Turk J Endocrinol Metab. 2020;24:115-121

Serum 25(OH) Vitamin D Levels in Severely Obese Patients Evaluated Before Bariatric Surgery

Bariatrik Cerrahi Öncesi Değerlendirilen Ciddi Obezitesi Olan Hastalarda Serum 25(OH) Vitamin D Seviyeleri

Hatice Gizem GÜNHAN, Meliha Melin UYGUR*, Eren İMRE*, Onur ELBASAN*, Dilek GOGAS YAVUZ*

Marmara University Pendik Training and Research Hospital, Clinic of Internal Medicine, İstanbul, TURKEY
*Marmara University Faculty of Medicine, Department of Endocrinology and Metabolism İstanbul, TURKEY

Abstract

Objective: Obesity is a risk factor for vitamin D deficiency, which is reported to be detected differently in each population. This study aimed to evaluate the 25(OH) vitamin D (25(OH)D) levels, intact parathormone (iPTH) levels, and their relationship with body mass index (BMI) in obese patients, screened prior to bariatric surgery. **Material and Methods:** This retrospective study comprised of 1.082 obese patients (41±10 years, female/male: 823/259) who were candidates for bariatric surgery. BMI, waist circumference (WC), serum 25(OH)D, iPTH, calcium, phosphorus values of these patients were recorded from patient files. **Results:** BMI, WC, iPTH, and 25(OH)D levels were 48±8.9 kg/m², 128±11.9 cm, 64±36 pg/mL, and 15±18 ng/mL, respectively. Mean 25(OH)D level of 79.1% of the patients belonged to the deficiency range. Very low 25(OH) vitamin D levels (<10 ng/mL) were witnessed among 40.9% (443/1.082) of the study group. Female obese subjects possessed significantly lower serum 25(OH)D levels as compared to male obese patients. Significant negative correlations were perceived between 25(OH)D levels and iPTH (r=-0.34, p<0.0001), BMI (r=-0.20, p<0.0001), and waist circumferences (r=-0.14, p=0.002) in the whole group. Multivariate analysis indicated that BMI to be an independent risk factor for vitamin D deficiency. **Conclusion:** A high rate of vitamin D deficiency was documented in our morbidly obese patients who were candidates for bariatric surgery. BMI is a determinant of 25(OH)D levels. It is essential to screen for vitamin D deficiency and possible osteomalacia among the candidates for bariatric surgery of obese patients and should be treated appropriately before bariatric surgery.

Keywords: Obesity; vitamin D; bariatric surgery; vitamin D deficiency

Özet

Amaç: Obezite, her popülasyonda farklı sıklıkta saptandığı bildirilen vitamin D eksikliği için bir risk faktörüdür. Bu çalışmada, bariatrik cerrahi öncesi değerlendirilen obez hastalarda 25(OH) vitamin D (25(OH)D) düzeyleri, intakt parathormon (iPTH) düzeyleri ve bunların beden kitle indeksi (BKİ) ile ilişkilerinin değerlendirilmesi amaçlanmıştır. **Gereç ve Yöntemler:** Bariatrik cerrahi öncesinde değerlendirilen 1.082 morbid obez hasta (41±10 yaş, kadın/erkek: 823/259) verileri retrospektif olarak değerlendirildi. BKİ, bel çevresi (BÇ), serum 25(OH)D, iPTH, kalsiyum, fosfor değerleri hastaların dosyalarından kaydedildi. **Bulgular:** BKİ, BÇ, iPTH, 25(OH)D düzeyleri sırasıyla 48±8,9 kg/m², 128±11,9 cm, 64±36 pg/mL, 15±18 ng/mL idi. Ortalama 25(OH)D düzeylerinin, hastaların %79,1'inde yetersiz olduğu tespit edilmiştir. Çalışma grubundaki tüm hastaların %40,9'unda (443/1.082) çok düşük 25(OH)D vitamini seviyesi (<10 ng/mL) vardı. Obez kadınlarda 25(OH)D vitamin düzeyleri, obez erkeklere kıyasla anlamlı olarak düşük bulunmuştur. 25(OH)D vitamin düzeyleri iPTH ile ters orantılı izlenmiştir (r=-0,34, p<0,0001), tüm grupta 25(OH)D vitamin düzeyleri BKİ ve BÇ ile negatif korelasyon göstermiştir (r=-0,20, p<0,0001) (r=-0,14, p=0,002). Multivaryant analiz, BKİ'nin D vitamini eksikliği için bağımsız bir risk faktörü olduğunu göstermektedir. **Sonuç:** Bariatrik cerrahi için aday olan morbid obez hastalarımızda yüksek oranda D vitamini eksikliği gözlemledik. BKİ, 25(OH)D seviyelerinin belirleyicisidir. BKİ ile 25(OH)D vitamin düzeyleri negatif korelasyon göstermektedir. Bariatrik cerrahiye aday olan obez hastalar, D vitamini eksikliği ve olası osteomalazi açısından değerlendirilmeli ve bariatrik cerrahi öncesi uygun şekilde tedavi edilmelidir.

