

Study

of serum levels of insulin-like growth factor $_{-1}$, insulin – like growth factor binding protein $_{-1}$ and $_{-3}$, prealbumin and aminoterminal propeptide of type $_{-1}$ procollagen in infants and children with protein energy malnutrition.

Thesis

Submitted for Fulfillment of PhD Degree
in Pediatrics

By

Almahdi Mohamed Alatrouni

MB . B . CH (Egypt)

Spuervisors

Prof Dr. Antonio Carrascosa Lezcano.

Prof and Head of Pediatrics. Dept., Vall d' Hebron Hospital,
UAB , Spain.

Prof Dr. Mohamed Amro Hamam.

Prof of Pediatrics, University of Tanta, Egypt.

Prof Dr. Aisha Abdel – Lattef.

Prof of Clinical Pathology, University of Tanta, Egypt.

U.A.B

2004

Table of Contents

	Page
Introductation	1
Review of literatures	
Protein energy malnutrition	3
Insulin- like growth factors	49
Prealbumin	73
Aminoterminanl propeptide of type-1 Procollagen	77
Patients and Methods	85
Results	94
Discussion	119
Summary and Conclusion	130
References	133

Acknowledgment

My gratitude and thanks should be submitted to God for his kind support to me.

It is a great honour for me to take this opportunity to express my most profound gratitude and my deepest respect to prof Dr Antonio Carrascosa Lezcano, Prof. and Head of Pediatrics, Vall d' Hebron Hospital, UAB, Spain, for proposing the idea of this study, for his guidance, kind supervision and encouragement.

I'm also grateful to Prof. Dr. Mohamed Amro Hamam, Prof. of Pediatrics, Tanta University and to Prof. Dr. Aisha Abdel - Lattef , Prof. of Clinical Pathology , Tanta University, Egypt, for supervising this work and for their great help.

I'm very thankful to Dr. Adel Erfan, Assistant Prof. of Pediatrics, Tanta University, Egypt, for his Kind help.

My deep thanks to all the staff members and my colleagues in the Gastroenterology Unit of Pediatric Department, Tanta University. Egypt , for their kind help and cooperation.

Almahdi

List of Abbreviations

aa	amino acid
ACTH	adreno corticotrophic hormone
ADH	antidiuretic hormone
ALS	acid labile subunit
CSF	cerebro spinal fluid
DNA	deoxy ribonucleic acid
FSH	follicle stimulating hormone
GH	growth hormone
HAM	height for age median
Hb	haemoglobin
IGF _s	insulin-like growth factors
IGFBP _s	insulin-like growth factors binding proteins
I. V.	intravenous
KDa	kilodalton
Kwo	kwashiorkor
LH	leutinizing hormone
M	marasmus
Mkwo	marasmic kwashiorkor
M6P	mannose – 6 – phosphate
mRNA	massenger ribonucleic acid
MUAC	mid upper arm circumference
PEM	protein energy malnutrition
PICP	carboxy terminal propeptide of type 1 procollagen
PINP	amino terminal propeptide of type 1 procollagen
RBP	retinol binding protein
TSF	triceps skin fold
TTR	transthyretin
WAM	weight for age median
WHO	world health organization.

Introduction

Protein energy malnutrition (PEM) is a range of pathological conditions arising from coincident deficiency of proteins and calories in varying proportions occurring mostly in infants and young children.

According to Welcome classification, PEM is classified into mild form (underweight) and severe form (marasmus, kwashiorkor or marasmic kwashiorkor) (**Wellcome, 1970**).

The assessment of nutritional condition may be done through clinical examination, anthropometric measures or biochemical tests.

The insulin-like growth factors (IGF_S), are defined as polypeptide growth factors secreted by the liver and other tissues in response to stimulation by growth hormone (GH) (**Guyton, 1996**).

