MEDICAL CHANNEL

Original Article

THE ASSOCIATION OF BODY MASS INDEX WITH VITAMIN D STATUS AND PARA-THYROID HORMONE LEVELS IN HEALTHY ADOLESCENTS AND YOUNG ADULTS

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ABSTRACT

Objective: To test the hypothesis whether low levels of serum vitamin D and high levels of parathyroid hormone is associated with elevated BMI.
Material & Methods: This study was carried out in the Department of Biochemistry, BMSI, JPMC, Karachi. Total 90 healthy adolescents and young adults were selected with their consent, after selection they were categorized as non-obese and obese on the basis of their BMI.
Results: The result showed that obese subjects had significantly low levels of 25(OH) vitamin D and higher levels of iPTH (P<0.001) when compared to non-obese subjects. It was found that only 26 subjects were vitamin D sufficient having vitamin D > 30 ng/ml and they have normal BMI level (22.32 kg/m^2). 56 subjects showed vitamin D insufficiency as they have vitamin D concentration 10-30 ng/ml and these subjects categorized as overweight or pre-obese according to their mean BMI level (28.63 kg/m^2), while 8 subjects showed vitamin D deficiency because they have vitamin D < 10 ng/ml and they were severely obese subjects with BMI 37.48 kg/m^2.
Conclusion: In our study 62% of our subjects consisted on adolescents and young adults showed insufficient status of vitamin D while 9% were showed deficient status with higher levels of iPTH and most of these have high BMI.

Key Words: Obesity, Body Mass Index (BMI), Vitamin D status, 25 hydroxy (OH) vitamin D, Intact parathyroid hormone (iPTH), Intracellular calcium [Ca^{+2}] i.

INTRODUCTION:

According to the WHO Expert Consultation (2004)[1], Obesity defined as a body mass index (BMI) > 30kg/m^2 is one of the most prevalent health problems worldwide, a key risk factor for diabetes, is widely used for Caucasian populations. However, its appropriateness for Asian populations has been questioned. Kim et al., (2011)[2] suggested additional public health action points for Asian populations, i.e. a BMI of 23 kg/m^2 or higher represents increased risk and a BMI of 27.5 kg/m^2 or higher represents high risk. Recently, it was reported that the BMI cutoff values for South Asians and Chinese associated with an incidence of diabetes equal to that associated with Caucasian individuals with a BMI of 30 kg/m^2 are 24 and 25 kg/m^2, respectively.[3]

Obesity is associated with a lower concentration of 25-hydroxy vitamin D and a higher concentration of parathyroid hormone (PTH) in adults.[4] According to Ogden et al., (2006)[5], 17.1% of children and adolescents were obese based on a BMI at or above the 95th percentile. Peak bone mass is attained during pubertal skeletal growth, a period of time that has been associated with increased risk of vitamin D deficiency).[6] In studies of obese adolescents in the United States, vitamin D deficiency has been correlated with

greater weight and elevated BMI. However, specific data on the relation between vitamin D status and body fat indexes in this age group were lacking. Given the significance of bone mass accretion during adolescence and the prevalence of obesity, identification of factors associated with vitamin D status among obese adolescents is critical.[7]

Obesity is an increasingly prevalent condition in industrialized societies. Grethen et al., (2011)[8], reported that in year 2007, all but one state in the United States had a prevalence of obesity greater than 20%, and 30 states had a prevalence of at least 25%. In a 2008 report on obesity from Europe, 35.9% of the population over age 18 were overweight (BMI = 25–29.9 kg/m^2), and 17.2% were obese (BMI > 30kg/m^2).[9] Obesity is associated with an increased prevalence of a number of diseases including type 2 diabetes, hypertension, hypercholesterolemia, osteoarthritis, gastroesophageal reflux disease (GERD), sleep apnea, and chronic renal disease.[8]

Vitamin D, a key regulator of bone metabolism, is thought to play an important role in adipogenesis and the prevention of a variety of diseases, including osteoporosis, cancer, diabetes, and immune disorders.[10] It is derived from skin exposure to sunlight (vitamin D3) or food supplements (vitamins D2 or D3) and undergoes successive hydroxylation in the liver and kidneys to give rise to its active metabolite 1, 25 dihydroxy vitamin D [1, 25(OH) vit D] [11].

