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Original Article

Biochemistry Section

Hypovitaminosis D Implicated in the Development of Stress, Metabolic Syndrome and Hepatic Steatosis among Health Science Undergraduates attending a Tertiary Care Institute in Tamil Nadu, India

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ABSTRACT

Introduction: Vitamin D deficiency is prevalent worldwide and its association with stress has become an emerging problem. A collection of linked physiological, biochemical, clinical, and metabolic risk factors is known as the Metabolic Syndrome (MS). High stress level is found associated with vitamin D deficiency and features of metabolic syndrome symptoms.

Aim: To estimate the prevalence of vitamin D deficiency, perceived stress, metabolic syndrome and hepatic steatosis among health science Undergraduate (UG) students and also to evaluate the association of vitamin D with perceived stress score, calcium, phosphorus, components of metabolic syndrome and indicators of liver steatosis.

Materials and Methods: This cross-sectional study was conducted at SRM Medical College, Hospital and Research Centre, Chennai, India, from February 2022 to August 2022. A total of 80 health science UG students in the age group of 19-25 years were included. The parameters included Fasting plasma glucose, Triglycerides (TGL), High Density Lipoprotein Cholesterol (HDLC), Gamma-glutamyl Transferase (GGT), phosphorus, calcium, and a Perceived Stress Scale (PSS) score scale. Data were statistically analysed using Pearson's correlation test and Receiver Operating Characteristic (ROC) curve was used to assess the relationship of vitamin D with stress, metabolic syndrome and liver steatosis.

Results: In the present study, majority 56 (70%) had vitamin D deficiency, 23 (28.75%) had insufficiency and 1 (1.25%) had sufficiency. An estimated 6 (7.5%) of students experienced low stress, 63 (78.75%) experienced moderate stress and 11 (13.75%) experienced high perceived stress. Indicators of metabolic syndrome occurred in 13 (16.25%) of the population. Nearly 6 (7.5%) of the participants displayed manifestation of fatty liver. A negative association was found between vitamin D with stress score, Body Mass Index (BMI), waist circumference, Blood Pressure (BP), phosphorus, fasting plasma glucose, TGL, HDLC, GGT, Fatty Liver Index (FLI) score.

Conclusion: In the present study, vitamin D deficiency was most prevalent (70%), followed by metabolic syndrome, high stress and hepatic steatosis. Vitamin D showed a negative correlation with stress score, BMI, waist circumference, BP, phosphorous, fasting plasma glucose, TGL, HDLC, GGT and FLI score.

Keywords: Body mass index, Fatty liver, Stress score, Vitamin D

INTRODUCTION

Vitamin D is one of the fat soluble vitamin whose functions as a prohormone [1]. A 1,25-dihydroxyvitamin D is the biologically active form of vitamin D. This type of vitamin D however, does not accurately reflect tissue levels. Therefore, 25-hydroxy vitamin D which is stable is typically employed for vitamin D analysis. It is one of the dietary components that could produce neuroregulatory effects [2]. Serotonin, dopamine and noradrenaline are among the neurotransmitters that are altered by vitamin D shortage [3]. Vitamin D also plays a role in neuroimmunomodulation and neuroplasticity [4].

