



Nutritional Deficiencies in Severe Obesity: a Multiethnic Asian Cohort

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Abstract

Background Micronutrient deficiencies are highly prevalent in patients seeking metabolic-bariatric surgery (MBS), although literature remains scant in Asia. In this study, we assess the prevalence of nutritional deficiencies in patients with clinically severe obesity in Singapore and examine factors associated with the deficiencies.

Methods This is a prospective, observational study of 577 consecutive patients scheduled to undergo MBS. Nutritional profile including renal panel, calcium, phosphate, intact parathyroid hormone (iPTH), 25-hydroxyvitamin D (25(OH)D), vitamin B12, folate, ferritin, iron studies, hemoglobin, albumin, and alkaline phosphatase were analyzed.

Results Mean age was 40.6 ± 10.3 years, 61.2% female, and mean BMI 42.4 ± 8.4 kg/m². 92.9% had suboptimal vitamin D levels; of which 25.6% had vitamin D insufficiency (25(OH)D < 30 mcg/L), 57.5% had vitamin D deficiency (25(OH)D < 20 mcg/L), and 9.8% had severe vitamin D deficiency (25(OH)D < 10 mcg/L). Younger age, female gender, and higher BMI were independent factors associated with lower 25(OH)D. There was an inverse relationship between iPTH and 25(OH)D, with an inflection point at 25(OH)D of approximately 20 mcg/L.

Folate deficiency was present in 31% and vitamin B12 deficiency in 9.5% of the cohort. Serum ferritin levels were low in 29.3%. 25(OH)D, ferritin, serum iron, and albumin were also significantly higher in Chinese compared to Malay and Indian patients.

Conclusion Vitamin D deficiency was the most common micronutrient deficiency observed in this multi-ethnic Asian cohort presenting for MBS. Ethnic differences in nutritional status were observed.

Keywords Nutritional deficiencies · Obesity · Bariatric surgery · Vitamin D deficiency · Parathyroid hormone

Introduction

Obesity is a major public health challenge with established health risks. Although incidence of obesity appeared to have stabilized in some high-income Western countries, obesity prevalence rates continue to rise at an alarming rate in the

developing world, including many parts of Asia [1]. Among the high income English-speaking countries, rates of severe obesity, as defined by body mass index (BMI) ≥ 35 kg/m², continue to rise [1].

Paradoxically, nutritional deficiencies are often observed in patients with clinically severe obesity despite ample energy excess [2]. High prevalence of micronutrient deficiencies have been reported in patients seeking metabolic-bariatric surgery (MBS), with common deficiencies being iron, vitamin B₁₂, folate, and vitamin D [3–6]. Appropriate preoperative nutritional assessment allows for deficiencies to be detected and corrected prior to surgery.

Although prevalence of nutritional deficiencies have been widely reported in Western countries, literature remains scant in the Asian setting, with one study showing that electrolyte and nutritional deficiencies are common in Chinese patients seeking MBS [7]. This concern is particularly relevant as China and India, the two most populous countries in the world, had the highest numbers of obese children in 2015 [8], and the epicenter of the obesity-diabetes pandemic appears to have shifted to Asia

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[9], with the rate of MBS in Asia having increased by over fourfold from 2004 to 2009 [10]. Singapore has a multiethnic Asian society consisting of three main ethnic groups: Chinese, Malays, and Indians. The cultural background and traditional diets of the various ethnicities differ significantly, although they live under relatively similar environmental conditions. The diverse cultural and ethnic mix within the city-state allows an exciting opportunity to study potential ethnic differences in the prevalence of micronutrient deficiencies in a cohort with clinically severe obesity.

The primary aim of this study was to assess the prevalence of nutritional deficiencies in MBS patients with clinically severe obesity in a multi-ethnic Asian cohort who live in Singapore. Secondary aims of the study included examination of the differences in micronutrient deficiencies between the various ethnic groups and exploration of factors that were associated with the deficiencies.

Methods

In this observational study, data were extracted from a prospective detailed bariatric surgery database in a tertiary hospital in Singapore. The study cohort consisted of consecutive patients with clinically severe obesity that were scheduled to undergo primary sleeve gastrectomy (SG) or gastric bypass (GB) from September 2008 to November 2017. These

patients' demographics, full nutritional and metabolic profile are systematically collected in a web-based data repository (REDCAP) [11]. The study was approved by our hospital's Institutional Review Board.