Vitamin D deficiency is also an important worldwide public health problem.[12] Although the most-studied and best-known function of vitamin D, together with parathyroid hormone (PTH), is related to bone metabolism[13], many studies show evidence of the relationship between obesity and low levels of 25(OH) vitamin D (the best indicator of clinical levels of vitamin D). Factors known to influence 25(OH) vitamin D concentrations include race, vitamin D intake, sun exposure, adiposity, age and physical activity.[14] In obese people, low levels of 25 (OH) vitamin D can be attributed mainly to: a) the lower bioavailability of the vitamin, due to its sequestration by adipose tissue[15]; b) the dilution of ingested or cutaneously synthesized vitamin D in the enlarged fat mass[16]; c) low sun exposure, due to mobility limitations or the low sun exposure of large areas of the body[17]; or d) a low intake of calcium and vitamin D. The frequently observed increases in PTH serum concentrations in obese individuals could be explained by a compensatory mechanism in response to low circulating levels of 25(OH) vitamin D.[14]

Vitamin D deficiency occurs at serum 25 (OH) vitamin D levels persistently lower than 10 ng/ml and results in marked calcium malabsorption, negative calcium balance, secondary hyperparathyroidism, increased bone turnover, a large increase in serum 1, 25 –dihydroxy vitamin D in response to an increase in 25 D substrate, and osteomalacia in adults and rickets in children.[8]

Multiple mechanisms have been proposed to explain the association of obesity with hypovitaminosis D, including lack of sunlight exposure from physical inactivity[18] and sequestration of vitamin D in subcutaneous fat depots[19], while Wortsman et al.[15], reported that the capacity of the skin to produce vitamin D is not altered in obesity. However, the increase in serum vitamin D after sun exposure was 57% less in obese compared with non-obese subjects suggesting a decreased bioavailability of vitamin D because of its deposition in body fat compartments, given that vitamin D is fat soluble. Young et al., (2009)[20], observed that higher BMI and subcutaneous adipose tissue were associated with lower 1, 25-dihydroxyvitamin D, after controlling for 25[OH] vitamin D levels, suggesting a more complex relationship between vitamin D and adiposity than simply attributing this association to vitamin D bioavailability.

Another hypothesis suggests a negative feedback inhibition of 25(OH) D synthesis in liver by the increased level of 1, 25(OH)$_2$ D. Alteration of the vitamin D endocrine system in obese subjects is characterized by secondary hyperparathyroidism which is associated with enhanced renal tubular reabsorption of calcium and increased circulating 1, 25 (OH)$_2$ D which causes a feedback inhibition of 25 (OH) D synthesis.[21] However, some studies have reported an inverse correlation between BMI and serum 1, 25 (OH)$_2$ D,[22] casting a doubt on the hypothesis of negative feedback inhibition.[23]

Vitamin D and parathyroid hormone (PTH) are well known for their essential role in bone metabolism and calcium homeostasis. The main sources of vitamin D are ergocalciferol and cholecalciferol, the former normally available in food and the latter produced in the skin by ultraviolet radiation of 7-dehydrocholesterol. Both of these compounds are hydroxylated in the liver to 25-hydroxyvitamin D (25-OH Vit D), which is the major circulating metabolite precursor to the hormonally active form, 1, 25-dihydroxy-vitamin D.[24]

It has become increasingly clear that the vitamin D endocrine system is related to obesity in adults. Obesity has been found to be associated with lower levels of serum 25 (OH) vitamin D[23] and higher levels of serum PTH[25], thus PTH has been postulated as an independent predictor of obesity. [26]

A low vitamin D intake was associated with increased body mass index, however, excess body fat results in its increased sequestration and low availability and, as a consequence, low serum 25(OH) vitamin D levels.

MATERIAL & METHODS:

This study was carried out in the Department of Biochemistry, BMSI, JPMC, Karachi. Total 90 subjects age ranging between 12 to 25 years were taken from local Karachi population, from different educational institutes and by joining BMI camps established by Abbott Laboratories (Pakistan) Ltd.