It was found that 68% of South Asian population had vitamin D deficiency [5].Vitamin D deficiency has been linked to increased levels of stress and depression, according to previous research [6-8]. Stress is estimated to affect 29.6% [9] of people worldwide and 11.6% of people in India during Coronavirus Disease 2019 (COVID-19) [10]. Vitamin D deficiency affects the serotoninergic system, which affects serotonin metabolism and contributes to the maintenance of circadian rhythm, both of which are critical components in the emergence of depressive and stress symptoms [11]. Poor sun exposure, skin pigmentation, age related skin thinning, inadequate food intake, antiepileptic medications and malabsorption are the main causes of vitamin D insufficiency, which is the most prevalent cause of hypocalcaemia [12]. Low serum vitamin D has been found to be associated with various types of metabolic syndrome [13]. Lack of vitamin D is frequently linked to Non Alcoholic Fatty Liver Disease (NAFLD) [14]. In peripheral tissues, including hepatocytes, vitamin D lowers free fatty acid induced insulin resistance [15]. Thus, intrahepatic lipid accumulation caused by low vitamin D levels may contribute to the pathogenesis of NAFLD [16]. Lack of vitamin D can impair cells' ability to convert proinsulin to insulin [17]. This insulin resistance is responsible for development of metabolic syndrome [17]. NAFLD is pathophysiologically characterised by hepatic fat accumulation with alcohol consumption [18]. A non invasive tool called the FLI is used to stratify a population's risk of developing NAFLD [19].

As vitamin D deficiency, fatty liver, metabolic syndrome and the occurrence of stress are interrelated especially among young people, and no study has been conducted to evaluate this interrelation of vitamin D with stress, liver steatosis and metabolic syndrome in Chennai, Tamil Nadu. Hence, present study was conducted to estimate the prevalence of vitamin D deficiency, perceived stress, metabolic syndrome and fatty liver in health science UG students and to evaluate the association of vitamin D_2 with stress score, calcium, phosphorus, components of metabolic syndrome and indicators of hepatic steatosis.

MATERIALS AND METHODS

This cross-sectional study was done in SRM Medical College Hospital and Research Centre, Kattankulathur, Chennai, Tamil Nadu, India, from February 2022 to August 2022.As part of the study protocol, each participant's written informed consent was obtained, which was carried out in accordance with the approval of the Institutional Ethics Committee (IEC no: 8272/IEC/2022).

Inclusion criteria: Medical and paramedical UG students between the age group of 18- 25 years formed the study group.

Exclusion criteria: Students with a history of neurological disorders and on treatment for the same, on vitamin D supplements, thyroid dysfunction, diabetes mellitus, hypertension, postgraduates (PGs), health science UG students during their study holidays and examination period were excluded from the study.

Sample size calculation: Sample size calculated was 25, by using the formula:

$n=4\ pq/d^2$

n=Sample size, p=prevalence of stress (56.25%), [20], q=100-p,

d=20% precision.

n=4*56.25*43.75/20*20

n=25

But, in present study, sample size taken was 80.

Study Procedure

Percieved stress score: All participants were screened using a self reported perceived stress scale [21]. The 10-question PSS is a valuable and efficient way of identifying participants at risk for perceived stress. PSS scores are obtained by reversing responses (e.g., 0=4, 1=3, 2=2, 3=1 and 4=0) to the four positively stated items (items 4, 5, 7, and 8) and then summing across all scale items. Scores ranging from 0 to 13 indicates low stress, 14 to 26 moderate stress and 27 and 40 represents high perceived stress.

Metabolic syndrome: was diagnosed when any of the three criteria were present- waist circumference > 90 cm (male), >80 cm (female), BP ≥140/90 mm/Hg, TGL ≥150 mg/dL, HDLC <40 mg/dL (male), <50 mg/dL (female), fasting blood glucose ≥100 mg/dL [22].

Liver steatosis: In order to quantify liver steatosis, FLI was used. Based on their FLI scores, the participants were divided into three groups: FLI 30 was considered to be NAFLD free, FLI of 30 to 59 was considered to be intermediate FLI, and FLI 60 was considered to be NAFLD positive. It is calculated by the following formula:

$$FLI=(e^{0.953\times loge(triglycerides)+0.139\times BMI+0.718\times loge(GGT)+0.053\times waistcircumference-15.745})/(1+e^{0.953\times loge(triglycerides)+0.139\times BMI+0.718\times loge(GGT)+0.053\times waistcircumference-15.745})\times 100$$ [23].