In humans, there are two main forms of IGF_S: Insulin-like growth factor₋₁ (IGF₋₁) and insulin-like growth factor₋₁₁ (IGF₋₁₁). The most important of these is IGF₋₁, its synthesis is GH dependent, and its plasma levels are very sensitive to changes in GH availability (**Berne et al, 1998**).

The IGF_S circulate in plasma in complex with a family of binding proteins that extend the serum half-life of the IGF peptides, transport the IGF_S to target cells and modulate the

interaction of the IGF_S with surface membrane receptors (**Reiter and Rosenfeld, 1998**).

There are six IGF – binding proteins (IGFBP_S) designated IGFBP₋₁ to IGFBP₋₆. They are designated on the basis of their amino acid sequence (**Berne et al, 1998**).

IGFBP₋₁ is generating much interest, because it possesses properties that are a typical for a classical binding protein. It is an important modulator of IGF activities (**Martina et al, 1997**).

IGFBP₋₃ is the major IGFBP in the circulation (**Boisclair et al, 2001**).

The prealbumin is a protein synthesized by the liver. It plays an important role in the plasma transport of vitamin A, and also involved in the transport of thyroid hormones (**Silverman and Christenson, 1994**)

The aminoterminal peptide of procollagen, are removed during processing of collagen and released into the circulation. The level of procollagen peptides may provide a clinically useful index of growth (**Raisz et al., 1998**).

- Aim of work :

The aim of work is to evaluate serum levels of IGF₋₁ , IGFBP₋₁ , IGFBP₋₃ , prealbumin and aminoterminal propeptide of type 1 procollagen in malnourished children and demonstrate the effect of malnutrition on these parameters.

Review of Literature

Protein Energy Malnutrition

Protein energy malnutrition (PEM) is a range of pathological conditions arising from coincident lack , in varying proportions , of protein and calories occurring most frequently in infants and young children and commonly associated with infection **(WHO,1973)**

PEM is a serious problem in the developing countries , where more than half of the deaths of children under five years are related directly or indirectly to malnutrition (**Waterlow , 1994**)

PEM may be said to range in severity from mild , through moderate to severe degree . The mild and most of the moderate degrees are subclinical and can only be detected by anthropometric and biochemical tests . These early Stages are characterized by growth failure and possibly some retardation of mental development . The best way to identify such children early is by regular weighing and plotting the weights on growth chart to show flattening of the weight curve . The severe degree of PEM ranges in type of clinical picture in spectrum , marasmus (M), kwashiorkor (kwo) and marasmic kwashiorkor (M kwo) **(El-Mougy , 1999)**

In the developing countries , some combination of these types of malnutrition is almost always found . This is why energy malnutrition is no longer dissociated from protein malnutrition . Since several vitamin and mineral deficiencies are associated with PEM, American authors prefer to use the term multideficiency disease (**Brasseur et al, 1994**)

Protein energy malnutrition often coexists with micronutrient deficiencies (**Gracey , 1996**)

Ballabriga (1985) reported that malnutrition results from multiple deficiencies , not necessarily limited to lack of proteins or calories , but also involving other associated or separate factors such as deficiency of trace elements , such as copper and zinc.

Prevalence of PEM

Malnutrition is one of the principal causes of childhood morbidity and mortality , approximately 50% of the 10 million deaths each year in developing countries occur due to malnutrition in children younger than 5 years (**Lin and Santoro, 2002**).

In 1987, **the Subcommittee on Nutrition of the Administrative Coordinating Council of the United Nations** , in a publication on the world's nutritional status , estimates that over one billion persons are suffering from mild to severe degrees of PEM (**UNACC/SCN,1987**)

Severe malnutrition in infants is common in areas with insufficient food , inadequate knowledge of feeding techniques or poor hygiene (**Curran and Barness , 2000**) . It is estimated that 2.5% of children under five years are severely malnourished and 20% are moderately malnourished (**Barness , 1992**).