Normal healthy adolescents (12-18 years) and young adults (19-25 years) of either sex with or without positive family history of obesity having BMI 18.5-29.99 and BMI >30. Subjects were required to be free of significant medical illnesses and taking no medications. Subjects using sunscreen and excessive clothing like boorka or abaya (veiled) were excluded. Subjects with any dermatological problem, liver and kidney disorder, GIT disturbance or with any known endocrinological disorder, pregnant females and subjects on any drug therapy were also excluded.

After selection the subjects were classified into non- obese and obese according to their body mass index (BMI). Subjects having BMI 20-24.99 kg/m^2 were classified as non- obese group while those with BMI >25 kg/m^2 were classified as obese group. In subsequent analysis, obese group was subdivided into Overweight or Pre-obese as grade-I having BMI 25-29.99 kg/m^2, moderately obese as grade-II having BMI 30-34.99kg/m^2 and severely obese as grade-III having BMI ?35.

Calculation of BMI:

Body mass index was calculated by the following formula;

BMI= weight in Kg/ height in m^2

Before calculating BMI, weight and height were measured in

kilogram and meters respectively while the subjects were in light clothing and without shoes using weighing with height scale machine (MIC Health Scale made in China). Adolescents BMI were calculated according to International cut off points for body mass index for overweight and obesity by sex between 2 and 18 years.[27]

RESULTS:

Subjects (non-obese, obese) were divided into Adolescents (12-18 years) and Young adults (19-25 years) with respect to their age difference (Table-1) moreover group of healthy non-obese subjects (n=40) was consisted of 14(35%) adolescents and 26(65%) young adult subjects. Where as the group of healthy obese subjects (n=50) was consisted of 23 (46%) adolescents and 27(54%) young adult subjects. Thus the presence of obesity is almost similar in both adolescents and young adults.

Anthropometrical parameters of non-obese and obese subjects were compared in Table-2. The mean values of age of non-obese and obese subjects were showing non-significant difference. The mean values of weight and height of obese subjects were showed highly significant difference (P<0.001). Obesity was identified on the basis of BMI, thus obese subjects 31.71±0.58 have significantly (P<0.001) higher BMI than non-obese subjects 22.42±0.18. The mean values of other adiposity measures like waist circumference, hip circumference, waist hip ratio of obese subjects showed significant difference (P<0.001) when compared to non-obese subjects.

Biochemical parameters between non-obese and obese subjects were compared in Table-3. The mean value of 25-OH vitamin D was significantly low (P<0.001) while serum iPTH value was significantly high (P<0.001) in obese as compared to non-obese subjects thus obese subjects showing vitamin D insufficiency with higher levels of iPTH while serum calcium and phosphate showed non-significant difference.

Table-4 shows the correlation coefficient of BMI with biochemical parameters. Serum 25-OH vitamin D showed highly significant (P<0.001) negative correlation (r = -0.820) with BMI, while iPTH showed highly significant (P<0.001) positive correlation (r = 0.859). Serum calcium showed somewhat significant (P<0.05) negative correlation with BMI (r = -0.253) while non-significant negative correlation was observed when compared serum phosphate with BMI. This table clearly indicates that the BMI has statistically significant negative correlation with serum level of 25(OH) vitamin D and significant positive correlation with iPTH. Figure-1 and 2 showed graphical presentation of correlation of BMI with 25 (OH) vitamin D and iPTH respectively.

Low levels of 25-OH vitamin D and higher levels of iPTH were observed in all three grades of obesity with respect of BMI. Table-5 indicated that mean values of 25-(OH) vitamin D were 17.58±0.55, 15.09±0.61 and 12.02±0.82 in grade-I, II and III respectively, significantly different (P<0.001) to each other and showed that as the obesity increases in terms of BMI vitamin D levels decreases. Similarly the mean iPTH values in these three grades of obesity were 35.91±0.80, 39.74±0.69 and 42.66 ±1.30 showed highly significant difference (P<0.001) when compared to each other and it can be observed that iPTH level rises as the BMI rises.