Anahtar kelimeler: Obezite; vitamin D; bariatrik cerrahi; vitamin D eksikliği

Address for Correspondence: Hatice Gizem GÜNHAN, Marmara University Pendik Training and Research Hospital, Clinic of Internal Medicine, İstanbul, TURKEY
Phone: +90 216 625 45 45 **E-mail:** drgizemgunhan@gmail.com

Peer review under responsibility of Turkish Journal of Endocrinology and Metabolism.

Received: 08 Oct 2019 **Received in revised form:** 29 Feb 2020 **Accepted:** 13 Apr 2020 **Available online:** 29 Apr 2020

DOI: 10.25179/tjem.2019-71778

Introduction

Vitamin D deficiency is a global epidemic, increasing at an alarming rate in both sunny and less sunny countries (1). Obesity, another epidemic disease, is known to be a risk factor for vitamin D deficiency (2). A strong relationship between obesity and vitamin D deficiency is well documented (2). Vitamin D deficiency, commonly seen with obesity, indicates the correlation between adipose tissue and vitamin D deficiency. However, the reasons for the relationship between obesity and low 25-hydroxyvitamin D [25(OH)D] levels have not been fully explained (3). The risk factors in obese people were predicted to be reduced outdoor activity, decreased sunlight exposure, and consuming food containing less vitamin D (3). A hypothesis suggested that vitamin D, being a fat-soluble molecule, could be sequestered in body fat, thereby lowering its bioavailability in case of obesity (4). Another hypothesis opined a large amount of dilution in adipose tissue might contribute to vitamin D deficiency in obese people. A small group of obese and non-obese women has confirmed this proposition (5).

Research among various populations has proved the relation of low serum vitamin D levels with high body mass index values (6-8). The information on the serum 25(OH) vitamin D levels before bariatric surgery in Turkey is limited. In a cross-sectional study about vitamin D status among adults reported from Turkey, 69% of the patients with BMI>30 kg/m^2 were found to be suffering from vitamin D deficiency (9).

The most effective treatment method for morbidly obese patients, bariatric surgery is associated with malabsorption of nutrients and vitamins (10,11). As the risk of vitamin D deficiency also increases after bariatric surgery, 25(OH)D levels were measured for the obese patients who were referred to our clinic for obesity surgery. Preoperatively low vitamin D levels have been demonstrated as an independent risk factor of vitamin D deficiency in the postoperative period.

This retrospective study aimed to evaluate 25(OH)D levels, iPTH, and their association with body mass index (BMI) in severely obese patients who were candidates for bariatric surgery and determined the frequency of vitamin D deficiency and secondary hyperparathyroidism related to vitamin D deficiency. We also aimed to explore the risk factors accompanying vitamin D deficiency in this population.

Material and Methods

Patient Selection

This retrospective study population included 1082 obese patients who were evaluated for bariatric surgery between 2016-2018 years in Marmara University Pendik Hospital endocrinology polyclinic.

Exclusion criteria for the present study were patients with renal insufficiency (creatinine >1.5 mg/dL) or hepatic disease, systemic inflammatory diseases, malignancy, and who use medicine affecting vitamin D metabolism. The study was approved by the Marmara University School of Medicine's local ethics committee (09.2019.877).

Demographic and laboratory data were recorded from patients' files.

