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Original Research Article

A study to see association between vitamin d level and obstructive sleep apnea

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ABSTRACT

Introduction: Obese patients have low levels of serum 25-hydroxy vitamin D due to feedback inhibition of hepatic synthesis of the metabolite by increased circulating 1,25(OH) vitamin D. Obese individuals have more physical activity which limits their exposure to sunlight resulting in lower levels of 25(OH)D. Sleep fragmentation in OSA leads to daytime drowsiness, fatigue and hence decreased outdoor activity contributing to the same. Hence, OSA aggravates obesity and obesity aggravates OSA creating a vicious cycle and together contribute to the depletion of serum vitamin D level.

Materials and Methods: Patients attending the special clinic of sleep were included in the study and were screened using STOP-BANG scoring system for OSA Patients with score of >2 were included in the study and further underwent polysomnography test. Among the study population, cases had an apnea-hypopnea index (AHI) > 5 in polysomnography and controls had AHI <5. Controls were further matched for age, sex and BMI with cases. Vitamin D Level was tested in both cases and controls for comparison using arterial blood sample.

Results: Total ninety-three patients were included in the study, out of whom 59 were cases which formed the OSA group, had mean age of 48.02 ±8.435 years, mean body mass index (BMI) 33.73 ±7.48 kg/m2, mean neck circumference 37.8 cm ±5.08 Mean vitamin D level in the case and control was 21.02 ± 7.27 and 24.48 ± 6.92 respectively with a p value < 0.05, with a negative correlation of AHI with serum vitamin D level ($p< 0.001$, $r = -0.286$).

Conclusion: Different mechanisms play a role in OSA patients affecting. This study shows inverse relationship between vitamin D level and AHI (apnea-hypopnea index) which was statistically significant and vitamin D level was higher in controls than cases. Thus it can be said that 25(OH)D levels and OSAS are related, but it is difficult to establish a direct causal association between them.

1. Introduction

Sleep disordered breathing characterized by repetitive, incomplete or total obstruction of the upper respiratory tract combined with hypopnea and apnea during sleep, contributing to an intermittent decrease in the blood oxygen saturation and hypercapnia is defined as obstructive sleep apnea (OSA).[1] Symptoms of OSA include daytime sleepiness, fatigue, inattention, headaches and even memory loss during the day, which can seriously affect the quality of life and life expectancy.[2] Gold standard diagnostic procedure for diagnosing OSA is polysomnography.[3] OSA can lead to various other complications such as cardiovascular, cerebral, pulmonary, vascular and multisystem pathophysiological changes.[4,5]

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Shahare et al and Erden et al found a higher prevalence of 25(OH)D deficiency in patients of obstructive sleep apnea.[6,7]

Obese individuals have more subcutaneous fat and vitamin D is stored in fat tissues of the body so there is decreased release of 25(OH)D into the circulation.[8]

In obese individuals low level of serum vitamin D is due to feedback inhibition of hepatic synthesis of the metabolite by increased circulating 1,25(OH)D.

Obese individulas have restricted physical activity which limits their sunlight exposure leading to lower 25(OH)D concentrations.[9]

OSA patients have nocturnal hypoxia leading to sleep fragmentation which causes symptoms of daytime sleepiness and fatigue. It can further cause decreased outdoor activity, reduced sunlight exposure and a reduction in 25(OH)D synthesis . Studies have reported that one hour of sleep disorder can decrease daytime activity by three percent, and with loss of one hour of sleep, the probability of obesity rises by eighty percent .Poor quality of sleep or lack of sleep in obstructive sleep apnea aggravates obesity forming a vicious cycle of obesity and obstructive sleep apnea.

There is increased autonomic nervous system activity due to repeated hypo apnea and obstruction of upper airway in patients of obstructive sleep apnea during night ,mainly sympathetic nerve activity.[10]

Increased sympathetic activity can inhibit vagus activity which affects gastrointestinal mobility and gastrointestinal hormones secretion which affects absorption and metabolism of 25(OH)D.