The mean values of serum calcium were within the normal range in all three grades of obesity but the mean value of calcium in

TABLE-1
DISTRIBUTION OF STUDY SUBJECTS ACCORDING TO AGE

S. No	Groups	Non-obese n=40	Obese n=50
1	Adolescents (12-18Y)	14(35%)	23(46%)
2	Young Adults (19-25Y)	26(65%)	27(54%)

TABLE -2
COMPARISON OF ANTHROPOMETRICAL PARAMETERS BETWEEN NON-OBESE AND OBESE SUBJECTS
Values are expressed as mean ± s.e.m

Parameters	Non Obese (n=40)	Obese (n=50)
Age (Years)	19.80±0.54	19.32±0.48 NS
Weight (kg)	57.80±1.32	89.66±2.07*
Height (m)	1.59±0.01	1.68±0.01*
BMI (kg/m^2)	22.42±0.18	31.71±0.58*
Waist (cm)	72.00±1.05	95.14±1.52*
Hip (cm)	89.70±1.10	108.40±1.55*
W/H ratio	0.80±0.008	0.87±0.005*

NS=non-significant. *P<0.001 when compared to non-obese. W/H ratio=Waist hip ratio.

TABLE - 3
COMPARISON OF BIOCHEMICAL PARAMETERS BETWEEN NON-OBESE & OBESE SUBJECT
Values are expressed as mean ± s.e.m

Parameters	Non Obese (n=40)	Obese (n=50)
25-(OH)D (ng/ml)	32.28±0.88	15.19±0.48*
iPTH (pg/ml)	20.90±0.46	39.12±0.64*
Serum Calcium (mg/dl)	9.28±0.11	9.02 ±0.11 NS
Serum Phosphate (mg/dl)	4.74±0.07	4.54±0.09 NS

NS= non-significant. *P<0.001 when compared with non-obese.

TABLE - 4
CORRELATION BETWEEN BMI AND BIOCHEMICAL PARAMETERS

Parameters	BMI (r-value)
25(OH) D	-0.820**
iPTH	0.859**
Serum Calcium	-0.253*
Serum Phosphate	- 0.152

** CORRELATION IS SIGNIFICANT AT THE P< 0.001LEVEL.
*CORRELATION IS SIGNIFICANT AT THE P< 0.05 LEVEL.

FIGURE-1
ASSOCIATION BETWEEN BMI & SERUM 25(OH) VITAMIN D

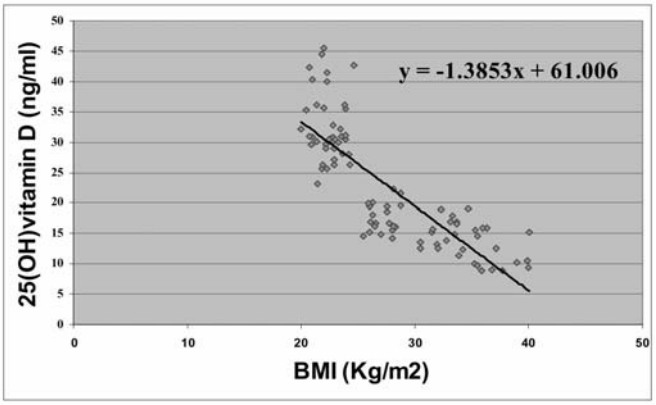
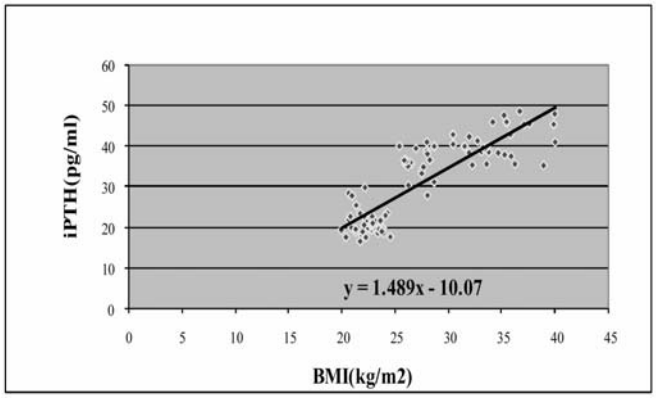


FIGURE-2
ASSOCIATION BETWEEN BMI & SERUM iPTH



grade-III was somewhat lower and showed significant difference (P<0.001) with remaining grades of obesity. Normocalcaemia in presence of low levels of 25(OH) vitamin D and high levels of iPTH in our obese subjects clearly indicate the presence of compensatory normalization of serum calcium level by iPTH. The mean values of serum phosphate in all three grades of obesity showed non-significant difference.

