

"Study Aetiological, Clinical and Metabolic Profile of Hypocalcaemia in Adults"

Dr.Sanjay Gulhane¹, Dr. Asmita More²

¹Associate Professor, Dept. of Medicine, Dr R N Cooper Hosp & H B T Medical College, Juhu, Mumbai, India

²Senior Resident, Department of Medicine, L T M General Hosp & L T M Medical College, Sion, Mumbai, India
corresponding author: Dr. Asmita More

Abstract:

Aims:

To study clinical presentations , ascertain etiological factors and associated metabolic parameters in patients with hypocalcaemia

Material and Methods: Amongst 236 patients having signs and symptoms of hypocalcaemia were evaluated and 100 patients were enrolled.

Result and Discussion: 54% patients were females. Average age in females was 31.74 years. Majority of females (85.18%) were in reproductive age group, six were lactating mothers. Perioral tingling was the commonest clinical presentation in 80% of total patients. Trousseau's sign is having 80% sensitivity. Sedentary lifestyle, lack of exercise, inadequate sunlight exposure, Burkha, multiparity, inadequate dietary intake of calcium were major contributors for Vitamin D deficiency in Women. Vitamin D insufficiency (<30ng) was found in 74% total patient. 60% patients had ECG changes suggestive of QTc prolongation.

Conclusions: Adolescent and young adults are the main age groups who presented with hypocalcaemia and should be worked up for metabolic and genetic diseases. Females have more symptomatic hypocalcaemia than men. Before starting anticonvulsants, supplementation with Vitamin D along with Calcium is must as there is high prevalence of Vitamin D insufficiency and hypocalcaemia. Calcium and Vitamin D supplementation to be considered as a part of standard treatment in cases of CNS tuberculosis where patients are given anticonvulsants and antituberculous drugs together.

Date of Submission: 21-05-2018

Date of Acceptance: 05-06-2018

I. Background and Introduction

Calcium is classified as an "Alkaline Earth Metal" which are located in Group 2 elements of the Periodic Table. Calcium makes up 1%-2% of adult human body weight. Over 99% of it is stored in bones and teeth with the rest stored in blood, muscle, and other tissues. Normal calcium homeostasis is important for the various physiological function of the body. Ringer (1883) showed that calcium was essential for myocardial contraction. McLean and Hastings (1934) showed that this myocardial contraction was the responsibility of the ionized calcium. Whereas protein bound and citrate bound calcium had no effect. Ionized calcium is necessary for blood coagulation and nerve function (Ganong, 2003). It is important to maintain ionized calcium at a near normal concentration, especially during surgery and in critically ill patients (Drop, 1985)¹. Hypocalcaemia may be an asymptomatic laboratory finding or a life threatening metabolic disturbance. The symptoms of hypocalcaemia often reflect the key role of calcium in the process of nerve conduction and the muscle function. Low plasma calcium results in increased neuromuscular excitability. Paresthesia, a tingling sensation, usually present around the mouth, fingers and toes is a common symptom of hypocalcaemia. Leg cramps or Muscle cramps, are due to sustained muscle contractions, can progress to tetany. Convulsions, which may be either focal or generalized, can be a manifestation of hypocalcaemia at any age. Hypocalcaemia is defined as serum calcium levels less than 8.5mg/dl.

The most common cause of hypocalcaemia in primary care is vitamin D deficiency, which depending on population demographics may have prevalence as high as 50%. Hypocalcaemia presents in primary and secondary care, it has a prevalence of 18% in all patients in hospital and 85% in the intensive care unit.²

Vitamin D Deficiency as Pandemic

Estimated 1 billion people are affected with low Vitamin Levels and hypocalcaemia worldwide ³. 64% of women in multinational study in 18 countries: S. America, Europe, The Middle East, Asia, Australia are found to have Vitamin D deficiency⁴. U.S. study showed 84% of Boston men and women > 65 yrs. had 25(OH) D of < 20 ng/ml ⁵. 50% Pregnant women and 65% of infants in one of the Boston study were having vitamin D

deficiency⁶. Vitamin D plays a key role in handling calcium in body and serum Calcium is one of the cheapest investigation readily available to indirectly assess Vitamin D status. So this study was under taken to know the demographic profile, clinical profile, metabolic parameters and etiological profile of the patients with laboratory finding of hypocalcaemia in a tertiary care centre.

II. Methodology of Serum Calcium measurement

Sample Requirements and Precaution:

Total calcium is usually measured in serum or plasma in heparinised whole blood. Blood is drawn from a vein in which the blood is free flowing (i.e without a tourniquet) because venous stasis can result in loss of fluid across the wall of the vein and a relative increase in protein bound calcium. The distribution of calcium between being protein bound or in free solution is dependent on [H⁺] (pH). Because this can change invitro, measurements of serum calcium should be made rapidly after the blood has been drawn and ideally be performed within 30 minutes.

Falsely high Sr Calcium can be seen in following situation:

Liver or renal failure or in patients with lipemic or haemolysed specimens. **Venous occlusion** of the arm during venipuncture may increase the total concentration of serum calcium by up to 0.3 mmol/L. **Posture:** If the patient stands up from a supine position, there may be an increase of 0.05 to 0.20 mmol/L in serum calcium. **Exercise:** if just done before venipuncture tends to increase serum calcium. **Gender:** Men 15 to 45 years of age tend to have serum calcium levels 0.02 to 0.05 mmol/L higher than similarly aged women. **Seasonal variation:** Postmenopausal women, however, have higher levels of calcium in winter as compared to summer.

Falsely low Sr Calcium may also be seen in patients with liver or renal failure or in patients with lipemic or haemolysed specimens and is due to increase in plasma protein concentration caused by hemodynamic changes.

