

# Controversies in vitamin D: deficiency and supplementation after Roux-en-Y gastric bypass surgery

Kerstyn C Zalesin<sup>†</sup>,  
 Wendy M Miller,  
 Katherine E Nori Janosz,  
 Jose Yanez,  
 Kevin Krause,  
 David L Chengelis &  
 Peter A McCullough

<sup>†</sup>Author for correspondence  
 William Beaumont Hospital,  
 Division of Nutrition and  
 Preventive Medicine,  
 4949 Coolidge  
 Highway Royal Oak,  
 Michigan 48073, USA  
 Tel.: +1 248 655 5900  
 Fax: +1 248 655 5901  
 kzalesin@beaumont.edu

Current vitamin D recommendations are insufficient and a higher intake is necessary in the general population. The requirements of bariatric surgery patients can be augmented by longstanding obesity coupled with, gastro-intestinal malabsorption. Vitamin D deficiency promotes metabolic bone disease and may increase risks for a multitude of other medical conditions. This article reviews some controversies surrounding vitamin D and proposes a management strategy for bariatric surgery patients.

Vitamin D deficiency is a worldwide concern that is becoming increasingly recognized as a public health threat. Certain populations are at greater risk for vitamin D deficiency including the obese and those with gastro-intestinal malabsorption, which exemplifies bariatric surgery patients. Bariatric surgery is the most potent tool available in the treatment of obesity and its inherent comorbidities and is becoming increasingly accepted by physicians and patients alike. Roux-en-Y gastric bypass (RYGB) is the gold standard in the surgical treatment of obesity, succeeding by utilizing restrictive and malabsorptive surgical techniques, which may promote vitamin D deficiencies [1]. The impact of vitamin D deficiency is great; although early stages may be asymptomatic, progression to metabolic bone disease (MBD) can occur with time [2]. Ironically, middle-aged women, who comprise a large proportion of bariatric surgery patients and who benefit greatly from surgical weight loss, are at the greatest risk from the consequences of bone loss [3]. There is developing consensus that current vitamin D recommendations are insufficient and a higher intake of vitamin D is necessary in the general population, yet the requirements of vitamin D after bariatric surgery remains elusive. This article reviews vitamin D controversies and proposes a management strategy for bariatric surgery patients.

## Vitamin D source

Vitamin D is synthesized in the epidermis from 7-dehydrocholesterol and catalyzed by ultraviolet-B (UVB) radiation (wavelengths 290–315 nm) from sunlight. It is subsequently hydroxylated by the liver and then the kidney to become 1 $\alpha$ , 25-dihydroxyvitamin D<sub>3</sub>, which is the active form of vitamin D. Adequate sunlight exposure is capable of providing ample supply of

vitamin D. It is estimated that 10–15 minutes of sunlight will produce the equivalent of 3000 IU of vitamin D<sub>3</sub> [4]. However, with the increasing utilization of sunscreens and a decrease in outdoor activities, reliance on natural light is an inadequate source of vitamin D for much of today's population [5]. In addition, between November and February, natural sunlight exposure in the northern latitudes (greater than 35th parallel) is unable to produce adequate levels of vitamin D [5]. Food sources, including fortified milk, margarines, certain cereals and orange juice, as well as fatty fish and egg yolks, are likewise insufficient sources of vitamin D, as most of the population does not consistently consume large enough quantities to suffice [6].

## Ergocalciferol (vitamin D<sub>2</sub>) versus cholecalciferol (vitamin D<sub>3</sub>)

There are two forms of commercially available vitamin D: ergocalciferol (vitamin D<sub>2</sub>) and cholecalciferol (vitamin D<sub>3</sub>). Initially these formulations were thought to be equivalent; however, recent studies identify cholecalciferol as more effective in raising serum levels of 25-hydroxyvitamin D [7]. Cholecalciferol's potency to improve serum 25-hydroxyvitamin is estimated to be threefold, but could be as high as tenfold [7]. Differing potencies result from a greater molecular stability of cholecalciferol compared with ergocalciferol, as well as a more biologically active receptor binding with cholecalciferol [8]. Many commercially available vitamins are reformulating their products to incorporate cholecalciferol as the predominant source of vitamin D, but this has not been universally embraced. Prescription vitamin D utilized by clinicians for severe hypovitaminosis D treatment are predominantly formulated with ergocalciferol, as there is limited availability of higher-dose cholecalciferol.

**Keywords:** bariatric surgery, cholecalciferol, metabolic bone disease, obesity, vitamin D



### Vitamin D & obesity

The relationship between adiposity and vitamin D deficiency was first recognized over 30 years ago [9]. In recent years, a number of studies continue to validate this relationship. Arunabh and colleagues found an inverse association between percentage body fat and serum 25-hydroxyvitamin D levels in 410 healthy women [10]. Similarly, Yanoff and colleagues found that the prevalence of hypovitaminosis D increased in parallel with BMI for both black and white subjects in a group of 379 otherwise healthy adults [11]. The majority (60%) of 279 morbidly obese adults seeking gastric bypass surgery were found to have a serum 25-hydroxyvitamin D level of 20 ng/ml or less [12], providing further evidence of the inverse correlation between 25-hydroxyvitamin D and BMI.

Various theories regarding the etiology of vitamin D deficiency in obesity have been postulated. These include avoidance of sun exposure in obese individuals [13], enhanced production of 1,25-hydroxyvitamin D with a resultant negative feedback on hepatic synthesis of 25-hydroxyvitamin D [14], as well as increased uptake of circulating vitamin D into adipose tissue [15]. As vitamin D is fat-soluble, it is reasonable to speculate that obese individuals have decreased bioavailability of vitamin D due to sequestering in adipose tissue.

To assess some of the theories regarding vitamin D deficiency in obesity, Wortsman and colleagues compared the effect of whole-body ultraviolet radiation and a pharmacologic dose of 1,25-hydroxyvitamin D in 19 healthy, normal weight subjects versus 19 healthy, obese subjects [16]. Following whole-body irradiation, the content of the vitamin D<sub>3</sub> precursor 7-dehydrocholesterol in the skin of obese and nonobese subjects did not differ significantly, nor did its conversion to previtamin D<sub>3</sub> after irradiation *in vitro*. After 24 h, however, the incremental increase of vitamin D<sub>3</sub> was 57% lower in obese subjects as compared with nonobese subjects. Therefore, an inverse relationship between BMI and serum vitamin D<sub>3</sub> levels following irradiation was identified. Similarly, there was an inverse correlation between BMI and serum 1,25-hydroxyvitamin D following a 50,000 IU oral dose of 1,25-hydroxyvitamin D. The authors concluded that obesity-associated hypovitaminosis D is likely due to its deposition in body fat, which leads to decreased bioavailability of vitamin D.

### Vitamin D & its association with other medical conditions

Vitamin D is proving to be important in the prevention of many chronic disease states, including some cancers, autoimmune disorders, and cardiovascular disease. Multiple studies of persons living at higher latitudes, with less natural exposure to UVB solar radiation, demonstrate an increased risk for some cancers, multiple sclerosis and hypertension [17–25]. It has been proposed that sun exposure augments levels of 1,25-dihydroxyvitamin D<sub>3</sub>, which regulates cell growth and inhibits cancer cell proliferation in an autocrine and paracrine fashion [26], or possibly by reducing angiogenesis, increasing cell differentiation and apoptosis of cancer cells and reducing metastases [27,28]. Vitamin D behaves as a hormone rather than a vitamin, by exerting immunomodulating properties on many cells receptors and tissues, including islet cells, heart muscle, skeletal muscle, active T and B lymphocytes, breast, colon and prostate. In multiple sclerosis, higher vitamin D intake has been associated with disease stabilization and a reduced risk of developing disease [29,30]. In Type I diabetes, 1,25-dihydroxyvitamin D<sub>3</sub> has been shown to reduce risk of disease through the down regulation of cytokines and lymphocyte proliferation, thus reducing overall  $\beta$ -cell destruction [31]. A Finnish study involving 10,366 children demonstrated that a higher intake of vitamin D (2000 IU/day) in the first year of life reduced development of Type I diabetes by a rate ratio of 0.22 (range: 0.05–0.89) [32]. Several epidemiologic and animal studies show vitamin D intake is inversely associated with autoimmune diseases such as rheumatoid arthritis, inflammatory bowel disease, and systemic lupus erythematosus (SLE). An 11-year study of 30,000 women, found lower daily intake of vitamin D (<200 IU/day) was associated with a 33% increase in the development of rheumatoid arthritis [33].