Under aseptic precaution 5 mL of fasting venous blood sample was collected in serum and sodium fluoride vaccutainers. Beckman Coulter auto analyser was used to measure fasting plasma glucose (70-110 mg/dL), TGL (≥150 mg/dL), HDLC (<40 mg/dL in men, <50 mg/dL), GGT (5-40 U/L), calcium (8.6-11 mg/dL) and phosphorus (3.3-4.5 mg/dL) [24-27]. Vitamin D analysis samples stored at -20°C were estimated using Bio-Rad Enzyme-Linked Immunosorbent Assay (ELISA) reader and washer. Vitamin D level from 0-10 ng/mL is considered deficient, from 1030 ng/mL is insufficient, above 30 ng/mL is sufficient [28].

STATISTICAL ANALYSIS

The Statistical Package for the Social Sciences (SPSS) version 26.0 software was used to analyse both parametric and non parametric data. Frequencies and percentages were used to express categorical variables. The Pearson correlation equation was used to calculate the correlation coefficient of vitamin D status with the measured parameters. The p-value <0.05 was deemed statistically significant. Receiver Operating Characteristic (ROC) curve was used to assess the relationship of vitamin D with stress, metabolic syndrome and liver steatosis.

RESULTS

The study included 80 health science UG students, consisting of 33 females and 47 males, aged between 19 and 25, with a mean age of 20.2±1.03 years. Out of the 80 participants, 56 (70%) had vitamin D deficiency, 23 (28.75%) had insufficient vitamin D levels and only one had adequate vitamin D. Among the 80 health science UG 6 (7.5%) with mean score of 8.33±4.22 experienced low stress, 63 (78.75%) experienced moderate stress and 11 (13.75%) experienced high perceived stress [Table/Fig-1].

Vitamin D level	N (%)	Mean vitamin D level
Sufficient	1 (1.25%)	33.62
Insufficient	23 (28.75%)	13.85±3.94
Deficient	56 (70%)	4.72±2.19
PSS	**N (%)**	**Mean PSS scores**
High	11 (13.75%)	28.72±1.67
Moderate	63 (78.75%)	18.82±1.78
Low	6 (7.5%)	8.33±4.22
Metabolic syndrome	**N (%)**	
Present	13 (16.25%)	
Absent	67 (83.75%)	
Liver steatosis	**N (%)**	
Present	6 (7.5%)	
Absent	74 (92.5%)	

[Table/Fig-1]: Sample distribution for vitamin D level, presence of metabolic syndrome, liver steatosis and PSS among UG health science students.

10 (91%) of the participants with high stress scores had vitamin D deficiency, 1 (9%) had insufficiency and none had adequate levels. In the moderate stress score, 43 (68.25%) of the subjects lacked enough vitamin D, 19 (30.15%) had insufficient levels [Table/Fig-2].

Vitamin D (ng/mL)	High stress (11)	Moderate stress (63)	Low stress (6)
Sufficient	0	1 (1.58%)	0
Insufficient	1 (9%)	19 (30.15%)	3 (50%)
Deficient	10 (91%)	43 (68.25%)	3 (50%)

[Table/Fig-2]: Vitamin D levels among health science UG students with different stress scores.

Among high stress level, the mean for sufficient, insufficient and deficient vitamin D levels were 0, 10.69 and 4.36±1.65. In moderate stress, the mean were 33.62, 14.10±4.22 and 4.78±2.31. In low stress, the mean were 0, 13.30±2.10 and 5.12±2.70, respectively [Table/Fig-3].

Vitamin D (ng/mL)	High stress 11 (13.75%)	Moderate stress 63 (78.75%)	Low stress 6 (7.5%)	p-value
Sufficient	0	33.62	0	-
Insufficient	10.69	14.10±4.22	13.30±2.10	0.697
Deficient	4.36±1.65	4.78±2.31	5.12±2.70	0.824

[Table/Fig-3]: Vitamin D levels among health science UG students with different stress scores with mean values.