In 2000, the WHO estimated that malnourished children numbered 181.9 million, or 32%, in developing countries. In South Central Asia and Eastern Africa, about one half the children have growth retardation due to PEM. This is 5 times the prevalence in the western world (**WHO, 2000**).

The prevalence of PEM is lowest during the first six months of life , due to the fact that breast feeding is the rule in this period and is considered satisfactory from the nutritional point of view .

In addition , the risk of external infections , especially those causing diarrhea is also decreased in these infants. On the other hand , in the second six months of life , the incidence of malnutrition increases as breast milk becomes insufficient to meet all dietary requirements , and the supplements given are mostly watery fluids of negligible nutritional value . This is partly due to economic reasons and partly due to ignorance (**Osman et al . 1978**).

In the western societies , primary PEM is hardly seen (**Owen, and lippman , 1977**) . While malnutrition secondary to acute and chronic diseases is commonly seen , with a 25% to 60% prevalence in hospitalized pediatric patients (**Hendricks et al 1995**). Inadequate caloric intake , inadequate absorption and assimilation , failure of utilization , or increased metabolic needs are the basis for this type of malnutrition (**Shamir and Wilschanski, 1998**)

Classification of PEM

Malnutrition may be acute or chronic , reversible or irreversible (**Curran and Barness , 2000**) . Many classifications have been used over the past several decades to assess nutritional status of large number of children.

[1] Classification based on the weight

1- Gomez classification

Gomez et al (1956) classified PEM into three stages depending on the percentage of expected weight for age .

% of expected weight for age	grade of PEM
> 90 %	Normal
89 – 75 %	First degree
74 – 60 %	Second degree
< 60 %	Third degree

Table (A-1) Gomez classification of PEM (Gomez et al , 1956)

The main drawback of this classification is that it assumes that all children of certain age should have the same weight . It also includes actively malnourished children and those who are underweight as a result of malnutrition in the past . So , Gomez classification overestimates the prevalence of malnutrition (**Kiju et al , 1991**)

2- Jelliffe classification :

Jelliffe (1966) classified PEM into four levels :

% of expected weight for age	Level of PEM
> 91 %	Normal
90 – 81 %	First level
80 – 71 %	Second level
70 – 61 %	Third level
60 % or less	Fourth level

Table (A-2) Jelliffe classification of PEM (Jelliffe , 1966)

Both Gomez and Jelliffe classifications considered normal those children above 90 % of expected weight for age , while children below 60 % were classified as nutritional marasmus .

3- Wellcome classification :

Garrow (1966) and Wellcome (1970) classified PEM depending on the presence or absence of edema and the deficit in body weight .

State of malnutrition	Body weight as % of standard	Edema
Simple underweight	80 – 60 %	Absent
Marasmus	< 60 %	Absent
Kwashiorkor	80 – 60 %	Present
Marasmic kwashiorkor	< 60 %	Present

Table (A-3) Wellcome classification of PEM (Wellcome, 1970)

4- Buzina classification :

In 1980 , **Buzina** has shown that body weight is a good indicator of nutritional status only at the extremes , i.e severe PEM or gross obesity .

Nutritional status	Weight / Age %
Overweight	> 110 %
normal	90 – 110 %
Mild PEM	85 – 90 %
Moderate PEM	75 – 85 %
Severe PEM	< 75 %

Table (A-4) Buzina classification (Buzina , 1980)

[2] classification based on length

The increase in length is a measure of growth in children . Undernutrition , especially when prolonged , is manifested by slower growth and short stature . However , the immediate effect of malnutrition is reflected on weight , which decreases in relation to length (**Shukry and Kamel . 1974**) . A balanced prolonged low caloric diet results in growth retardation , both in weight and length , and this may lead to nutritional dwarfism (**Brasseur et al , 1994**)

The modified Jelliffe classification in 1968 was based on weight for length , exactly similar to that of weight for age , but this classification gave no consideration to nutritional dwarfism ,

where weight per length is normal , but both are markedly below the expected for age (**Jelliffe , 1968**)