Hypertension rates are higher in both the US and Europe for people living at higher latitudes [8]. Krause *et al.* found that exposing patients to UVB radiation for 3 months had a more than 180% increase in 25-hydroxyvitamin D levels, which resulted in a 6 mmHg decrease in diastolic and systolic blood pressures, similar to the effects of a single blood pressure medication [34]. The mechanism by which vitamin D alters blood pressure is not completely understood. However, a study by Li *et al.*, observed mice with higher 1,25-dihydroxyvitamin D<sub>3</sub> that effectively downregulated renin

and angiotensin, which decreases blood pressure, therefore reducing long-term cardiovascular risk [35]. Several observational studies report that young adults with vitamin D deficiency are at greater risk of congestive heart failure compared with young adults with adequate vitamin D stores [36,37]. Similarly, two studies involving postmenopausal women found that higher 25-hydroxyvitamin D levels were associated with decreased myocardial infarctions and ischemic heart disease [38].

#### ***Metabolic bone disease & vascular calcification***

Liberation of calcium, phosphorous and other substrates from bone may lead to accelerated vascular calcification. Multiple studies indicate that calcification occurs at the necrotic core of atherosclerotic lesions that span the subintimal to vascular medial layers of the arterial wall [39,40]. Vascular calcification thus implies anatomic presence of atherosclerosis. Greater degrees of vascular calcification suggest a greater overall burden of atherosclerosis in the vascular tree. Several studies have linked osteoporosis and MBD associated with chronic kidney disease to accelerated vascular calcification [41]. While there are no data linking calcium, phosphorus, vitamin D and parathyroid hormone (PTH) to changes in atherosclerosis in bariatric patients, this could be a long-term concern. It may represent somewhat of a paradox, since many of the metabolic changes that occur after bariatric surgery are thought to be favorable to atherosclerosis stabilization and regression, while the development of bone disease in bariatric patients could theoretically worsen vascular atherosclerosis and vascular calcification over the longer term. Clearly, studies of vascular calcification are needed in this group of patients.

#### **Vitamin D deficiency: a link to metabolic bone disease**

The relationship between vitamin D deficiency and bone disease is well described. In a study of community-dwelling patients with hip fractures, half had concomitant vitamin D deficiency while a third had secondary hyperparathyroidism [42]. Vitamin D supplementation slows bone loss in postmenopausal women [43], and has been found to protect against weakness and fall risk [44], and reduce secondary hyperparathyroidism [45] in the same population. Calcium absorption and homeostasis is facilitated through a vitamin D mechanism. With a vitamin D

deficiency, gastro-intestinal calcium absorption is hindered. As a compensatory response to lower calcium, PTH production stimulates kidney tubule reabsorption, which maintains serum calcium concentrations. The action of PTH stimulates 1,25-dihydroxyvitamin D levels, which in the early stages, while the process is asymptomatic, leads to an alteration of bony architecture depleting calcium stores resulting in poor mineralization of bone content, hence promoting bone loss and fracture risks. With advanced deficiency, diffuse arthralgias, myalgias and muscular weakness can mimic various rheumatologic or orthopedic conditions, thus confounding the diagnosis [46]. By definition, MBD encompasses the spectrum of secondary hyperparathyroidism, osteomalacia and osteoporosis. The gold standard of differentiating these conditions is with an iliac crest bone biopsy with double tetracycline labeling, yet this technique is not clinically utilized in most cases. Bone-specific markers can be used as a tool to clinically aid in discriminating osteomalacia from osteoporosis. Serum predictors of these processes include: a low 25-hydroxyvitamin D, which is the best assessment of body storages of vitamin D, elevated 1,25-dihydroxyvitamin D and PTH, and bone-specific alkaline phosphatase and osteocalcin, which are markers of osteoblastic bone formation. Urinary N-telopeptides (u-NTX), indicate bone resorption facilitated through osteoclastic function, as well as inhibited urinary calcium excretion less than 100mg/day. Anti-resorptive treatments used in osteoporosis do not benefit osteomalacia, which may be partially reversible with supplemental vitamin D, making this distinction of great importance. To maximize intestinal calcium and downregulate PTH secretion, serum 25-hydroxyvitamin D levels should be maintained within an optimal normal range.

#### ***Recommendations***

The Food and Nutrition Board (FNB) of the Institute of Medicine currently recommends daily intake levels of 200 IU from birth to age 50 years, 400 IU from the ages of 51–70 years, 600 IU for ages over 70 years, and 800 IU for institutionalized or homebound individuals [47]. These recommendations arose from early research emphasizing prevention of rickets and are now recognized as insufficient [48]. Higher concentrations of vitamin D are necessary to prevent bone loss, fractures and other potentially serious medical conditions. Studies indicate that the minimum daily intake for the adult

population should be closer to 1000 IU daily [49], while the upper limit (UL), which is currently acknowledged at 2000 IU/day, may actually be as high as 10,000 IU/day [50].

Optimal dosing of vitamin D has been found to be a key factor in differentiating fracture risk reduction. In a placebo-controlled study, using 400 IU of cholecalciferol daily was not observed to reduce fracture risk [51]. However, a recent meta-analysis utilizing 700–800 IU/daily of cholecalciferol demonstrated a reduced risk for hip fractures of 26% and risk of nonvertebral fracture by 23% compared with placebo. The authors concluded that fracture risk reduction correlates with optimal serum 25-hydroxyvitamin D and requires dosing at levels greater than currently recommended [52]. Evolving recommendations in the general population identify 25-hydroxyvitamin D at 32 ng/ml or greater as an optimal range capable of maximally suppressing PTH levels, thus, limiting bone loss [53]. This concentration is higher than the established norm on most laboratories reference ranges, which guides current treatment.

#### ***Bariatric surgery & vitamin D***

MBD is a known consequence of prolonged vitamin D deficiency in other malabsorptive conditions [54], and is well documented after gastrectomy procedures [55]. However, many physicians are unaware of this potential complication and, thus, do not adequately screen or promptly diagnose MBD with RYGB surgery [56]. The duodenum and jejunum are sites of calcium absorption, which is processed through a vitamin D-related transport mechanism. After RYGB, the remaining distal small bowel compensates and absorbs calcium, albeit less efficiently. Calcium carbonate is inefficiently absorbed owing to the lack of stomach acidity, therefore calcium citrate is the preferred form of calcium supplementation after RYGB, yet this form of calcium is less desirable owing to its bulky composition. Risks of vitamin D deficiency become amplified by poor intake of vitamin D and calcium-rich foods in the postoperative setting, owing to the common development of lactose intolerance and dietary preference after surgery [57]. In addition, malabsorption of fat-soluble vitamins may occur owing to ineffective mixing of bile salts with fat, exacerbating the deficiency [58]. As a result of these physiologic changes, this population will require a greater daily intake of vitamin D to maintain serum levels and will continue to

exhibit lifetime risks for these problems. We reviewed the literature for studies of vitamin D deficiency and secondary MBD outcomes after bariatric surgery.