Baseline laboratory investigations were performed in the fasted state prior to surgery. The blood tests include renal panel, calcium, phosphate, intact parathyroid hormone (iPTH), 25-hydroxyvitamin D (25(OH)D), vitamin B12, folate, ferritin, iron studies, hemoglobin, albumin, and alkaline phosphatase.

Statistical Plan

Variables were extracted, explored, and presented as frequency (%) for categorical data, whereas continuous data were presented as either mean (S.D.) for parametric distribution or median (interquartile range) for non-parametric distribution. One-way ANOVA and Pearson χ^2 test were used where appropriate, to compare baseline characteristics between the ethnicities. All analyses were performed using SPSS software (version 21; IBM Corporation, Armonk, NY).

Results

A total of 577 patients were included in the study. Mean age was 40.6 ± 10.3 years (range 18–66), with 61.2% being female. Ethnic composition of the cohort consists primarily of

Table 1 Demographics and characteristics of population and ethnic subgroups

| Patient characteristics | Total (n = 577) | Chinese (n = 234) | Malay (n = 167) | Indian (n = 143) | p value* |
|--|--------------------|----------------------|--------------------|---------------------|----------|
| Age, years | 40.6 (10.3) | 40.4 (10.8) | 41.0 (9.8) | 40.5 (9.8) | 0.943 |
| Gender (% female) ^a | 61.2% | 52.1% | 70.1% | 70.6% | < 0.001 |
| Ethnicity (n, %) | | | | | |
| Chinese | 234 (40.6%) | | | | |
| Malay | 167 (28.9%) | | | | |
| Indian | 143 (24.8%) | | | | |
| Others | 33 (5.7%) | | | | |
| BMI, kg/m ^{2a} | 42.4 (8.37) | 40.6 (7.7) | 44.7 (8.1) | 42.0 (8.7) | < 0.001 |
| Systolic blood pressure, mmHg | 129 (15) | 129 (15) | 130 (15) | 127 (16) | 0.067 |
| Diastolic blood pressure, mmHg | 81 (11) | 80 (11) | 80 (11) | 81 (11) | 0.818 |
| Glycemic status (%) | | | | | 0.328 |
| Normal | 43.9 | 39.9 | 48.4 | 41.4 | |
| Pre-diabetes | 15.3 | 15.4 | 15.5 | 16.4 | |
| Type 2 diabetes | 40.8 | 44.7 | 36.0 | 42.1 | |
| % with hypertension | 56.9 | 64.0 | 53.8 | 49.6 | 0.136 |
| % with dyslipidemia | 38.6 | 42.7 | 39.8 | 31.7 | 0.188 |
| % with liver imaging | 52.3 | 52.2 | 52.2 | 52.2 | 0.994 |
| % with fatty liver (of those with imaging) | 95.2 | 94.1 | 97.6 | 93.1 | 0.404 |

Data presented as mean (S.D.) or median (IQR) unless otherwise stated

*p value calculated using one-way ANOVA (for continuous variables) or chi-square test (for categorical variables)

^a Denotes significant differences between the groups ($p < 0.05$)

Chinese (40.6%), Malay (28.9%), and Indian (24.8%), with other ethnicities representing only 5.7%. Baseline weight was 108.3 kg with mean BMI 42.4 kg/m² (S.D 8.4). Mean BMI in the Malay cohort was 44.7 kg/m², significantly higher than the Chinese (mean BMI 40.6 kg/m²) and Indians (mean BMI 42.0 kg/m²) ($p < 0.001$ and $p = 0.023$ respectively) (Table 1).

The biochemical parameters of the study cohort and prevalence of laboratory abnormalities and nutritional deficiencies are summarized in Table 2. The prevalence of vitamin deficiency is very high in the pre-surgical cohort (Table 3). 92.9% had suboptimal vitamin D levels; of which 25.6% had vitamin D insufficiency (25(OH)D < 30 mcg/L), 57.5% had vitamin D deficiency (25(OH)D < 20 mcg/L), and 9.8% had severe vitamin D deficiency (25(OH)D < 10 mcg/L). Correspondingly, raised iPTH levels suggestive of secondary hyperparathyroidism were observed in 34.7% of the cases. Serum alkaline phosphatase, another marker of nutritional bone health and bone turnover, was increased in 11.4% of the patients. Hypocalcemia (2.1%), hypercalcemia (3.5%), and hypophosphatemia (4.7%) were less common. Of the 14 patients with hypercalcemia, 13 had mildly elevated calcium levels (2.47–2.64 mmol/L) with normal iPTH levels. One patient had hyperparathyroidism with serum calcium of 2.88 mmol/L and iPTH of 47.8 pmol/L.

