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The formation of cholecalciferol (Vitamin D3) in skin depends on solar UVB to break the B ring of 7-dehydrocholesterol. Its discovery more than a century ago resulted from the identification of rickets as due to deficient sunshine in latitudes far from the equator, exacerbated by the air pollution, factory work and indoor living. Rickets resulted from defective endocrine control of blood calcium, and was accompanied by epidemic tuberculosis from failure of the D3-dependent first-line immune system. The influenza pandemic of 2018 revealed the need for D3 to fight viruses. Half a century later the systemic hormone role of 1,25(OH)D3 of renal origin, under control of PTH, was a major stimulus to understanding the mechanism of action via the VDR-RXR heterodimer. It was soon realised that 1,25(OH)D3 is also produced and acts locally in many organs and tissues provided that there are adequate reserves of the (protein-bound) blood storage form, 25(OH)D. This is the common pool for 1-hydroxylation by any cells that need local activation of VDR for induction of specific genes. In the case of the immune system, the trigger is foreign proteins recognised as 'non-self'. Local production and action of 1,25(OH)D, and then its local destruction by 24-hydroxylation must all occur below the 'endocrine radar', so as not to interfere with systemic calcium control. Coronaviruses through their 'spike' protein are internalised by interacting with the ACE-2 receptor, which in turn is down-regulated by Vitamin D. In the process, 25(OH)D is hydroxylated to the active 1,25(OH) D, which must later be degraded to 1,24,25(OH)D. So it is to be expected that when 25(OH)D reserves are low at the onset of infection, they will fall further, allowing virus to enter the cells and trigger a cytokine storm and other damage. Blood PTH will rise to claim any residual 25(OH)D for the dominating systemic role in calcium homeostasis. It follows that intake of vitamin D3 should always be much more than the minimum claimed by the globally-active endocrine system. Unfortunately, the UK's Specialised Advisory Committee on Nutrition (SACN), does not recognise this. It is dominated by nutritionists, even though food sources of D3 are for most non-existent, and of D2, the vegetable substitute, highly variable. The 400IU of D3 reluctantly recommended for those 'at risk', based on endocrinology alone, is grossly inadequate; 4,000IU daily is needed to maintain a blood 25(OH)D at more than 30 ng/ml (75 nmol/l), and provide sufficient reserve for its many autocrine and paracrine functions. The dangers of letting the dominant endocrine function of 1,25(OH)D in ionic calcium control dictate the level of D3 supplements, have once again been underlined by the Covid-19 disaster.

Bone and Mineral Metabolism

VITAMIN D, DIABETES AND ENERGY METABOLISM

Factors Associated With Low Bone Mineral Density in Adults With Type 1 Diabetes: A Cross-Sectional Study

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Context: Individuals with type 1 diabetes (T1D) have a two- to threefold increase in fracture risk at any site, and up to a sevenfold increase in hip fracture risk compared to those without diabetes. The mechanisms accounting for this bone fragility are not yet fully understood.
Objectives: 1) To determine factors associated with low bone mineral density (BMD) in patients with T1D; 2) To assess the association between skin advanced glycation end products (AGEs) and low BMD in patients with T1D.
Methods: These are preliminary data from patients with T1D included in a cross-sectional study aiming at comparing the prevalence of vertebral fractures between adult patients with T1D from two tertiary care centers and age- and sex-matched controls without diabetes. Patients were eligible if they were aged ≥20 years and had a diagnosis of T1D for at least 5 years. Patients were classified as having a low BMD if Z-score was ≤-2.0 at any site (lumbar spine, femoral neck, total hip, radius) in patients aged <50 years or if T-score was ≤-1.0 at any site in patients aged ≥50 years or in postmenopausal women. Skin AGEs (surrogate marker of overall including bone AGEs) were measured by skin autofluorescence (AGE Reader ®). Unpaired t-tests or Chi-squared tests were used to compare characteristics between patients with or without a low BMD. Variables associated with a low BMD were determined by univariate analysis and were subsequently included in a multivariate logistic regression analysis if p<0.1 in the univariate analysis. All variables were tested for multicollinearity.
Results: 106 patients with T1D were included (mean age 45.2±15.0 years; mean BMI 26.3±5.1 kg/m^2; 54.7% women; mean duration of diabetes 28.2±13.6 years; 44.3% with a microvascular complication). Mean HbA1C over the past 3 years was 7.5±0.8%. A third of the patients (31.1%) had a low BMD (3 patients using Z-score; 30 patients using T-score). Patients with a low BMD were older (58.3 vs 39.3 years, p<0.001), had a lower mean HbA1C over the past 3 years (7.3% vs 7.6%, p=0.047), a longer diabetes duration (36.1 vs 24.6 years, p<0.001), higher skin AGEs (2.50 vs 2.03, p<0.001), a higher prevalence of microvascular complications (63.6% vs 37.7%, p=0.02) and a higher prevalence of abnormal albumin to creatinine ratio (ACR ≥2.0) on the day of assessment (38.7% vs 11.8%, p=0.003). In multivariate regression analysis, age (p<0.001), abnormal ACR (p=0.003) and lower mean HbA1C over the past 3 years (p=0.02) remained significantly associated with a low BMD. Skin AGEs were correlated with age (r=0.56) and diabetes duration (r=0.47).
Conclusion: In this population with T1D, a low BMD was independently associated with older age, abnormal ACR and, unexpectedly, with a lower mean HbA1C over the past 3 years, but not with skin AGEs.