Availability of Vitamin D</th>
<th>From Sunlight</th>
<th>Northern latitude</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td>Air pollution</td>
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<td></td>
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<td>Modest clothing</td>
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<td>Pigmented skin</td>
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<td>Use of sunscreens</td>
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<td>Heliophobia</td>
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<td></td>
<td></td>
<td>Lack of outdoor activities</td>
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<td>From Diet</td>
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<td>Vegetarian diet</td>
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<td></td>
<td></td>
<td>Malabsorption (eg, coeliac disease, cystic fibrosis, biliary obstruction)</td>
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<td></td>
<td></td>
<td>Use of colestyramine</td>
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<tr>
<td>Impaired Metabolism</td>
<td>Reduced Synthesis</td>
<td>Elderly</td>
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<td></td>
<td></td>
<td>Renal impairment</td>
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<td></td>
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<td>Hepatic impairment</td>
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<td>Increased Breakdown</td>
<td></td>
<td>antifungals : ketoconazole</td>
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<td></td>
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<td>anti-tubercular drugs: rifampicin, INH</td>
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<td></td>
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<td>anti-convulsants: phenytoin</td>
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<td></td>
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<td>HAART (highly active anti – retroviral therapy)</td>
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<td>Glucocorticoids</td>
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**Table-2**: Clinical manifestations of vitamin d deficiency.

<table>
<thead>
<tr>
<th>Symptoms</th>
<th>Signs</th>
<th>Dynamic Signs</th>
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<tbody>
<tr>
<td>PAIN: generalized aches and pains, more in proximal muscles, more in lower limbs; frequent muscle cramps.</td>
<td>Tenderness: over lower rib cage, anterior tibial surface, wrist</td>
<td>Wall-to-Occiput Distance (WOD)</td>
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<tr>
<td>Weakness predominantly of proximal muscles; and of lower limbs; inability to squat, to get up after performing namaaz, to use Oriental style toilets; to lift heavy weights above shoulder level</td>
<td>Gait</td>
<td>- Ideally, the occiput should touch the wall when one stands erect, next to a straight vertical wall, ie, WOD is zero in normal individuals.</td>
</tr>
<tr>
<td>Precipitating factors for Limited Vitamin D Availability /Metabolism</td>
<td>- Waddling gait</td>
<td>- A WOD &gt;0 implies an occult thoracic vertebral fracture, and may suggest osteoporosis or osteomalacia</td>
</tr>
<tr>
<td>- prolonged illness, prolonged indoor stay, childbirth, lactation, winter, liver disease, use of sunscreen, use modest clothing with limited exposure to sunlight.</td>
<td>- Squat test</td>
<td>Hand Insinuation Test</td>
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<td></td>
<td>- Inability to squat</td>
<td>- Inability to get up from squatting position without using support</td>
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J Pak Med Assoc
Vitamin D deficiency: Diagnosis and patient centred management

...through an early morning, fasting sample, in conjunction with serum calcium, phosphorus, alkaline phosphatase, and PTH levels.

Economic considerations mean that PTH assays are not always possible. Surrogate markers of vitamin D deficiency include elevated alkaline phosphatase. The former is limited by its lack of accuracy, and the latter, by lack of availability. Densitometric methods of assessing bone health are meant to diagnose osteopenia or osteoporosis, not osteomalacia or vitamin D status. However, osteomalacia has classic radiographic abnormalities, such as microfractures, Loosers zones, and generalized osteopenia, which manifest with severe forms of deficiency.

25 OHD assays are done by high performance liquid chromatography (HPLC) tandem mass spectrometry (both gold standards), radioimmunoassay, and chemiluminescent protein binding assay. One should be aware of the coefficient of variation of the assay being used.

Management

The drug of choice for management, and prevention, of vitamin D, is cholecalciferol. (Vitamin D3). Ergocalciferol (vitamin D2) is also used in some countries. Cholecalciferol is available in a wide range of formulations and doses (Table-3) Detailed information about these is necessary as wide variation in content and bioavailability has been reported. Preparations from reputed manufacturers should always be preferred.

The choice of dose, route of administration, and duration of therapy may sometimes seem confusing to clinicians, who read conflicting advice from various authors. An understanding of the different setting in which these...
researchers work, explain the discrepancy between their findings. Vitamin D replacement therapy should be planned in a patient-centred manner, based upon available evidence, while keeping social and financial relation in mind. Some of the factors to be considered are include in Table-4.