About 13 (16.25%) of the population displayed signs of metabolic syndrome. Metabolic syndrome was present in 12 (21.4%) participants with vitamin D deficiency, 1 (4.3%) participant with vitamin D insufficiency, and in none of the participants with sufficient vitamin D levels [Table/Fig-4].

Metabolic syndrome	Vitamin D deficient	Vitamin D insufficient	Vitamin D sufficient
Present	12 (21.4%)	1 (4.3%)	0
Absent	44 (78.5%)	22 (95.6%)	1

[Table/Fig-4]: Vitamin D levels among health science UG students with metabolic syndrome.

Among participants with metabolic syndrome, the mean for sufficient, insufficient and deficient vitamin D levels were 0, 10.39 and 3.97±1.68. In participants without metabolic syndrome, the mean were 33.62, 14.01±3.96 and 4.93±2.29, respectively [Table/Fig-5].

Metabolic syndrome	Vitamin D deficient	Vitamin D insufficient	Vitamin D sufficient	p-value
Present	3.97±1.68	10.39	0	0.04*
Absent	4.93±2.29	14.01±3.96	33.62	0.001*

[Table/Fig-5]: Vitamin D levels among health science UG students with metabolic syndrome with mean values.

Nearly 6 (7.5%) population displayed manifestation of liver steatosis. Features of liver steatosis was present in 5 (9.8%) participant with vitamin D deficiency, 1 (4.3%) participant with vitamin D insufficieny [Table/Fig-6].

Liver steatosis	Vitamin D deficient	Vitamin D insufficient	Vitamin D sufficient
Present	5 (9.8%)	1 (4.3%)	0
Absent	51 (91.07%)	22 (95.6%)	1

[Table/Fig-6]: Vitamin D levels among health science UG students with features of NAFLD.

Among participants with features of NAFLD, the mean for sufficient, insufficient and deficient vitamin D levels were 0, 10.69 and 3.16±1.43. In participants without the features of NAFLD, the mean were 33.62, 13.85±3.94 and 4.81±2.19, respectively for sufficient, insufficient and deficient vitamin D levels [Table/Fig-7].

Liver steatosis	Vitamin D deficient	Vitamin D insufficient	Vitamin D sufficient	p-value
Present	3.16±1.43	10.69	0	0.009*
Absent	4.81±2.19	13.85±3.94	33.62	0.001*

[Table/Fig-7]: Vitamin D levels among health science UG students with features of NAFLD with mean values.

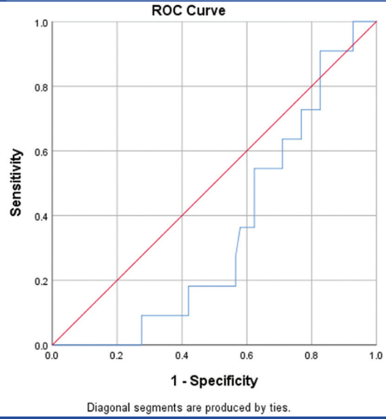
Vitamin D was correlated positively with calcium but this relation was statistically non significant. Vitamin D had a significant negative correlation with BMI, waist circumference, and FLI score. Vitamin D was also negatively correlated with stress score, BP, FPG, GGT, TGL, HDLC and phosphorus but this relation was statistically not significant [Table/Fig-8].

Correlation of vitamin D with	r value	p-value
Stress score	-0.101	0.373
BMI (kg/m^2)	-0.335	0.002*
Waist circumference (cm)	-0.337	0.002*
Calcium (mg/dL)	0.177	0.117
Phosphorus (mg/dL)	-0.021	0.851
Fasting plasma glucose (mg/dL)	-0.022	0.846
TGL (mg/dL)	-0.149	0.187
HDLC (mg/dL)	-0.033	0.770
GGT (IU/L)	-0.035	0.760
FLI score	-0.237	0.034*
Systolic blood pressure (mmHg)	-0.093	0.412
Diastolic blood pressure (mmHg)	-0.216	0.054

[Table/Fig-8]: Pearson's Correlation analysis of vitamin D2 with stress score, BMI, waist circumference, FLI score, BP and biochemical parameters in UG students (n=80).