#### **Review of the RYGB literature**

There is great variation in the literature with respect to the relationship of vitamin D and MBD after RYGB surgery (Table 1). Coates and colleagues evaluated 25 postoperative RYGB patients and compared bone turnover markers with 30 obese controls [59]. Patients in the control group had a greater BMI than those in the postoperative group measured at  $48 \pm 7$  and  $32 \pm 5$  kg/m<sup>2</sup>, respectively. A significant increase of u-NTX measured at  $93 \pm 38$  versus  $24 \pm 11$  nM/mmolCr, ( $p < 0.001$ ), as well as a higher osteocalcin, measured at  $11.6 \pm 3.4$  versus  $7.6 \pm 3.6$  ng/ml ( $p < 0.001$ ), among surgery compared with control cases. A subgroup analysis evaluated 15 patients (12 women and three men) prospectively for 9 months from surgery and likewise noted an increase in u-NTX scores with time,  $174 \pm 168\%$  at 3 months ( $p < 0.01$ ) and  $319 \pm 187\%$  at 9 months ( $p < 0.01$ ). All postoperative patients were instructed to take a vitamin supplement with calcium (1200 mg daily) and vitamin D 400–800 IU daily. The subgroup lost  $37 \pm 9$  kg and had a  $29 \pm 8\%$  decrease in BMI ( $p < 0.001$ ). Bone mineral density (BMD) scores among this group were significantly decreased at the hip ( $7.8 \pm 4.8\%$ ;  $p < 0.001$ ), trochanter ( $9.3 \pm 5.7\%$ ;  $p < 0.001$ ) and total body ( $1.6 \pm 2.0\%$ ;  $p < 0.05$ ) after surgery. Other markers of bone metabolism, such as PTH serum calcium and 24-h urinary calcium, were unchanged between control and postoperative groups. 25-hydroxyvitamin D levels were low in both groups, yet unchanged with surgery. These results indicate that bone turnover may be noted as early as 3 months after RYGB surgery, with the hip being the most affected site, and suggests that vitamin D is not the only mediator of increase bone turnover after bariatric surgery. The authors recommend supplementation of calcium and vitamin D as well as screening for MBD in this population.

Youssef *et al.* recently published the effects of RYGB on calcium, alkaline phosphatase, PTH, and 25-hydroxyvitamin D [60]. The study enrolled 193 female patients and prospectively followed them for 2 years. Daily calcium citrate 1200 mg with vitamin D 400 IU were recommended daily for all subjects. They noted 53.3%

**Table 1. Studies assessing vitamin D and markers for metabolic bone disease with Roux-en-Y gastric bypass surgery.**

Study	Design	Duration	n	Supplement use	Outcomes: 25(OH)D/bone markers	Outcomes: BMD	Study recommendations	Study weaknesses	Ref.
Coates et al.	Retrospective control	2 years	25 RYGB 30 CNT	1200 mg Ca <sup>2+</sup> 400–800 IU vitamin D	↑ uNTX, OC* Similar 25(OH)D	N/A	Supplement Ca <sup>2+</sup> & vitamin D; reasonable to screen BMD in at-risk patients	Small n	[59]
	Prospective	9 months	15 RYGB		↑ uNTX*	↓ TH, trocater, total body*		Small n, short duration	[59]
Johnson et al.	Prospective, case controlled	3 years	232 RYGB	1200 mg Ca <sup>2+</sup> 800 IU vitamin D	Similar 25(OH)D, PTH Ca <sup>2+</sup>	BMD at TH and LS at 1 year*, similar at year 2	MBD annual screening	Poor follow-up, RYGB BPD analyzed together	[61]
Ott et al.	Retrospective control	10 years	26 RYGB 7 CNT	MVI & Ca <sup>2+</sup> vitamin D	↓ Ca <sup>2+</sup> , 25(OH)D ↑ Alk Phos*	↓ FN# ↑ LS	Further studies to define extent and prevalence of problem	Wt loss between study and CNT groups different; small n	[64]
Johnson et al.	Prospective	5.7 ± 2.5 years	41 LL-GBP	1200 mg Ca <sup>2+</sup> 800 IU vitamin D	↓ Vitamin D, ↑ PTH in the LL-GBP compared with SL-GBP	N/A	Keep 25-OH vitamin D ≥30 ng/ml Aggressively screen & treat deficient vitamin D	No baseline data	[63]
		3.1 ± 3.6 years	202 SL-GBP						

\*Statistical significance; #Not statistically significant.

Alk phos: Alkaline phosphatase; BMC: Bone mineral content; BMD: Bone mineral density; BPD: Biliopancreatic diversion; CNT: Control; def: Deficiency; FN: Femoral neck; LL-GBP: Long limb gastric bypass; LS: Lumbar spine; MBD: Metabolic bone disease; MVA: Multivitamin; n: Sample size; N/A: Not available; OC: Osteocalcin; PTH: Parathyroid hormone; RYGB: Roux-en-Y gastric bypass; SL-GBP: Short limb gastric bypass; TH: Total hip; uNTX: Urinary N-telopeptide; Wt: Weight.



**Table 1. Studies assessing vitamin D and markers for metabolic bone disease with Roux-en-Y gastric bypass surgery. (cont.)**

Study	Design	Duration	n	Supplement use	Outcomes: 25(OH)D/bone markers	Outcomes: BMD	Study recommendations	Study weaknesses	Ref.
Goode <i>et al.</i>	Retrospective observational, controlled	3 years	44 RYGB 65 CNT	Not defined	N/A	Similar BMD in premenopausal, Postmenopausal ↓ FN, ↑ LS*	Further studies to examine if ↑ vitamin D can prevent MBD	Small n	[62]
	Prospective	6 months	13 RYGB with ↓ BMD 13 CNT	1200 mg Ca <sup>2+</sup> 8 µg vitamin D	↑ PTH, uNTX 6 months* ↑ 25(OH) D* Similar OC	Similar LS BMD and BMC		Short duration of follow-up	[62]
Youssef <i>et al.</i>	Prospective observational	2 years	193 female RYGB	1200 mg Ca <sup>2+</sup> 400 IU vitamin D	↑ PTH *	N/A	Aggressive and early supplementation after RYGB, screen Ca <sup>2+</sup> metabolism pre-op	Defined vitamin D def. <20 ng/ml, no baseline data	[60]
Sánchez-Hernández <i>et al.</i>	Prospective observational	3 years	64 RYGB	No routine supplements	↑ 25(OH)D ↓ Alk phos, PTH after RYGB*	N/A	Further studies	Small n	[65]
Ybarra <i>et al.</i>	Prospective control	3 years	64 RYGB, 80 obese CNT	No routine supplements	Similar Ca <sup>2+</sup> , alk phos, PTH, 25(OH)D	N/A	Vitamin D supplementation is needed in obese	No baseline data	[66]
de Prisco <i>et al.</i>	Case series, retrospective observational	10–12 years	3 RYGB 1BPD	Varied	↑ PTH, 1,25 vitamin D, alk phos ↓ Ca <sup>2+</sup> , 25 vitamin D	N/A	Increase awareness, supplement and screen MBD	Case series	[67]

\*Statistical significance; †Not statistically significant.

Alk phos: Alkaline phosphatase; BMC: Bone mineral content; BMD: Bone mineral density; BPD: Biliopancreatic diversion; CNT: Control; def: Deficiency; FN: Femoral neck; LL-GBP: Long limb gastric bypass; LS: Lumbar spine; MBD: Metabolic bone disease; MVA: Multivitamin; n: Sample size; N/A: Not available; OC: Osteocalcin; PTH: Parathyroid hormone; RYGB: Roux-en-Y gastric bypass; SL-GBP: Short limb gastric bypass; TH: Total hip; uNTX: Urinary N-telopeptide; Wt: Weight.

of patients had an elevated PTH level with mean time to development after surgery at 9.1 months. There was a 2.5-fold elevated risk in the African–American population compared with the Caucasian population ( $p < 0.05$ ), and a 1.8-times higher risk in subjects aged over 45 years compared with younger counterparts ( $p < 0.05$ ), to develop secondary hyperparathyroidism. Vitamin D deficiency, which was defined as less than 20 ng/ml, was described in 18.2% of the patients, while 30% of patients with secondary hyperparathyroidism had concomitant vitamin D deficiency. This study likewise identified factors other than vitamin D deficiency as predictive of MBD, namely age and race. The authors cautioned that aggressive supplementation with calcium and vitamin D is necessary due to cumulative effects of malabsorption with hypovitaminosis D magnifying risks of MBD.

