LITERATURE REVIEW

a. Body Water and Development of Oedema

Water is the most important solvent in human body the metabolism of which is maintained by several mechanisms that control water intake and output, but is balanced principally through excretion of water by the kidney. Total body water (TBW) as a percentage of body weight changes with age, decreasing rapidly in early life. At, birth, TBW drops dramatically to approximately the adult level of 55-60% of body wt at 1yr of age.

TBW has been measured in vivo in infants and children before, during and after recovery from severe PEM by the technique of isotope dilution method, using either tritiated water or deuterium oxide as the isotope. Alternatively, TBW has been measured directly (in vitro study) in whole body analyses of infant and children in varying nutritional state at the time of death.\(^\text{16}\)

On the basis of results of isotopic and body composition studies and also by tissue analysis, it was concluded that there was overhydration in both types of severe malnutrition i.e. marasmus and kwashiorkor and that expansion in extracellular fluid accounted for most of the increase in body water. However, a study by Patrick J. , Reeds, Jackson and Picou (1975)\(^\text{17}\) showed that TBW\% was increased in malnourished children with oedema but after loss of oedema TBW\% was the same before and after recovery from PEM.

In PEM, pitting oedema first appears on the feet and lower legs (on dependent parts) and later it becomes generalized. Ascites is typically absent.
The pathogenesis of oedema in kwashiorkor and marasmic kwashiorkor still remains controversial but several mechanisms have been put forward to explain it. Similar to other several clinical situations leading to oedema, the oedema of kwashiorkor and marasmic kwashiorkor cannot occur in the absence of sodium and water retention. One proposed explanation given by Klahr & Alleyne in 1973 is shown below:

![Diagram of the pathogenesis of oedema in kwashiorkor and marasmic kwashiorkor]

- Decreased protein intake
  - Hypoalbuminaemia.
    - Decreased Plasma Volume
      - Decreased Cardiac Output
        - Decreased arterial BP.
        - Decreased renal blood flow & GFR
          - Increased renin angiotensin
            - Increased aldosterone
              - Increased tubular reabsorption of salt & water
              - Decreased peritubular hydrostatic pressure
        - Decreased filtered load of salt & water

OEDEMA
As there is low plasma colloid oncotic pressure because of hypoalbuminaemia, there may be lack of water inside blood vessels despite having overhydration (in interstitial space) leading to oedema. It is specially striking during gastroenteritis which occurs commonly with PEM.

To find out the plasma renin activity (PRA) in PEM, a study comprising 52 children with kwashiorkor, 28 with marasmus and 21 healthy children was undertaken in a hospital in South Africa and PRA was measured by bio-assay. PRA was significantly increased in children with kwashiorkor and marasmus compared with healthy children and in children who died, compared with survivors. No strict causal relationship could be found between plasma renin activity and the degree of oedema in kwashiorkor. Increased renin activity was attributed to a terminal change in cardiovascular function.

In a similar type of study conducted at Harare, Zimbabwe showed that effective plasma renin activity was higher in children with kwashiorkor and increased activity was attributed to several physiological changes associated with PEM. One hundred twenty six children with kwashiorkor and 20 children attending well baby clinics were enrolled in the study.

In a study conducted at PGIMR, Chandigarh glomerular and renal tubular functions were studied in 16 subjects with grade II, III and IV PEM and in control subjects GFR was lower in PEM. Acidification capacity of renal tubule was also impaired to significant extent in them. There was no alteration in the concentrating
capacity of the kidney. These changes were reversible after short-term nutritional rehabilitation.21

To conclude, the total body water as percentage of total body weight increase in PEM especially in kwashiorkor and marasmic kwashiorkor, because of decreased renal perfusion probably as a result renin-angiotensin-aldosterone system that gets activated leading to overhydration and development of oedema. The pathogenesis of oedema and plasma renin activity in PEM especially kwashiorkor is yet to be clarified.

**b. Potassium**

Potassium is the major intracellular cation having a vital role in the human body. Intercellular concentrations of potassium approximates 150 mEq/l of cell water. The extracellular concentration of potassium (4mEq/l) creates a large concentration difference across the cell membranes. The difference between intercellular and extracellular potassium, sustained by the action of Na-K AT Pase is important for maintaining the resting membrane potential difference across the cell membrane. Potassium is critical for the excitability of nerve and muscle cells and for the contractility of cardiac, skeletal and smooth muscle. Because of its intracellular osmotic contribution, potassium is also important for the maintenance of cell volume. A daily intake of 1-2 Eq/ Kg body weight is recommended. Absorption of potassium is reasonably complete in the upper gastrointestinal tract. Aldosterone plays a key role in the renal and extrarenal handling of potassium. Similarly, acid base balance affects intracellular shifts of potassium. Systemic acidosis results in the movement of potassium out of cells, alkalosis produces the opposite effect. Chronic potassium balance is primarily regulated by the kidneys.
With the use of radiation of natural isotope 40K, total body potassium (TBK) was determined which is in the range of 40-45 mmol/kg. Oedematous children tend to have particularly low values of TBK/Kg as the low values of potassium capacity and potassium content are simply as a result of oedema. There is an inverse correlation between TBK and extracellular fluid volume.

During rehabilitation, the patients of PEM retain more potassium in comparison to nitrogen in the range of 3:1. As 3:1 is a normal tissue realtionship, it is concluded that there is potassium deficiency and not simply tissue loss in PEM.

In a study performed at Agra by Kalra K. et al, estimation of electrolytes were done in 126 children with malnutrition. the cases were divided into four clinical groups: undernutrition marasmus, nutritional oedema and kwashiorkor. Serum potassium levels ranged from 3.2 to 6 mEq/L. Serum potassium levels were low in 21.3% of non-oedematous children as contrasted to 33.3% of oedematous group. The overall mean values in non-oedematous and oedematous groups were 4.80 and 4.18 mEq/L respectively.22

A similar type of study was conducted in Egypt by Said A et al to find comparatively the electrolytes in plasma and electrolytes in PEM. The study revealed that plasma potassium is markedly lower than normal in all groups of malnourished subjects. RBC potassium was significantly lower than normal in severe kwashiorkor and marasmic kwashiorkor but was high in marasmus.23