BMI was calculated by the weight of the patients in kilograms divided by the square of their height in meters. BMI was classified according to World Health Organization's criteria as BMI 30-34.9 kg/m^2 is class I obesity, BMI 35-39.9 kg/m^2 is class II obesity, BMI≥40 kg/m^2 is class III (extreme) obesity (12).

Waist circumference (WC) was measured from the midpoint of the distance between arcus costarum and superior iliac crest (12).

Biochemical Parameters

Serum 25(OH)D concentrations were measured with high-performance liquid chromatography method (Recipe Chemicals, Germany). According to Endocrine Society, 2011 guidelines, vitamin D deficiency was defined as a 25(OH)D below 20 ng/mL, vitamin D insufficiency as a 25(OH)D of 21-29 ng/mL (13). The determination of iPTH was made by using immunochemiluminescence assay (Modular Analytics E170; Roche Diagnostics, Germany). The upper limit in the case of normal serum PTH was 72 pg/mL. Serum phosphorus and calcium levels were measured with an enzymatic colorimetric assay method (Roche Diagnostics, Germany).

Statistical Analysis

All the statistical analyses were made using SPSS (Statistical Package for the Social Sciences) version 20.0. Descriptive data was stated as frequencies (%) for categorical data, means, and standard deviations (SD) for continuous data with a normal distribution. A comparison of one group with another was made with Student's t-test. We used Spearman's correlations for nonparametric values and two-tailed probability values to predict the strength of the relationship between variables.

A stepwise multivariate analysis was performed to determine clinical parameters that were risk factors for serum 25(OH) vitamin D levels. Age, BMI, and WC were included in the model as independent variables. The statistical significance level was accepted as $p<0.05$. All of the results were stated as mean±SD.

Results

The demographic characteristics and biochemical results of the study groups according to gender were illustrated in Table 1. Mean BMI was calculated as 48±8.9 kg/m^2 in the whole group. Patients were divided according to the obesity classification: 18 (1.66%) patients belonged to class I, 132 (12.2%) patients belonged to class II, whereas, 932 (86.1%) patients were considered as extreme obesity. Statistical analysis showed an insignificant difference between the BMI of male and female groups.

Mean serum 25(OH)D level was 15±18 ng/mL, belonged to the deficiency range. In the entire study population, 25(OH)D level ≥30 ng/mL was observed in 6.9% (n:75) of the patients, while the remaining 93.1% (n:1007) were in the range of vitamin D deficiency or insufficiency.

Vitamin D insufficiency frequency was 14% (n:151), deficiency frequency was 79.1% (n:856) in the whole study group. 25(OH)D levels less than 10 ng/mL were recorded among 40.9% of the patients (n:443), which was considered to be a severe vitamin D deficiency state (Figure 1).

In female patients, 25(OH) vitamin D levels were lower (13±85 ng/mL) compared to the male patients (17±12 ng/mL) significantly ($p=0.0002$).

According to obesity classification, serum 25(OH) vitamin D levels were 14.0±9.1 ng/mL, 21.1±13.7 ng/mL, and 10.9±9.1 ng/mL in extremely obese, class II, and class I obese patients, respectively. 25(OH) vitamin D level was significantly ($p<0.001$) lower in extremely obese patients than class II obese patients.

There were negative correlations between serum 25(OH) vitamin D levels and BMI ($r=-0.20$, $p<0.0001$), waist circumference ($r=-0.14$, $p=0.002$), and serum iPTH ($r=-0.34$, $p<0.0001$) (Figure 2).

Patients were classified into three groups according to 25(OH)D levels: 25(OH)D<20 ng/mL in group 1, 20-29 ng/mL in group 2 and 30-88 ng/mL in group 3. Clinical and laboratory parameters compared between the groups were represented in Table 2.

A model of stepwise multivariate analysis elucidated age, gender, WC, and BMI as variables and risk factors for serum 25(OH)D levels. This model ($r^2=2.19\%$, $p=0.0022$) demonstrated the significant contribution ($p=0.02$) of BMI as an independent risk factor for serum 25(OH)D levels in obese patients.

Serum iPTH, calcium, and phosphorus mean values were normal, and there were no differences between female and male subjects.

Table 1. Demographic and laboratory results of the patients in the study group.