Johnson *et al.* prospectively monitored BMD, calcium, PTH and vitamin D and compared baseline results to annual postoperative findings for 2 years subsequently [61]. Calcium intake recommendations were 600–1000 mg with 400–800 IU of vitamin D per day. A total of 226 patients, who had undergone RYGB, and seven who underwent biliopancreatic diversion (BPD), were included in a combined analysis, with each patient serving as their own control. They found that 15 patients were osteopenic preoperatively, and three subjects developed osteopenia within the first year. None of the study patients had or developed osteoporosis. At the 1 year evaluation ( $n = 116$ ), total forearm BMD had decreased  $0.55 \pm 2.43\%$  ( $p = 0.03$ ), radius BMD increased  $1.85 \pm 4.06\%$  ( $p = 0.008$ ), while total hip and lumbar spine BMD decreased by  $9.27 \pm 3.42\%$  ( $p < 0.001$ ), and  $4.53 \pm 3.83\%$  ( $p < 0.001$ ), respectively. At the second year ( $n = 37$ ), BMD at the total forearm decreased an additional  $3.62 \pm 3.56\%$  ( $p < 0.001$ ), while no significant further losses at the total hip or lumbar spine were appreciated. At the third year follow-up ( $n = 12$ ), there were no statistically significant losses noted at total forearm, radius bone, total hip or lumbar spine. In fact, BMDs at the spine and hip areas were not significantly different from baseline after the first year, indicating that there may be regain in BMD in some patients over time at the hip, spine and total forearm locations among the remaining small sample. Calcium trended in a declining pattern, while PTH and 25-hydroxyvitamin D levels both increased after surgery; however, none of these

parameters were significantly changed. This study demonstrates that the rate of bone loss is greatest after the first year, and plateaus or even slightly improves in subsequent years. This bone loss appeared partially independent from a vitamin D mechanism, as there was no association between vitamin D or PTH levels to BMD results in this study. The authors indicate that bone loss is not an ongoing process after the first year; however, they do advocate annual screening to detect MBD and BMD changes in individuals at increased risk.

Goode *et al.* assessed 44 females (23 were premenopausal and 21 postmenopausal), 3 or more years following RYGB [62]. There was an average weight loss of 31% and a current BMI average of  $34 \text{ kg/m}^2$ . A comparison of bone mineral content (BMC), bone turnover markers, PTH levels and 25-hydroxyvitamin D levels with an age- and weight-matched historical control group who had previously been assessed for bone mass ( $n = 65$ ). This study achieved a 72% follow-up rate and found no difference in BMC in premenopausal groups ( $42 \pm 5$  years); however, in postmenopausal women ( $55 \pm 7$  years), BMC was higher in the lumbar spine ( $p < 0.05$ ) and lower in the femoral hip ( $p < 0.001$ ). A subgroup of 13 postoperative RYGB patients with a mean BMI of  $34 \text{ kg/m}^2$ , seven premenopausal and six postmenopausal, with low BMCs, were provided supplements of 1200 mg of calcium and  $8 \mu\text{g}$  of vitamin D per day for 6 months, while BMC and serum bone markers were monitored. This group was compared with a 13-member weight-matched control group, seven premenopausal and six postmenopausal, who had previously completed a 6-month unsupplemented weight-maintenance study. No difference in BMC was noted in the subgroup analysis (100% follow-up rate) with supplementation. PTH and serum markers of bone turnover were higher in the RYGB group ( $p < 0.001$ ), yet were not significantly altered with supplementation. While there was a significant increase in 25-hydroxyvitamin D in RYGB patients with supplementation ( $p < 0.0001$ ), no differences in 25-hydroxyvitamin D or osteocalcin were demonstrated between control and postoperative groups. This study found MBD risks to be more prominent with postmenopausal status at cortical bone sites, namely the femoral neck and radius, and raised the concern that standard vitamin D and calcium supplementation may be insufficient to suppress PTH and prevent bone loss after bariatric surgery.

Direct correlation of vitamin D levels and markers of MBD after surgery have been noted. In another 243-subject study led by the Johnson group [63], a prospective evaluation of the effects of RYGB, both long limb ( $n = 41$ ) (LL-GBP), defined as a Roux limb greater than 100cm, and short limb, defined as 100cm or more ( $n = 202$ ) (SL-GBP), on calcium, vitamin D and PTH was compiled. BMI levels were greater in the LL-GBP measuring  $60.6 \pm 8.3 \text{ kg/m}^2$ , as opposed to the SL-GBP group, which was  $49.1 \pm 8.8 \text{ kg/m}^2$ . All study subjects were supplemented with 1200 mg of calcium and 800 IU of vitamin D. Patients in the SL-GBP were followed for a mean of  $3.1 \pm 3.6$  years, while the LL-GBP group was followed for  $5.7 \pm 2.5$  years ( $p < 0.0001$ ). They found that the average 25-hydroxyvitamin D level was lower in the LL-GBP group,  $16.8 \pm 10.8 \text{ ng/ml}$ , while the SL-GBP group levels were  $22.7 \pm 11.1 \text{ ng/ml}$  ( $p = 0.0022$ ). The average PTH levels were higher in the LL-GBP group  $113.5 \pm 88.0$  compared with SL-GBP  $74.5 \pm 52.7 \text{ pg/ml}$  ( $p = 0.0002$ ). Study patients had normal calcium levels without differences between SL and LL-GBP groups. In patients with low vitamin D levels, (defined as  $<8.9 \text{ ng/ml}$ ), 89% had an elevated PTH, (defined as  $>65 \text{ pg/ml}$ ). In patients with a vitamin D level up to  $8.9 \text{ ng/ml}$ , 58% had an elevated PTH. When evaluating 25-hydroxyvitamin D at less than  $30 \text{ ng/ml}$ , 55.1% had secondary hyperparathyroidism while those with vitamin D level up to  $30 \text{ ng/ml}$ , 28.5% had secondary hyperparathyroidism ( $p = 0.0007$ ). A linear correlation revealed that as vitamin D levels decrease ( $p = 0.005$ ) PTH levels linearly increase ( $p < 0.001$ ), which highlighted a direct relationship of bone turnover and vitamin D deficiency in this postoperative setting. This trend appeared more prominent the longer patients were followed after RYGB. The LL-GBP population had a greater risk for hypovitaminosis D and secondary hyperparathyroidism, indicating that a greater surgically imposed malabsorption produces greater risks for MBD. The authors recommended maintaining 25 hydroxyvitamin D levels greater than  $30 \text{ ng/ml}$ .

Ott *et al.* retrospectively evaluated 26 female patients who had undergone RYGB surgery 10 years before and lost an average of  $41.2 \text{ kg}$  [64]. They compared bone parameters with seven control patients who underwent a calorie-restricted weight-loss program and lost  $9.8 \text{ kg}$ , which is significantly less than the

surgery group ( $p = 0.0016$ ). Serum calcium was lower in the postoperative group measured at  $4.3 \pm 0.03$  versus  $4.6 \pm 0.06 \text{ mEq/l}$  ( $p = 0.002$ ). Serum alkaline phosphatase was greater in the postoperative groups compared with the control group,  $121.0 \pm 7.6$  versus  $87.3 \pm 8.3 \text{ U/l}$  ( $p = 0.018$ ). 25-hydroxyvitamin D levels were lower among postoperative patients measured  $24.3 \pm 1.6$  versus  $35.9 \pm 3.4 \text{ ng/ml}$  ( $p = 0.008$ ). Serum osteocalcin tended to lower but did not reach a significant value measuring  $12.6 \pm 1.2$  versus  $9.5 \pm 1.9 \text{ } \mu\text{g/ml}$  ( $p = 0.078$ ). Most postoperative patients were using a multivitamin after surgery and eight were using an additional calcium and vitamin D supplement, which was not defined. BMD was increased at three sites in the lumbar spine, while decreased at the femoral neck measuring  $0.90 \pm 0.05 \text{ g/cm}^2$  versus  $0.03 \pm 0.06 \text{ g/cm}^2$ , among RYGB patients and controls, respectively ( $p = 0.067$ ). This study illustrates the evolution of MBD after RYGB correlating with vitamin D deficiency and strongly recommends further studies to better define the relationship.