In a study conducted by A.Rao and A. Cherian in Nigeria renal tubular function was assessed in PEM. The study consisted of 9 cases of marasmus, 15 cases of kwashiorkor and marasmic kwashiorkor and 14 control subjects. Serum potassium was significantly lower in both patient groups.24
A study conducted in Nigeria to find out plasma electrolyte concentration in children with PEM and prolonged diarrhoea showed a significant decline in plasma potassium. Values were found to be statistically significant at $p<0.001$ when compared to controls.\(^2^5\)

The total body potassium and serum electrolyte concentration of malnourished children in Cape Town was studied. The TBW was almost always low and a particularly low TBK appear to influence the prognosis. During the early stage of recovery of malnourished children on three levels of potassium intake, the total body potassium and potassium retention were measured. A potassium intake of 2m Eq/Kg/day resulted in significantly greater potassium retention than one of 3m Eq/Kg/day. At higher levels of intake 15m Eq/Kg/day did not result in an absolute increase in potassium retention and was not recommended because of its theoretical dangers although it may have stimulated an increase in potassium capacity.\(^2^6\)

Muscle electrolytes in PEM was studied to find out changes in salt and water composition in various types of PEM. Out of ten children with marasmus and eight children with kwashiorkor the alternation was confined to the later. The marasmic child with equivalent or more severe nutritional wasting than the child with kwashiorkor, maintained a more normal muscle electrolyte concentration. The pathophysiology of the altered muscle composition in kwashiorkor remains unclear.\(^2^7\)

The relationship between intracellular and extracellular potassium in normal and malnourished subjects was studied in leucocytes. Leucocyte potassium was measured in normal subject and in malnourished children with or without oedema both on admission and during recovery. In nonoedematous
malnourished children the potassium content was low (328 mmol/Kg dry solids) and took 2-3 weeks of rehabilitation to return to normal (374 mmol/Kg dry solids). Leucocytes from oedematous children had normal intracellular potassium values. However, 5 days on a maintenance diet reduced the intracellular potassium in the children with kwashiorkor to a value similar to that found in marasmus. Plasma potassium was significantly lower in kwashiorkor (3.43) than in marasmus (4.74).

The relationship between external potassium and internal potassium in normal leucocytes was measured, and the values found in severe malnutrition compared with normal. It was found that in nonoedematous malnutrition intracellular potassium was low compared to the predicted value, whereas in kwashiorkor, although the mean value were normal; no realtionship between external potassium and intracellular potassium could be demonstrated. It was concluded with this study that in the leucocyte, malnutrition alters either the passive permeability of the membrane to potassium or the active transport of potassium or both.28

A study was conducted in Malawi to find out the influence of potassium supplementation and correct dose of potassium that should be given in kwashiorkor. It was a randomized, double blind, placebo controlled clinical trial of high potassium supplementation in 99 children with kwashiorkor. Control consisting of 51 children received a standard potassium intake of 4.7 mmol/kg/day. The intervention group, which consisted of 48 patients received 7.7 mmol kg/day. Both groups were treated in the hospital based Nutrition Rehabilitation Centre and received a standard treatment regime of mild feeds, mineral and vitamin supplements and antibiotics. There was no significant difference in length of hospitalisation or time for resolution of oedema between groups. The case fatality rate was reduced by 33% in the high potassium intervention group (13/48) compared to controls (21/51). There was a significant reduction on the late deaths (13 in controls Vs 3 in intervention group, odds ratio 5.3, 95% confidence interval 1.2-31.0) but no intervention group also had
significantly fewer presumed septic episodes. (3vs18, odds ratio 8.9, confidence interval 2.2-50.9) respiratory symptoms and new skin ulcerations than controls from this study was concluded that the high potassium supplementation reduced mortality and significant morbidity in kwashiorkor. This may be due to improved myocardial and immune function from earlier repletion of intracellular potassium. Researchers came into a conclusion that initial phase of treatment of kwashiorkor be increased from 4 to 8 mmol/kg/day.\textsuperscript{29}

**Insulin and potassium**

Insulin is one of the hormones regulating the level of plasma potassium. The serum immunoreactive insulin (IRI) concentration and glucose disappearance rate-constants after intravenous glucose administration were measured on admission and during recovery from protein energy malnutrition. A high potassium intake resulted in a considerable increase in the serum IRI levels early in the treatment period. There was a definite relationship between potassium depletion and measurements of insulin secretion. The results were found to be consistent with the hypothesis that impaired insulin release in children suffering from PEM is partly the result of potassium depletion.\textsuperscript{30}

**Pancreatic duct function and level of potassium in PEM.**

In order to study the pancreatic duct function in malnutrition, twenty-three children with recurrent episodes of diarrhoea and chronic malnutrition were studied in Bombay, India. These children were subjected to pancreatic stimulation with pancreozymin and secretin. Grade I malnourished children as per Gomez classification, formed the control group. The water output from pancreas increased in malnourished children (\(p<0.05\)). It correlated significantly to cationic transport (\(p<0.01\)). Sodium and potassium together accounted for significant proportion of
water output in pancreatic fluid. Potassium transport increased with increasing severity of malnutrition and may be responsible for the hypokalaemia observed in malnourished children. Pancreatic secretion of bicarbonate decreased in severe malnutrition in spite of increased flow rate of pancreatic secretion. This is probably due to defective bicarbonate secretion likely to be located at pancreatic duct epithelial cell membrane.\(^{31}\)

In summary, most of studies mentioned in literature show a decrease in plasma potassium along with decrease in total body potassium. Decrease of plasma potassium is one of the poor prognostic factors in PEM.

c. Sodium

Sodium is the bulk cation of the extracellular fluids and is the principal osmotically active solute responsible for the maintenance of intravascular and interstitial volumes. Though cell membranes are relatively permeable to it, sodium is mainly distributed in the extracellular compartment with the help of Na-K ATPase system. Intracellular concentrations are maintained at levels of approximately 10m Eq/L and extracellular concentrations of approximately 140m Eq/L. Absorption from gastrointestinal tract occurs by Na-glucose co-transport which is facilitated by Na-K ATPase system which is an active process.

Plasma sodium is the main factor determining plasma osmolarity and plasma osmolarity is determined by a balance between water intake and water loss. Renal regulation of sodium depends on a balance between glomerular filtration and tubular reabsorption. Out of total amount of sodium filtered by the kidneys less than 1% is excreted in the urine and remaining 99% is reabsorbed along the length of the renal tubule, representing the result of highly efficient regulatory process. A fixed proportion of filtered sodium is reabsorbed in the
proximal convoluted tubule (approximately two thirds) and the fine regulation of sodium balance probably occurs throughout distal nephron in the distal convoluted tubules and the collecting ducts.