We divided our subjects on the basis of their serum vitamin D concentration or their vitamin D status, Figure-3 showed percent distribution of subjects according to their vitamin D status.

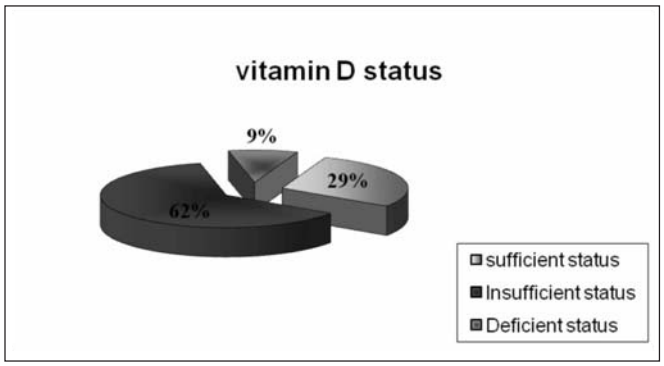
The interrelationship of BMI and iPTH in different vitamin D status showed in Table-6. On the basis of reference values, the cutoff value for vitamin D deficiency in children, adolescence, and adults is generally set at 10ng/ml so we categorized the study subjects in deficient status (?10ng/ml), insufficient status (10-30ng/ml) and sufficient status (>30 ng/ml). According to this cutoff point, 8subjects(9%) from the study group were included in deficient group, 56 subjects (62%) showed insufficient status and only 26

TABLE – 5
COMPARISON OF BIOCHEMICAL PARAMETERS AMONG DIFFERENT GRADES OF OBESITY
Values are expressed as mean ± s.e.m

Parameters	Grade I BMI 25-29.99 (n=20)	Grade II BMI 30-34.99 (n=16)	Grade III BMI ³35 (n=14)
25 (OH) D (ng/ml)	17.58±0.55	15.09*±0.61	12.02*§±0.82
iPTH (pg/ml)	35.91±0.80	39.74*±0.69	42.66*§±1.30
Serum Calcium (mg/dl)	9.26±0.22	9.07 ^{NS}±0.19	8.63*§±0.17
Serum Phosphate (mg/dl)	4.41 ±0.17	4.56 ^{NS} ±0.16	4.69 ^{NS}±0.18

NS= non-significant. Grade-I= Over weight, Grade-II= Moderately obese, Grade-III= Severely obese. *P<0.001 when compared with grade I obesity. §P<0.001 when compared with grade II obesity.

FIGURE-3
DISTRIBUTION OF SUBJECTS ACCORDING TO THEIR VITAMIN D STATUS



subjects (29%) showed sufficient status of vitamin D. The mean value of BMI of those subjects who showed sufficient status of vitamin D was 22.32±0.24, while the mean values of BMI of those who showed insufficient and deficient status were 28.63±0.64 and 37.48±0.68 respectively.

These values showed highly significant difference when compared to each other. As expected mean 25-OH vitamin D level of subjects showed sufficient status was 34.90±0.99 significantly higher than the mean values of 25-OH vitamin D of those who showed insufficient and deficient status 19.00±0.72 and 9.56±0.23 respectively. These values showed highly significant difference (P<0.001) when compared to each other. Those who showed insufficient and deficient status of vitamin D also showed raised mean iPTH levels and showed highly significant difference when they compared to each other.

TABLE - 6
THE INTERRELATIONSHIP OF BMI AND iPTH IN DIFFERENT VITAMIN D STATUS
Values are expressed as mean ± s.e.m

	Sufficient status (>30 ng/ml)	Insufficient status (10-30 ng/ml)	Deficient status (£10ng/ml)
n(%)	26(29%)	56(62.2%)	8(9%)
BMI (kg/m^2)	22.32 ±0.24	28.63* ±0.64	37.48*§ ±0.68
25 (OH) D (ng/ml)	34.90 ±0.99	19.00* ±0.72	9.56*§ ±0.23
iPTH (pg/ml)	20.25 ±0.64	38.45* ±0.57	44.82*§ ±0.1.51

*P<0.001 when compared with Vitamin D sufficient status. §P<0.001 when compared with Vitamin D insufficient status.