If any error is suspected, the measurement is to be redone; blood should be drawn following an overnight fast because the daily intake of calcium may contribute to the serum calcium concentration as much as 0.15 mmol/L.

In true hypocalcaemia, parathyroid hormone concentrations should be high if the parathyroids are appropriately responding to the reduced negative feedback of calcium or low if these glands are the cause of the problem. "Normal" concentrations of parathyroid hormone in this context are inappropriate and thus abnormal. A high concentration of parathyroid hormone in the presence of normal renal function suggests deficiency of vitamin D or calcium malabsorption.

This study was conducted in a tertiary care centre over period of 24 months after obtaining the permission from Institution ethics committee. All patients complaining of or having suspected signs and symptoms of hypocalcaemia were enrolled and were evaluated during the first contact in Emergency Medical Services (EMS), Out Patient Department (OPD) or in Indoor Patient Department (IPD). All patients enrolled were evaluated in detailed after obtaining informed consent. Patient with Age >12 years and corrected Serum Ca⁺⁺ < 8.5 meq [Corrected Calcium = 0.8 X (Normal serum albumin (=4) - Pt's Albumin) + Serum Ca] were included. Those with Chronic renal disease(diagnosed earlier or diagnosed during hospital stay), patients already receiving Ca and Vitamin D supplements, patients receiving chronic antacid therapy causing hypocalcaemia and patients not willing for the further investigation and workup and those not consenting for study were excluded.

III. Assays and Normal Range

Serum Calcium: Direct calorimetric method for determination of Serum Calcium by **OCPC** method was used.

Vitamin D: Chemiluminescent immunoassay (**CLIA**) technology for determining 25(OH) D and 125I radioimmunoassay (**RIA**) for estimation serum 1, 25-hydroxyvitamin D [1, 25(OH) D3] was used.

Parathyroid hormone level (intact PTH): Assay utilized **CLIA** technology

For the purpose of the study,

Sr Calcium: 8.5-10.5mg/dl is considered as normal range.

Sr PTH (intact): 10-51 pg/ml is considered normal.

Hypocalcaemia: Sr. Calcium levels below 8.5mg/dl.

Vit D sufficiency: Sr 25(OH) D levels above 30 ng/ml.

Vit D insufficiency: Sr 25 (OH) D levels below 20 ng/ml

Vit D deficiency: Sr 25 (OH) D level below 10 ng/ml

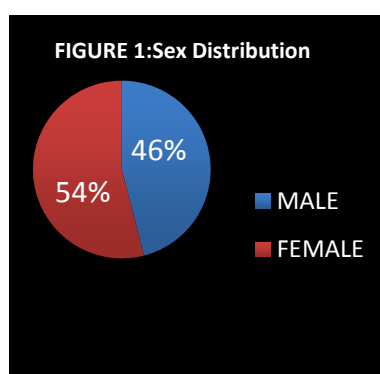
Hypoparathyroidism: Sr intact PTH levels below 10 pg/ml

Hypomagnesaemia: Sr Mg levels less than 1.5mg/dl

Observations and Results

This was a prospective study carried out in the tertiary care center in patients diagnosed to have hypocalcaemia. Data analysis was done by using statistical methods with application of Students ‘t’ test wherever indicated. Amongst 236 patients evaluated, 100 patients were enrolled. The demographic data of patients is included in the study are as shown in Table 1, it reveals that the maximum no. of patients (38) were in the age group of 20- 30 years .The age ranged from 14 years to 71 years. The youngest patient was of 14 yr. age was diagnosed as Down’s syndrome with mental retardation with Vitamin D deficiency .The eldest patient was a 71 year old female suffering with atypical pneumonia with Vitamin D deficiency. Among the patients enrolled 74% patients were Hindu and 26% were Muslims by religion.

Parameters	
No. of cases n=100	Percentage
Age (yrs)	
12-20	12(12.0%)
21-30	38(38.0%)
31-40	22(22.0)
41-50	8(8.0%)
>51	20(20.0%)
Sex (%)	
Male	46(46.0%)
Female	54(54.0%)
Religion	
Hindu	74(74.0%)
Muslim	26(26.0%)



As shown in TABLE 1 & FIGURE 1, out of total patients (n=100), 54% patients were females (n=54). Average age in females was 31.74 years and in males 36.73 years.

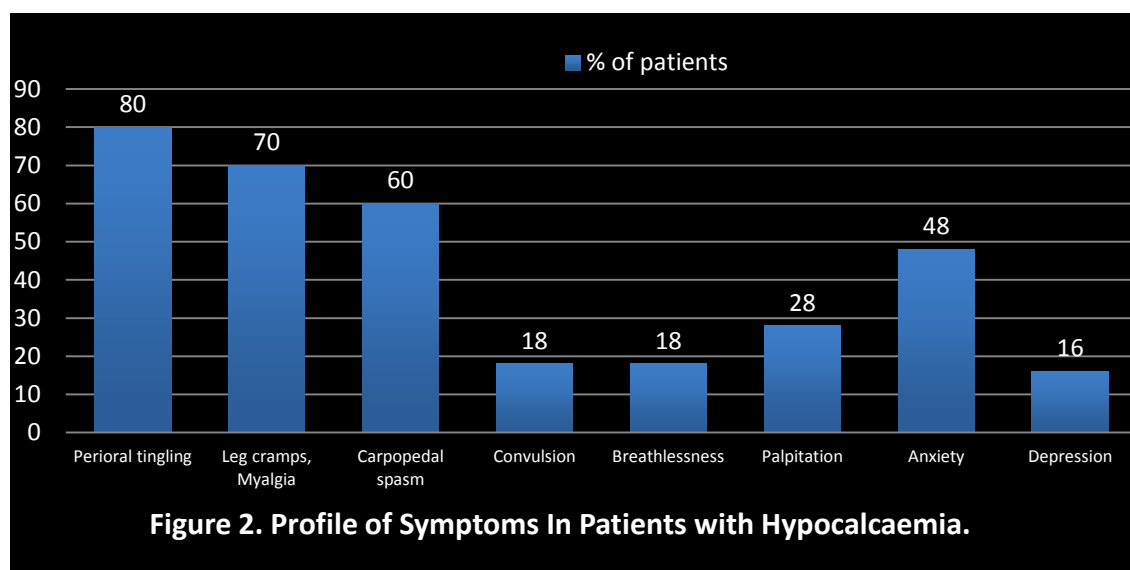
Parameters	Females [Total(N=54)]
Married	48
Unmarried	6
Multiparous	42
Uniparous	6
Lactating	12
Burkha/Purda Users	22
Non-Vegetarian	18
Skeletal Abnormalities	28