As there is increase in extracellular fluid in PEM, one would expect total body sodium to be increased also and there is evidence that is so. Paradoxically, the increase in total body Na is sometimes accompanied by hyponatraemia, which is particularly likely to occur in marasmic kwashiorkor. There is an excess of Na in an even greater excess of water. To have a low Na in plasma, it should either be diluted in the ECF or diverted out of it whatever may be explanation for hypotonicity (because of low Na), the fact remains that hyponatraemia is a very bad prognostic sign in PEM.32

A study was conducted by Kalra K. et al in India to estimate electrolytes in 126 children with malnutrition. They were divided in to four clinical groups: undernutrition marasmus, nutritional oedema and kwashiorkor. Serum sodium levels ranged from 120 to 163mE/L. there was no significant difference in serum sodium levels in children with or without oedema.22

To find out the derangement in sodium transport in cases PEM, intracellular electrolytes and sodium transport were measured in leucocytes obtained from malnourished children. In the presence of oedema leucocyte sodium and potassium were raised. The total flux and glycoside-sensitive portion were increased. Loss of oedema was associated with reductions in all these measurements. In marasmus, glycoside-sensitive sodium efflux was reduced compared to recovered values. Sodium was increased and potassium decreased. It was later concluded that at least two defect in sodium transport may occur in PEM, an increased passive permeability in kwashiorkor and a reduced active transport for sodium in marasmus.33
To find the clinical, biochemical & bacteriological profile in acute diarrhoea in PEM, 287 cases of acute gastro-enteritis admitted to the paediatric words of Lok Nayak Jai Prakash Narayan Hospital (India) were included in a study. Children with chronic or intractable diarrhoea were excluded and clinical, biochemical and bacteriological profile of 171 malnourished and 116 normal nourished children with acute diarrhoea were presented. AGE in normal nourished children was more common under 1 year of age, however, malnourished children at all ages were affected. Severe dehydration was more often seen in grade III malnourished children. Serum sodium levels were significantly lower in grade III malnutrition but did not seem to affect the outcome. On the other hand, hypokalaemia in malnourished children was more often fatal. Bacteriological profile was significantly different in malnourished children but again did not affect the outcome. Young age, severe dehydration and hypokalaemia were responsible for significantly increased mortality among malnourished children with AGE.34

In a study conducted by A.Rao and A. Cherian in Nigeria renal tubular function was assessed in PEM. The study consisted of 9 cases of marasmus, 15 cases of kwashiorkor and marasmic kwashiorkor and 14 control subjects. Serum sodium was not significantly between the patient groups. Serum K. was significantly lower in both patient groups.24

**Membrane transport of Na and K in PEM**

The total ouabain insensitive and ouabain sensitive Na and K adenosine triphosphatase activity in the erythrocyte membrane of protein calorie malnourished children with marasmus and kwashiorkor were compared for the enzyme activity in apparently healthy children (normal) Na⁺ and K⁺ contents of erythrocyte and plasma were also determined in these patients. Specific activity
(units per milligram of membrane protein) of ouabain sensitive Na\(^+\) and K\(^+\) adenosine triphosphatase was significantly higher in erythrocyte membrane preparations from children with kwashiorkor but not from children with marasmus. After 4 to 5 weeks of treatment with diets sufficient in protein and calories the specific activity of the enzyme was lower as compared to that on admission. Erythrocyte and plasma Na\(^+\) content microgram 10 cells and microgram per millilitre of plasma) in children with kwashiorkor were not different from those in normal children, however there was reduction in K\(^+\) content of erythrocyte and plasma of these children. After treatment erythrocyte Na\(^+\) and K\(^+\) and plasma K\(^+\) in children with kwashiorkor increased significantly. In marasmic children erythrocyte Na\(^+\) was higher as compared to normal but there were no differences in K\(^+\) content of either erythrocytes or plasma in these children.\(^{35}\)

In a similar type of study carried out in Jamaica, erythrocytes of normal and malnourished children, both marasmic and oedematous (kwashiorkor) were equilibrated in standard incubation medium and their ion transport via the Na-K pump and the pathways of passive permeation were measured as unidirectional fluxes of 86 Rb (as a congener of K) and 22 Na. Cells of children with kwashiorkor exhibited a 69 percent higher ouabain sensitive K(Rb) influx (pump rate) than these of normal of marasmic children. When allowance was made for cytoplasmic Na concentration, the pump rate was slower in younger (12 months and under) normal children than in older children. Judged by the same criterion, cells of older marasmic children also had a slower steady-state pump activity. The passive permeation of K through the residual leak pathway (i.e. ouabain-and-bumetanide insensitive influx) and Na permeation (ouabain- bumetanide-insensitive Na efflux) were greater in malnourished children than in normal children by a factor of two of more during treatment for malnutrition, both Na\(^+\) pump activity and ouabain binding increased rapidly in marasmic children.
Passive permeation didn't return to normal levels in malnourished children during the period of hospitalisation.\textsuperscript{36}

To conclude, plasma sodium is decreased in PEM though the total body sodium may actually be increased as a result of increase in extra cellular fluid. In other words, there is an excess of sodium in even greater excess of water. Most of studies mentioned in available literature mention the decrease in serum Na as one the poor prognostic factors in PEM.

d. Serum Protein and Albumin

In a child with PEM, total body protein is reduced but some organs, such as brain and heart, are less affected while others, e.g. muscle and fat in marasmus, are more severely affected. Plasma proteins are reduced and in kwashiorkor, the greatest reduction is in the albumin fraction.\textsuperscript{37}

No measurements have been made of rates of protein synthesis in individual tissues in children with PEM, but animal experiments have shown that on low protein diets or during fasting there is a large reduction in the rate of protein synthesis in muscle. This could be regarded as an adaptation, which protects the aminoacid supply to other more essential tissues. In rats after several days of fasting there is an increase in muscle protein breakdown. Therefore, that muscle is in negative N balance.\textsuperscript{38}

During recovery from PEM, the rate of whole body protein synthesis increases dramatically to levels well above normal, in just the same ways as the rate of \(O_2\) consumption. A linear relationship has been found between rates of protein synthesis and of weight gain.\textsuperscript{39} It is probable that during recovery some tissues have priority over others; albumin for example, clearly has a high priority.
Skeletal growth seems take off only after normal weight for height has been restored.\textsuperscript{40}