ROC analysis for development of stress [Table/Fig-9]. A vitamin D cut-off value of 6 ng/mL responded to 18% sensitivity and 52% specificity for the development of stress. Students with low vitamin D or ≤6 ng/mL were shown to be 2.08 times more likely to develop stress when the odds ratio to predict the stress level was calculated (p=0.22, 95% CI=0.6-6.8) [Table/Fig-10].

Marker	Cut-off value	Sensitivity (%)	Specificity (%)	AUC	95% CI	p-value
Vitamin D	6 ng/mL	18%	52%	0.351	0.21-0.48	0.114



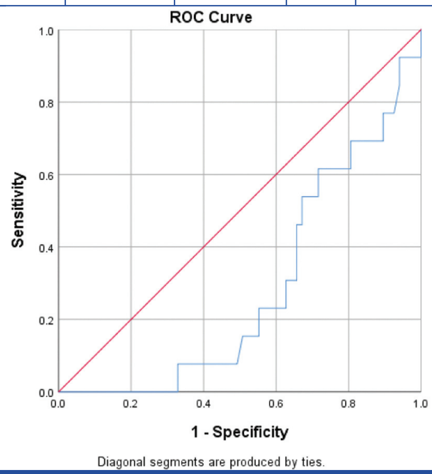
[Table/Fig-9]: ROC analysis to determine cut-off of vitamin D for development of stress.
AUC: Area under the ROC curve; CI: Confidence interval

Variables	Case % (high perceived stress)	Control % (Moderate and low stress)	Total %	Odds ratio	95% CI	p-value
Low vitamin D	9 (82%)	32 (46%)	41 (51%)	2.08	0.6-6.8	0.22
Normal vitamin D	2 (18%)	37 (54%)	39 (49%)			

[Table/Fig-10]: Low vitamin D (<6 ng/mL) as a risk factor for developing stress.

ROC analysis to determine cut-off of vitamin D for risk of metabolic syndrome shown in [Table/Fig-11]. A vitamin D cut-off value of 6 ng /mL responded to 15% sensitivity and 53% specificity for the development of metabolic syndrome. Students with low vitamin D or ≤6 ng/mL were shown to be 6.3 times more likely to develop MS when the odds ratio to predict the risk for MS was calculated (p=0.02, 95% CI=1.3-31) [Table/Fig-12].

Marker	Cut-off value	Sensitivity (%)	Specificity (%)	AUC	95% CI	p-value
Vitamin D	6 ng/mL	15%	53%	0.286	0.15-0.41	<0.01



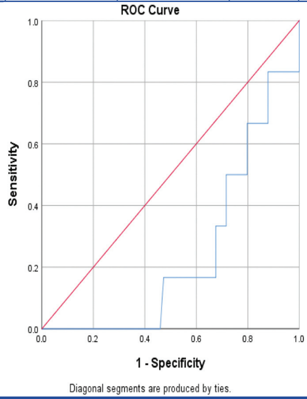
[Table/Fig-11]: ROC analysis to determine cut-off of vitamin D for risk of metabolic syndrome.

Variables	Case % (with metabolic syndrome)	Control% (without metabolic syndrome)	Total %	Odds ratio	95% CI	p-value
Low vitamin D	11 (85%)	31 (46%)	42 (52%)	6.3	1.3-31	0.02
Normal vitamin D	2 (15%)	36 (53%)	38 (47%)			

[Table/Fig-12]: Low vitamin D (<6 ng/mL) as a risk factor for metabolic syndrome.

ROC analysis fo development of NAFLD [Table/Fig-13]. A vitamin D cut-off value of 6 ng /mL responded to 16% sensitivity and 50% specificity for the development of NAFLD.

