

# Frequency of Occurrence of Hypocalcemia in Various Disorders

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**Objective:** To determine the relative frequency of occurrence of hypocalcemia in various disorders.

**Study Design:** It is across-sectional/ descriptive study.

**Settings and Duration:** The study was carried out at Armed Forces Institute of Pathology, Rawalpindi from April 1999 – April 2000.

**Material and Methods:** In this study one hundred patients with hypocalcemia (Serum Total Calcium < 2.10 mmol/L) were selected irrespective of the age and sex. The history and physical examination was carried out for each patient.

The blood specimen was analyzed for serum calcium, phosphate, albumin, alkaline phosphate, magnesium, urea, creatinine, electrolytes, PTH, and blood bicarbonate according to the requirement to find the etiology.

**Results:** The chronic renal failure was found in 49%, rickets in 21%, hypoparathyroidism in 8%, infections in 7%, acid-base disorders 3%, malignancies 4%, miscellaneous diseases 5%, unknown in 3%.

**Conclusion:** Chronic renal failure and rickets are most frequently associated with hypocalcemia in our clinical setup. Hypocalcemia is also associated with other disorders like infectious diseases, acid-base disorders, malignancies, and miscellaneous diseases which include acute pancreatitis, magnesium deficiency, aplastic anaemia, diabetes mellitus and hypertension. The lowest calcium levels were found in hypo-parathyroidism and there was significant difference in means of the calcium levels in various disorders causing hypocalcemia i.e 0.001, as analysed by the application of statistical test ANOVA.

**Keywords:** Hypocalcaemia, Chronic renal failure, Rickets.

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## Introduction

Hypocalcemia is a common condition in our country because of low socio-economic status, nutritional insufficiency, malabsorption, multiple pregnancies and vitamin D deficiency.<sup>1</sup> It has been found that the prevalence of hypocalcemia is about 18% in all patients in a hospital and 82% in intensive care units.<sup>2</sup> A wide range of disorders leads to hypocalcemia in addition to those mentioned above. These include chronic renal failure, hypo-proteinemia, pancreatitis, nephrotic syndrome. Hormonal imbalance like diabetes mellitus<sup>3</sup>, hypoparathyroidism<sup>4</sup>, hyper and hypothyroidism, Cushing's disease, Addison's disease, deficiency of growth hormone,<sup>5</sup> androgens, and also of oestrogen in post menopausal women. Drugs like bisphosphonates<sup>6</sup>, alcohol may lead to hypocalcemia. In addition to these increased demands as in lactation<sup>7</sup> may also cause hypocalcemia. Calcium level is also influenced by concentrations of minerals specially phosphate and magnesium.<sup>8</sup>

The blood calcium is maintained by the action of parathyroid hormone and vitamin D on the kidneys, bones and gastrointestinal tract. Parathyroid hormone stimulates calcium resorption in the kidney and calcium release from bone. It also stimulates renal production of 1, 25-dihydroxyvitamin D (calcitriol) from 25-hydroxyvitamin D. 1, 25-Dihydroxyvitamin D is the most active form of vitamin D, and it acts on the gastrointestinal tract to increase calcium absorption. Vitamin D is obtained mainly through synthesis in the skin, with a small contribution from the diet. Skin synthesis requires exposure to ultraviolet light and is reduced by skin pigmentation.

Calcium is essential for wide range of metabolic processes, however most of it about 99% reside in skeleton which serves as its dynamic reservoir whereas remaining 1% exist in the extra cellular tissue. In plasma it is found in free form about 50%, bound to plasma proteins 40% and complexed form 10%. It is important for the coagulation, neuromuscular transmission, hormone secretion, cell division such as coagulation, neuromuscular transmission, hormone

secretion and cell division. Recently it has been found to be critical for apoptosis, chemotaxis, gene expression, water and mineral balance etc.<sup>9</sup> So hypocalcemia may lead to serious complications such as seizure, tetany, ventricular arrhythmias<sup>10</sup>, laryngospasm. Frequent clinical findings of hypocalcaemia include muscle cramps, paresthesia, tingling sensations in hands and feet, chronic diarrhoea abdominal pain, bone pain, fractures, dry skin, patchy hair, transverse ridging of the nails and enamel, weight loss and alopecia.<sup>2</sup>

The frequency of occurrence of hypocalcemia in different disorders varies in different parts of the world. Only a few studies have been found regarding the frequency of various causes of hypocalcaemia in general population<sup>10</sup> Therefore, a study was designed to determine the frequency of various diseases causing hypocalcemia.