Cicely Williams, in her original description of kwashiorkor, implied that deficiency of protein in the baby's food could be a main cause of the syndrome. The hallmark of kwashiorkor is oedema. Accordingly to the "Classical" theory, an inadequate intake of protein leads to low plasma albumin concentration, which in turn cause oedema. This theory has been contested from several points of view that hypoalbuminaemia is not the major factor determining the presence of oedema and that there is no real evidence of dietary protein deficiency. The resolution of this question is of some importance from the point of view of diagnosis and prevention. Although it is clearly multifactorial with electrolyte disturbance- potassium deficiency and sodium retention - playing and important role, it is contended that the classical theory is essentially correct. On the dietary side, recent experimental work supports the earlier relative excess of energy.\textsuperscript{41}

The role of dietary protein deficiency in kwashiorkor is uncertain, although it has been shown not to be involved in the famine oedema of adults. A study of six different diets given to 103 children with oedematous malnutrition showed that the rate of loss of oedema was strongly correlated with the dietary energy intake ($r=0.75$) but not with the protein intake ($r = 0.03$). 66 patients given a very low protein diet (2.5% protein energy) lost oedema as fast as those given five times as much protein. The energy intake above which oedema resolved and below which oedema accumulated was 245-270 KJ/kg/day. Because energy deficiency is not invariably associated with oedema it cannot be the only factor involved and the necessary dietary component(s) must therefore have been present in surfeit in all the therapeutic diets. It is suggested that protein deficiency is not the cause of the oedema of kwashiorkor and that there is no need to postulate a different pathogenesis for this oedema from starvation oedema of adults.\textsuperscript{42}
It is now well established from several experiments that the catabolic rate of albumin in serve PEM is reduced to about half the rate found after recovery.\textsuperscript{43} Cohen & Hansen also demonstrated that the total albumin pool was decreased to about 50 percent of the recovered value and that the decrease appeared to be proportionately greater in the extravascular than in the intravascular pool. Similar experiments in adults showed a decrease in catabolic rate occurred in normal adults after a week or more on a low protein diet before any significant loss of total body nitrogen had occurred.\textsuperscript{44}

In a study on malnourished and recovered children receiving high or low protein diets. James and Hay (1968)\textsuperscript{45} established that with a low protein diet the rate of synthesis was lower in the malnourished than in the recovered child thus confirming a previous finding by Cohen & Hansen (1962)\textsuperscript{43} Albumin synthesis rose and fell promptly when protein intake was increased or decreased and these changes in catabolic rate occurred after a lag period of about a week. It was thus concluded from these studies that a reduction in protein intake is followed by a decrease in synthesis of albumin and that synthesis or plasma concentration of albumin.

Gammaglobulin metabolism, unlike that of albumin was unaffected by nutritional state, and in the pressure of infection the synthesis rate was greatly increased.\textsuperscript{43} When adults were placed on a low protein diet gamma-globulin concentration is markedly reduced in severe PEM\textsuperscript{46} and studies have shown a 50 percent reduction in its rate of synthesis in protein-deprived rats.

To establish the validity of measurement of serum albumin concentration as a measure of nutritional state, 161 body composition studies were performed in 102 patients simultaneously with protein electrophoresis. The body cell mass
represented by the exchangeable potassium to total body water ratio correlated significantly \((p<0.001)\) with the serum albumin concentration \((r = 0.59)\) and significantly \((p<0.001)\) to total protein \((r = 0.59)\). However in both cases the 95% confidence limits about the regression were wide. In 24 of 54 patient (44%) with a normal nutritional state, as defined by body composition, the serum albumin was normal. In 12 of 107 (11.2%) patient with malnutrition, the serum albumin was normal. Serum albumin did not consistently reflect the significant body composition changes observed. The data indicate that serum albumin is a valid measure of nutritional state for epidemiological survey however, due to the low sensitivity and specificity it is a poor parameter for evaluating the individual patient's nutritional state.\(^{47}\)

To find the practical significance of serum albumin analyses in the assessment of nutritional status, a prospective longitudinal study was conducted at Kampala, Uganda which comprised a total of 98 children, 27 of which had either pitting oedema or moon face. The study concluded that in kwashiorkor, hypoalbuminaemia should be regarded as a marker of susceptibility of a malnourished children to oedema and serial weight records as the role index of nutritional status can be misleading.\(^{47}\)

In a similar study done at PGIMR, Chandigarh, biochemical tests for serum albumin, glucose, urea nitrogen, amylase and total protein was performed in 264 children using micromethods. It was found that BUN and amylase decreased significantly \((p<0.01)\) in mild and moderate degrees of malnutrition with no progressive decline with fall in body weights. Serum albumin showed a progressive decline with decrease in body weights \((p<0.01)\). Using multivariate analysis, a multiple regression equation was constructed to predict the body weight as percentage of expected for age from the values obtained for urea nitrogen, amylase and albumin. It was found that the calculated weights matched with 95
percent confidence limits with the actual weight expressed as percentage of expected for age.\textsuperscript{49}

In a study conducted at Nigeria, eleven plasma biochemical parameters were estimated in a total of 28 children with protein energy malnutrition, seven children in each category of marasmus, kwashiorkor, marasmic kwashiorkor and undernutrition with ages between 8 and 48 months. The estimations were performed on admission and 8 to 24 days after treatment at the Obafemi Aolowo University Teaching Hospital Complex, Nigeria. Plasma sodium, potassium, chloride, bicarbonate and albumin levels were significantly (\textit{p}<0.05) higher after treatment than on admission. Calcium however showed no significant change. Total protein and cholesterol were significantly (\textit{p}<0.05) raised after treatment for all the PEM types except undernutrition and kwashiorkor respectively. Globulin, urea were significantly raised after treatment for kwashiorkor (\textit{p}<0.05).\textsuperscript{50}