Improvements in both vitamin D levels and markers for MBD have been correlated by researchers after RYGB. Sánchez-Hernández *et al.* sought to elucidate the prevalence of hypovitaminosis D in the obese population and to chronicle vitamin D, calcium homeostasis and PTH levels after surgery [65]. A total of 64 patients were prospectively followed after short-limb (60 cm Roux limb) RYGB for an average of 36 months postsurgery. Calcium and vitamin D levels were not routinely provided postoperatively, but were supplemented if a deficiency was recognized. Vitamin D, PTH, calcium and alkaline phosphatase levels were routinely measured after surgery. Calcidiol levels improved by an average of 28% ( $p < 0.0005$ ), while a decline in alkaline phosphatase at -53% ( $p < 0.0005$ ), and PTH at -74% ( $p = 0.001$ ) were appreciated. Calcium and phosphorous levels remained unchanged. These results suggest RYGB surgery effectively augments vitamin D concentrations and will, in turn, effectively suppress PTH levels to minimize bone losses.

A surgical cohort was compared with a control group of 80 obese subjects in a study produced by the same group led by Ybarra, who assessed 25-hydroxyvitamin D and PTH levels, over a mean of 36 months postoperatively [66]. No difference between surgical and nonsurgical populations with respect to calcium, alkaline phosphatase, PTH and calcidiol levels were



identified. Irrespective of surgical status, the greater the vitamin D deficiency, the higher the risk of secondary hyperparathyroidism, indicating that obesity, not surgery, is the greater risk factor for MBD as predicted by vitamin D status. The study concludes that in subjects with obesity, vitamin D deficiency should be screened and treated if found.

Most studies comparing vitamin D and MBD markers evaluated relatively short durations after surgery (within the first few months to years). One small case series [67], however, retrospectively evaluated four postoperative patients after bariatric surgery, (three of whom underwent RYGB, the other BPD) at an average of 8–12 years after surgery. All patients were middle-aged women and three of the four were African-American, with an average weight loss of 41.8 kg. Calcium and vitamin D supplementation varied in all subjects, one patient used no routine supplementation, and the others varied from 100 IU daily to 50,000 IU weekly of ergocalciferol. All patients had hypocalcemia, marked elevations in PTH with extremely low levels of 25-hydroxyvitamin D, elevated 1,25-dihydroxyvitamin D and elevated alkaline phosphatase. The authors observed a striking association of vitamin D, PTH levels and MBD cautioning that shorter studies have limited capabilities of identifying these trends. They further proposed that physicians should aggressively screen this population closely for early MBD and respond with an increased dose of vitamin D.

More malabsorptive surgical weight-loss procedures such as the BPD and the duodenal switch have described an exacerbation of vitamin D deficiency with associated reduction of BMD postoperatively, presumably due to the more extreme malabsorption of vitamin D [68,69].

### Discussion

Much of the research indicates there is an accelerated rate of bone loss after bariatric surgery; however, this process may not be based exclusively on a vitamin D mechanism. Speculations of other proposed mechanisms include: thyroid, PTH-related peptide or even direct cytokine interactions between adipocytes and osteoclastic bone cells capable of directly stimulating resorption facilitated through IL-1, IL-6, TNF $\alpha$ , IL-11 and prostaglandin E<sub>2</sub> [70,71]. Alternatively, adiponectin, an adipose regulatory protein that increases after bariatric surgery, has been suspected in playing a role in stimulating bone resorption with weight loss [72].

Body weight, a major determinant of bone mass, amplifies bone density in the obese particularly at weight bearing locations. Traditionally, obesity has been regarded as protective against osteoporosis [73]. Perhaps, with surgically induced weight-loss, an accelerated loss in bone mass is the direct result of the loss of the protective effect that obesity once provided bone density. Supporting this, researchers have identified accelerated bone losses coinciding with the period of most rapid weight-loss, which plateau with weight stabilization [61]. This concept has been echoed in the medical weight-loss literature as well. Weight loss produced by a very low-calorie diet in a morbidly obese population resulted in an initial (2 months) rapid 22.4 kg loss. There was a coinciding 3.3% decline in BMC as well as an increase in MBD markers such as: serum osteocalcin and hydroxyproline:creatinine ratio within this time frame. However, when reassessed at 8 months, after an additional modest weight loss of 7.3 kg, no further changes in BMC were appreciated. This study demonstrates that the rapidity of weight loss coincides with the greatest losses of BMC [74]. This may indicate that bone loss after weight loss is a natural process, owing to the minimized mechanical forces that the skeleton is required to support. The processes that govern bone metabolism with weight loss may, in fact, be heterogeneous. How these influences stimulate osteoblastic and osteoclastic cellular shifts remains unclear. The result promotes bone remodeling and exerts an evolutionary change on the skeleton, often promoting bone losses. The key to unraveling the mechanisms behind the process, which appears to be at least partially dependent of vitamin D, may allow effective preventative treatments.

Vitamin D requirements after RYGB may be accentuated by multiple mechanisms and augments MBD risks. Antiquated preventative vitamin D supplementation was employed with all these studies, which is becoming recognized as suboptimal, even for the general population. Consistent with this tide of change, much of what is reported as normal by laboratory standards appears to be insufficient by newly evolving recommendations of 25-hydroxyvitamin D serum concentration at 32 ng/ml or greater. Achieving this concentration will require higher than standard dosing of vitamin D [53]. In addition, many of the studies used cut-offs for normal levels, which are suboptimal by these standards, and patients may in fact have been deficient in vitamins D, in spite

of being labeled as normal. These confounding variables make the established research difficult to interpret.

Most of these studies assessed short-term outcomes after bariatric surgery. The two long-term case-series, however, noted a more striking association between vitamin D deficiencies and MBD after RYGB surgery. This may indicate that vitamin D deficiency produces MBD that can only be fully appreciated after many years, which is beyond the scope of many of these studies.

Other confounding challenges come into play with the interpretation of data. DXA testing has been criticized as inaccurate with obesity and weight loss. The surrounding fatty tissues, as well as osteoarthritic changes, can falsely elevate BMD, which will overinflate bone density with obesity and overestimate bone losses with weight or fatty tissue losses [75]. Likewise, there has been controversy surrounding laboratory reproducibility of vitamin D concentrations, because of an unacceptable interlaboratory variability with analysis of the same specimen [76], which confounds interpretation of these results.

No standardized recommendations exist for vitamin D supplementation after bariatric surgery. Bone loss after surgery seems to be a dynamic process; the mechanism is not defined and may be multifactorial. The role of vitamin D deficiency as it applies to postoperative bone loss is not fully understood, nor has supplemental use been proven to reverse this process. Nonetheless, it seems prudent to screen and correct a vitamin D deficiency both before and after bariatric surgery in order to maximize those variables that are modifiable. Early recognition and prompt treatment of vitamin D deficiency may prove to be fundamental in prevention and/or treatment of MBD in this population and may play a role in prevention of other chronic medical illnesses. At this time, we do not have any established guidelines for postoperative RYGB patients with respect to vitamin D supplementation and the prevention of MBD and more research needs to be carried out to clarify this.