	Total group (n:1082)	Female (n:823)	Male (n:259)	p (female vs male)
Age (years)	41±10	41±11	41±10	0.65
BMI (kg/m^2)	48±8.9	49±9	47±8.5	0.0562
Waist circumference (cm)	128±11.9	128±12.6	135±9.9	<0.0001
25(OH)D (ng/mL)	15±18	13±8.5	17±12	0.0002
iPTH (pg/mL)	64±36	65±36	60±33	0.0574
Serum calcium (mg/dL)	9.7±3.9	9.7±4.3	9.5±0.44	0.9781

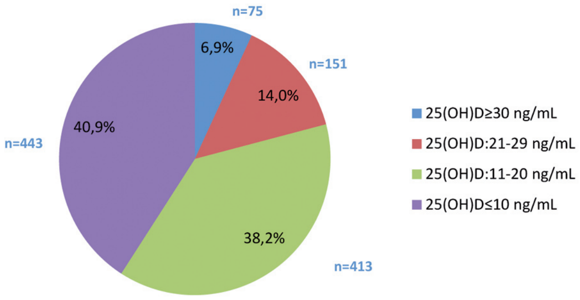
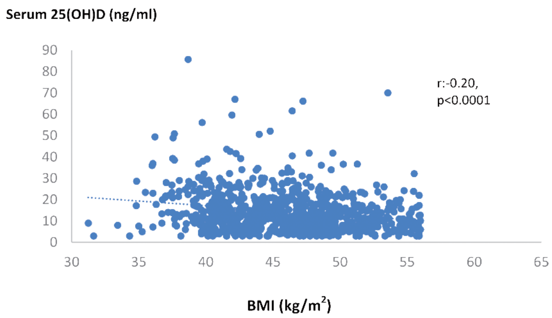


Figure 1: Distribution of serum 25(OH)D levels in the whole study group (n:1082).



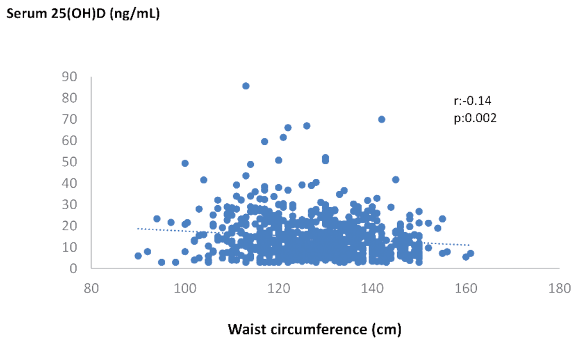


Figure 2: Correlation of serum 25(OH)D with BMI and WC.

Discussion

According to the recent reviews in the literature, this study contains one of the largest subject groups evaluated before bariatric surgery.

One small study was reported incorporating one hundred ninety-nine patients before bariatric surgery in Turkey (14). In this study, it was reported that severe vitamin D deficiency was diagnosed in 47.2% of the patients. The present study documented one of the highest vitamin D deficiency levels in obese patients who were candidates for bariatric surgery. A significant frequency of patients (40,9%) had severe vitamin D deficiency, 25(OH)D level being under 10 ng/mL.

Hypovitaminosis D is prevalent in patients who are candidates for bariatric surgery. It has been reported in 41-98% of preoperative patients (15). Previous studies reported prior to bariatric surgery, deficiency of vitamin D levels was perceived among 55.3% Brazilian obese population (15), 53.6% in Iranian (16), 75.7% Singaporean (17), and 97.5% in Austrian (18) obese patients.

In this study, the multivariate analysis concluded that BMI is an independent risk factor for vitamin D deficiency in obese patients, and we also observed a negative correlation between BMI and serum 25(OH) vitamin D levels, which was in agreement with previous studies. This negative correlation was shown similarly in former studies, and one of the predisposing factors of vitamin D deficiency has been described as obesity. Brock *et al.* showed that (19) high BMI relevant to low vitamin D levels (20-25). Results obtained from various other studies in Turkey had also supported this theory (26-28).