**Loading Dose / 'Curative' Dose**
A loading dose of vitamin D is required to correct vitamin D deficiency. Such doses are used in documented deficiency, irrespective of severity of symptoms, and can be prescribed to persons with classic symptoms of vitamin D deficiency, even if supporting biochemical evidence is not available, or cannot be sought because of financial limitations.

At least three formulae are available to calculate vitamin D requirements (Table-5). These equations can be used to decide safe, initial loading doses.

A loading dose of 50000-60000IU once a week for 8 weeks, 5000 IU daily for 8 weeks, is suggested as a loading dose. Intramuscular vitamin D is not recommended by any professional organization now, and its use should be restricted to specific clinical situation where oral therapy is not possible, not tolerated, expected not be effective. Megadoses should never be prescribed in absence of documented vitamin D deficiency.11

Faster loading regimes can also be used in severity symptomatic individuals whose quality of life is significantly impacted by vitamin D deficiency. Such regimes provide 50000-60000 IU of vitamin D every alternate day, or twice a week, till normal vitamin D levels are attained.

The total dose required can be calculated from the equations listed in Table-5. Using an extreme scenario, an adolescent weighing 75 kg, with undetectable vitamin D (< 2.6 ng/ml) will need 37×75×30 = 83250 IU to reach 30 ng /ml. An adult of the same weight, with undetectable vitamin D, may require 100×75×30= 225000 IU to reach the same target. These equations assume complete absorption of the drug. The effort of various preparations may vary, based upon their quality and bioavailability.

**Maintenance Dose / 'Preventive' Dose**
Small doses of vitamin D are required to maintain healthy levels, in asymptomatic persons, as well as in person who have successfully received loading doses. Adults require at least 600 IU vitamin D per day, to maximize musculo-skeletal function. However, adults aged > 70 years, require higher doses (800 IU/day). Person who are obese or have malabsorption are on drugs known to interfere with the metabolism of vitamin D, need 2-3 times higher doses of vitamin D.

The maintenance tolerable upper limits of vitamin D, not to be exceeded without medical supervision, or without monitoring facilities, should not be more than 4000 IU/day for adults, given as a daily dose, or 5000 IU capsules twice weekly, or a 60000 IU tablet or sachet once monthly, usually suffices.12 The choice of preparation usually depends upon patient preference and physician experience. Small daily doses may be more physiological than infrequent megadoses.

**Monitoring of Therapy**
Ideally, therapy should be monitored by assessment of serum PTH, calcium and vitamin D.13 The aim of vitamin D therapy is to suppress PTH to normal levels. In most instances, however, lack of availability, access or affordability mean that alternate methods of monitoring have to be sought.

Clinical symptoms such as improvement in pain at the anterior tibia have been shown to correlate with reductions in PTH. Apart from symptomatic improvement, one can monitor therapy with regular urinalysis to rule out calcium crystalluria, which may be suggestive of hypercalcaemia

Patients who cannot be monitored regularly in an ideal manner should be prescribed lower, but more frequent doses of oral vitamin D3.

**Side Effects of Therapy**
High doses of vitamin D may be often be associated with headache, nausea, constipation and other gastrointestinal disturbances. Case reports of vitamin D addiction and toxicity have been published from South Asia.

One should inform patients about possible side effects of therapy, and encourage them to seek medical advice if any disturbing adverse event occurs. Adequate fluid intake must be advised, especially in summer months.

**Conclusion**
Vitamin D deficiency is a major endocrine and metabolic public health problem. It is tragic that such an easily identifiable, preventable and treatable condition continues to affect a large number of our country women and men. While public awareness about the importance of vitamin D has increased in recent years, much more needs to be done, a concerted, and sustained, educational campaign should be led by endocrinologists to encourage sunlight exposure through healthy, socially acceptable, outdoor activities, we must shed our
heliophobic habits to take advantage of the abundant sunshine given to us by nature.

At the same time, awareness should be spread about the symptoms of vitamin D deficiency (and vitamin D intoxication, too).

This will help improve health care seeking behaviour. Physicians should prescribe vitamin D responsibly, in a patient-centred manner, following available evidence, and keeping socioeconomic factors in mind. In case of doubt, lower daily doses may be safer than single megadoses. Pragmatic use of vitamin D, which corrects symptoms, should diffuse the message of vitamin D health in the community, and initiate a virtuous cycle of early health care seeking behaviour, timely diagnosis and correction of vitamin D deficiency, and better health for all.

References