Obstructive sleep apnea patients suffer from hypoxia, obstruction of upper airways and increased abdominal pressure for longer time that could lead to gastroesophageal reflux and gastric ischemia, affecting absorption of 25(OH)D.[11] comorbidities associated with OSA such as obesity and metabolic syndrome like elevated systemic inflammation, dyslipidemia, secondary hyperparathyroidism, hypogonadism, insulin resistance overlaps with Vitamin D deficiency.[12]

Low levels of vitamin D in circulation causes poor musculoskeletal function.[13] Tone of muscles of upper airway play a major role in patients of obstructive sleep apnea[14] and patients of obstructive sleep apnea have poor function of skeletal muscles maintaining the patency of upper airway during sleep due to low 25(OH)D levels. Low vitamin D concentrations can cause tonsillar enlargement due to Inflammation of airway, chronic rhinitis, and repeated upper airway infections,[15] which further contributes to OSA incidence and severity.

It is also suggested that vitamin D reserve may be depleted due to chronic low grade inflammation in untreated OSA patients which is supported by Ligouri et al who reported a markedly increased level of 25(OH)D after seven days of continuous positive airway pressure use in male obstructive sleep apnea patients.[16]

2. Material and Methods

This is a case–control prospective study, conducted in the Department of tuberculosis and Respiratory Medicine and department of endocrinology, Jawaharlal Nehru Medical College, AMU, Aligarh, UP. Institutional ethical committee approval was obtained for this study.

2.1. *Inclusion criteria*

1. Patients between thirty to sixty years of age having sleep related complains.
2. Patients having positive consent for polysomnography.

2.2. *Exclusion criteria*

1. Patients less than 30 years of age and more than 60 years of age
2. Patients with known vitamin D deficiency
3. Patients with other medical conditions causing Vitamin D deficiency such a Cushing's syndrome, hyperthyroidism, hypothyroidism, hyperparathyroidism, diabetes mellitus
4. Patients on vitamin D supplements
5. Critically ill patients

2.3. *Sample Technique*

Clinical history and demographic data was screened using STOPBANG questionnaire scoring system. Patients with score >2 were included in the study and subjected to polysomnography.

Cases had apnea hypoapnea index more than five and controls had apnea hypoapnea index less than five. Age, sex and body mass index (BMI) was matched for both cases and controls.

Figure 1 represents the flow chart of selection of study population.

2.4. *Investigations*

2.4.1. *Sleep study*

Study population was subjected to sleep study during night in hospital level one sleep lab with PHILIPS ALICE 6 LDe system with 32 leads.

Parameters recorded were as follows:

1. Nasal pressure
2. Respiratory effort
3. Body position
4. Pulse transit time
5. Snoring
6. Airflow
7. Oxygen saturation (sao2)

8. Electrocardiogram

Various parameters used were:

Apnea: No airflow for more than ten seconds. apnea can be central or obstructive.

Hypoapnea thirty percent or more reduction in airflow from basline for more than ten seconds or four percent or more reduction in oxygen saturation from baseline.

Apnea-hypopnea index: number of apnea or hypoapnea events/hour of reported sleep time.

American academy of sleep medicine criteria was used for diagnosing OSA:

Apnea-hypopnea index more than five but less than fifteen is mild obstructive sleep apnea

Apnea-hypopnea index more than or equal to fifteen but less than thirty is moderate obstructive sleep apnea

Apnea-hypopnea index more than or equal to thirty is severe obstructive sleep apnea

2.4.2. Serum vitamin D level testing

Arterial blood samples were tested from both cases and controls.

Amount of blood taken for sampling: five mililitre.

Transportation: samples were sent to lab at room temperature in plain vials for analysis

Process of sampling: done using a Beckman Coulter Access 2 machine working on the principle of chemiluminescence-immunoassay (CLIA).

The reference value taken was twenty five to eighty nanogram per deciliter for vitamin D for this study.

2.4.3. Statistical Analysis

SPSS version 25.0 was used for data analysis. Numerical variables were presented as mean +/- SD with 95% CI, non-numerical variables were presented as frequency of distribution. ANOVA test and Student's t-test was used to compare the mean of variables between different groups. For calculating frequency of distribution chi square test was used. $p<0.05$ was considered to be ststistically significant To establish an association between AHI and vitamin D level Pearson correlation coefficient was calculated.

3. Observation and Results

Ninety three patients were subjected to polysomnography, fifty nine patients were found to have AHI >5 and 34 were found to have AHI <5 and were taken as cases and controls respectively. Among the cases 15 were mild, 17 were moderate and 27 were severe OSA patients.