Even though the correlation between obesity and decreased 25(OH) vitamin D concentrations is fully conversant, the mechanisms that explain the relation were yet to be unearthed. Sequestration of 25(OH) vitamin D in adipose tissue coupled with the volumetric dilution of 25(OH) vitamin D in the total body tissue volume may be responsible for low vitamin D levels. Due

Table 2. Clinical and laboratory characteristics of patients according to serum 25(OH)D level.

	Group 1 (25(OH)D<20 ng/mL) (n:776)	Group 2 (25(OH)D 20-29 ng/mL) (n:199)	Group 3 (25(OH)D 30-88 ng/mL) (n:107)	p (group 1 vs group 2 and 3)
Age (years)	41,2±10,2	43±10,4	45,9±11,3	0.78
BMI (kg/m²)	48,6±6,8	45,8±6,9	45,4±7,5	<0.0001
25(OH)D (ng/mL)	10,2±4,4	23,7±2,7	41,3±12,6	<0.0001
iPTH (pg/mL)	67,7±40	55,1±26,4	48,7±28	<0.0001

to limited outdoor exercises of obese individuals, there is less contact with sunlight, which leads to less vitamin D synthesis from the skin, which may be another possible reason. It is presumed that both 1-α hydroxylation and 25-hydroxylation disorders, alterations in the binding of vitamin D to proteins, and increased metabolic clearance of 25(OH) vitamin D may be due to the mechanisms that cause low vitamin D (29). Further research is required on this subject. In our study, vitamin D levels were lower in female patients than in male patients. Though there was no information regarding the lifestyle of the patients, we assume that women spend more time in the house compared to men, and women's clothing habits may be responsible for this.

Guidelines strongly suggest it is essential to keep vitamin D levels in normal ranges to protect bone and muscle strength (13). Vitamin D and other vitamin deficiencies are frequent due to malabsorption after bariatric surgery, which may be associated with increased muscle weakness and increased risk of fractures (30). Vitamin D deficiency is known to be associated with muscle dysfunction, increased risk of diabetes mellitus, cardiovascular disease, multiple sclerosis, and cancer (31-40). Based on all this, it can be claimed that the restoration of vitamin D levels in the normal range can help to reduce the metabolic load.

There is limited data on vitamin D deficiency frequencies in obese patients who are candidates for bariatric surgery in Turkey. High rates of vitamin D deficiency were determined in our study, and this is the largest cohort to be published about Turkish patients before bariatric surgery.

There were some limitations of our study; the data were collected retrospectively, the information on contact time with sunlight and nutrients intake was not analyzed. Moreover, there was no comparison with non-obese controls.

Preoperative vitamin D deficiency may stimulate or aggravate postoperative vitamin D deficiency. Considering that deficiency of vitamin D is common in obese patients in Turkey, estimation of the levels of 25(OH) vitamin D can be recommended, and deficiency state must be treated appropriately before bariatric surgery (41).

Conclusion

We found that vitamin D deficiency was very high among obese patients who were candidates for bariatric surgery in our center. BMI is an independent risk factor for vitamin D deficiency in obese patients. Supplementation of vitamin D should be considered in all obese patients and candidates for bariatric surgery.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authors Contributions

Idea/Concept: Dilek Gogas Yavuz; Control/Supervision: Dilek Gogas Yavuz; Data Collection and/or Processing: Hatice Gizem Günhan, Meliha Melin Uygur, Eren İmre, Onur Elbasan,; Analysis and/or Intepretation: Dilek Gogas Yavuz, Hatice Gizem Günhan; Literature Review: Hatice Gizem Günhan, Dilek Gogas Yavuz; Writing the Article: Hatice Gizem Günhan, Dilek Gogas Yavuz; Critical Reviewing: Dilek Gogas Yavuz.