Waterlow (1972) classified PEM based on the concepts of height for age and weight for height . In this classification , children are classified into normal , stunted (height deficit for age), wasted (weight deficit for height) or both (stunted and wasted) . Grades of stunting are defined by height for age , value greater than 95 % (grade 0) , 95 – 90 % (grade 1) , 90 – 85 % (grade 2) , less than 85 % (grade 3) . While grades of wasting are defined by weight for height , value greater than 90 % (grade 0) , 90 – 80 % (grade 1) , 80 – 70 % (grade 2) , less than 70 % (grade 3) . So , the author called the present malnutrition “wasting” and the past malnutrition “stunting” .

Mclaren and Read (1975) described the weight / height ratio for age index based on the fact that weight for height is not completely independent for age especially in children in the first year of life , the children were classified into five groups :

group	Observed weight as % of ideal weight / length / age
Over weight	> 110 %
Normal range	90 – 110 %
Mild PEM	85 – 90 %
Moderate PEM	75 – 85 %
Severe PEM	< 75 %

Table (A-5) McLaren and Read classification of PEM (McLaren and Read, 1975)

[3] classification based on clinical signs :

- McLaren scoring system for PEM :

McLaren et al (1967) applied a simple scoring system for classification of severe forms of PEM. No anthropometric measurements were used in this system , except that an upper limit of 75 % of expected weight for age is applied to patients with marasmus .

Signs present	Points
Edema	3
Dermatitis	2
Edema + dermatitis	6
Hair changes	1
Hepatomegaly	1
Serum albumin or protein (g/ml)	
< 1.00 < 3.25	7
1.00 – 1.49 3.25 – 3.99	6
1.50 – 1.99 4.00 – 4.74	5
2.00 – 2.49 4.75 – 5.49	4
2.50 – 2.99 5.50 – 6.24	3
3.00 – 3.49 6.25 – 6.99	2
3.50 – 3.99 7.00 – 7.74	1
≥ 4.00 ≥ 7.75	0

0 – 3 marasmus

4 – 8 marasmic Kwashiorkor

9 – 15 Kwashiorkor

Table (A-6) McLaren classification of PEM (McLaren et al , 1967)

- Thangkul scoring system for PEM :

Thangkul et al (1980) applied modification for the McLaren system to help rating the severity of PEM .

Weight / height	Edema	Score
80 %	+ ve	5
70 – 80 %	+ ve	4
70 %	+ ve	3
< 70 %	- ve	1
Dermatosis	+ ve	2
Serum albumin (gmdl)	Serum protein (gmdl)	
1.0	3.25	5
1.0 - 1.4	3.25-3.99	4
1.5 – 1.9	4.00-4.75	3
2.0 – 2.4	4.75-5.49	2
2.5 – 2.9	5.50-6.24	1
3.0	6.25	0

1 – 3 marasmus

4 – 7 marasmic Kwashiorkor

> 8 Kwashiorkor

Table (A-7) Thangkul scoring system for PEM (Thangkul et al, 1980)

Etiology of PEM

Protein energy malnutrition is a disease caused by a complex of dietary, infective and environmental factors. Poverty, inequality, poor food distribution and production and lack of knowledge are the underlying causes, but the interaction of nutrition and infection plays the most important role (**Latham , 1990)**

Protein energy malnutrition can be broadly separated in two categories. primary and secondary. Primary PEM is due to inability of the individuals and population groups to produce and consume the necessary foods for maintenance of health in their environment (**Viteri , 1991**).

Secondary PEM is the consequence of a primary pathologic condition that either impairs the food intake and utilization or increases nutrient loss or increase protein and caloric requirements :

- Defective food intake :

- chronic repeated vomiting .
- Anorexia : infections, renal or hepatic disease .
- Mechanical : cerebral palsy, corrosive oesophageal stricture , cleft palate , pyloric stenosis .
- Iatrogenic .