**Prognostic value of serum protein and albumin**

In a study performed at Agra by K. Kalra et al, estimation of serum proteins and electrolytes were done in 126 children with malnutrition. The cases were divided into four clinical group undernutrition, marasmus, nutritional oedema and kwashiorkor. Total serum proteins were below 6.5 gm\% in 63 out of 80 cases of marasmus and all the eighteen undernourished children. In oedematous groups i.e. nutritional oedema and kwashiorkor, serum protein levels were below normal in all the 28 cases and none of them showed serum protein levels above 6.5 gm\%. Serum albumin was less than 3 gm\% in all children with nutritional oedema, while in undernourished and marasmic children, serum albumin levels were within normal range in 6 & 16 cases respectively.\textsuperscript{22}
To measure the prognostic value of clinical, anthropometric and biological indicators of PEM in hospitalised children, a hospital based, follow up study was undertaken in paediatric hospital in Zaire. Patients were followed from admission to discharge of death of a cohort of children. 1129 patients were admitted consecutively between August 1986 and October 1988. Mortality was higher in wasted children and in those with a mid-upper arm circumference (MUAC) of <125 mm, a serum albumin <16 gm/l and oedema. After multivariate analysis, serum albumin was the best predictor of subsequent risk of dying. MUAC and oedema, however still contributed considerably to evaluation of mortality.\textsuperscript{51}

In a similar type of study conducted in Zaire, few biochemical markers were used in an attempt to predict mortality in children admitted to hospital in Kivu, Zaire for PEM. Data for 39 children who died showed significantly lower levels of albumin (1.61 vs 2.53 gm/dl; $p < 0.001$), transferrin (82.1 vs 167.7 mg/dl; $p < 0.001$), and transthyretin (6.49 vs 9.87 mg/dl; $p < 0.001$) but not retinol-binding protein than for the 199 survivors. Relative risk of dying for each indicator was about 4. This study helps to discriminate among hospitalised subjects at risk and to identify those in need of more intensive nutritional support to prevent early death.\textsuperscript{52}

To conclude, serum protein and albumin are significantly decreased in PEM and the decrease is more marked in serum albumin. Other components of proteins may be normal, low or even be increased. Various studies mentioned in available literature take serum albumin as one of the poor prognostic factors in PEM. Decrease in oedema is thought be the cause of oedema in PEM but few studies have proposed alternative hypotheses.

e. Glucose
It is increasingly becoming clear that a deficiency in energy intake is a major factor among the dietary causes of PEM. There is general agreement that fasting blood glucose is lower in malnourished children than in recovered or normal children, though there is wide variation in the blood glucose levels in various studies. The immediate past dietary intake of energy and the subject's requirement for energy are uncontrolled variables that affect the actual blood glucose level after a standard 8 hours fast. Other factors that determine the level of blood sugar on fasting are the level of glycogen stores and the rate of its breakdown in the liver and the rates of gluconeogenesis and peripheral utilization of glucose.

Several studies have shown conflicting results about the level of glycogen in PEM. Studies by Waterlow et al (1960)\textsuperscript{53} showed high glycogen store in kwashiorkor while the study conducted by Alleyne (1969)\textsuperscript{54} showed that this is not the case for all type of PEM. Later it was shown that glycogen oxidation is decreased and was completed earlier in PEM compared with recovered patients. The fall in plasma glucose occurred earlier in the malnourished but the final level reached was the same in the children before and after recovery from malnutrition.\textsuperscript{55} Despite a 50 percent reduction in glycogen stores, the malnourished child on fasting was able to maintain blood glucose levels similar to those after recovery. It may be one good example of metabolic adaptation in PEM probably as a result of increased activity of glucose - 6 phosphatase.\textsuperscript{54}

Apart from breakdown of available glycogen stores, PEM patients can maintain blood glucose levels to a significant extent by producing glucose from non-carbohydrate sources i.e. by gluconeogenesis. After depletion of glycogen stores, oxidation of fat, which is by far the largest energy source is the major energy source. Both brain and RBC strictly require glucose as the source of energy and gluconeogenesis from 3-carbon substrates fulfils this requirement. In a study
conducted by Kerr et al (1974).\textsuperscript{56} An attempt has been made to measure in the malnourished and recovered children during the transition from the fed to the fasting state, the contribution to glucose production from glycerol, from lactate, pyruvate and amino acids derived from glucose, which are partially oxidised and hence available for synthesis of glucose. A maximum of 8 percent of glucose production could have been provided from breakdown of portion and the corresponding value for recovered child was 16 percent. In both the cases about 20 percent could have been derived from glycerol and the rest 70% of glucose production in the malnourished and 60% in recovered child must have been derived from efficient recycling of product of glycolysis.

Mild to moderate hypoglycaemia is quite common in cases of PEM; has no risk of mortality but symptomatic profound hypoglycaemia is life threatening and requires urgent treatment. A blood sugar below 3 mmol/l (50 mg/dl) carries a high mortality. Symptomatic hypoglycaemia is more common in marasmus where energy stores are depleted. It also occurs more frequently if feeding is infrequent and is often associated with septicaemia in cases of PEM.\textsuperscript{57}

\textbf{Infection hypothermia and hypoglycaemia}

In Jamaica, near hypothermia (temperature below normal but above 95\textdegree F.) occurs in about 50\% of admitted children with PEM but is regarded as a relatively benign condition.\textsuperscript{58} In Uganda, it also occurs more often in severely wasted children but is associated with a high mortality rate\textsuperscript{59} In May be due to lower ambient temperature during the night in Uganda. Hypothermia (rectal temp <35\textdegree) frequently occurs in children with gram negative septicaemia which is quite common in cases of PEM and also may be associated with hypoglycaemia. Hypothermia is a manifestation of thermoregulatory control and decreased energy stores. In addition emaciation leads to reduced total specific thermal insulation.
In an attempt to study the incidence and clinical association of hypoglycaemia among paediatric admissions, a study was carried out in an acute medical paediatric service in Maputo, Mozambique. Of 603 children, 43 children (7.1%) were hypoglycaemic, 16 of these with plasmodium falciparum malaria had a shorter illness and a higher incidence of convulsions and focal neurological signs than those with other diagnoses, but were less likely to die. Hypoglycaemia also complicated PEM, pneumonia, encephalitis, intestinal parasitic infection and nephritic syndrome. 25 of the 603 children died; 7 (16.3%) of 43 with hypoglycaemia and 18 (3.2%) of 560 who were normoglycaemic with relative risk of death being 5.8 (95% confidence interval 2.25 to 14.93).  

To study the hypoglycaemia associated with severe kwashiorkor, a study was conducted in South Africa. Despite abundant stores of glycogen glycogenolysis was found to be impaired. Plasma glucagon levels were relatively low and it is suggested that this might be secondary to either a pancreatic alpha cell defect or inadequate sympathetic stimulation.  