Linear regression has shown that younger age, female gender, and higher BMI were independent factors that were associated

with lower 25(OH) D levels. Patients at lowest BMI quartile (BMI < 37.2 kg/m²) had significantly higher 25(OH)D compared with those at highest BMI quartile (BMI > 46.6 kg/m²), 25(OH)D level 19.8 mcg/L vs. 16.3 mcg/L ($p < 0.001$). There appears to be an inverse relationship between iPTH and 25(OH)D, with an inflection point observed at 25(OH)D level of approximately 20 mcg/L. (Fig. 1) Serum ALP level did not correlate with 25(OH)D or BMI. However, ALP was positively correlated with iPTH ($r = 0.177$, $p = 0.002$), even after adjustment for 25(OH)D and BMI.

Other micronutrient deficiencies were also prevalent, with folate deficiency seen in 31% and vitamin B12 deficiency in 9.5%. Ferritin levels, a marker of iron stores in the body, were low in 29.3% of the cases, low iron levels in 32.7%, and corresponding raised total iron binding capacity in 27.9% of the cohort.

Stratification of the laboratory results by ethnicity revealed significant differences between the three major ethnicities (Table 2). 25(OH)D levels were lower among Indian and Malay patients as compared to Chinese counterparts ($p = 0.001$ and $p = 0.002$ respectively using Tukey's B test). The prevalence of vitamin D deficiency and severe vitamin D deficiency were also higher in Malay and Indian compared to Chinese patients ($p < 0.001$ and $p = 0.007$ respectively) (Table 3). Ferritin, serum iron, and albumin levels were also significantly higher in Chinese compared to Malay and Indian counterparts (Table 2).

Table 2 Prevalence of nutritional deficiencies, stratified by ethnic subgroups

| Biochemical parameter (reference interval) | Total | | | Mean (stratified by ethnicity) | | | <i>p</i> value (one-way ANOVA) |
|--|----------|---------------|------------------------|--------------------------------|-------|--------|-----------------------------------|
| | <i>n</i> | Mean (S.D.) | % deficient/(elevated) | Chinese | Malay | Indian | |
| Calcium (2.09–2.46 mmol/L) | 433 | 2.28 (0.10) | 1.8 | 2.28 | 2.27 | 2.35 | 0.203 |
| Phosphate (0.94–1.40 mmol/L) | 427 | 1.20 (0.18) | 4.9 | 1.18 | 1.22 | 1.22 | 0.065 |
| iPTH (0.9–6.2 pmol/L) | 374 | 5.96 (3.90) | (34.7) | 5.48 | 6.05 | 6.16 | 0.321 |
| 25(OH)D (10.1–40.3 mcg/L) | 449 | 18.1 (7.7) | | 20.4 | 17.0 | 16.7 | < 0.001 ^a |
| Folate (> 13.4 nmol/L) | 388 | 20.5 (11.9) | 31 | 21.8 | 19.2 | 20.4 | 0.228 |
| Vitamin B12 (145–637 pmol/L) | 453 | 272 (118) | 9.5 | 275 | 284 | 252 | 0.080 |
| Ferritin (47–452 mcg/L) | 433 | 112.1 (107.2) | 29.3 | 151.5 | 97.5 | 67.7 | < 0.001 ^b |
| Iron (11–32 μmol/L) | 440 | 13.9 (7.7) | 32.7 | 15.2 | 12.6 | 13.1 | 0.008 ^c |
| Total iron binding capacity (44–73 μmol/L) | 430 | 68 (11) | (27.9) | 66 | 67 | 71 | 0.001 ^d |
| Hemoglobin | | | | | | | |
| Male (14.0–18.0 g/dL) | 193 | 14.7 (1.7) | 23.3 | 14.7 | 14.7 | 14.6 | 0.979 |
| Female (12.0–16.0 g/dL) | 304 | 13.1 (1.1) | 15.8 | 13.4 | 13.1 | 12.7 | 0.001 ^e |
| Albumin (40–51 g/L) | 454 | 39.6 (3.5) | 47.1 | 40.6 | 38.8 | 38.9 | < 0.001 ^f |
| Alkaline phosphatase (39–99 U/L) | 437 | 73.4 (22.0) | (11.4) | 71.4 | 72.5 | 77.9 | 0.108 |