Table 1 summarizes the characteristics of study population

Figure 1 shows the flow diagram for selecting study population

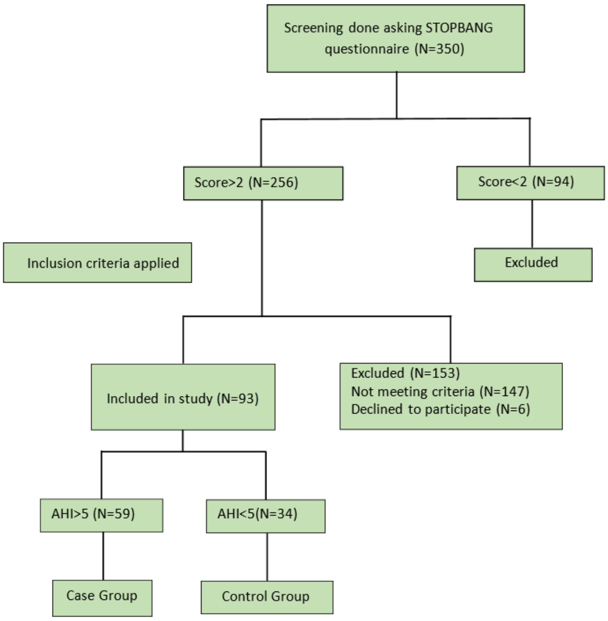

Figure 1: Flow diagram of study population selection

3.1. Relation between AHI and age

Figure 2 shows age distribution of study population.

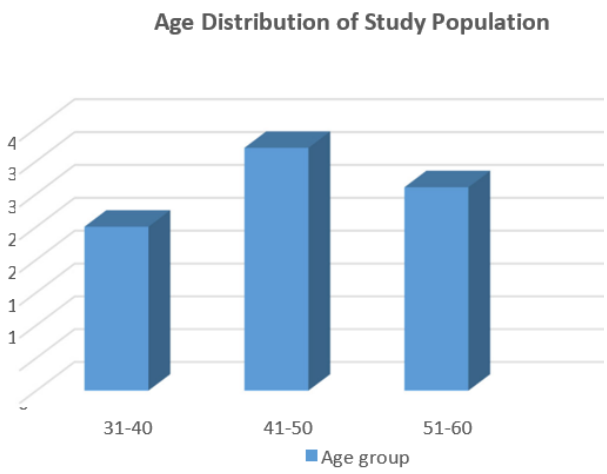

Figure 2: Chart showing age distribution of the study population

Prevalence and severity of OSA increases with age as shown in Figure 3.

In this study we found mean AHI highest in patients between 51-60 years {48.72+/-(29.63)} which was followed by patients in forty-one to fifty years of age {45.46 +-(32.35)} and patients in 31-40 years of age {31.08 +-(26.5)} which are shown in chart 4. Increase in age was found to be associated with higher AHI on comparison of mean AHI using ANOVA test in different age groups (F value 8.62 and

Table 1: Table summarizing characteristic features of cases and controls

S.No.	Profile		Case	Control
1.	Total		59	34
2.	Age (years)		47.97±8.42	46.35±7.29
3.	Sex	M	50	28
		F	9	6
4.	Weight (kg)		86.9±18.14	78.81±16.94
5.	Height (cms)		159.63±19.6	162.62±13.56
6.	BMI (kg/m2)		33.73±7.48	29.66±4.88
7.	Neck circumference (cms)		37.87±5.08	29.53±2.6
8.	Mean AHI		43.13±30.21	4.43±0.65
9.	Vitamin D (ng/dl)		21.02±7.27	24.48±6.9

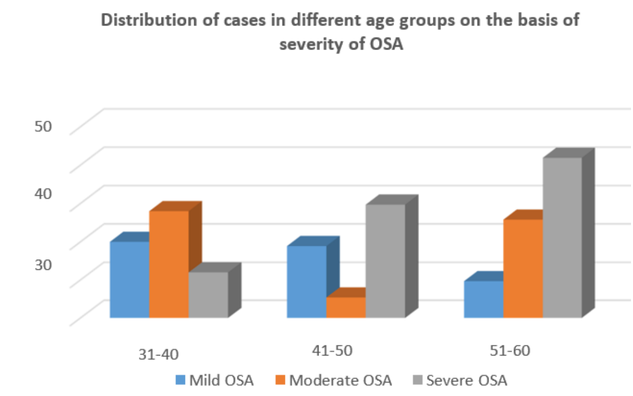

Figure 3: Chart showing classification of patients according to severity of obstructive sleep apnea

p< 0.05).