## Materials and Methods

One hundred patients of hypocalcemia were included in this cross sectional study to determine the frequency with which different diseases cause hypocalcemia.

**Inclusion criteria:** All consecutive patients found to be hypocalcaemic after routine investigations at Armed Forces Institute of Pathology Rawalpindi (AFIP) were selected irrespective of age and sex.

**Exclusion criteria:** All those subjects found to have factitious hypocalcaemia on subsequent laboratory investigations.

### Data Collection Procedure:

**Sampling Technique:** Purposive sampling was done patient having confirmed hypocalcemia were selected irrespective of age and sex.

The hypocalcemia was established after the serum calcium was corrected for albumin concentration, by applying correction formula<sup>10</sup>. The patients with corrected serum calcium below the lower limit of normal reference range were contacted. Their consent was taken for clinical assessment and further investigations. Most of the ambulatory patients managed to come to the laboratory while the blood samples of those who were hospitalised were collected directly from the wards. The history and physical examination was carried out. This included demographic features and related general and physical findings according to the proforma designed for this purpose.

Specimen collection for hypocalcemic patients: 10 ml of fasting blood was collected from each individual from antecubital fossa by clean venepuncture using sterile disposable syringe with minimal stasis. It was immediately transferred to a clean container with cap without any anticoagulant.

The blood was allowed to clot. Soon after clot formation, the serum was separated by centrifugation at 3000 rpm for 15 min and analysed mostly as fresh sample.

The subjects with confirmed hypocalcemia were investigated further for the first line of investigations, i.e. serum phosphate, and Alkaline Phosphatase (ALP). The additional investigations were carried out to get clues for the cause such as urea and creatinine for renal pathology, PTH for parathyroid abnormality, magnesium for deficiency, alanine amino transferase (ALT) for liver disorders, bicarbonate for acid base disorder according to the indications and the first line investigations to find out the aetiology.

**Specimen collection for PTH:** As there is nocturnal rise of intact PTH, blood sample were collected by venepuncture in the morning after an overnight fast. The samples were immediately transferred to tube containing ethylene diamine-tetra-acetic acid (EDTA) as an anticoagulant and placed in an ice container. Soon after clotting, the plasma was separated from the cells by using a refrigerated centrifuge. The fresh sample was analysed or stored at 2-8° C, to be analysed preferably on the very next day.

**Specimen collection for blood gases:** For bicarbonate analysis the arterial blood sample was taken in a heparinized syringe from radial artery. The sample was kept in ice and analyzed within 15 minutes.

**Techniques for measuring analytes:** Serum Calcium: was measured colourimetrically using O-Cresolphthalein complexone method (CPC) kit by Horizon Company (USA). Phosphate by Menarini Diagnostic kit, Albumin by using bromocresyl green method. ALP by kinetic method Magnesium by using kit of Croma/Linear chemicals (Spain) and Creatinine: was estimated by Jaffee's kinetic method on Mirco lab 200. Urea was analysed by using enzymatic- UV kit by Labsystems on RA – 1000 discrete autoanalyzer. Electrolytes: Sodium and Potassium were estimated on Corning flame photometer model 410c using Inomat controls manufactured by Croma-Linear Chemical (Spain) and the measurement of parathyroid hormone (PTH) was carried out using Immulite intact PTH kit (USA) on Immulite Automated Analyser. The kit is based on the principle of a solid phase, two site (biterminal) chemiluminescent assay. Bicarbonate: Bicarbonate was measured by ion selective electrode (ISE) using Corning blood gas analyser model 278.

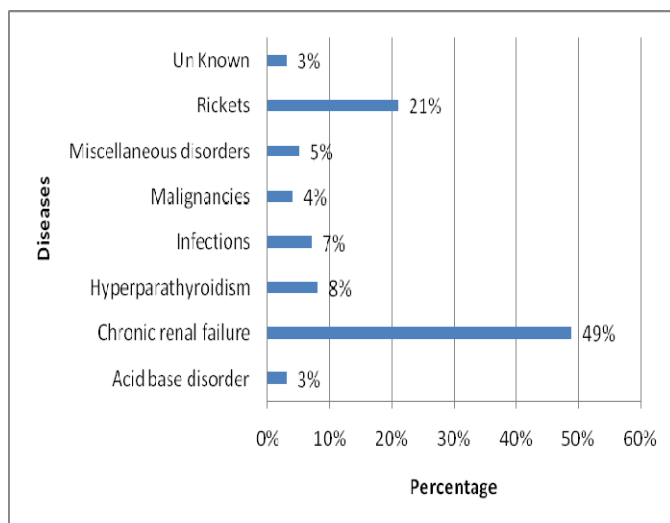
All the analyses were carried out under similar conditions with respect to instruments, kits, temperature, incubation etc. The samples were run in batches along with bi-level (high and low level) control for each parameter to ensure analytical accuracy and precision.