Average age in females was 31.74 years. Majority of females (85.18%) were in reproductive age group (n=46).Among 54 females 6 were unmarried and came for short stature in endocrine outdoor department .48 females were married (88.88%).In the study group 12 (22.22%) were lactating mothers. 81.48% of females had low (below 30ng/ml) Vitamin D levels as compared to 56.52% of males.

Clinical features and relevant history:

According to Figure 2, Perioral tingling was the commonest clinical presentation in 80%. Muscular pain was present in 70% of all patients. Carpopedal spasms were the third most common presentation. Palpitation, breathlessness and convulsion were present in 28%, 18% and 18% patients respectively. Anxiety is one of the

neuropsychiatric manifestations in 48% patients. Perioral tingling sensation was also common in both sex groups. In females, Perioral tingling sensation was marginally more than men. Anxiety and depression was marginally more in men.



Dietary factors and gastrointestinal factors:

Amongst total 100 patients, 46 patients had mix diet. However 54 patients were only on vegetarian diet. Low milk and milk product intake, low fruit intake and high carbohydrate diet was found in vegetarian patients. Even, oil used to prepare food was not fortified with Vitamin D. This all were contributory factors for low Serum calcium and low Vitamin D diet which resulted into hypocalcaemia. Mix diet consisted of adequate Nonvegetarian food twice a week. Alcohol consumption was seen in 26 patients, all were men. 12 of them also had low serum Magnesium levels (<1.5mg/dl) & 14 had Vitamin D levels low (<30ng/ml). Poor dietary intake was also present in alcoholics. 2 patients had multiple loose motions per day (chronic) since 2 years and one diagnosed as Crohn’s disease on the intestinal biopsy while other was undiagnosed, they had carpopedal spasms, perioral tingling sensation and leg cramps during presentation. Patients Body mass index was less than 18 suggesting malnutrition. They were put on oral high dose Calcium and weekly Vitamin D supplements.

Profile of patients presenting with convulsion (n=18).

18 patients had history of convulsion on admission. 12 were females and 6 were males. Among 18 patients, 14 patients were symptomatic prior to convulsion and had carpopedal spasm and perioral numbness. 10 patients also had leg cramps intermittently. 16 patients had neuropsychiatric symptoms only i.e. anxiety in 10 patients and depression in 6 patients. Clinically, Trousseau’s sign and Chvostek’s sign was present in 16 of the 18 patients. The final diagnosis which was reached after through investigations of these patients presenting of convulsions were as follows: Drug induced Vitamin D Deficiency (n=6), Vitamin D Insufficiency (n=8) and idiopathic Hypoparathyroidism (n=2) and hypomagnesaemia (n=4).

Profile of patients in intensive care unit:

SYMPTOMS→ DIAGNOSIS↓	FEVER (16)	JAUNDICE (10)	OLIGURIA (20)	ABDOMINAL PAIN (16)
LEPTOSPIROSIS	8	6	8	2
MALARIA	4	4	4	2
AFI	2	0	2	2
PNEUMONIA	2	0	2	0
PANCREATITIS	0	0	2	8
OTHERS	0	0	6	2

Table no.3: Correlation of symptoms and diagnosis of patients admitted in intensive care (n=30).

30 patients having sign and symptoms of hypocalcaemia were critically ill and requiring intensive

care, were also enrolled in the study. As shown in table 3, Fever was presenting symptom in 16 patients in intensive care. Acute abdominal pain was presenting symptom in 16 patients. Further workup revealed that, 8 had Leptospirosis, 4 had malarial infestation, 2 were undiagnosed acute febrile illness with acute respiratory distress syndrome, and 4 had Respiratory tract infection (Pneumonia). Among the intensive care patients 8 had acute alcohol induced Pancreatitis with SIRS.

Table 4: Drug History

ETIOLOGY	DRUGS	No.	VIT D
Tuberculosis	Antituberculous	n=8	
Cervical lymphadenopathy	INH+RCIN+ETB+PZA	2	I
Abdominal lymphadenopathy	INH+RCIN+ETB+PZA	2	I
Disseminated	INH+RCIN+ETB+PZA	2	I
Pulmonary+CNS tuberculoma	INH+RCIN+ETB+PZA+T.Phenytoin	2	D
	Antiepileptic's	n=8	
Seizure disorder with psychosis	Phenytoin, Clobazam	2	D
Idiopathic generalized epilepsy	Phenytoin	4	D
Idiopathic hypoparathyroidism	Valproate, Clobazam	2	I
Preeclamsia	Inj MgSO4	2	I

INH=Isoniazid, Rcin=Rifampicin, PZA=Pyrazinamide, ETB=Ethambutol. Vitamin D Status I = Insufficiency D = Deficiency

8 patients were diagnosed case of tuberculosis were on antituberculous medications (as per Table 4).The drugs included –Isoniazid, Rifampicin, Ethambutol and Pyrazinamide. All 8 patients on anti- tuberculous treatment (ATT) had low Vitamin D levels (< 30ng/ml).Among these 8 patients, 6 had Vitamin D insufficiency (30-10ng/ml) and 2 had Vitamin D deficiency (<10ng/ml). 2 patient, postpartum female with preeclampsia developed convulsion on second day postpartum, they were given Inj. MgSO4 as per Pritchard's regime predelivery .On further investigation they were having underlying Vitamin D insufficiency.