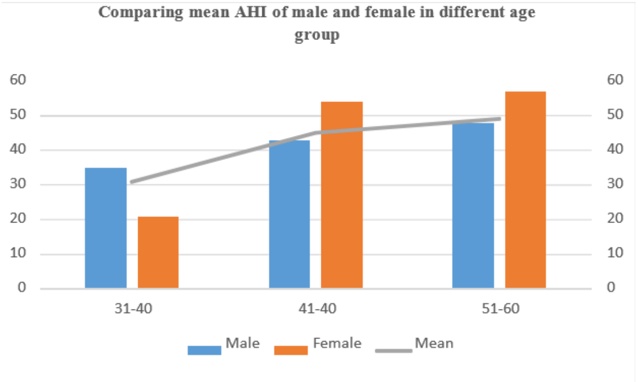

Figure 4: Chart showing comparison of apnea hypoapnea index of different age groups between men and women

3.2. Co-relation between AHI and vitamin D

In this study we found that mean vitamin D levels were decreasing as severity of with increasing severity of obstructive sleep apnea increased as follows:

Levels of mean 25(OH)D

OSA group: 24 12 +/-6 27 ng/dl

Moderate OSA group: 20.09 +/- 7.55 ng/dl

Severe OSA group: 19.89 +/- 7.36 ng/dl

p value was less than 0.05 using ANOVA test so this data was found to be statistically significant.

Figure 5 shows results of correlation between apnea hypoapnea index and vitamin D level which was a negative correlation using pearson correlation test and it was statistically significant (p <0.001, r= -0.286).

Controls were found to have higher mean vitamin D levels (4.48 +/- 6.92) than cases (21 .02+/- 7.27) (p<0.05 for F statistics, t value =2.246, p<0.027, df =88). Highest level of vitamin D in control and case was 12ng/dl and 10ng/dl and lowest level was 47ng/dl and 37ng/dl in control and case respectively. (Figure 6)

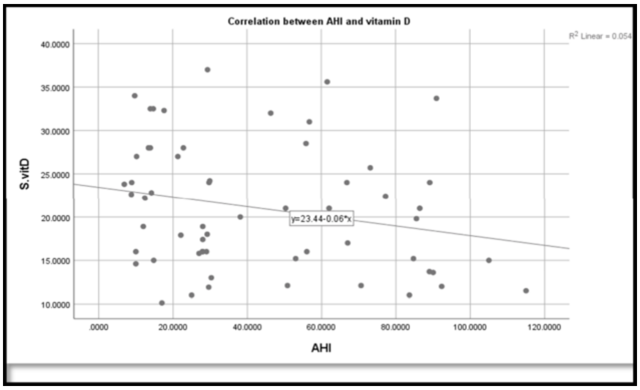

Figure 5: Chart showing correlation between apnea hypoapnea index and level of vitamin D

3.3. Relation between AHI and obesity

Figure 7 shows the classification of patients according to severity of OSA.

Obesity class III had maximum number of severe OSA patients followed by obesity class II, obesity class I, over weight and normal (Figure 8). Severity of obesity and severity of OSA were found to be statistically significant (fisher's test, F = 24.118, p< 0.05). And