**Data Analysis:** After establishing the aetiology, the data was segregated into sub- groups of age and sex to

determine the prevalence of disease accordingly. Relative frequency was calculated for each group of disorders by entering the data in SPSS version 13 and statistical test ANOVA was applied. Frequency bar chart was prepared in Microsoft Excel software program.

## Results

The results of the study showed that the predominant diseases associated with hypocalcemia are chronic renal failure (49%) and rickets (21%). As shown in Fig.I different diseases were grouped into main disorders. The main groups are chronic renal failure, rickets, hypoparathyroidism, infectious diseases, malignancy, acid base disorders in descending order of frequency of causing hypocalcaemia.



**Figure I : Frequency of different disorders causing hypocalcemia along with a percentage**

The smaller groups including malignancies, acid base disorders and miscellaneous disorders were further found to consist of diseases as follows:

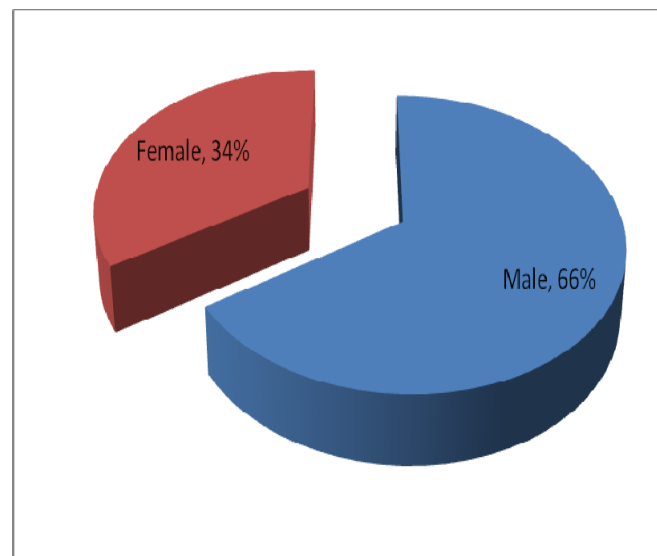
The malignant lesions (n=4) causing hypocalcemia, included multiple myeloma (n=2), acute myeloid leukemia (n=1) and prostatic carcinoma (n=1).

Acid based disorders were found to be 3% which include chronic airway obstructive diseases 2% respiratory distress syndrome 1%.

The miscellaneous diseases causing hypocalcemia 5% included one patient each of acute pancreatitis, magnesium deficiency, aplastic anaemia, hypotension and diabetes mellitus.

After segregating the data into different groups, the gender wise frequency of hypocalcemia exhibit male

preponderance with the ratio of about 2:1 as shown by figure II.



**Figure II: Frequency of hypocalcemia in male and female**

More variations were found in serum calcium level in males and that the minimum level was lower in males than found in females as shown by table I below.

**Table I : Gender wise distribution of serum calcium level in hypocalcemic patients**

| Sex    | N   | Corrected<br>Calcium level<br>(Mean) | Std.<br>Deviation | Min. | Max. |
|--------|-----|--------------------------------------|-------------------|------|------|
| Male   | 66  | 1.9289                               | .12154            | 1.54 | 2.07 |
| Female | 34  | 1.9454                               | .08275            | 1.63 | 2.08 |
| Total  | 100 | 1.9345                               | .10974            | 1.54 | 2.08 |

The frequency of hypocalcemia in relation to age groups as shown in table II, reveal lowest frequency 7% in age group of 16-35 years then it progressively increases below and above this age group i.e. 6-15years and 36-55years to 13% and 12% respectively. The frequency was highest below 6 years was 23% and above 55 years was 26%.

The corrected serum in various age groups reveal minimum calcium level below 6years of age viz 1.54 mmol/l and above 55years i.e. 1.56mmol/l. In the age group of 16-25years it is also low i.e. 1.58mmol/l. The minimum calcium level is comparatively higher in age group of 26-45 years viz 1.80-1.88mmol/l. as shown in table II.