References

1. Binkley N, Ramamurthy R, Krueger D. Low vitamin D status: definition, prevalence, consequences, and correction. Endocrinol Metab Clin North Am. 2010;39:287-301. [Crossref] [PubMed] [PMC]
2. Pereira-Santos M, Costa PRF, Assis AMO, Santos CAST, Santos DB. Obesity and vitamin D deficiency: a systematic review and metaanalysis. Obes Rev. 2015;16:341-349. [Crossref] [PubMed]
3. Migliaccio S, Di Nisio A, Mele C, Scappaticcio L, Savastano S, Colao A; Obesity Programs of nutrition, Education, Research and Assessment (OPERA) Group. Obesity and hypovitaminosis D: causality or casualty? Int J Obes Suppl. 2019;9:20-31. [Crossref] [PubMed] [PMC]
4. Need AG, Morris HA, Horowitz M, Nordin C. Effects of skin thickness, age, body fat, and sunlight on serum 25-hydroxyvitamin D. Am J Clin Nutr. 1993;58:882-885. [Crossref] [PubMed]

5. Carrelli A, Bucovsky M, Horst R, Cremers S, Zhang C, Bessler M, Schrope B, Evanko J, Blanco Silverberg SJ, Stein EM. Vitamin D storage in adipose tissue of obese and normal weight women. J Bone Miner Res. 2016;32:237-242. [Crossref] [PubMed] [PMC]
6. Liu S, Song Y, Ford ES, Manson JE, Buring JE, Ridker PM. Dietary calcium, vitamin D and the prevalence of metabolic syndrome in middle-aged and older U.S. women. Diabetes Care. 2005;28:2926-2932. [Crossref] [PubMed]
7. Savastano S, Barrea L, Savanelli MC, Nappi F, Di Somma C, Orio F, Colao A. Low vitamin D status and obesity: role of nutritionist. Rev Endocr Metab Disord. 2017;18:215-225. [Crossref] [PubMed]
8. Vimaleswaran KS, Berry DJ, Lu C, Tikkanen E, Pilz S, Hiraki LT, Cooper JD, Dastani Z, Li R, Houston DK, Wood AR, Michaëlsson K, Vandenput L, Zgaga L, Yerges-Armstrong LM, McCarthy MI, Dupuis J, Kaakinen M, Kleber ME, Jameson K, Arden N, Raitakari O, Viikari J, Lohman KK, Ferrucci L, Melhus H, Ingelsson E, Byberg L, Lind L, Lorentzon M, Salomaa V, Campbell H, Dunlop M, Mitchell BD, Herzig KH, Pouta A, Hartikainen AL, Genetic Investigation of Anthropometric Traits-GIANT Consortium; Streeten EA, Theodoratou E, Jula A, Wareham NJ, Ohlsson C, Frayling TM, Kritchevsky SB, Spector TD, Richards JB, Lehtimäki T, Ouwehand WH, Kraft P, Cooper C, März W, Power C, Loos RJF, Wang TJ, Järvelin MR, Whittaker JC, Hingorani AD, Hyppönen E. Causal relationship between obesity and vitamin D status: bi-directional Mendelian randomization analysis of multiple cohorts. PLoS Med. 2013;10:e100138. [PubMed]
9. Hekimsoy Z, Dinç G, Kafesçiler S, Onur E, Güvenç Y, Pala T, Güçlü F, Ozmen B. Vitamin D status among adults in the Aegean region of Turkey. BMC Public Health. 2010;10:782. [Crossref] [PubMed] [PMC]
10. Bal BS, Finelli FC, Shope TR, Koch TR. Nutritional deficiencies after bariatric surgery. Nat Rev Endocrinol. 2012;8:544-556. [Crossref] [PubMed]
11. Ziegler O, Sirveaux MA, Brunaud L, Reibel N, Quilliot D. Medical follow up after bariatric surgery: nutritional and drug issues. General recommendations for the prevention and treatment of nutritional deficiencies. Diabetes Metab. 2009;35:544-557. [Crossref] [PubMed]
12. Yumuk V, Tsigos C, Fried M, Schindler K, Busetto L, Micic D, Toplak H; Obesity Management Task Force of the European Association for the Study of Obesity. European guidelines for obesity management in adults. Obes Facts. 2015;8:402-424. [Crossref] [PubMed] [PMC]
13. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, Murad MH, Weaver CM; Endocrine Society. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab. 2011;96:1911-1930. [Crossref] [PubMed]