^a 25(OH)D higher in Chinese compared with Malay ($p = 0.001$) or Indian ($p = 0.002$)

^b Ferritin higher in Chinese compared with Malay or Indian ($p < 0.001$ in both cases)

^c Iron higher in Chinese compared with Malay ($p < 0.012$)

^d Total iron binding capacity higher in Indian compared with Chinese ($p = 0.001$) or Malay ($p = 0.005$)

^e Hemoglobin higher in Chinese females compared with Indian females ($p < 0.001$)

^f Albumin higher in Chinese compared with Malay ($p < 0.001$) or Indian ($p = 0.002$)

Table 3 Vitamin D status, stratified by ethnicity

| Vitamin D status | Total | Chinese (<i>n</i> = 178) | Malay (<i>n</i> = 129) | Indian (<i>n</i> = 119) | <i>p</i> value (χ^2 test) |
|--|-------|---------------------------|-------------------------|--------------------------|---------------------------------|
| Severe vitamin D deficiency (25(OH)D < 10 mcg/L) | 9.8% | 3.9% | 12.4% | 14.3% | 0.007 |
| Vitamin D deficiency (25(OH)D < 20 mcg/L) | 67.3% | 53.4% | 76.7% | 77.3% | < 0.001 |
| Vitamin D insufficiency (25(OH)D < 30 mcg/L) | 92.9% | 92.7% | 93.8% | 92.4% | 0.717 |

Discussion

To our knowledge, our study is the largest reported thus far in Asia, which allowed us to examine the ethnic differences in the prevalence of nutritional deficiencies in those with clinically severe obesity. The study findings revealed significant differences in 25(OH)D, ferritin, iron, and albumin levels between the ethnic groups. We have previously reported our T2DM cohort, and showed that there were no significant ethnic differences in glycemic or metabolic outcomes after bariatric surgery [12]. Some of the findings were consistent with other reports in the literature, which also identified higher ferritin levels in Chinese (men 236 and women 92 mcg/l), compared to Indians (men 132 and women 50 mcg/l), and Malays (men 175 and women 85 mcg/l) [13]. The study postulated that the differences in ferritin levels were due to reduced iron intake and binding of non-hem iron to phytates in Indians. Our data also suggest a trend towards lower vitamin B12 in Indians, compared to Malays and Chinese ($p = 0.08$), which is also consistent with a previous study in Singapore [14].

Another recent study examined the effect of ethnicity on 25(OH)D in the cohort of community-dwelling adults in Singapore and found that Malay and Indian ethnicities have lower 25(OH)D levels, compared with Chinese [15]. In the study, several factors were postulated to explain the variation in 25(OH)D levels, including differences in culture, diet, and sun exposure [15]. Similar to our study, factors associated with lower 25(OH)D levels included age ≤ 65 years, female gender, and having higher BMI. Other factors identified to be associated with lower 25(OH)D levels included higher HbA1c and higher levels of education and income [15].