**Table II: Frequency of hypocalcemia along with corrected calcium level in various age groups**

| age groups years | N   | Corrected Calcium level (Mean) | Std. Deviation | Min. | Max. |
|------------------|-----|--------------------------------|----------------|------|------|
| Below 6 years    | 23  | 1.9058                         | .13799         | 1.54 | 2.01 |
| 6-15 yrs         | 13  | 1.9638                         | .04556         | 1.88 | 2.07 |
| 16-25 yrs        | 7   | 1.8857                         | .16531         | 1.58 | 2.05 |
| 26-35 yrs        | 7   | 1.9514                         | .03436         | 1.88 | 1.98 |
| 36-45 yrs        | 12  | 1.9492                         | .06142         | 1.80 | 2.01 |
| 46-55 yrs        | 12  | 1.9717                         | .07346         | 1.77 | 2.08 |
| Above 55 Years   | 26  | 1.9298                         | .12774         | 1.56 | 2.04 |
| Total            | 100 | 1.9345                         | .10974         | 1.54 | 2.08 |

**Table III: Statistical analysis of degree of hypocalcaemia in different disorders**

| disorders               | N   | Mean   | Std. Deviation | Std. Error | Max. |
|-------------------------|-----|--------|----------------|------------|------|
| Acid base disorder      | 3   | 1.9333 | .02309         | .01333     | 1.96 |
| Chronic renal failure   | 49  | 1.9650 | .06155         | .00879     | 2.08 |
| Hypoparathyroidism      | 8   | 1.6562 | .12603         | .04456     | 1.92 |
| Infections              | 7   | 1.9743 | .01988         | .00751     | 2.01 |
| Malignancies            | 4   | 1.9650 | .01291         | .00645     | 1.98 |
| Miscellaneous disorders | 5   | 1.9620 | .04712         | .02107     | 2.00 |
| Rickets                 | 21  | 1.9430 | .09888         | .02158     | 2.07 |
| Un Known                | 3   | 1.9400 | .05292         | .03055     | 1.98 |
| Total                   | 100 | 1.9345 | .10974         | .01097     | 2.08 |

Although there are differences in mean value of calcium in different hypocalcemic disorders, however the lowest calcium was found in hpo-parathyroidism as revealed by table 3 above .The statistical analysis after the application of ANOVA test revealed that there is significant difference in the mean calcium level of these disorders.i.e 0.001 as shown in table 4 below:

**Table IV: Shows the results of statistical analysis after applying ANOVA test**

| Corrected Calcium level | Sum of Squares | df | Mean Square | F     | Sig. |
|-------------------------|----------------|----|-------------|-------|------|
| Between Groups          | .608           | 7  | .087        | 4.100 | .001 |
| Within Groups           | 1.950          | 92 | .021        |       |      |
| Total                   | 2.558          | 99 |             |       |      |

## Discussion

The study showed that a broad range of disorders can lead to hypocalcemia. Chronic renal failure is the commonest cause (49%). It has been reported, that a very few studies are available with quantitative data on the prevalence of hypocalcaemia and its causes<sup>10-12</sup>. However, our finding is consistent with that of various other studies reporting the causes of hypocalcaemia separately. A study in Singapore reported that 24.4% of patients at end stage renal disease on haemodialysis had hypocalcemia.<sup>13</sup> The reports from a study conducted at the Kidney Centre, Karachi (Pakistan) showed the incidence of hypocalcemia of 47% in such patients. In another study it was reported that hypocalcaemia was, present in 66% in the chronic kidney diseases and 24% with vitamin D deficiency<sup>10,14</sup>. Multiple factors may cause hypocalcemia in chronic renal failure (CRF). It has been suggested by recent evidence that phosphate retention is being the primary factor leading to decrease synthesis of 1, 25 dihydroxy-cholecalciferol in the kidney apart from loss of renal tissue, restricted diet in CRF, and renal loss of calcium. As mentioned above studies on spectrum of diseases causing hypocalcaemia are a few, many of the reviewers concluded that common causes in order of prevalence are renal failure, vitamin D deficiency, hypomagnesemia, pancreatitis, hypoparathyroidism<sup>11,14</sup>. This is also more or less consistent with our findings in addition to other findings in our study mentioned below. Incidence of rickets has been detected to be 21% in the present study. Although it is the second most important cause of hypocalcemia constitutes about of all hypocalcemic patients, yet it is the commonest cause of hypocalcemia in children. The most vulnerable age is below 4 years; however some of the patients were above this age. Current findings on rickets are supported by a number of studies done in different parts of the world. According to a study in France on European population, 24% of the neonates born to mothers who did not receive any supplement of vitamin D in pregnancy had vitamin D deficiency, whereas sub-

clinical deficiency was stated to be 63%. Hypocalcemia was present in 9% of these neonates.<sup>15</sup> Another study in North Yemen showed that 27% of children under five years had rickets. High incidence of vitamin D deficiency has also been reported in children under two years of age in Mecca (Saudi Arabia) despite of abundant sunlight.<sup>16</sup> Possibly because they are kept wrapped in cloths. Increased skin pigmentation is set to be another cause of hypocalcemia<sup>2</sup>