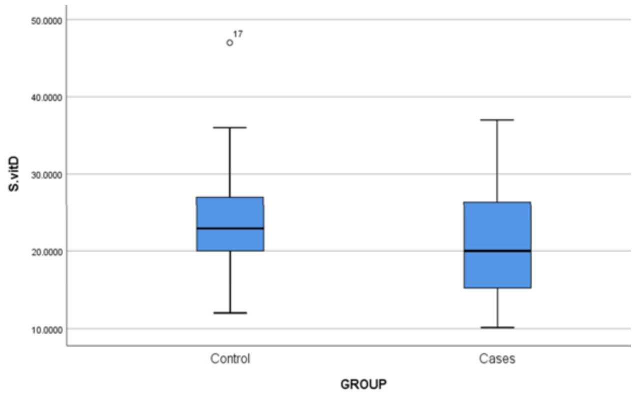

Figure 6: Chart showing mean levels of vitamin D in study population

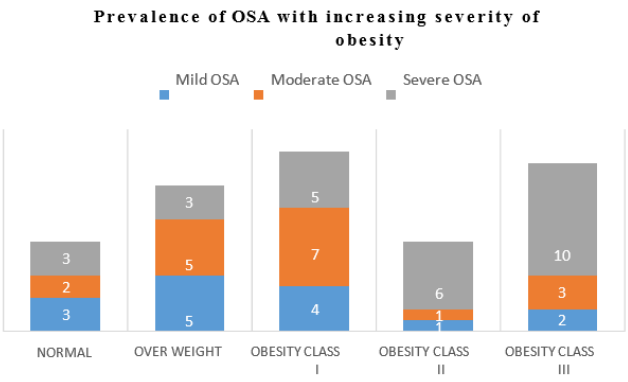

Figure 8: Chart showing Prevalence of obstructive sleep apnea with increasing severity of obesity

having positive correlation using pearson's correlation test (r=0.434, P<0.05) (Figure 9).

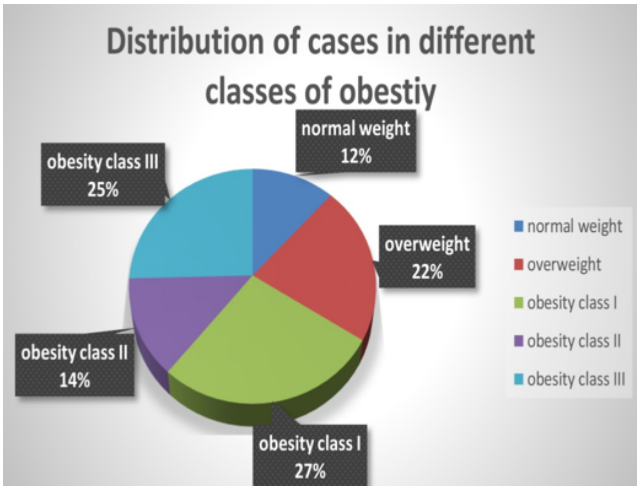

Figure 7: Chart showing pie diagram of cases according to obstructive sleep apnea severity and obesity

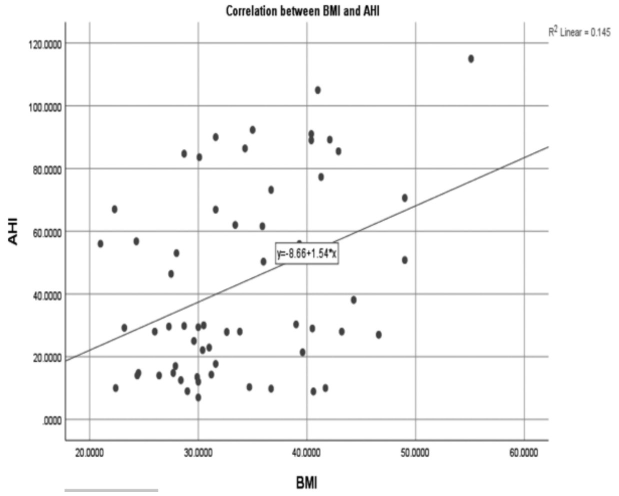

Figure 9: Chart showing scattered dot-plot diagram with a positive correlation between body mass index and apnea hypoapnea index

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4. Discussion

Most common sleep disordered sleeping is obstructive sleep apnea and is associated with many other comorbidities such as cardiovascular, metabolic, hormonal disorders and inflammatory derangements.

Fifty nine OSA cases with mean age 48.029 ±8.435 years, neck circumference 37.8 ±5.08 cm and BMI 33.73 ±7.48 kg/m2 were compared with thirty four matched controls.

Liguori et al[17] studied comparison of ninety two obstructive sleep apnea patients and had 50 controls matched for age and sex. A case control study was also done by Tomiyana et al[18] with a comparable study population.

Vitamin D level was inversely associated with numerous obstructive sleep apnea parameters as documented with polysomnography, including apnea hypoapnea index, baseline oxygen concentration and also time spent below ninety percent oxygen saturation and desaturation index.