Gastrointestinal infections are one of the commonest causes of death in cases of PEM. A survey which measured the blood sugar levels in 868 infants with dehydration from gastroenteritis (age of patients ranged 2-35 months) showed that in 7.9% of cases blood sugar level were 0-50mg % and in 10.2 % they were over 200mg%. Hypoglycaemia was more common in malnutrition and a high mortality was found in hypoglycaemia. Hypothermia was associated with abnormal blood sugar levels. No correlation was found between blood sugar and serum sodium.  

**Insulin, glucagon and glucose in PEM**
Young Wister rats were used as an experimental model to determine the effects of PEM on glucose tolerance and insulin release. Malnourished rats presented some of the features commonly found in human PEM, such as failure to gain weight, hypoalbuminaemia, fatty infiltration of the liver and intolerance of oral and intravenous glucose loads. The rate of disappearance of glucose from the gut lumen was greater in the malnourished rats but there was no significant difference in portal blood glucose concentration between normal and malnourished rats 5 and 10 min after an oral glucose load. Insulin resistance was not thought to be the cause of the glucose intolerance in the malnourished animals since these rats had a low fasting plasma insulin concentration with a normal fasting blood glucose concentration and no impairment in their hypoglycaemic response to exogenous insulin administration. Furthermore, fasting malnourished rats were unable to correct the insulin-induced hypoglycaemia despite high concentration hepatic glycogen. Malnourished rats had lower peak plasma insulin concentrations than normal control animals after provocation with oral and intravenous glucose, intravenous tolbutamide and intravenous glucose plus aminophylline. This was not due to a reduction in the insulin content of the pancreas or potassium deficiency. Healthy weanling rats, like the older malnourished rats had a diminished insulin response to intravenous glucose and intravenous tolbutamide. However, their insulin response to stimulation with intravenous glucose plus aminophylline far exceeded that of the malnourished rats. Thus the impairment of insulin release demonstrated in the malnourished rats can't be ascribed to a 'functional immaturity' of the pancreas.\(^6^3\)

In Poland fasting blood serum insulin glucose and K\(^+\) ions concentrations were estimated in 50 children with protein calorie malnutrition. These children were born with the normal body weight or with symptoms of intrauterine dystrophy 40 healthy children of the same age with normal chronologic body weight were included in the control group. The results of immunoreactive insulin
(IRI), glucose and K ions concentrations were evaluated statistically by student's t test. The statistically significant lowering of the IRI level and statistically insignificant lowering in glucose and K ions were found in children with malnutrition of compared to control group.64

**Growth hormone and glucose in PEM**

In a similar type of study conducted by Nirmala Vashi et al, to find growth hormone secretion in malnutrition, 20 children of 8 months to 12 years were selected; 5 with frank kwashiorkor, 13 with undernutrition and 2 with marasmus. Ten normal matched for age and sex was used as controls. Common factors of the study were gross growth retardation below the 3rd percentile of the ICMR standard. Human growth hormone was measured 24 hours after admission in most cases. Hypoglycaemia was induced by administration of crystalline insulin 1 unit/kg and blood collected at 0, 30, 60 and 90 minutes. The mean growth hormone level at 60 minutes was 19.2 ± 7.2 in millimicrogram/ml and fell within the normal limits. This suggested that growth retardation in malnutrition has no relation to the hormonal control but is due essentially to the lack of amino acids and calories necessary for growth.65

Plasma human growth hormone levels were assessed in 15 infants with PEM. Following insulin induced hypoglycaemia, argentine and L-dopa provocation tests and intravenous glucose tolerance test. Fasting hGH levels were high in 85.7% of the cases. An adequate hHG response to stimulation was obtained in only 42.8% of the cases with insulin induced hypoglycaemia; in 52.2% with arginine; in 30.8% with L-dopa. Response to at least one type of provocation was obtained in all 5 cases to which all three tests were applied. Exaggerated or delayed responses to provocation stimuli were also encountered in a number of the cases. Intravenous glucose tolerance test did not lead to suppression in hHG
recreation to increase in insulin secretion in these subjects. The results indicate that marasmic PEM may lead to defects in the hGH secretary function of the hypothalamopituitary axis.\textsuperscript{56}

**Infection and prediction of mortality in PEM**

Relative risk (RR) of death associated with various factors was studied by Briend et al in Matlab, Bangladesh (1987). Among these female gender has RR of 26, no breast feeding 2.1, any diarrhoea 4.8, diarrhoea 11.3, ARI 11.6 and oedema 84.1 and MUAC less than or equal to 10 cm 48.0.\textsuperscript{67} In a study in rural Uganda, anthropometric measurements were used to predict mortality. Out of 96 deaths, weight for age \textless 2S.D. could predict 40 deaths, weight for height \textless 2 S.D. 12 deaths and MUAC < 12.5 cm 25 deaths.\textsuperscript{68}

A prospective study was undertaken to study the clinical profile and pattern of infection in 90 Ethiopian children with severe PEM. Study group consisted of 44(49%) with marasmus, 29 (32% ) with marasmic kwashiorkor and 17 (19% ) with kwashiorkor. Their age ranged from 4 to 60 months and the median age at admission was 11.5, 15 and 20 months respectively. Over 80% patients were infected and lungs were the commonest sites. Bacterial pathogens predominantly gram negative enteric organisms were isolated from 36% of blood and 37% of urine specimens. Tuberculosis and non-typhoidal Salmonellae showed a higher tendency of causing disseminated disease. Rickets and overt vitamin a deficiency were seen in 37% and 17% of the patients respectively. Septicaemia, gastroenteritis, pneumonia and disseminated TB accounted for an overall case fatality rate of 32%. Mortality was higher in children with serum protein of 5 gm % or less.\textsuperscript{69}
A study was carried out in paediatric ward of the regional hospital in Moundou, Chad, between June 1992 and May 1993 to assess the prevalence of PEM in children under 5 years of age and its relationship with various diseases and in hospital mortality. A total of 1050 children ranging in age from 1 to 59 months were hospitalised in the ward during the study period and included in the study. Nutritional status was assessed using weight for height and height for age charts. Diarrhoea, dehydration, malaria, anaemia, acute respiratory infection and meningitis accounted for 85.5% of underlying diseases and for 76% of deaths. Malnutrition was more prevalent in children under than over 2 years of age. The prevalence of malnutrition was highest in children with ARI or diarrhoea (61.3% and 89.8% respectively). Mortality was significantly higher in severely malnourished children and PEM children with respiratory infection especially at ages under 1 years. Death was attributed to malnutrition in 30% of cases.70