The current study showed 8% cases of hypoparathyroidism were due to thyroidectomy, or parathyroidectomy. The incidence of permanent hypoparathyroidism has been reported to be from 0.4 to 13.8% after total thyroidectomy, and 0.2 – 1.9% of after sub total thyroidectomy<sup>17</sup> A study in Pakistan reported temporary hypocalcemia in 31 and overt hypocalcemia in 7 out of 48 cases of sub total thyroidectomy. However sub-clinical hypocalcemia was found in 16.5% of these patients<sup>18</sup>. Total calcium may fall after the surgery due to temporary hemodilution owing to the fluid shifts resulting in low albumin, whereas ionised calcium usually remains unaffected<sup>18</sup>.

The post parathyroidectomy hypocalcemia was 1% in the present study. In another study transitory hypocalcemia was found in 22%, while permanent hypocalcemia in 2% after parathyroidectomy.<sup>19</sup>

In our study 7% of the hypocalcemic patients were due to various infections. Reports from other investigations have also shown association of infectious diseases with hypocalcemia. Different studies reported high incidence in bacterial pneumonia, measles, toxic shock syndrome, leprosy and tuberculosis<sup>20</sup>. It may be due to nutritional deficiency in such patients.

The current study showed malignancies in 4% of the cases as a cause of hypocalcaemia. Leukemias can also lead to hypocalcemia particularly with chemotherapy resulting in tumour lysis syndrome. Plasma exchange therapy commonly done in multiple myeloma and other malignancies may lead to hypocalcemia<sup>21</sup>. Probably hypocalcemia occurs due to therapeutic interventions in these malignancies.

Acid base disorders are found in 3% of the cases. The blood pH, protein and anion level effects the total calcium leading to hypocalcaemia.<sup>9</sup>

The miscellaneous diseases causing hypocalcemia found in the present study include acute pancreatitis, magnesium deficiency, aplastic anaemia, type 1 diabetes mellitus and hypotension.<sup>22</sup>

Hypocalcemia in acute and chronic pancreatitis may occur due to release of lipase, glucagon, gastrin, shock, hypoproteinemia. Gastro-intestinal disorders such as coeliac disorders<sup>23</sup>, liver disease, pancreatic insufficiency, diarrhoea also lead to electrolyte imbalance including that of calcium. Sufficient supply of 25-hydroxy D to the kidney require adequate GIT

absorption, and adequate liver function for the first hydroxylation step of vitamin D3 synthesis.<sup>11</sup>

Sometime the blood calcium may remain in normal range but it is maintained at the expenses of the bones, being the dynamic reservoir. Severe total body deficiency of calcium can exist without hypocalcemia. Hypocalcemia may be due to the physiological conditions, like pregnancy and lactation which require extra calcium, hence can lead to negative balance unless additional supplements are provided.<sup>7</sup> Nutritional imbalance frequently occurs with nutrition support therapies.<sup>24,25</sup> Many studies showed that calcium intake in various populations especially in women and children is low. In nutritional evaluation of working adult women in Kuala Lumpur, calcium intake was found to be 57% of recommended daily intake<sup>26</sup>. The low intake of calcium may be due to multiple factors. In the higher social classes, the modern diet has replaced the traditional diet such as milk and milk products like lassi, butter etc. with sophisticated drinks like coca-cola and other beverages. While in the lower social classes the unavailability and skipping of food can cause low calcium status of the body. In old people lack of physical activity, decreased appetite whereas in the young, imbalance food such as potatoes chips rice and fat rich Western style diet<sup>27</sup> have been reported to be among the causative factors.

The significance of determining the frequency of various diseases which can trigger towards potentially dangerous life threatening conditions of hypocalcemia lies in its great clinical implications regarding prevention and therapeutic management of such disorders.

## Conclusion

Chronic renal failure and rickets are most frequently associated with hypocalcemia in our clinical setup. Hypocalcemia is also associated with other disorders like infectious diseases, acid-base disorders, malignancies, and miscellaneous diseases which include acute pancreatitis, magnesium deficiency, aplastic anaemia, diabetes mellitus and hypertension. The lowest calcium levels were found in hypoparathyroidism and there was significant difference in means of the calcium levels in various disorders causing hypocalcemia i.e 0.001, as analysed by the application of statistical test ANOVA.

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