Marker	Cut-off value	Sensitivity (%)	Specificity (%)	AUC	95% CI	p-value
Vitamin D	6 ng/mL	16%	50%	0.244	0.09-0.39	<0.03



[Table/Fig-13]: ROC analysis to determine cut-off of vitamin D for development of NAFLD.

Students with low vitamin D or ≤6 ng/mL were shown to be five times more likely to develop NAFLD when the odds ratio to predict the NAFLD was calculated (p=0.15, 95% CI=0.5-44.8) [Table/Fig-14].

Variables	Case % (with NAFLD)	Control % (without NAFLD)	Total %	Odds ratio	95% CI	p-value
Low vitamin D	5 (83%)	37 (50%)	42 (52.5%)	5	0.5-44.8	0.15
Normal vitamin D	1 (17%)	37 (50%)	38 (47.5%)			

[Table/Fig-14]: Low vitamin D (<6 ng/mL) as a risk factor for NAFLD.

Female students had a higher incidence of high perceived stress (18% vs 11%), vitamin D deficiency (84% vs 59%) and metabolic syndrome characteristics (18% vs 10%) than their male counterparts. Males were more likely than females to have fatty liver symptoms (8.5% vs 6.06%).

DISCUSSION

A lack of vitamin D is a global problem [29]. COVID-19 induced modifications in lifestyle have resulted in widespread mental health consequences. A sedentary lifestyle and lack of sun exposure have contributed to an increase in vitamin D deficiency. Vitamin D promotes the production of neurotransmitters such as dopamine and norepinephrine and contributes to psychological health [30]. The results of the present study showed that just one participant had acceptable vitamin D levels, while 28.75% had inadequate levels and 70% had vitamin D insufficiency.

As of late, stress has become a major cause for concern [31]. An extended period of not going to school and staying indoors during the COVID-19 pandemic has had a profound impact on many students [32]. A study found that 6% of Indian students reported high perceived stress and 45% experienced mild stress [33], whereas in the present study, 7.5% of the enrolled students experienced low stress, 78.75% moderate stress and 13.75% high perceived stress. Also, In a study, university students in India were found to have normal (15.6%), mild (33.8%), moderate (35.4%), severe (13.2%), and excessive (2.8%) stress levels [34]. A correlation between low vitamin D levels and the development of depressive symptoms was demonstrated in a study [35]. A research found that patients with high stress had hypovitaminosis D [36]. In the current study, it was observed vitamin D deficiency to be high among participants (91%) with high perceived stress score. Also, vitamin D has correlated negatively with the stress scores. Students with low vitamin D or <6 ng/mL were shown to be 2.08 times more likely to develop stress when the odds ratio to predict the stress level was calculated (p=0.22, 95% CI=0.6-6.8). Hence, reduced vitamin D levels are found to be associated with higher stress scores.

The prevalence of metabolic syndrome was found to be 8.7% among young adults in India [37]. A higher percentage of metabolic syndrome (16.25%) has been reported in the present analysis. In a research, vitamin D deficiency was found to be linked to metabolic syndrome [13]. Vitamin D deficiency causes several risk factors such as hypertension, hyperlipidaemia, hyperglycaemia and insulin resistance that leads to metabolic syndrome. The present study has observed 92% of vitamin D deficiency prevalent among participants with metabolic syndrome. Students with low vitamin D or <6 ng/mL were shown to be 6.3 times more likely to develop metabolic syndrome when the odds ratio to predict the risk for metabolic syndrome was calculated (p=0.02, 95% CI=1.3-31). A study found 78.3% of young adults with metabolic syndrome suffering from vitamin D deficiency [38].