#### *Optimal treatment*

In the William Beaumont Hospital Weight Control Center, Royal Oak, Michigan, we monitor RYGB patients after surgery. A daily diet high in calcium with vitamin D is recommended to all postoperative patients. Judicious sunlight exposure (10–15 min, 2–3 days per week) is a plentiful source of vitamin D and

could be considered complimentary therapy when seasonally available, unless otherwise contraindicated. Supplementation with calcium citrate (1200–1500 mg/day) and vitamin D (cholecalciferol 1200–2000 IU/daily) is recommended for prophylaxis to all our postoperative RYGB patients, although this amount varies depending on patient preference of dietary supplements. We feel that aggressive screening of vitamin D concentrations and markers of MBD are an indispensable part of a postoperative regimen. A screening protocol and treatment algorithm has been instituted at our center to deal with this prevalent concern (Box 1). We define mild deficiency as a 25-hydroxyvitamin D at 20–31 ng/ml, moderate deficiency as 11–19 ng/ml, and severe deficiency state is defined as a level of 10ng/ml or under. Our tiered treatment of escalating cholecalciferol intake is recommended depending on the degree of deficiency identified, ideally shooting for a 25-hydroxyvitamin D of greater than 32 ng/ml without elevation of MBD markers. Levels are repeated within 6–12 weeks of treatment or until normalized, at which time preventative doses are reinstated and monitored for efficacy. Routine MBD screening is recommended with our algorithm at yearly intervals or sooner if elevated markers of MBD are identified. This MBD screening panel includes (Box 1) PTH, osteocalcin, bone-specific alkaline phosphatase and u-NTX. Bone densitometry via dual x-ray absorptiometry is recommended every other year, especially in populations with baseline risk factor for osteoporosis.

#### **Expert commentary**

History teaches us that classic vitamin D deficiency produces osteomalacia in adults and rickets in children, which can be prevented with low-dose vitamin D supplementation. This lesson inspired a public policy reformation and

#### **Box 1. Proposed screening for metabolic bone disease after Roux-en-Y gastric bypass.**

- Bone-specific alkaline phosphatase
- 25-hydroxyvitamin D
- Parathyroid hormone
- Osteocalcin
- Urine N-telopeptides
- Bone densitometry

*Postoperatively – screen yearly or when significant deficiency is identified.*

mandated routine supplementation of milk that virtually eliminated the problem. In recent years, however, there has been a re-emergence of osteomalacia [77]. Reasons for this recurrence are likely multifactorial, relating to the many cultural changes that we, as a society, have experienced. This implies current standards are insufficient and greater intake of vitamin D is now required. The Current Food and Nutrition Board of the Institute of Medicine recommendations are inadequate and are in urgent need of revision. Vitamin D toxicity may produce adverse events such as hypercalcemia with metastatic calcinosis including nephrolithiasis, which are fortunately rare, yet require consideration and therapeutic monitoring [78]. Patients with vitamin D deficiency may even require higher doses of vitamin D until their total body stores have been repleted. As physicians, it is imperative that patients with these risks be identified and screened for vitamin D deficiency.

### Future perspective

While obesity rates continue to rise and traditional treatment modalities fail, bariatric surgery rates will likely increase. The combined effect of obesity and RYGB treatment may place some individuals at a greater risk of vitamin D deficiency accompanied by the potential sequelae of MBD and various other medical conditions. Vitamin D is now recognized as a critical nutrient. There is now a compelling need to establish optimal therapy and guidelines for supplementation both within the general population and in those patients with bariatric surgery. Physicians need to become increasingly aware of the shortcomings associated with current vitamin D intake and current intake recommendations. Improving food fortification is one possible means of improving supplementation and creating greater public awareness is necessary. An efficient marker of early bone disease that can be readily employed for screening to identify

### Executive summary

- Vitamin D deficiency promotes risks for metabolic bone disease (MBD).
- Vitamin D is also proving to be important in the prevention of many chronic disease states, including some cancers, autoimmune disorders and cardiovascular disease.
- Cholecalciferol (vitamin D<sub>3</sub>) appears more potent than ergocalciferol (vitamin D<sub>2</sub>).
- Current recommendations for vitamin D intake are insufficient.
- Evolving recommendations identify 25-hydroxyvitamin D levels of 32 ng/ml or greater as an optimal range capable of maximally suppressing parathyroid hormone levels limiting bone loss.
- Vitamin D requirements after Roux-en-Y gastric bypass (RYGB) may be accentuated by multiple mechanisms and a greater daily intake of vitamin D is necessary to maintain optimal serum levels.
- Bariatric surgery patients exhibit lifetime risks for vitamin D deficiency and the development of MBD.
- Screening and treating this deficiency early may effect a reduction of MBD and potentially reduce scores of other medical conditions associated with vitamin D deficiency.
- Bariatric surgery patients are at a disproportionate risk for bone loss and MBD.
- These patients appear to lose the protective effect on bone mass granted by obesity owing to the combination of surgically induced weight loss and postoperative anatomic and physiologic modifications. The relationship between vitamin D deficiency and MBD in this population is not well described.
- Vitamin D deficiency may contribute to MBD after surgery; however, it may not be the sole mediator of this process. Cytokine and cellular interaction of inflammatory mediators are other potential mechanisms that may play a role in this process, leading to MBD in this unique population.
- Aggressive monitoring and supplementation with calcium citrate and vitamin D should be implemented since cumulative effects of malabsorption with low vitamin D can significantly magnify other mediators in the process of MBD.
- More research is required to understand the interaction of vitamin D and bone loss after surgery and to clarify if optimal dosing can promote improvements in MBD risks and bone loss.
- We believe it is important to maximize all modifiable risks with such potentially severe consequences. From our current vantage point, the risks of not optimizing vitamin D are too great to be ignored.

MBD in its early stages would also be clinically useful. Screening and treating this deficiency early may effectuate a reduction of MBD and potentially reduce scores of other medical conditions associated with vitamin D deficiency.

#### Financial disclosure

*The authors have no relevant financial interests, including employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties related to this manuscript.*

#### Bibliography

Papers of special note have been highlighted as of interest (•) or of considerable interest (••) to readers.