Table 5:Post-Surgical Causes:

Thyroid Surgery	Type	n=12
Total Thyroidectomy	Mutinodular Goitre	4
	Pappillary CA	6
	Medullary CA	2
Parathyroid Surgery	Parathyroid adenoma	2

CA:→Carcinoma

As per table 5, 12 patient undergone neck surgeries, 10 had total thyroidectomy and 2 had parathyroid adenoma surgery. Etiology is as per in the table no.5, all patients had persistent hypocalcaemia due to post-surgical hypoparathyroidism .

Comorbid Illness: 2 patients had chronic obstructive lung disease. 4 patients were Diabetic on regular oral hypoglycaemic medications. 10 had hypertension and on regular visits with controlled blood pressure on medications.

On examination: All patients on admission were clinically evaluated for signs suggesting neuromuscular irritability. General examination for other signs of hypocalcaemia like ophthalmic, skeletal and ectodermal changes was done. The finding was as follows. (Figure 2)

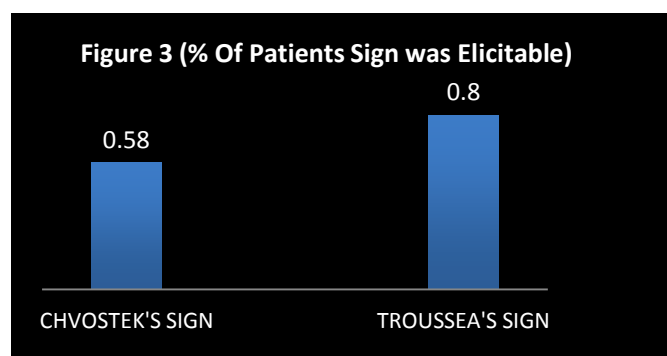


Figure3:-Specific signs of hypocalcaemia:

Data from Figure 3 reveals that 80% patients were examined had Trousseau's sign. The difference between male and female cases was comparable but statistically not significant. General examination revealed that pallor was present in 60% (n=60) of patients. 70.4% of females had pallor as compared to 47.8% of males. Icterus was present in 34% which included patients of Leptospirosis and Malaria with multiorgan dysfunction, acute febrile illness, Alcoholic liver disease, acute pancreatitis patients. Pedal edema in 12%, lymphadenopathy in 2% and cyanosis in 2%.

Ophthalmic examination, Cataract was seen in 18 patients.10 out of that 18 were of age more than age of 40, with mean age of 61.6years.And 8 out of 18 were below age 40yrs (early onset of cataract) with mean age of 23yrs.Skeletal abnormalities in the form of short stature, Genu valgum, skeletal dysplasia's, malunited or nonunited fractures were present. Total 36 patients had skeletal abnormalities, females (n=28) and males (n=8). Patients were evaluated for causes of short stature, 61.1% had Vitamin D insufficiency (10-30ng/ml) and 27.77% had severe Vitamin D Deficiency (below 10ng/dl), 11.11% had different causes like constitutional, familial or endocrine.

Table 6: Body Mass Index (BMI) of Patients

BMI(Kg/M ²)	No. Patients (%)
<18.5	38%
18.5—25	30%
>25	2%

Table 6, suggest that 38% of the patients were malnourished [BMI less than 18.5 (kg/ m²)]. Only 2% patients were having BMI >25.They were diagnosed with Pseudopseudohypoparathyroidism.

Investigations: Anaemia, (Haemoglobin level less than 11gm/dl), was found in 26% patients. Average haemoglobin was 10.46gm/dl .Leucocytosis and thrombocytopenia was present in critically ill patients.

Table7: Blood parameters of patients of hypocalcaemia

Diagnosis	No. of Male	No. Female	Total
Vitamin D Deficiency	4	12	16
Insufficiency	22	32	54
Hypomagnesaemia	22	18	40
Hypoparathyroidism			
Acquired	6	8	14
Idiopathic	2	0	2
Pseudopseudohypoparathyroidism	2	0	2
Critical Illness Related	22	8	30

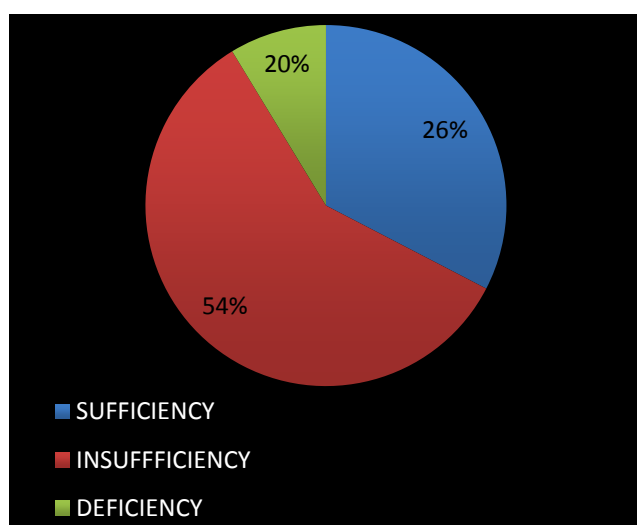


Figure 5. Vitamin D status in hypocalcaemic patients

According to this table no.7, most of the patients had hypovitaminosis D i.e.74%, Insufficiency in 54%

of patients and Deficiency in 20% of patient. Vitamin D deficiency and insufficiency was a major cause of hypocalcaemia in females compared to males. Critical illness related hypocalcaemia is a special category of all causes of hypocalcaemia, because normal interactions between the organs are impaired or altered, and cannot maintain calcium equilibrium.