According to a study, chronic stress was proposed as a risk factor for the development of metabolic syndrome [39]. It was found that 8% of the population with high levels of stress exhibited signs of metabolic syndrome [40]. In the present study, 27.3% of participants with high levels of stress, 14.28% of participants with moderate levels of stress and only one participant with low levels of stress had metabolic syndrome. Thus, the role of stress in the development of metabolic syndrome can be studied. In the present study, vitamin D was positively correlated with calcium and negatively correlated with stress score, BMI, waist circumference, BP, phosphorus, fasting plasma glucose, TGL, HDLC, GGT and FLI score. The present results correlate with a study that found low vitamin D levels to be linked to hypertension development and high BP [41]. In Asian Indian women, higher blood glucose values are linked to lower vitamin D levels [42]. A prevalence of 15% of Impaired Fasting Glycaemia (IFG) was found in the present study. A study conducted, showed high prevalence of hypovitaminosis D existing among IFG subjects [43]. Higher levels of TGL are found to be associated with low vitamin D levels [44] which are also similar to the findings in the present study. The enzyme lipoprotein lipase which aids in reducing TGL is upregulated by vitamin D metabolites as was shown in a study [45]. Vitamin D deficiency leads to a decrease in HDLC which may cause cardiovascular risk in suspectible individuals [46]. A study reported, decreasing HDLC levels with decrease in vitamin D [47]. The present study has a conflicting results regarding HDLC in relation to vitamin D. This could be due to the younger age of the enrolled participants.

The NAFLD is thought to be the hepatic analogue of metabolic syndrome [48]. A prevalence of 7.5% of fatty liver was found in the present study. A higher prevalence of 62.5% was found in the study [49]. Vitamin D, particularly the active form 1,25 (OH) D and the Vitamin D Receptors (VDR), are involved in a variety of immune-inflammatory and metabolic processes [50]. Vitamin D levels were found to be one of the most significant factors in NAFLD pathogenesis [51]. 70% of NAFLD patients were deficient in vitamin D, according to a study [52]. According to findings of the present study, the entire population affected by fatty liver manifestations was discovered to be deficient in vitamin D. Students with low vitamin D or <6 ng/mL were shown to be five times more likely to develop NAFLD when the odds ratio to predict the stress level was calculated (p=0.15, 95% CI=0.5-44.8). Higher stress levels, vitamin D deficiency as well as metabolic syndrome were more frequently reported among young women when compared with their counterparts [53-55]. The features of fatty liver were more among males than in females (8.5% vs 6.06%). Similarly, in the present study, it was observed female students with a higher incidence of high perceived stress, vitamin D deficiency and metabolic syndrome characteristics than their male counterparts. An imbalance in the levels oestrogen, progesterone is considered as the main cause of high stress levels among female participants.

It is important that students view stress reduction techniques and educational initiatives to develop useful and healthy coping mechanisms. A diet rich in fruits, vegetables, legumes, whole grains, low fat dairy and low calorie products can be followed. Optimal vitamin D supplementation and exposure to sunlight can facilitate to decrease stress and the development of metabolic derangements.

Limitation(s)

The evaluation was based primarily on a self reported questionnaire and its results were not confirmed by a semi-structured interview. Since, only one scale (PSS) and no psychometric procedures were utilised, it is possible that the current study is insufficient to establish a greater validity.

CONCLUSION(S)

In the present study, a high prevalence (70%) of vitamin D deficiency was observed among young health science UG. A lack of vitamin D among students was correlated with metabolic syndrome, features of fatty liver and perceived stress. This pandemic of hypovitaminosis D can be attributed to reduced outdoor activities and environmental factors that reduce exposure to sunlight. Hence, it is crucial to learn healthy ways to deal with stress, increase one's exposure to natural environments and consume a diet high in fibre and low in calories. Vitamin D supplementation has been linked to improved mood and reduced stress, as well as reduced risk of metabolic disturbance. Hence, educational initiatives to develop useful, healthy coping mechanisms, a balanced diet, optimal vitamin D supplementation and exposure to sunlight can facilitate in decreasing stress and the development of metabolic derangements.

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