Mean level of vitamin D was found to be significantly lower in cases than controls which was further decreasing with increasing severity of OSA , thus had a negative correlation between apnea hypoapnea index and serum vitamin D level.

To find a relation between OSA and vitamin D levels a meta analysis was done by Upala et al.[19]

Liguori et al. showed that the levels of vitamin D in cases of obstructive sleep apnea was significantly lower as compared to controls.[17]

In a study done by Chen et al on women they found that as severity of obstructive sleep apnea increased vitamin D levels decreased.[20]

Vitamin D levels were found to be higher in non obstructive sleep apnea group than obstructive sleep apnea group by Kerley et al, in Caucasian population.[21]

Mete and his coworkers[22] reported that 78% patients of OSA with AHI > 30 Were deficient in vitamin D (20mg/dl) as compared to 50% among controls with AHI < 5.

Kheirandish-Gozal and colleagues[23] conducted a study on pediatric patients with a mean age between 6.5-7.2 years with OSA and found a significant correlation between apnea hypoapnea index and vitamin D level.(r = 20.285; p=0.001).

Adenotonsillar hypertrophy leading to upper airway inflammation is a major contributor of OSA in children as shown by Bozkurt NC Et al in their study.[12]

However there are studies which do not show any significant association between severity of obstructive sleep apnea and vitamin D level such as done by Salepci et al, Yassa et al,[24] and Goswami et al.[25]

This study included patients between thirty to sixty years of age. largest number of patients were in age group between forty one to fifty years (39.8%). mean AHI in patients of 51-60 years of age was highest {48.72 ±29.63} compared to 31.08 ± 26.5 in patients between 31-40 years of age which was found to be statistically significant showing that increase in age can be a significant risk factor for obstructive sleep apnea.

Ancoli-Israel et al conducted a study using home polysomnography on probability sample of 427 individuals between sixty five to ninety five years of age. They found that apnea hypoapnea index equal to or greater than 10 was found in seventy percent males and fifty six percent females which was approximately three times higher than prevalence estimates of obstructive sleepapnea in middle age.[26]

Nearly twice higher Prevalence of obstructive sleep apnea in patients of age group 65-100years of age with a 95% as that of middle age was shown by Bixler et al in their study.[27]

Duranet al. and Littner et al., showed similar results suggesting that increasing age can pose to be a risk factor for obstructive sleep apnea.[28,29]

A positive and statistically significant correlation between apnea hypoapnea index and body mass index was also found in this study (r=0.434, P <.05) as maximum number of patients fell into class III obesity group suggesting OSA is more common among obese and with increasing obesity severity of obstructive sleep apnea also worsens .

Morbidly obese patients have twelve to thirty times higher incidence of obstructive sleep apnea than general population.

A ten percent weight gain is associated with an approximate thirty two percent increase in apnea hypoapnea index and ten percent weight loss associated with twenty six percent decrease in apnea hypoapnea index.[30] Odds of developing moderate to severe OSA increases by 6 fold with 10% increase in weight.

However, Ancoli-Israel et al. found that changes in BMI were not significantly associated with changes in AHI.[26]

As it is already known from literature that increasing age, female sex and obesity are the risk factors for Vitamin D deficiency, we can expect decreasing trend in serum 25(OH)D level with increasing severity of obstructive sleep apnea. However, it is difficult to establish a direct causal association between them and further larger studies are required for the same.

5. Conclusion

This study concluded that association between severity of obstructive sleep apnea and levels of 25(OH)D is statistically significant. it was also found that as severity of OSA increases, vitamin D level decreases. Increase in age and body mass index also pose as risk factors for obstructive sleep apnea which are associated with low 25(OH)D levels. To benefit the patients, further larger studies should be done to understand the biological processes and relationship between the severity of obstructive sleep apnea and level of vitamin D and establish appropriate screening methods, diagnostic methods and necessary intervention.

6. Limitations

1. Small study population.
2. Various parameters like sun exposue and dietary habits were not assessed.
3. Metabolic biomarkers such as parathyroid hormome levels, lipids and glycemic indices were not assessed

7. Informed Consent

Written informed consent was obtained from the patients who agreed to take part in the study.

8. Conflict of Interest

None.

9. Source of Funding

None.

10. Acknowledgement

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