**Hyperglycaemia and PEM**

In a study conducted by Anju Seth & S. Aneja in New Delhi, India, out of 50 patients included in a series of patients with malnutrition grade III and IV based on IAP classification with dehydrating gastro-enteritis, 5 patients (10%) were found to be hyperglycaemics. All children with hyperglycaemia were under 1 year of age and had moderate dehydration. Serum sodium levels were normal in all patients presenting with hyperglycaemia except one who had hyponatraemia. Serum potassium was normal in all cases. This was one of the rare studies conducted in India with occurrence of hyperglycaemia without associated hyponatraemia in infantile gastro-enteritis.71

In a similar type of study conducted by Piyush Gupta et al in New Delhi, India, transient hyperglycaemia was found in 4.7% of children presenting with
hyperglycaemia (glucose level of ≥150mg/dl). Out of 758 children (1 month to 6 years) with acute illness, disease wise prevalence in neurological disorders, septicaemia, respiratory illnesses and diarrhoea was 7.9, 7.6, 4.2 and 3.0 percent respectively. A interesting finding was that family history of diabetes mellitus did not predispose towards developing transient hyperglycaemia. The demographic profile and severity of illness did not affect the prevalence, extent and the rate of normalisation of associated hyperglycaemia. The mortality in hyperglycaemics was double (13.9%) as compared to 6.9% in non-hyperglycaemics but the difference was insignificant (p>0.05). Though it was concluded from the study that transient hyperglycaemia occurs in 4.5% of patients with acute paediatric illnesses, it did not significantly correlate with the clinical profile and severity of the illness and had no immediate prognostic significance.72

In summary, the serum glucose level is decreased in PEM as a result of decreased amount of substrates. Mild to moderate hypoglycemia is quite common in PEM but severe hypoglycemia which carries a high mortality is less common.

f. Calcium

Ninety-nine percent of Ca++ is found on bone and of the reminder almost 1% is within the intracellular compartment and around 0.1% within the extracellular fluid. Although only a tiny fraction of the body store of Ca++ is within the extracellular fluid, the plasma Ca++ is closely controlled. The large store of Ca++ in bone is in the form of hydroxyapatite crystals. Although only about 1% of the body store Ca++ is found outside bone the Ca++ in solution plays a vital role in controlling the activity of excitable tissues, Extracellular Ca++ influences neuromuscular transmission and cardiac muscle excitability. The normal total plasma Ca++ is around 5 m Eq/l(10mg/dl) but only the free ionised Ca++ is physiologically active. Since half of the Ca++ in plasma is bound to protein and
other anions, the free ionised Ca\(^{++}\) is around 2 m Eq/1 (5 mg/dl). The availability of ionised Ca\(^{++}\) is influenced by the presence of other electrolytes; HCO\(_3\) and phosphate reduce the availability, change in plasma Ca\(^{++}\) are not always followed by a similar change in the ionised Ca\(^{++}\) as an increase in plasma albumin concentration will increase total plasma Ca\(^{++}\) without any change in the ionised Ca\(^{++}\). A low plasma Ca\(^{++}\) associated with hypoalbuminaemia is not indicative of hypocalcaemia as the physiologically active ionised Ca\(^{++}\) may be normal. This situation is very likely to occur in PEM in which hypoproteinaemia often occur.\(^7\)

In spite of large differences in intake the concentration of ionised Ca\(^{++}\) in plasma and extracellular fluids is regulated within narrow limits by the combined activity of three hormones, parathyroid hormone, calcitonin and the vitamin D metabolite 1, 25- dihydroxycholecalciferol.\(^7\)\(^4\),\(^7\)\(^5\)

Parathyroid hormone increases plasma Ca\(^{++}\) by stimulating bone resorption, increasing renal resorption, and stimulating the production of active form of vitamin D (1, 25-dihydroxycholecalciferol) form its inactive form (25-hydroxycholecalciferol).

As the intracellular concentration of Ca\(^{++}\) is 1000 times lower than the extracellular, the constancy of the cytoplasmic Ca\(^{++}\) concentrations of great importance, since it plays a crucial role in the integrated control of membrane permeability, the cellular response to stimulation and intracellular signalling.\(^7\)\(^6\),\(^7\)\(^7\) 'Calcium pump' maintains the large concentration gradient across cell membrane and some claim that the body as a whole this pump is responsible for a larger oxygen uptake than the Na-pump.\(^7\)\(^8\). A breakdown in this vital pump as a result of hypoxia leads to accumulation of intracellular Ca\(^{++}\) and serious cell damage that could be a component of 'sick cell syndrome' in serum PEM.
The calcium intake of Third World child will be limiting after the first six months of life and at one year, when both intake and calcium concentration of breast milk begin to fall off, it will be difficult for the child's requirement to be met. Though cow's milk has a concentration of calcium four times that of human milk, the weaning foods are likely to contain interfering factors such as phytic acid that significantly reduces calcium absorption.

Rickets is not a typical feature of PEM, because in the absence of bone growth, the classical changes in rickets do not occur. Bhattacharyya and Dutta (1976) in Calcutta has described 'atrophic' rickets in PEM which has marked decalcification and thinning out of bone cortex with remarkable absence of classical cupping and spraying of the mataphyses, which becomes striking in the process of healing during recovery form PEM. In a study conducted by Salimpour (1980), similar results were found and malnutrition also tended to disguise the characteristic biochemical changes of rickets.