- substance abuse.

- Impaired food absorption :

- Gastric and small bowel diseases

- pancreatic diseases .

- Liver and biliary diseases .

- parasitic diseases.

- Increased nutrient loss :

- persistent diarrhea .

- protein losing enteropathy .

- Increased requirements and abnormal metabolism :

- Inflammatory diseases.

- Fever .

- organic diseases e.g liver cirrhosis and congenital heart disease .

- congenital metabolic disorders (**El-Mougy , 1999)**

- Interaction between nutrition and infection :

The relationship between repeated infections and PEM is well established among populations who live in areas where malaria , and respiratory and diarrheal diseases are endemic. The importance of skin infections and communicable diseases of

childhood , especially measles , as precipitating causes of acute and severe PEM has also been documented (**Matta , 1978**)

Besides the metabolic effects of infectious process , infection are accompanied by a significant reduction in food intake due to anorexia and also most cultures restrict food from sick individuals especially children . Nutrient loss due to diarrhea and increased energy loss due to fever , will aggravate the already unfavorable nutritional condition (**Viteri , 1991**). On the other hand , malnutrition makes the infection worse due to unhealthy mucosal surfaces which allow easy introduction of microorganisms , also the poor immune system permits rapid multiplication of invading organisms , and the recovery is slow as the body is less able to repair the damaged tissues (**El-Mougy , 1999**)

Diarrhea affects the nutritional status of the child in different ways , first by losing appetite , then by associated vomiting , severe dietary restriction and malabsorption (**Puri and Chandra, 1985**). Diarrhea and PEM are directly linked with each other , severe episodes of diarrhea in children , particularly those under 2 years , if not managed properly , result in weight loss and malnutrition . Also , the malnourished children are more likely to suffer from more severe and prolonged diarrhea . So , diarrhea is both a cause and an effect of malnutrition. (**Guerrant et al , 1992**)

Intestinal parasites may also causing PEM due to chronic diarrhea , also it interferes with digestion and absorption by blockade of villi and secretion of antiproteolytic enzymes (**Benjamin and Fernando , 1988**) . The most common intestinal

parasite in this age is the *Giardia lamblia* . prolonged infection with this parasite has been associated with PEM (**Roberts , 1993**).

Assessment of the nutritional status

Nutritional assessment is the evaluation of an individual status and requirements . It is a means by which the undernourished (or overnourished) child can be identified , the nutritional effects of therapy and the efficacy of nutritional interventions monitored and the prevalence of under or over nutrition in a group established (**Reilly , 1998**)

Nutritional assessment was used first in surveys of the nutritional status of populations, especially those in developing countries . More recently there has been much interest for nutritional assessment in developed countries as a result of increasing awareness that malnutrition is common in hospital and community populations of children (**Moy et al , 1990**) , and the growing awareness of the clinical and functional consequences of malnutrition (**Lennard - Jones , 1992**)

There are five principal approaches to nutritional assessment : anthropometric , dietary , clinical , biochemical and functional .

- Anthropometric Nutritional Assessment :

Discussion about the adequacy of a particular anthropometric standard for the classification of PEM among different genetic / ethnic groups has taken place . **The world Health organization (WHO)** , after considering different options and the scientific

evidence about optimal growth patterns of different populations , has adopted the **National Centre for Health Statistics (NCHS)** standards as a universal yardstick for evaluating growth of children throughout the world (**Waterlow et al , 1977**)

There are three basic measurements (body height , weight . and age) are recommended by **WHO (1983)** , and these are used to derive the following indices : height for age (low height for age “stunting” is an index of chronic malnutrition) ; weight for age ; weight for height (low weight for height “wasting” is an index of acute malnutrition (**Reilly , 1998**)

In clinical practice , the body weight , height and age , these anthropometric indices are useful but can be limited as , for example , when a child has ascites , fluid retention , or a large solid tumor , such conditions can confound weight-based anthropometric indices . The mid-arm circumference and skin fold thickness (notably over the triceps) has been proposed for the identification and classification of PEM of various degrees and severity (**Potter et al , 1995**)