A patient could have one or more causes of hypocalcaemia. Patient receiving multiple drugs like proton pump inhibitors, antacids and antibiotics can lead to low calcium levels. Also there can be transient alkalosis which can precipitate hypocalcaemia symptoms even if total calcium appears normal. Patients receiving blood transfusions i.e. citrated blood can cause hypocalcaemia.⁷ patients admitted in intensive care received transfusion in this study.

ECG Changes: On admission ECG changes in terms of QTc prolongation and arrhythmia was evaluated .60% patients had QTc prolongation (corrected QT more than 0.45sec).The patient having QTc as 0.56sec had corrected serum calcium of 5.8mg/dl and was diagnosed as Vitamin D deficiency. There was no major difference noted in QTc prolongation of patients treated outdoor, indoor or intensive care unit. Arrhythmia was found in 10 patients of intensive care and one patient admitted indoor. The patient who was admitted as case of palpitation was found to have multiple VPC (Ventricular Premature contractions) and only abnormality was low calcium levels.

IV. Discussion

A total of 236 patients evaluated, 100 patients could be enrolled in the study.136 patients who were excluded were cases of Chronic renal disease (n=108), patients not willing for further investigations or admission (n=28). There were 12 patients in age group of 12-20years, 38 patients in age group of 20-30 years, 22 patients in 31-40 years, 8 in 41- 50 years age group and 20 in age more than 50 years. Low Vitamin D was the commonest cause in both younger and older patients. Among the patients of age group of 12-20 years(youngest age group) the diagnosis were as follows- Disseminated tuberculosis with Drug induced hypocalcaemia, Dietary Vitamin D deficiency with short stature , Idiopathic Hypoparathyroidism, Down's syndrome with Vitamin D deficiency and Pseudohypoparathyroidism. The older group (age >50 years) suffered from causes like Vitamin D insufficiency, alcohol related hypomagnesaemia or critically illness related hypocalcaemia. Marwaha et al have reported Vitamin D deficiency in healthy Indians above 50 years of age from North India.⁷ More than half of individuals in above study were on Vitamin D and calcium supplementation, but in inadequate dosages.⁷In our study 54 patients were females with average age 31.74 years. Majority of females (85.18%) were in reproductive age group. Among 54 females, 11% were unmarried and had presenting complaint of short stature (in endocrine outdoor department). 89% females were married, all women were multiparous and 22.22% were lactating mothers. A Mumbai based study conducted by Deepak et al in January to December 2011, reveals that women between the age group of 12 – 35 years have a higher deficient value of Vitamin D as compared to men across age groups. Of a total of 33,444 people screened, 82.54% people showed abnormal low values. Among them 65.84% (n=18176) were females, 30.83% (n=8510) were males, 3.33% were children^{8,9}

Harinarayan CV et al¹⁰ have studied 25(OH) D and BMD in women of reproductive (WR) age group and post-menopausal women (PMW) in South India. They have reported Vitamin D deficiency in 76% in WR, 70% in PMW, insufficiency in 16.5% in WR and 23% in PMW. In this study there is Vitamin D deficiency which coexists with low BMD. As per S.P.S. Teotia & M. Teotia et al, "Nutritional vitamin D-deficiency is the commonest nutritional bone disease prevalent in Indian mother." They found that it is due to inadequate exposure to sunlight (UVB 290-315nm) in the mothers who also had repeated pregnancies and prolonged lactation. According to study done by Marwaha et al "High prevalence of hypovitaminosis D was observed in pregnancy, lactation and infancy with no significant inter-trimester differences in serum 25(OH) D levels".¹¹

Among total patients, 23% patients had mix diet in form adequate Nonvegetarian food twice a week. In this study out of 54 females, 11 were Muslim by religion and used Burkha. Burkha is a black coloured dress worn to completely cover the body before getting outdoors as a part of customs. As per observations by Marwaha et al "All women, house bound, living in crowded localities and dark alleys, with covered-up style of clothing and *purdah* and thus, deprived of sun exposure are at the highest risk of developing vitamin D deficiency".¹¹

Perioral tingling was the commonest clinical presentation in 80% of total patients, followed by leg cramps ,carpedal spasms, anxiety, palpitations, breathlessness and convulsions in a decreasing order. Anne L. Schafe et el⁹ "The hallmark of acute hypocalcaemia is neuromuscular irritability". However no study mentioned about the frequency of occurrence of symptoms. Patients were enrolled from Outpatient department (OPD) (n=34), Inpatient department (IPD) (n=36) and Medical intensive care unit (MICU) (n=30). Among patients coming to OPD, 28 were females and 6 were male who presented with complains of body ache, leg cramps, perioral tingling and palpitations. Vitamin D levels were found low (<30ng/ml) in 30 of 34 patients. Of the 30

patients admitted in Medical Intensive Care unit(MICU- table 4), One patient had snake bite following which he had acute renal shutdown ,he received haemodialysis alternate day for 24 days after which, he started having urine output and recovered completely. According to Robert et al¹² "Patients with non-traumatic acute kidney injury, developed hypocalcaemia in early course of illness." The cause may be related to excessive calcium loss through kidney and inadequate active Vitamin D synthesis.