14. Topaloğlu O, Evren B, Yoloğlu S, Şahin Ş, Sahin İ. The frequency of vitamin D deficiency in obese patients on bariatric surgery wait list: is there any association with co-existence of prediabetes or diabetes? Turk J Endocrinol Metab. 2019;23:229-239. [Crossref]
15. Vivan MA, Kops NL, Fülber ER, de Souza AC, Fleuri MASB, Friedman R. Prevalence of vitamin D depletion, and associated factors, among patients undergoing bariatric surgery in Southern Brazil. Obes Surg. 2019;29:3179-3187. [Crossref] [PubMed]
16. Asghari G, Khalaj A, Ghadimi M, Mahdavi M, Farhadnejad H, Valizadeh M, Azizi F, Barzin M, Hosseinpanah F. Prevalence of micronutrient deficiencies prior to bariatric surgery: Tehran Obesity Treatment Study (TOTS). Obes Surg. 2018;28:2465-2472. [Crossref] [PubMed]
17. Ong MW, Tan CH, Cheng AKS. Prevalence and determinants of vitamin D deficiency among the overweight and obese Singaporeans seeking weight management including bariatric surgery: a relationship with bone health. Obes Surg. 2018;28:2305-2312. [Crossref] [PubMed]
18. Krzizek EC, Brix JM, Herz CT, Kopp HP, Schernthaner GH, Schernthaner G, Ludvik B. Prevalence of micronutrient deficiency in patients with morbid obesity before bariatric surgery. Obes Surg. 2018;283:643-648. [Crossref] [PubMed]
19. Brock K, Huang WY, Fraser R, Ke L, Tseng M, Stolzenberg-Solomon R, Peters U, Ahn J, Purdue M, McCarty C, Ziegler RG, Graubard B. Low vitamin D status is associated with physical inactivity, obesity and low vitamin D intake in a large us sample of healthy middle-aged men and women. J Steroid Biochem Mol Biol. 2010;121:462-466. [Crossref] [PubMed] [PMC]
20. Giovannucci E, Liu Y, Rimm EB, Hollis BW, Fuchs CS, Stampfer MJ, Willett WC. Prospective study of predictors of vitamin D status and cancer incidence and mortality in men. J Natl Cancer Inst. 2006;98:451-459. [Crossref] [PubMed]
21. Freedman DM, Chang SC, Falk RT, Purdue MP, Huang WY, McCarty CA, Hollis BW, Graubard BI, Ziegler RG. Serum levels of vitamin D metabolites and breast cancer risk in the prostate, lung, colorectal, and ovarian cancer screening trial. Cancer Epidemiol Biomarkers Prev. 2008;17:889-894. [Crossref] [PubMed] [PMC]
22. World Health Organization International Agency for Research on Cancer. IARC Working Group Reports Volume 5. Vitamin D and Cancer. Lyon, France: WHO Press; 2008:201.
23. Scragg R, Camargo Jr CA. Frequency of leisure-time physical activity and serum 25- hydroxyvitamin D levels in the US population: results from the Third National Health and Nutrition Examination Survey. Am J Epidemiol. 2008;168:577-586. [Crossref] [PubMed] [PMC]
24. Burgaz A, Akesson A, Oster A, Michaëlsson K, Wolk A. Associations of diet, supplement use, and ultraviolet B radiation exposure with vitamin D status in Swedish women during winter. Am J Clin Nutr. 2007;86:1399-1404. [Crossref] [PubMed]
25. Abbas S, Linseisen J, Slanger T, Kropp S, Mutschelknauss EJ, Flesch-Janys D, Chang-Claude J. Serum 25-hydroxyvitamin D and risk of post-menopausal breast cancer--results of a large case-control study. Carcinogenesis. 2008;29:93-99. [Crossref] [PubMed]
26. Tosunbayraktar G, Bas M, Kut A, Hasbay Buyukkaragoz A. Low serum 25(OH)D levels are associated to higher BMI and metabolic syndrome parameters in adult subjects in Turkey. Afr Health Sciences. 2016;15:1162-1169. [Crossref] [PubMed] [PMC]