The mid-arm circumference is one of the simplest anthropometric indices not based on weight and height. A classification system based on 80 , 70 and 60 % of the standard used to distinguish mild , moderate and severe PEM (**Jelliffe, 1968**)

The degree of subcutaneous fat reflected by skin fold thickness , and the size of the muscle mass estimated by arm circumference are indirect indicators of calorie and protein reserves (**Gibson , 1990**)

The advantage of these anthropometric measurements that they are simple , non invasive , inexpensive , portable and suitable for pediatric use. The practical disadvantages of nutritional anthropometry relate to the need for training , quality control . and the difficulty of accurately measuring small changes in nutritional status , for example , functional changes indicative of the development of malnutrition are often measurable before detection by anthropometry (**Gibson , 1990**)

- Dietary Nutritional Assessment :

Assessment of the nutritional status based on dietary intake should take into account current and past food intake. Dietary assessments should be done by a pediatric dietitian who has the skills to ensure that all aspects of intake are considered, including assessment of the quantities of food eaten. Specific foods which appear to cause vomiting, diarrhea, malabsorption etc...must also be identified and food should not only refer to that taken at meals but also include snacks eaten . Recording dietary intake can be done in a number of ways with the aim of measuring quality and quantity of food consumed and the macro-and micronutrients ingested . Food tables or computer programs are used to calculate intake of individual nutrients . Dietary assessment of an infant of

less than 6 months should include assessment of the mother's nutritional status while pregnant and her lactational performance if she is breast – feeding. This may require weighing the infant before and after a feed (**Clark , 1998**)

- Clinical Nutritional Assessment :

Severe nutritional deprivation is easily detectable on clinical examination . Physical examination should be interpreted in association with anthropometric , dietary , and biochemical nutritional assessment. Physical signs usually don't appear until malnutrition has been prolonged and severe . Evidence of muscle and fat wasting is usually obvious . In addition, less obvious findings , as changes in skin turgor , hair consistency and liver and parotid enlargements are associated with protein deficient diets . Specific signs of vitamin deficiencies must be searched for . In addition to vitamins , the well recognized deficiency syndromes of iron , iodine and minerals must be extended to include syndromes of trace element deficiencies (**Weaver , 1998**)

- Biochemical Nutritional Assessment :

Biochemical nutritional assessment requires measurement of nutrient concentrations in the blood , urine , other fluids or tissues. There is an optimal concentration of nutrients within the body , below and above which deficiency and toxicity can occur. It must be remembered that changes in circulating concentration of many nutrients occur only when tissue stores

have been depleted and normal blood concentrations don't necessarily indicate normal nutritional status (**Robinson , 1998**)

- Functional Nutritional Assessment :

Functional abnormalities in children with PEM may include impairment of wound healing , immunocompetence , and muscle function .

- Wound Healing :

Wound healing is delayed in the malnourished patient , causing inadequate or incomplete wound closure . Protein deficiency contributes to poor wound healing by diminishing fibroblast proliferation , proteoglycan and collagen synthesis , vascularization , lymphatic formation , and wound remodeling (**Pollack , 1979**) When protein deficiency is prolonged , edema secondary to low serum albumin concentrations may develop and further impair fibroplasia . Hypoalbuminemia also may impair wound healing by disrupting amino acid , zinc and fatty acid transport (**Dickhaut et al, 1984**). Several vitamins are also necessary for wound healing to occur . Ascorbic acid is essential for hydroxylation of proline in collagen synthesis . Deficiency of ascorbic acid results in improper sequencing of amino acids , impairment in procollagen chain secretion and reduction in collagen polymerization . Retinol , pyridoxine , riboflavin , thiamin , and tocopherol also have a function in wound healing (**Megan and Veldee , 1999**)