18% patients had history of convulsion (Grand mal, Petit mal, or focal) at the time of admission (6 males and 12 females). Age ranged from 16 years to 64years.10 patients were already diagnosed and were on anticonvulsant medication which included -Phenytoin (n= 8), Sodium Valproate and Clobazam (n=2). Among 18 patients having convulsion and hypocalcaemia, anxiety, carpopedal spasm and perioral numbness were preceding the occurrence of convulsions. So, if the symptoms were earlier recognized and treated, convulsion could have been prevented. The final diagnosis which was reached after the through investigations of these 18 patients were as follows: 6 had drug induced Vitamin D Deficiency, 8 had Vitamin D Insufficiency, 2 had idiopathic Hypoparathyroidism and 2 had Pseudo- hypoparathyroidism. According to Lorraine A. Fitzpatrick et al^{9,13} "patients with idiopathic hypoparathyroidism or pseudohypoparathyroidism may develop neurological complications, including calcifications of the basal ganglia and other areas of the brain, and extrapyramidal neurologic symptoms".

8 patients were diagnosed case of Tuberculosis (table 5).All were on antituberculous medications which included Isoniazid, Rifampicin, Ethambutol and Pyrazinamide. All 8 patients had drug induced hypovitaminosis D (< 30ng/ml).One patient who had CNS tuberculosis was also on antiepileptic medication i.e. Phenytoin. In spite of on regular treatment pt developed convulsion and was hospitalized .On the day of admission her blood sample was collected and analyzed. She had Sr phenytoin levels in normal therapeutic range, but her serum calcium was very low. She was given intravenous Calcium Gluconate infusion on the day of admission, followed by Vitamin D and oral Calcium .Her convulsion responded to same .Her skeletal X-rays were suggestive of osteomalacia. Hypocalcaemia and osteomalacia have been described with prolonged therapy with anticonvulsants such as phenytoin or Phenobarbital^{14, 15}. These drugs like Phenytoin and Rifampicin are inducers of cytochrome P450 (CYP450), causing increased vitamin D degradation. They also decrease calcium resorption in the gut¹⁵. Decreased circulating levels of calcidiol are also observed in patients treated with drugs such Carbamazepine, Isoniazid, Theophylline and Rifampicin, as a result of induction of CYP450 enzyme activity, which metabolizes calcidiol to inactive vitamin D metabolites^{14,15,16,17}.According to study of Gniatkowska-Nowakowska¹⁵ on 126 patients of epilepsy, about risk of fracture in children with epilepsy than in children without epilepsy. The frequency of fractures is 2-3 times greater in children with epilepsy than in the control group. Osteoporosis and osteopenia is more often present in children who have taken Anti-Epileptic Drugs.

One patient, case of preeclampsia, developed convulsion on day 2 of delivery .She was given Injection MgSO₄ as per Pritchard's regime predelivery .She developed oliguria post-delivery. When calcium values were checked for evaluation of cause of convulsion ,they were low (corrected Ca-6.4mg/dl).MgSO₄ injection is known to cause hypocalcaemia. Thus monitoring of the patient's Sr Mg and Sr Calcium is most important. Hypermagnesemia can also cause hypocalcaemia by both suppressing PTH secretion and blunting its peripheral actions. Moreover magnesium ions compete with calcium for reabsorption in the loop of Henle; thus renal loss of calcium contributes to hypocalcaemia. Similarly, asymptomatic hypocalcaemia is relatively frequent during magnesium sulfate tocolytic therapy. Indeed, only six cases of clinically important hypocalcaemia have been reported when magnesium is given for tocolysis¹⁴.

14 patients had undergone neck surgery (table 6) Post thyroidectomy patients were on thyroid replacements. All had postsurgical acquired hypoparathyroidism and hypocalcaemia. 8 patients were also having Vitamin D lower than 30ng/ml. Study conducted by Mazhar Iqbal et al¹⁸ at Karachi found that, frequency of hypocalcaemia in total thyroidectomy was 21.6% and was transient due to hypoparathyroidism. Kirkby-Bott J¹⁹ studied 166 patients from January 2006 to March 2009, at Hammersmith Hospital, London, undergone total thyroidectomy regarding the relation between preoperative vitamin D₃ levels and postoperative corrected calcium levels. The study concluded that, there is a significant difference in postoperative hypocalcaemia rates between those with vitamin D levels >20 ng/ml and those with a level of<10 ng/ml. Vitamin D deficiency leads to a delay in discharge owing to a higher likelihood of hypocalcaemia. Vitamin D₃ deficiency was also associated with significant longer hospital stay (median stay 2 days vs. 1 day).

In this study, Alcohol consumption was seen in 26 patients, all were men. 16 of them had low Sr Magnesium levels (<1.5mg/dl) & 14 had Vitamin D levels low (<30ng/ml). Malnutrition is common in alcoholics²⁰. Decreased dietary intake, as well as malabsorption and alterations in the metabolism of nutrients, are causes of nutrient deficiencies in alcoholism. Some of the effects of alcohol on the liver may be mediated by its actions on nutrient absorption and metabolism. As per study by Elisaf M and Liamis G²¹ in series of alcoholic patients (n = 127) admitted to department because of causes related to alcohol abuse, the incidence of true hypocalcaemia was 14.2%. It is known that acute alcohol consumption suppresses the secretion of PTH, leading

to hypocalcaemia. In addition, respiratory alkalosis (inducing renal PTH resistance) and hypomagnesaemia frequently observed in alcoholic subjects may also contribute to the development of hypocalcaemia.

On evaluation of patient for signs of neuromuscular irritability, 80% patients Trousseau's sign and in 58% patients Chvostek's sign was elicitable. Although the two signs have never been directly compared, Trousseau's sign is more specific for hypocalcaemia than Chvostek's sign. In study done by Kugelberg E et al²², 94% of patients with confirmed hypocalcaemia had a positive Trousseau's sign, whereas only 1% of healthy patients demonstrated a positive Trousseau's sign. Also, 29% of patients with laboratory confirmed hypocalcaemia had a negative Chvostek's sign.