DISCUSSION:

Vitamin D deficiency and obesity both are nutritional disorders of global importance. There are growing data from studies of young adults, elderly persons and youth in different countries that vitamin D deficiency is an unrecognized and prevalent health problem.[28, 29, 30] Multiple studies have been carried out about the prevalence of vitamin D deficiency, however the majority of these studies were limited to specific age group (especially elderly) and specific sex groups therefore elucidation of vitamin D status at the community level and in different climate of a country seems essential. One of the most important aims of this study was to observe the different vitamin D status in adolescence and young adults of our community and its relation to obesity. Several studies demonstrated that obese people have lower serum levels of vitamin D when compared to non-obese people.[15, 31]

Our results are consistent with previous investigations reporting a relationship between lower vitamin D concentrations and increasing body weight, BMI and percentage body fat. Results of our study (Table-3) showed a significant difference (P<0.001) in levels of vitamin D between obese and non-obese subjects these results matched and justified with the studies of Snijder et al, (2005)[4] who compared the levels of vitamin D between obese and non-obese people in a population based study and observed that the levels were significantly lower in obese individuals. Parikh et al (2004)[23] studied adults of both genders of various races and observed that the obese group displayed mean levels of serum 25-OH vitamin D (23.5±12.2 ng/ml) significantly lower than those observed in the non-obese group (31±14.4 ng/ml). In studies of Hypponen and Power (2006)[32] found lower level of 25 (OH) vitamin D in obese adults similarly Reinehr et al (2007)[24] reported lower vitamin D status in obese children before weight loss. Vitamin D insufficiency (subclinical vitamin D deficiency) is characterized by mild secondary hyperparathyroidism, normocalcaemia and normal bone mineralization. The initial fall in ionized plasma calcium stimulates parathyroid hormone secretion, which in turn stimulates renal 1?-hodroxylase and increase 1, 25(OH) vitamin D production. This restores serum calcium to the normal[2] set point for that individual but at the expense of increased bone turnover. We found (Table-3) non-significant difference (P>0.05) in serum calcium and phosphate level of obese and non-obese subjects. [31, 33]

Also found serum calcium and phosphate within normal limits. Evidence has been accumulating that obesity can also be the consequence of a low vitamin D status. Increased PTH levels, of which serum 25-OH vitamin D is an important determinant, promote calcium influx into the adipocytes. Available data indicate that adipocytes are target for PTH action, and chronic excess of PTH increases calcium burden of fat tissues suggesting that PTH increases entry of calcium into adipocytes.

In these cells intracellular calcium enhances lipogenesis. The anti-lipolytic effects of intracellular calcium in adipocytes is mediated primarily by activation of adipocytes phosphodiesterase (PDE) and reduction in cAMP levels, leading to a decrease in hormone-sensitive lipase (HSL) phosphorylation and consequently inhibition of lipolysis.[34]

The fact that iPTH was also associated with adiposity after adjustment for 25-OH vitamin D could suggest that iPTH also independently of 25-OH vitamin D contributes to the development of obesity.[35] Our results regarding to iPTH (Table-3) showed significant higher levels (P<0.001) of iPTH in obese than non-obese subjects. These results are in agreement with study of Reinehr et al (2007)[24] who found higher levels of iPTH in obese young children and declines with weight loss. Yanoff et al., (2006)[36] found significantly higher levels of iPTH in obese than non-obese subjects in a cross-sectional study related to the prevalence of hypovitaminosis D and secondary Hyperparathyroidism in obese black Americans.

Our results (Table-5) showed a consistency with Yanoff et al., (2006)[36] when we sub divided our obese subjects according to different BMI ranges. We found that as the obesity progress in terms of BMI, vitamin D status showed negative association with BMI while iPTH showed positive association with BMI.

CONCLUSION AND RECOMMENDATIONS:

To conclude, 62% of our study subjects consisted on adolescents and young adults showed vitamin D insufficiency while 9% were showed deficient status and most of these subjects showed significantly (P<0.005) higher levels of BMI and iPTH and these levels increases as the vitamin D status of our subject changed from sufficient to insufficient and deficient. However, calculation of exact prevalence of vitamin D insufficiency in obesity with other metabolic changes requires larger scale studies.

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