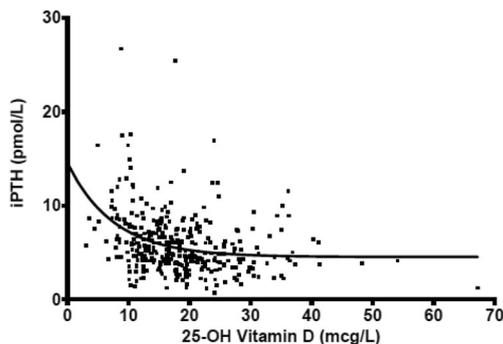


Fig. 1 Relationship between iPTH and 25-OH vitamin D levels

It is well known that clinically severe obesity is associated with vitamin D deficiency and secondary hyperparathyroidism [16]. Aggressive calcium and vitamin D supplementation is needed, although longitudinal studies still show marked bone loss and increase in bone turnover markers after metabolic-bariatric surgery (MBS) [17]. In our study, the prevalence of vitamin D deficiency was very high. Almost all patients had vitamin D insufficiency, more than two-thirds had vitamin D deficiency, and one in ten had severe vitamin D deficiency, with PTH elevation in 34.7%. A recent large study of a Western cohort also reported similar prevalence of vitamin D insufficiency of 97.5% and PTH elevation of 30.3% in individuals wishing to undergo bariatric surgery [6]. This finding has important implications given that the detrimental effect on bone is compounded after bariatric surgery. Although bone densitometry was not routinely performed in our study, bone mineral density appears to be directly correlated with vitamin D and inversely correlated with PTH levels [18]. Given the near-universal prevalence of vitamin D insufficiency, it may be argued that there is a role for routine pre-operative vitamin D supplementation prior to bariatric surgery. However, there is wide variability in the 25(OH)D levels, and the measurement of pre-operative 25(OH)D would still be useful to guide the intensity and duration of vitamin D supplementation and also to gauge response to supplementation.

In the normal-weight population, 25(OH)D levels are inversely associated with iPTH until 25(OH)D reaches 30 to 40 mcg/L, at which point iPTH levels begin to plateau at their nadir [19]. Our study also confirmed the inverse relationships between iPTH and 25(OH)D levels. Interestingly, the inflection point occurred at a lower 25(OH)D level of about 20 mcg/L. This finding is consistent with another large study from China (2588 healthy subjects with mean BMI 22.9 kg/m²) which showed a relatively steep increase in iPTH when 25(OH)D drops below 20 mcg/L. [20] Meanwhile, another study from Singapore involving healthy women showed inverse relationship between iPTH and 25(OH)D, with no threshold of 25(OH)D level at which iPTH plateaued [21]. Hence, it is important to replete vitamin D deficiency at least to a 25(OH)D level of above 20 mcg/L, in order to prevent secondary hyperparathyroidism and subsequent bone loss.

Our study has several limitations. Although the three different ethnic groups live within the same environment, they are culturally diverse, with different traditional diets. Lack of

data on dietary intake meant that we were unable to examine the link between diet and nutritional deficiencies reported in this study. Differences in baseline characteristics (e.g., gender and BMI) between the three ethnic groups may contribute to our study findings. We also did not have data on over-the-counter nutritional supplements, which could potentially also influence our results. Due to the cross-sectional design of our study, the findings only suggest associations, and further cohort studies may shed light on the causative factors that lead to nutritional deficiencies.

Chronic micronutrient deficiencies have detrimental long-term consequences, including nutritional anemias, metabolic bone disease, and neurological complications [22]. Medical insurance claims data from a large Western cohort has shown increased prevalence of iron, vitamin B12, and folate deficiencies after MBS, compared to before surgery [23]. Hence, nutritional monitoring and supplementation is key to reduce the risks of long-term complications after MBS. In our institution's clinical practice, nutritional deficiencies that were identified were replaced orally prior to surgery. The usual supplementation for vitamin D deficiency would be high-dose vitamin D2 (ergocalciferol). Oral iron formulations, folic acid, and vitamin B12 are also supplemented if deficient. The supplementation were continued after surgery, with close follow-up of the nutritional status. The ethnic differences in pre-operative nutritional levels, especially iron and vitamin D status, may have immediate implications in regard to the choice of surgical procedure, postoperative nutritional supplementation, and monitoring. Our data also suggest that the nutritional guidelines concerning MBS may need to be adapted depending on the ethnic group.

Conclusion

High prevalence of vitamin D deficiency associated with secondary hyperparathyroidism was observed in our multi-ethnic Asian cohort presenting for MBS. iPTH levels were negatively correlated with vitamin D at 25(OH)D < 20 mcg/L, a level below which vitamin D repletion should be aggressively undertaken to reduce risk of bone loss postoperatively. Our study provided the unique opportunity to study the prevalence of nutritional deficiencies in severe obesity in the multi-ethnic Asian population that live in the same environment and revealed ethnic differences in nutritional/metabolic status; notably 25(OH)D, ferritin, iron and albumin levels. Future prospective studies are needed to elucidate the factors that influence the nutritional status of this population.

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Compliance with Ethical Standards

Competing Interests The authors declare that they have no competing interests.

Ethical Approval Statement This article does not contain any studies with human participants or animals performed by any of the authors. For this type of study formal consent is not required.

Informed Consent Statement Does not apply.

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