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VITAMIN D STATUS IN PATIENTS ADMITTED IN A CLINIC OF ENDOCRINOLOGY

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(Abstract): Vitamin D deficiency has been known as a global health problem and there were reported moderate to strong inverse associations between 25(OH) D concentrations and cardiovascular diseases, serum lipid concentrations, inflammation, glucose metabolism disorders, weight gain, infectious diseases, multiple sclerosis, mood disorders, declining cognitive function, impaired physical functioning, and all-cause mortality. In Romania there are only a few published reports on vitamin D status among adult population. Aim: To evaluate vitamin D status in 440 patients those were admitted in our clinic for various endocrine pathology. Material and method: Serum 25-hydroxy vitamin D was measured using chemiluminescence assay. We categorized the vitamin D levels in 3 subgroups (deficiency, insufficiency and sufficiency). Results: In our study there was a high prevalence of both vitamin D deficiency and insufficiency, while optimal level was observed only in a very small number of patients. Conclusions: We demonstrated a high frequency of vitamin D deficiency in general population, especially in elderly and children. There are still many controversies regarding the optimal vitamin D status and the supplementation dosage, so long term large scale studies are needed regarding efficacy and safety. Keywords: VITAMIN D, OSTEOPOROSIS, PHOSPHO-CALCIC METABOLISM.

Vitamin D was long known to be essential in bone metabolism, and its main function is the regulation of calcium and phosphate homeostasis, in conjunction with PTH, the gut, kidney and bone being the principal target tissues. Vitamin D deficiency has been recognized as a pandemic with various health consequences (1). Low vitamin D status has been associated with an increased risk of type 1 diabetes mellitus, cardiovascular disease, certain cancers, cognitive decline, depression, pregnancy complications, autoimmunity and allergy (2, 3).

Vitamin D is a hormone precursor that is present in 2 forms: vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Both are produced by photolysis from naturally occurring sterol precursors. Vitamin D can be manufactured in the skin by way
of ultraviolet B rays. There is very little vitamin D production from November to May throughout Europe. Also, we expose less than 5% of our skin to the sun and the vitamin D production in the skin decreases 4 times with age. Very few foods in nature contain vitamin D. The flesh of fatty fish (such as salmon, tuna, and mackerel) and fish liver oils are among the best sources. Small amounts of vitamin D are found in beef liver, cheese, and egg yolks. The major pathologic complication of vitamin D deficiency is rickets (in children) or osteomalacia (in adults), which results mainly from the deficiency of calcium and phosphate required for bone mineralization. A low vitamin D level is an established risk factor for osteoporosis and increasingly recognized as an important factor in fall status among elderly patients (tab. I).

### TABLE I
Vitamin D levels and their impact on bone health

<table>
<thead>
<tr>
<th>Definition (vitamin D)</th>
<th>Serum 25(OH)D level</th>
<th>Impact on bone health</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deficiency</td>
<td>&lt; 25 nmol/L (&lt; 10 ng/mL)</td>
<td>Mineralization defect</td>
</tr>
<tr>
<td>Insufficiency</td>
<td>&lt; 50 nmol/L (&lt; 20 ng/mL)</td>
<td>Increased bone turnover and/or PTH</td>
</tr>
<tr>
<td>Sufficiency</td>
<td>50-75 nmol/L (20-30 ng/mL)</td>
<td>Neutral effect (bone turnover and PTH normalized), desirable benefits on fracture, falls and mortality</td>
</tr>
<tr>
<td>Sufficiency</td>
<td>&gt; 75 nmol/L (&gt; 30 ng/mL)</td>
<td>Desirable target in the fragile elderly due to optimal benefits on fracture, falls and mortality</td>
</tr>
<tr>
<td>Upper limit of adequacy</td>
<td>125 nmol/L</td>
<td>Possibility of adverse effects above this level</td>
</tr>
</tbody>
</table>

Vitamin D insufficiency is widespread (4), and is present in every region of the world, with a prevalence of 63.9% global and 57.7% in Europe (5). The rates of vitamin D deficiency are highest in the Middle East and South Asia (6). In elderly populations in Europe, vitamin D insufficiency is more common in the south than in the north, and more likely in women than in men (7).

In Romanian postmenopausal women, the mean concentrations of 25(OH)D were 20 ng/mL (50 nmol/L) and the prevalence of vitamin D deficiency was 32% (8), while in institutionalized seniors, we reported that mean concentrations of 25(OH)D were 28.5±10.8 nmol/L (9), far below the minimum 50 nmol/L that the Institutes of Medicine have set for everyone in the population. Our first study demonstrated 17,14% severe deficiency of 25(OH)D (10).

### MATERIAL AND METHODS
Our study included 440 patients referred to us for different endocrine problems and was conducted in the Endocrinology Clinic of Saint Spiridon Hospital in Iasi from January 2013 till March 2014. The patients’ ages ranged from 4 to 87 years. To determine vitamin D status we measured serum 25-hydroxyvitamin D3 (25-OH D3) by taking a single blood sample in the morning, in a fasting stage. Serum 25-OH D3 was measured by chemiluminescence assay with minimum detection limit of 3.0 ng/mL.

As seen in table I, we categorized vitamin D levels in 3 subgroups, based on the most recent studies – deficiency (< 10
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ng/mL); - insufficiency (10-20 ng/mL) and sufficiency (> 20 ng/mL)(11).