1. Gastrointestinal surgery for severe obesity. NIH Consens Dev Conf Consensus Statement 9(1), March 25–27 (1991).
- **Provides current rationale and framework for Roux-en-Y gastric bypass surgery as best evidence-based treatment strategy for obesity.**
2. Goldner WS, O'Dorisio TM, Dillion JS *et al.*: Severe metabolic bone disease as a long-term complication of obesity surgery. *Obes. Surg.* 12(5), 685–692 (2002).
3. Hamoui N, Kim K, Anthonie G *et al.*: The significance of elevated levels of parathyroid hormone in patients with morbid obesity before and after bariatric surgery. *Arch. Surg.* 138(8), 891–897 (2003).
4. Reichrath J: Sunlight, skin cancer and vitamin D: what are the conclusions of recent findings that protection against solar ultraviolet (UV) radiation causes 25-hydroxyvitamin D deficiency in solid organ-transplant recipients, xeroderma pigmentosum, and other risk groups? *J. Steroid Biochem. Mol. Biol.* 103(3–5), 664–667 (2007).
5. Holick MF: Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers and cardiovascular disease. *Am. J. Clin. Nutr.* 80(Suppl. 6), 1678S–1688S (2004).
6. Zitterman A: Vitamin D in preventative medicine: are we ignoring the evidence? *Br. J. Nutr.* 89, 552–572 (2003).
7. Armas LA, Hollis BW, Heaney RP: Vitamin D2 is much less effective than Vitamin D3 in humans. *J. Clin. Endocrinol. Metab.* 89, 5387–5391 (2004).
- **Demonstrates superiority of cholecalciferol to ergocalciferol in improving serum 25-hydroxyvitamin D in 20 healthy subjects.**
8. Grady LT, Thakker KD: Stability of solid drugs: degradation of ergocalciferol (vitamin D2) and cholecalciferol (vitamin D3) at high humidity and elevated temperatures. *J. Pharm. Sci.* 69, 1099–1102 (1980).
9. Rosenstreich SJ, Rich C, Volwiler W: Deposition in and release of vitamin D2 from body fat: evidence for a storage site in the rat. *J. Clin. Invest.* 50(3), 679–687 (1971).
10. Arunabh S, Pollack S, Yeh J, Aloia JF: Body fat content and 25-hydroxyvitamin D levels in healthy women. *J. Clin. Endocrinol. Metab.* 88(1), 157–161 (2003).
11. Yanoff LB, Parikh SJ, Spitalnik A *et al.*: The prevalence of hypovitaminosis D and secondary hyperparathyroidism in obese Black Americans. *Clin. Endocrin.* 64(5), 523–529 (2006).
12. Carlin AM, Rao DS, Mesleman AM *et al.*: Prevalence of vitamin D depletion among morbidly obese patients seeking gastric bypass surgery. *Surg. Obes. Relat. Dis.* 2(2), 98–103 (2006).
13. Compston JE, Vedi S, Ledger JE *et al.*: Vitamin D status and bone histomorphometry in gross obesity. *Am. J. Clin. Nutr.* 34(11), 2359–2363 (1981).
14. Bell NH, Epstein S, Greene A, Shary J, Oexmann MJ, Shaw S: Evidence for alteration of the vitamin D-endocrine system in obese subjects. *J. Clin. Invest.* 76(1), 370–373 (1985).
15. Liel Y, Ulmer E, Shary J, Hollis BW, Bell NH: Low circulating vitamin D in obesity. *Calcif. Tissue Int.* 43, 199–201 (1988).
16. Wortsman J, Matsuoka LY, Chen TC, Lu Z, Holick MF: Decreased bioavailability of vitamin D in obesity. *Am. J. Clin. Nutr.* 72(3), 690–693 (2000).
- **Study demonstrates diminished vitamin D bioavailability after dose-controlled whole-body irradiation and in obese subjects.**
17. Garland CF, Garland FC, Shaw EK, Comstock GW, Helsing KJ, Gorham ED: Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. *Lancet* 18(2), 1176–1178 (1989).
18. Garland FC, Garland CF, Gorham ED, Young JF: Geographic variation in breast *Cancer* mortality in the United States: a hypothesis involving exposure to solar radiation. *Prev. Med.* 19, 612–614 (1990).
19. Ahonen MH, Tenkanen L, Teppo L, Hakama M, Tuohimaa P: Prostate cancer risk and pre-diagnostic serum 25-hydroxyvitamin D levels (Finland). *Cancer Causes Control* 11, 847–852 (2000).
20. Hanchette CL, Schwartz GG: Geographic patterns of prostate cancer mortality. Evidence for a protective effect of ultraviolet radiation. *Cancer* 70(12), 2861–2869 (1992).
21. Apperly FL: The relation of solar radiation to cancer mortality in North America. *Cancer Res.* 1, 191–195 (1941).
22. Grant WB: An estimate of premature cancer mortality in the U. S. due to inadequate doses of solar ultraviolet-B radiation. *Cancer* 94(6), 1867–1875 (2002).
23. Hernan MA, Olek MJ, Ascherio A: Geographic variation of MS incidence in two prospective studies of US women. *Neurology* 51, 1711–1718 (1999).
24. Rostand SG: Ultraviolet light may contribute to geographic and racial blood pressure differences. *Hypertension* 30, 150–156 (1979).
25. Grant WB: An ecologic study of the role of solar UV-B radiation in reducing the risk of cancer using cancer mortality data, dietary supply data and latitude for European countries. In: *Biologic Effects of Light 2001*. Holick MF (Ed.). Kluwer Academic Publishing, Boston, MA, USA 266–267 (2002).
26. Holick MF: Vitamin D: Importance in the prevention of cancers, Type 1 diabetes, heart disease, and osteoporosis. *Am. J. Clin. Nutr.* 79(3), 362–371 (2004).
- **Highlights link of vitamin D deficiency to many other conditions.**
27. Mantell DJ, Owens PE, Bundred NJ, Mawer EB, Canfield AE: 1 $\alpha$ ,25-Dihydroxyvitamin D<sub>3</sub> inhibits angiogenesis in vitro and in vivo. *Circ. Res.* 87(3), 214–220 (2000).
28. Tangpricha V, Flanagan N, Whitlatch LW *et al.*: 25-hydroxyvitamin D-1  $\alpha$ -hydroxylase in normal and malignant colon tissue. *Lancet* 357, 1673–1674 (2001).
29. Mahon BD, Gorodon SA, Cruz J, Cosman F, Cantorna MT: Cytokine profile in patients with multiple sclerosis following vitamin D supplementation. *J. Neuroimmunol.* 134, 128–132 (2003).
30. Munger KL, Zhang SM, O'Reilly E *et al.*: Vitamin D intake and incidence of multiple sclerosis. *Neurology* 62(1), 60–65 (2004).
31. Casteels K, Waer M, Bouillon R *et al.*: 1,25-Dihydroxyvitamin D<sub>3</sub> restores sensitivity to cyclosporamide-induced apoptosis in non-obese diabetic (NOD) mice and protects against diabetes. *Clin. Exp. Immunol.* 112, 181–187 (1998).