Ophthalmic examination revealed that 18 patients had cataract, 10 patients were age more than 40 years and 8 were below 40 years. The diagnosis of these 8 patients were- Vitamin D deficiency, Pseudohypoparathyroidism, idiopathic hypoparathyroidism, and 2 were postoperative case of acquired hypoparathyroidism (surgery done for papillary Ca thyroid). All these 8 patients, hypocalcaemia was the common metabolic abnormality. Cataract is most commonly due to degenerative changes, but if found in young age metabolic causes should be looked for.

Short stature was present in 26 female and 10 male. When evaluated 22 patients had Vitamin D levels between 10-30 ng/ml and 10 patients were having Vitamin D deficiency (<10ng/ml). So all patients presenting to us with primary complaint of smaller height compared to peers should be thoroughly evaluated.

In this study, Vitamin D insufficiency was found in 54% of patients and Deficiency in 20% of patient. This suggests that a patient presenting with symptoms of hypocalcaemia, 75% chances that his Vitamin D levels are low. Patient will be benefit with Vitamin D and Calcium supplementation. According to CV Harinarayan et al²³ "Vitamin D deficiency is epidemic in India despite of plenty of sunshine. The interpretation of vitamin D levels should be done with the solar zenith angle, minimal erythemal dose, skin type, UV Index and geographical location". There may be a public health need to fortify Indian foods with vitamin D.

In a study done by Balasubramanian Ket al²⁴ and Rajeswari J et al²⁵ in northern India, most of the patient had undetectable serum 25(OH) D levels with serum parathyroid hormone (PTH) values more than four folds above upper limit of normal. They found, anticonvulsant and antituberculous therapy, fluoride excess, prolonged steroid therapy and bisphosphonates as precipitating cause for clinically overt rickets and osteomalacia. Almost one third of patients with osteomalacia have history of anticonvulsant, antituberculous therapy or steroid use in the immediate preceding years.

Rathore J et al²⁶ concluded that, VDR gene polymorphisms and hypovitaminosis D may predispose to MDR-TB. Lower serum 25(OH)D may increase time to MDR-TB sputum smear negativity.

Maximum-60% patients were found to have ECG changes in terms of QTc prolongation. The average calculated QTc was 0.45 sec. The QT interval was average 0.44 sec in outdoor, 0.455 sec in indoor patients and 0.475 sec in intensive care patients. No correlation was found with sex, hypokalemia, hypothyroidism or high creatinine. Acutely ill patients with QT prolongation have longer lengths of hospitalization and nearly three times the odds for mortality than those without QT prolongation²⁶.

Comparison between the outdoor, indoor and intensive care patients revealed that- there was difference in presentation. Carpopedal spasm and Perioral tingling was common in indoor and outdoor patients, however leg cramps, palpitation and anxiety was more common in intensive care patients. This may be primarily disease related complaints and not due to hypocalcaemia per se.

Maximum no. patients of outdoor and indoor group were detected to have Vitamin D levels low (<30ng/ml). However, Vitamin D levels were sufficient in most of the ICU patients that indicated that hypocalcaemia in intensive care is multifactorial. Out of 30 patients in intensive care, 20 developed oliguria, 14 patients received transfusion. Chernow B et al²⁷ studied 259 patients in ICU, of which 135 (64%) were hypocalcaemic and 75 (36%) were normocalcaemic. He concluded that "hypocalcaemia is a frequent finding in critically ill patients, determining ionized Ca⁺⁺ levels is useful because many ICU patients have alterations in both arterial pH and Sr. albumin levels; hypoalbuminemia, sepsis, red cell transfusions, and renal failure are predisposing factors for hypocalcaemia; and hypokalemic patients do less well clinically than normocalcaemic patients".

V. Conclusion

1. Patients presenting with symptoms suggestive of hypocalcaemia should be investigated and promptly treated.
2. Adolescent and young adults are the main age groups who presented with hypocalcaemia. Younger patients presenting with low serum calcium should be worked up for metabolic and genetic diseases and should be corrected early.
3. Females have more symptomatic hypocalcaemia than men. Sedentary lifestyle, lack of exercise, inadequate sunlight exposure, Burkha, multiparity, inadequate dietary calcium are major contributors for Vitamin D deficiency in women.

4. Perioral tingling sensation is the most common presenting symptom of hypocalcaemia. Leg cramps, muscle weakness, palpitation and convulsion are other important symptoms.
5. Patients presenting with palpitations should always be looked for QTc. If prolonged, Serum calcium should be estimated.
6. All cases presenting with convulsions should always have Serum Calcium included as one of the primary investigations, as it is a treatable cause of convulsion. Before starting anticonvulsants, supplementation with Vit. D along with Calcium is must as there is high prevalence of hypovitaminosis D and hypocalcaemia. Patients on anticonvulsants, antitubercular drugs and steroids should always be supplemented with Vitamin D and calcium tablets. Calcium and Vitamin D supplementation to be considered as a part of standard treatment in cases of CNS tuberculosis where patient are given anticonvulsants and antituberculous drugs together.
7. Serum Magnesium and calcium levels should always be monitored in patients with preeclampsia.
8. Patients who undergo total thyroidectomy should always be followed up for permanent post-surgical hypoparathyroidism and given benefit of Vitamin D and calcium for prevention of osteomalacia and early fracture. Also, patients are to be monitored for symptoms of hypervitaminosis.
9. Critically ill patients should be watched for low serum calcium as it is one of the prognostic markers for mortality.
10. Need of a national program similar to the interventions for deficiencies of Vitamin A and iodine to tackle the problem of Vitamin D deficiency.