27. Ozata M, Durmus O, Yilmaz MI, Bolu E, Erdogan M, Ozdemir IC. The renin-angiotensin-aldosterone system (RAAS) and its relation with calcium homeostasis in male obesity. Med Sci Monit. 2002;8:CR430-434. [PubMed]
28. Yildizhan R, Kurdoglu M, Adali E, Kolusari A, Yildizhan B, Sahin HG, Kamaci M. Serum 25-hydroxyvitamin D concentrations in obese and non-obese women with polycystic ovary syndrome. Arch Gynecol Obstet. 2009;280:559-563. [Crossref] [PubMed]
29. Vanlint S. Vitamin D and obesity. Nutrients. 2013;5:949-956. [Crossref] [PubMed] [PMC]
30. Corbeels K, Verlinden L, Lannoo M, Simoens C, Matthys C, Verstuyf A, Meulemans A, Carmeliet G, Van der Schueren B. Thin bones: vitamin D and calcium handling after bariatric surgery. Bone Rep. 2018;8:57-63. [Crossref] [PubMed] [PMC]
31. Plotnikoff GA, Quigley JM. Prevalence of severe hypovitaminosis D in patients with persistent, non-specific musculoskeletal pain. Mayo Clin Proc. 2003;78:1463-1470. [Crossref] [PubMed]
32. Glerup H, Mikkelsen K, Poulsen L, Hass E, Overbeck S, Andersen H, Charles P, Eriksen EF. Hypovitaminosis D myopathy without biochemical signs of osteomalacic bone involvement. Calcif Tissue Int. 2000;66:419-424. [Crossref] [PubMed]
33. Bischoff-Ferrari HA, Dietrich T, Orav EJ, Hu FB, Zhang Y, Karlson EW, Dawson-Hughes B. Higher 25-hydroxyvitamin D concentrations are associated with better lower-extremity function in both active and inactive persons aged>or =60 y. Am J Clin Nutr. 2004;80:752-758. [Crossref] [PubMed]
34. Visser M, Deeg DJ, Lips P; Longitudinal Aging Study Amsterdam Low vitamin D and high parathyroid hormone levels as determinants of loss of muscle strength and muscle mass (sarcopenia): the longitudinal aging study Amsterdam. J Clin Endocrinol Metab. 2003;88:5766-5772. [Crossref] [PubMed]
35. Wicherts IS, van Schoor NM, Boeke AJ, Visser M, Deeg DJH, Smit J, Knol DL, Lips P. Vitamin D status predicts physical performance and its decline in older persons. J Clin Endocrinol Metab. 2007;92:2058-2065. [Crossref] [PubMed]
36. World Health Organization International Agency for Research on Cancer. IARC Working Group Reports Volume 5. Vitamin D and Cancer. Lyon, France: WHO Press; 2008.
37. Mokry LE, Ross S, Ahmad OS, Forgetta V, Smith GD, Goltzman D, Leong A, Greenwood CMT, Thanassoulis G, Richards JB. Vitamin D and risk of multiple sclerosis: a Mendelian randomization study. PLoS Med. 2015;12:e1001866. [Crossref] [PubMed] [PMC]
38. Rhead B, Bäärnhielm M, Gianfrancesco M, Mok A, Shao X, Quach H, Shen L, Schaefer C, Link J, Gyllenberg A, Hedström AK, Olsson T, Hillert J, Kockum I, Glymour MM, Alfredsson L, Barcellos LF. Mendelian randomization shows a causal effect of low vitamin D on multiple sclerosis risk. Neurol Genet. 2016;2:e97. [Crossref] [PubMed] [PMC]
39. Wang L, Song Y, Manson JE, Pilz S, März W, Michaëlsson K, Lundqvist A, Jassal SK, Barrett-Connor E, Zhang C, Eaton CB, May HT, Anderson JL, Sesso HD. Circulating 25-hydroxy-vitamin D and risk of cardiovascular disease: a meta-analysis of prospective studies. Circ Cardiovasc Qual Outcomes. 2012;5:819-829. [Crossref] [PubMed] [PMC]
40. Takiishi T, Gysemans C, Bouillon R, Mathieu C. Vitamin D and diabetes. Endocrinol Metab Clin North Am. 2010;39:419-446. [Crossref] [PubMed]
41. Aills L, Blankenship J, Buffington C, Furtado M, Parrott J; Allied Health Sciences Section Ad Hoc Nutrition Committee. ASMBS Allied Health Nutritional Guidelines for the Surgical Weight Loss Patient. Surg Obes Related Dis. 2008;4:S73-S108. [Crossref] [PubMed]