Normal alkaline phosphatase level in PEM has also been mentioned by Reddy and Srikantia. Though calcium deficiency may be a common finding in PEM, it may not be a cause of linear growth because process of stunting my begin as early as 3 months of birth whereas the supply of calcium should be adequate for as long as the child is fully breastfed. (1981)

A study was conducted in Northern Nigeria to explore the relationship between protein nutritional status and the development of rickets in children. Using established and recently developed clinical and biochemical parameters, the diagnosis of rickets were confirmed in 16 children between ages of 10 months and years. Twenty-seven children lacking skeletal stigmata were selected as age and sex-matched controls to the ricketic patients. Several clinical, laboratory and anthropometric measurements designed to assess calcium homeostasis, skeletal
growth, and the extent of bone remodelling or resorption and protein nutritional status were moderately malnourished, their protein nutritional status was significantly better as measured by the serum prealbumin concentration (15.4 vs 12.5 mg/dl, \( p = 0.0012 \)) when compared with the severely malnourished children who were devoid of any indication of rickets than are children whose linear growth is impeded. The level of 1-25-dihydroxycholecalciferol in both groups were found to be higher than that mentioned in the literature.\(^{82}\)

Karla K. et al estimated serum calcium in 126 children with malnutrition. the cases were divided into four clinical groups: undernutrition, marasmus, nutritional oedema and kwashiorkor. Serum calcium was normal in 40% of cases in their series. The mean values of serum calcium and phosphorus were 9.4 and 4.38 mg% in non-oedematous group while the values were 8.8 and 4.22 gm% in oedematous group respectively.\(^{22}\)

In a study conducted by Rao A. and Cherian A in Nigeria, renal tubular function was assessed in PEM. The study consisted of 9 cases of marasmus, 15 cases of kwashiorkor and marasmic kwashiorkor and 14 control subjects. Serum (albumin adjusted) calcium and serum Mg did not show any significant change in the patients\(^{24}\)

In a study conducted in Nigeria, thirty children with kwashiorkor had mean ± serum plasma calcium of 7.15 ± 0.1 mg%, total proteins of 4.6 ± 0.17 gm/dl and albumin of 1.89 ± 0.11 gm/dl. These values are significantly lower \(( p<0.001)\) than the corresponding value of 9.07 ± 0.01, 7.3 ± 0.11 and 3.85 ± 0.07 observed in 30 other age matched normal controls. There was no significant statistical difference in plasma alkaline phosphatase levels in both groups. Correction of calcium for hypoalbuminaemia in the kwashiorkor group concluded that the observed
hypocalcaemia in kwashiorkor is merely apparent and is because of hypoalbuminaemia, the level of free or ionised calcium being normal.\textsuperscript{83}

To find out the calcium metabolism in children recovering from severe PEM, twenty pre-school children from severe oedematous PEM were studied during the initial 45 days of recovery. All children enrolled in the study received 4 gm/kg day of protein and 150 K cal/kg/day of energy from a milk-based recovery formula providing 130-140 K cal/kg/day of calcium. Study subjects were randomly allocated into two treatment groups once receiving intact milk formula and the other a lactose-free preparation. Both treatment groups showed a high efficiency of intestinal calcium absorption sustained even often the normalisation of weight for height and lean body mass. The presence of stool volume in the early period of recovery in the children receiving intact milk was not associated with higher faecal calcium losses. Urinary calcium excretion was within the range reported for healthy children under a normal diet. It was concluded that therapeutic amounts of calcium should be given to children with PEM well beyond the normalisation of body weight and lean body mass.\textsuperscript{84}

A study was conducted recently in Argentina to identify the influence of dietary calcium concentration on body size and bone composition in rats during recovery from malnutrition. At different levels of calcium in a diet containing 30% protein on the rehabilitation of body size from PEM and to find out the optimal calcium/protein ratio for attaining a normal body composition. During the study, weanling female Wistar rats were fed with protein free diet up to a weight deficit 20±1%. Then they were arranged in groups and fed diets with 30% protein and 0.0, 0.2, 0.4, 0.6, 0.9 or 1.2% calcium for 28 days. Food and deionized water were given ad libitum. Body weight and length were recovered every 3 days. At 28 days, the animals were sacrificed to determine femur composition. At 13 days of starting of study weight for age was within the normal range for rates consuming
≥0.6% calcium. At day 28, all groups showed adequate weight for age. Although length for age was during rehabilitated period, rate of weight gain improved when calcium was ≥0.9% femur length did not show significant differences between groups. Total femur calcium content and calcium/gm of dry weight tissue increased with increments in dietary calcium concentration and tended to plateau with 0.4% calcium. Calcium/protein ratio reached the highest value with 0.9% calcium. These findings showed that at a dietary protein level of 30% the calcium/protein ratio is a limiting factor in attaining of normal body size, this is achievable when calcium concentration is 1.2% and the calcium/protein ratio is 0.04.85

Erythrocyte membrane Ca-Mg ATPase is responsible for maintenance of calcium across cell membrane and maintains intracellular calcium, which is 1000 lower than that of extracellular compartment. In a study conducted at Nigeria, calmodulin free membrane was prepared from erythrocytes of kwashiorkor children and from healthy children of the same age. In the absence of calmodulin, the specific activity of Mg$^{++}$ dependent pumping ATPase (Ca-Mg ATPase) of kwashiorkor membrane was more than 40% lower than the specific activity of the normal enzymes, whose maximum velocity was increased by at least four-fold by the modulator protein. In contrast, the maximum velocity of the enzymes of kwashiorkor membrane was enhanced by calmodulin by about 1.5 times the basal activity of the normal enzymes and by 2 times the basal activity of the kwashiorkor enzymes. The affinity of the pump for ATP was lower in the membrane of kwashiorkor children in composition to normal membrane. A determination of dependence of activity of the pump on calcium in the absence or presence of calmodulin reveals that the affinity of the kwashiorkor enzymes for calcium is at least 70% lower than that of enzymes of normal membrane. These finding shows that the calcium pumping ATPase of kwashiorkor membrane is less functional than the enzymes of healthy erythrocytes.86
During the first stage of nutritional recovery the needs of undernourished infants in terms of protein calories percents are higher than normal leading to and accelerated catch-up. Consequently calcium and phosphorus balance increase proportionately to weight gain rate in order to attain a normal body composition. Because vitamin D is the one, which has a significant role in maintenance of serum calcium the question is whether vitamin D intake must also be increased during this accelerated catch-up growth period. A retrospective study was carried out to analyse the previous results in order to clarify the interrelationship between calcium absorption calcium retention and vitamin D intake total of 29 undernourished infants from 2 to 18 months of age, were fed ad libitum with one of two proprietary milk formulas containing, per 100 gm: calcium 0.50 and 1.17 gm; phosphorus 0.37 and 0.5 gm; vitamin D 350 and 400 IU; proteins 11.34 and 17 K Cal/100 K Cal of total diet respectively. Recommended dietary allowances (RDA) of calcium and vitamin D were calculated with reference to normal infants body weight and to 1000 K Cal of recommended dietary energy intake. Calcium intake was higher than the RDA and ranged between 60 and 413 mg/Kg/day; intake of vitamin D increased proportionately to food intake; calcium absorption ranged between 40 and 92% (mean 69.8±14.6).