References

- [1]. Prevalence of hypocalcaemia in patients attending the Olabisi Onabanjo University Teaching Hospital, Sagamu, South Western Nigeria African Journal of Biotechnology Vol. 5 (18), pp. 1675-1677, 18 September 2006
- [2]. Diagnosis and management of hypocalcaemia Mark S Cooper, Neil J L Gittoes BMJ 2008; 336:1298
- [3]. Hollick MF. Vitamin D deficiency. New England Journal of Medicine 2007; 357:266-281.
- [4]. Holick, Michael F. Vitamin D: the underappreciated D-lightful hormone that is important for skeletal and cellular health. Current Opinion Endocrinology Diabetes 2002 February 2002 - Volume 9 - Issue 1 - pp 87-98
- [5]. Joyce M. Lee. Vitamin D Deficiency in a Healthy Group of Mothers and Newborn Infants. Clinical Pediatric 2007.
- [6]. Bruce W. Hollis, Carol L. Wagner. Nutritional vitamin D status during pregnancy: reasons for concern. American Journal of Clinical Nutrition, 2004; 79: 820-5
- [7]. Marwaha RK, Tandon N, Garg MK, et al. Vitamin D status in healthy Indians aged 50 years and above. Journal of Assoc Physicians India (JAPI) .2011; 59:703-707.
- [8]. <http://modernmedicare.co.in/news/women-in-mumbai-have-a-higher-vitamin-d-deficiency-than-men-metropolis-study/study-conducted-by-metropolis-healthcare-ltd-from-january-to-december-2011>,
- [9]. Anne L. Schafer Bouillon RA, Auwerx JH, Lissens WD, Pelemans WK 1987 Vitamin D status in the elderly: seasonal substrate deficiency causes 1,25-dihydroxycholecalciferol deficiency Hypocalcemia: Diagnosis and Treatment. American Journal of Clinical Nutrition. 45:755-763
- [10]. Harinarayan CV, Alok Sachan, P. Amaresh Reddy, et al. Vitamin D status and Bone Mineral Density in Women of Reproductive and Postmenopausal age groups: A cross-sectional study from South India. J Assoc Physicians India 2011; 59:695-701.
- [11]. Marwaha K, Sripathy G. Vitamin D and Bone mineral density of healthy school children in northern India. Indian J Med Res 2008; 127:239-244.
- [12]. Robert A. Grossman, Nontraumatic Rhabdomyolysis and Acute Renal Failure England. Journal of Medicine. 1974; 291:807-811
- [13]. Fitzpatrick, L.A.: The hypocalcemic states. Disorders of Bone and Mineral Metabolism. M. Favus (ed), Lippincott Williams & Wilkins, Philadelphia, PA, pp. 568-588, 2002.
- [14]. George Liamis, Haralampos J. Milionis, Moses Elisaf: A review of drug-induced hypocalcaemia. J Bone Miner Metab (2009) 27:635-642.
- [15]. Gniatkowska-Nowakowska. Fractures in epilepsy children. Seizure, 2010 Jul; 19(6):324-5. (doi: 10.1016/j.seizure.2010.04.013.)
- [16]. Petty SJ, O'Brien TJ, Wark JD (2007) Anti-epileptic medication and bone health. Osteoporos Int 18:129-142
- [17]. Kovacs CS, Jones G, Yendt ER (1994). Primary hyperparathyroidism masked by antituberculous therapy-induced vitamin D deficiency. Clinical Endocrinology (Oxf) 41:831-836 discussion 837-839.
- [18]. Mazhar Iqbal Frequency of hypocalcaemia in total thyroidectomy, Journal of Surgery Pakistan (International) 15 (2) April - June 2010
- [19]. Kirkby-Bott J, Markogiannakis H, Skandarajah A, Cowan M, Fleming B, Palazzo F Preoperative vitamin D deficiency predicts postoperative hypocalcemia after total thyroidectomy. World Journal of Surgery. 2011 Feb; 35(2):324-30
- [20]. E Mezey. Alcoholic liver disease: roles of alcohol and malnutrition. American Journal of Clinical Nutrition, December 1980 Volume 33 no. 12 2709-2718
- [21]. Elisaf M, Liamis G, Liberopoulos E, Siamopoulos KC (2001). Mechanisms of hypocalcemia in alcoholic patients. Nephron 89:459-460
- [22]. Kugelberg E: The mechanism of Chvostek's sign. Archives of Neurology and Psychiatry. 1951; 65:511-517.
- [23]. Harinarayan C V, Joshi Sr. Vitamin D status in India-Its implications and remedial measures. Journal of Assoc Physicians India (JAPI) 2009; 57:40-48.
- [24]. Balasubramanian K, Rajeswari J, Gulab, Govil YC, Agarwal AK, Kumar A, et al. Varying role of vitamin D deficiency in the etiology of rickets in young children vs. adolescents in northern India. J Trop Pediatr 2003; 49 : 201-6.

- [25]. Rajeswari J, Balasubramanian K, Bhatia V, Sharma VP, Agarwal AK. Aetiology and clinical profile of osteomalacia in adolescent girls in northern India. *Natl Med J India* 2003;16 : 139-42.
- [26]. Rathored J, Sharma SK, Singh B, Banavaliker JN, Sreenivas V, Srivastava AK, Mohan A, Sachan A, Harinarayan, Goswami R. Risk and outcome of multidrug-resistant tuberculosis: vitamin D receptor polymorphisms and serum 25(OH)D. *Int Journal of Tuberculosis Lung Disease* 2012 Nov;16(11):1522-8. doi: 10.5588/ijtld.12.0122. Epub 2012 Sep 14.
- [27]. Chernow B, Zaloga G, McFadden E, Clapper M, Kotler M, Barton M, Rainey TG Hypocalcemia in critically ill patients. *Critical Care Medicine*.1982 Dec;10(12):848-5.

Dr.Sanjay Gulhane "Study an etiological, Clinical and Metabolic Profile of Hypocalcaemia in Adults."IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 17, no. 6, 2018, pp 25-35.