32. Hypponen E, Laara E, Reunanen A, Jarvelin MR, Virtanen SM: Intake of vitamin D and risk of Type I diabetes: a birth-cohort study. *Lancet* 358, 1500–1503 (2001).
- **Large study that showed that infants supplemented with vitamin D in the first year of life demonstrated a risk reduction for the development of diabetes.**
33. Merlino LA, Curtis J, Mikuls TR *et al.*: Vitamin D intake is inversely associated with rheumatoid arthritis: results from the Iowa Women's Health Study. *Arthritis Rheum.* 50, 72–77 (2004).
34. Krause R, Buhning M, Hopfenmuller W, Holick MF, Sharma AM: Ultraviolet B and blood pressure. *Lancet* 352, 709–710 (1998).
35. Li Y, Kong J, Wei M, Chen ZF, Liu S, Cao LP: 1,25-dihydroxyvitamin D<sub>3</sub> is a negative endocrine regulator of the renin–angiotensin system. *J. Clin. Invest.* 110 (2), 229–238 (2002).
36. Zittermann A, Schleithoff SS, Tendrich G, Berthold HK, Korfer R, Stehle P: Low vitamin D status: a contributing factor in the pathogenesis of congestive heart failure? *J. Am. Coll. Cardiol.* 4, 105–121 (2003).
37. Malabanan A, Veronikis IE, Holick MF: Redefining vitamin D insufficiency. *Lancet* 351, 805–806 (1998).
38. Bostick RM, Kushi LH, Wu Y, Meyer KA, Sellers TA, Folsom AR: Relation of calcium, vitamin D, and dietary food intake to ischemic heart disease mortality among postmenopausal women. *Am. J. Epidemiol.* 149(2), 151–161 (1999).
39. Hasegawa T, Ehara S, Kobayashi Y *et al.*: Acute myocardial infarction: Clinical characteristics and plaque morphology between expansive remodeling and constrictive remodeling by intravascular ultrasound. *Am. Heart. J.* 151(2), 332–337 (2006).
40. Demer LL, Tintut Y: Osteopontin. Between a rock and a hard plaque. *Circ. Res.* 84(2), 250–252 (1999).
41. Marcovitz PA, Tran HH, Franklin BA *et al.*: Usefulness of bone mineral density to predict significant coronary artery disease. *Am. J. Cardiol.* 98(6), 1059–1063 (2005).
42. LeBoff M, Kohlmeier L, Hurwitz S *et al.*: Occult vitamin D deficiency in postmenopausal women with acute hip fracture. *JAMA* 271, 1505–1511 (1999).
43. Ooms ME, Roos JC, Bezemer PD *et al.*: Prevention of bone loss by vitamin D supplementation in elderly women: a randomized double-blind trial *J. Clin. Endocrinol. Metab.* 80, 1052–1058 (1995).
44. Bishoff-Ferrari HA, Dawson-Hughes B, Willett WC *et al.*: Effects of vitamin D on falls: a meta-analysis. *JAMA* 291, 1999–2006 (2004).
- **Meta-analysis that demonstrated that vitamin D was associated with a risk reduction in falls in the elderly.**
45. Ricci TA, Chowdhury H, Heymsfield SB *et al.*: Calcium supplementation decreased bone turnover during weight reduction in obese postmenopausal women. *J. Bone Miner. Res.* 13, 1–6 (1998).
46. Reginato AJ, Falasca GF, Pappu R *et al.*: Musculoskeletal manifestations of osteomalacia: report of 26 cases and literature review. *Semin. Arthritis Rheum.* 28, 287–304 (1999).
47. Standard Committee on the Scientific Evaluation of Dietary Reference Intakes. Dietary reference intakes for calcium, phosphorus, magnesium, vitamin D, fluoride. National Academy Press, Washington, DC, USA 71–145 (1997).
48. Preece MA, McIntosh WB Tomlinson S *et al.*: Vitamin-D deficiency among Asian immigrants to Britain. *Lancet* 1, 907–910 (1973).
49. Hanley DA, Davison KS: Vitamin D insufficiency in North America. *J. Nutr.* 135, 332–337 (2005).
50. Hathcock JN, Shao A Vieth, Heany R: Risk assessment for vitamin D. *Am. J. Clin. Nutr.* 85(1), 6–18 (2007).
- **Risk assessment methodology employed to identify safe upper limits of vitamin D intake.**
51. Meyer HE, Smedshaug GB, Kvaavik E *et al.*: Can vitamin D supplementation reduce the risk of fracture in the elderly? A randomized controlled trial *J. Bone. Miner. Res.* 17(4), 709–715 (2002).
52. Bishoff-Ferrari HA, Willett WC, Wong JB *et al.*: Fracture prevention with vitamin D supplementation: A meta-analysis of randomized controlled trials *JAMA* 293(18), 2257–2264 (2005).
- **Meta-analysis demonstrating higher doses of vitamin D are necessary in osteoporosis fracture risk.**
53. Heaney RP: Functional indices of vitamin D status and ramifications of vitamin D deficiency. *Am. J. Clin. Nutr.* 80(Suppl.), 1706S–1709S (2004).
- **Provides evidence that low vitamin D levels (<80 nmol/l) are associated with lower calcium absorption, leading to osteoporosis and fracture risk. Identifies higher intake of vitamin D is necessary.**
54. Compston JE, Horton LWL, Laker MF *et al.*: Treatment of bone disease after jejunoileal bypass for obesity with oral 1 $\alpha$  hydroxyvitamin D<sub>3</sub>. *Gut* 21(8), 669–674 (1980).
55. Paakkonen M, Alhava EM, Karjalainen P: Bone mineral and intestinal calcium absorption after partial gastrectomy. *Scand. J. Gastroenterol.* 17(3), 369–372 (1982).
56. Basha BD, Rao DS, Han ZH, Parfitt AM: Osteomalacia due to vitamin D depletion: a neglected consequence of intestinal malabsorption. *Am. J. Med.* 108(4), 296–300 (2000).
57. Crowley LV, Seay J, Mullin G: Late effects of gastric bypass for obesity. *Am. J. Gastroenterol.* 79(11), 850–860 (1984).
58. Goldner WS, O'Dorisio TM, Dillon JS, Mason EE: Severe metabolic bone disease as a long-term complication of obesity surgery. *Obes. Surg.* 12(5), 685–692 (2002).
59. Coates PS, Fernstrom JD, Fernstrom MH, Schauer PR, Greenspan SL: Gastric bypass surgery for morbid obesity leads to an increase in bone turnover and a decrease in bone mass. *J. Clin. Endocrinol. Metab.* 89(3), 1061–1065 (2004).
60. Youssef Y, Richards WO, Sekhar N *et al.*: Risk of secondary hyperparathyroidism after laparoscopic bypass surgery in obese women. *Surg. Endosc.* 21(8), 1393–1396 (2007).
61. Johnson JM, Maher JW, Samuel I *et al.*: Effects of gastric bypass procedures on bone mineral density, calcium, parathyroid hormone and vitamin D. *J. Gastrointes. Surg.* 9(8), 1106–1110 (2005).
62. Goode LR, Brolin RE, Chowdhury HA, Shapses SA: Bone and gastric bypass surgery: effects of dietary calcium and vitamin D. *Obes. Res.* 12(1), 40–47 (2004).
63. Johnson JM, Maher JW, DeMaria EJ *et al.*: The long term effects of gastric bypass on vitamin D metabolism. *Ann. Surg.* 243(5), 701–705 (2006).
64. Ott MT, Fanti R, Malluche HH *et al.*: Biochemical evidence of metabolic bone disease in women following Roux-Y gastric bypass for morbid obesity. *Obes. Surg.* 2(4), 341–348 (1992).
65. Sánchez-Hernández J, Ybarra J, Gich I *et al.*: Effects of bariatric surgery on vitamin D status and secondary hyperparathyroidism: a prospective study *Obes. Surg.* 15(10), 1389–1395 (2005).
66. Ybarra J, Sánchez-Hernández J, Gich I *et al.*: Unchanged hypovitaminosis D and secondary hyperparathyroidism in morbid obesity after bariatric surgery. *Obes. Surg.* 15(3), 330–335(2005).



67. de Prisco C, Levine SN: Metabolic bone disease after gastric surgery for obesity. *Am. J. Med. Sci.* 329(2), 57–61 (2005).
68. Chapin BL, LeMar HJ Jr, Knodel DH, Carter PL: Secondary hyperparathyroidism following biliopancreatic diversion. *Arch. Surg.* 131(10), 1048–1052 (1996).
69. Hamoui N, Kim K, Anthone G *et al.*: The significance of elevated levels of parathyroid hormone in patients with morbid obesity before and after bariatric surgery. *Arch. Surg.* 138(8), 891–897 (2003).
70. Bell NH: RANK ligand and regulation of skeletal remodeling. *J. Clin. Invest.* 111(8), 1120–1122 (2003).
71. Kudo O, Fujikawa Y, Itonaga I *et al.*: Proinflammatory cytokine (TNF $\alpha$ /IL-1 $\alpha$ ) induction of human osteoclast formation. *J. Pathol.* 198(2), 220–227 (2002).
- **Demonstrates that elevated levels of inflammatory markers are stimulators of bone resorption.**
72. Lenchik L, Resister TC, Hsu FC *et al.*: Adiponectin as a novel determinant of bone mineral density and visceral fat. *Bone* 33(4), 646–651 (2003).
73. Krolner B, Ranlov P, Clemmese T *et al.*: Bone loss after gastroplasty for morbid obesity: side effect or adaptive response to weight reduction? *Lancet* 1, 956–957 (1982).
74. Hyldstrup L, Anderson T, McNair L, Breum L, Transbol I: Bone metabolism in obesity: changes related to severe overweight and dietary reduction. *Acta Endocrinol.* 129(5), 393–389 (1993).
75. Tothill P, Hannan WJ, Cowen S, Freeman CP: Anomalies in the measurements of changes in total bone mineral by dual x-ray absorptiometry during weight change. *J. Bone Miner. Res.* 12(11), 1908–1921 (1997).
76. Binkley N, Krueger D, Cowgill CS *et al.*: Assay variation confounds the diagnosis of hypovitaminosis D: a call for standardization. *J. Clin. Endocrinol. Metab.* 89(7), 3152–3157 (2004).
77. Chesney R: Rickets: An old form for a new century. *Pediatr. Int.* 43(5), 509–511 (2003).
- **Highlights resurgence of rickets.**
78. Vieth R, Chan PC, MacFarlane GD: Efficacy and safety of D3 intake exceeding the lowest observed adverse effect level. *Am. J. Clin. Nutr.* 73, 288–294 (2001).