RESULTS AND DISCUSSION

The distribution by age was various, with the majority of patients (53%) in the 50-70 years group, followed by 13% (4-18 years and over 70), 9% (30-40 years), 7% (40-50 years) and 5% (18-30 years) (fig 1). The mean (SD) serum 25OHD was 17.21 ng/mL, with 242 patients in the insufficiency group (fig. 2). We found a high prevalence of both vitamin D deficiency (25OHD < 10 ng/mL) -16% and insufficiency (25OHD=10-20 ng/mL) -55 % (fig 2).

In our study, vitamin D deficiency (<10 ng/mL) was observed in:
- 15% postmenopausal women;
- 18% patients with osteoporosis;
- 7% children and adolescents.

Vitamin D insufficiency (10-20 ng/mL) was found in:
- 54% postmenopausal women;
- 63% osteoporotic patients;
- 54% children and adolescents.

39% of children and adolescents presented vitamin D levels of 20-30 ng/mL but none of them had vitamin D sufficient levels (>30ng/mL).

Vitamin D sufficiency (> 30 ng/mL) was observed only at 12% of all studied patients.

Fig. 1. Distribution of patients by age group

Fig. 2. Distribution of serum 25OHD3

Fig. 3. Vitamin D deficiency in postmenopausal patients
There are many controversies regarding the definition of different categories of low vitamin D and of the precise estimation of optimal vitamin D status (usually, in Europe a threshold of 20 ng/mL is agreed, although in the USA a 30 ng/mL is favored). In our country, dietary sources of vitamin D are scarce and there is no fortification of food with vitamin D. After giving bread fortified with 5000 IU (125 mcg) to nursing home residents, the medium 25(OH)D seric concentration were significantly higher after 3, 6 and 12 months (12). Another study measured the bone mineral density (BMD) before and after 12 months of serving bread fortified with 800 mg calcium carbonate and 5000 IU vitamin D to nursing home residents. After 1 year the hip BMD grew with 24% of the initial value (13).

The greatest risk for bone and several major human diseases and preventable human health conditions are associated with 25OHD levels below 20 ng/mL (or 50 nmol/L). An estimated number of at least 1 billion (and probably many more) people around the world have 25OHD levels < 20 ng/mL (50 nmol/L), so that their bone health could be improved by vitamin D supplements that
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bring their 25OHD level above 20 ng/mL (50 nmol/L). Several authoritative meta-analyses indicate that a daily dietary vitamin D supplementation (600-800 IU D3) plus calcium reduces the risk of fractures and falls. Such vitamin D dose is likely to increase mean 25OHD levels by 6-16 ng/mL (15-40 nmol/L) and bring serum 25OHD to ≥ 20 ng/mL (> 50 nmol/L) in most subjects. It is no unlikely that even higher vitamin D supplements, bringing 25OHD levels to over 30 ng/mL (75 nmol/L) may convey further benefits without creating additional risk. This would however require vitamin D supplements ≥ 2,000 IU D3 per day for millions, if not billions of people, and until the completion of long term large scale RCTs the efficacy and safety of such interventions cannot be assured for the general population. Vitamin D supplementation (600-800 IU D3) plus calcium should be considered in elderly people (older than 75 years) with an increased fracture and/or fall risk, in particular people living in nursing homes. A Romanian study showed that after giving 200,000 IU Vitamin D 3 every 4 months for one year period, the 25(OH)D concentration grew 102%, but still didn’t reach optimal range (> 75 nmol/L)(15).

CONCLUSIONS
Our study confirms the pre-existing data in literature and is showing once more that only a small number of patients are in the safe range regarding vitamin D, the majority of patients being in the deficiency or insufficiency area. 20 ng/mL should be the minimal serum 25-OHD concentration at the population level and in patients with osteoporosis to ensure optimal bone health, all individuals below this threshold requiring vitamin D supplementation. Since in our country we have only a few published reports on vitamin D status, we need long term large scale studies regarding the efficacy and safety of the vitamin D supplementation.

REFERENCES
Gastrointestinal stromal tumour (GIST) is the most common mesenchymal neoplasm of the gastrointestinal tract, with a worldwide annual incidence of 11–18 per million. The clinical behaviour of GIST is variable, ranging from entirely benign to highly aggressive. Several factors can aid in the stratification of the risk of malignant behaviour for GIST, including anatomical location, tumour size, mitotic activity, and genotype. Approximately 80% of GISTs harbor oncogenic mutations in KIT, and 8–10% harbor oncogenic mutations in PDGFRA, which encode tyrosine kinase receptors. The discovery of these mutations has served as an excellent model for the development of effective molecularly targeted therapies for solid tumours. Specific genotypes, in part, predict the response to treatment with the tyrosine kinase inhibitors imatinib and sunitinib. However, ~10% of GISTs lack KIT and PDGFRA mutations (often referred to as ‘wild-type’ GISTs); such tumours are generally resistant to imatinib therapy. Recent insights into the biology of ‘wild-type’ GISTs have resulted in clinically significant subclassification of this heterogeneous group of tumours, a large subset of which are now known to represent succinate dehydrogenase-deficient GISTs. Recognition of this distinctive class of tumours has critical implications for prognosis, therapy, clinical follow-up, and genetic counselling. This review provides an update on the diagnosis and pathogenesis of these less common classes of GISTs, summarizes the clinical and pathological features associated with particular genotypes, and discusses mechanisms of resistance to targeted therapies. (Leona A Doyle & Jason L Hornick. Gastrointestinal stromal tumours: from KIT to succinate dehydrogenase. Histopathology 2014; 64: 53–67)