- Immune Function :

Protein energy malnutrition has been associated with decreased numbers of macrophages , T-cells , and B-cells ; impaired antibody responses and low immunoglobulin G levels ; depressed complement activity and the ability to opsonize bacteria ; depressed T-cell functions ; impaired nonspecific inflammation ; and an impaired ability of phagocytic cells to kill ingested bacteria . These impairments have also been observed after burn injury and have been shown to respond favorably to optimal protein energy support (**Alexander , 1986**)

- Muscle Function :

Muscle Function has been evaluated as an index of nutritional status , because it is susceptible to the effect of withdrawing nutrients and refeeding . Muscle degeneration in PEM is characterized by a decrease in muscle fibre diameter and maximal isometric contractile force (**Jeejeebhoy , 1988**) . Furthermore , the rate of relaxation after tetanic stimulation is significantly slowed in malnutrition , whereas muscle fatigability is increased (**Fong et al , 1989**) . The hand grip dynamometry described by **Russel et al (1984)** is one method to evaluate muscle function , as it involved some motivation , which may or may not be constant from one patient to the other or with the same patient during the course of illness . To obviate this problem in very ill patients , an electrical stimulation technique of the ulnar nerve at the wrist has been adapted . The result is the contraction of the

abductor pollicis longus muscle, which negates the cooperation of the patient and does not appear to be affected by sepsis , drugs , trauma , surgical intervention and anesthesia .

Kwashiorkor

Kwashiorkor is a term derived from the Ga-krobo – Abangbe – Megalube tribe of south Eastern Ghana and describes the sickness the older child gets when the next baby is born (**Konatey, 1991**) . Kwashiorkor has many other names, including mehl nahr schaden (Germany) , obwosi (Uganda) , diboba , m’buazki (Zaire) , culebulla (Mexico) , bouffissure d’Annam (Indochina) , depigmentation oedème syndrome , pellagroide beri berico (cuba) (**Manson and Apted , 1982**) . The first clinical description in the tropics was given in Kenya (**Procter , 1927**) . In Ghana , Cicely Williams first gave it its distinctive name , kwashiorkor or deprived child , and described its pathology (**Williams , 1933**)

- Etiology of Kwashiorkor :

Kwashiorkor caused by the feeding of a child with a diet very low in proteins , but which provides enough energy to satisfy the child’s needs . Therefor , kwashiorkor often is a disease of artificially fed or weaned children . Although kwashiorkor may occasionally be seen in breast-fed infants , these are probably children receiving small amounts of breast milk , and additional sugar or starches . As a rule kwashiorkor usually occurs in the

weaning and post weaning periods in the second and third years of life (**Behar and Viteri , 1978**) . Also , maternal deprivation due to birth of another infant , which not only deprives the child from breast feeding but also causes a psychological disorder . The child becomes apathic and loses the desire for food .

On the other hand , other factors may cause some children to develop kwashiorkor while others on the same diet develop marasmus , these factors include :-

(a) Free radicals :

Golden et al (1990) found that kwashiorkor results from an imbalance between the production of toxic free radicals and their safe disposal . Among the factors that increase free radicals are infection , toxins , sunlight , trauma and catalysts such as iron . Formation of free radicals is decreased by the anti oxidant function of vitamins A , C and E , ceruloplasmin , transferrin and zinc . The toxic effects of free radicals would be responsible for the cell damage seen in kwashiorkor such as edema , fatty liver , and skin lesions .

(b) Aflatoxin :

This is a fungal toxin found on grains stored in warm moist conditions . Aflatoxin have been incriminated in the etiology and pathogenesis of kwashiorkor . This was based on the similar geographic and climatic predilection of kwashiorkor and aflatoxins (**Maxwell et al , 1989**) , and on the remarkable

similarities in the biochemical , metabolic , immunological and pathological derangements observed in kwashiorkor and controlled studies on animals exposed to aflatoxin . It was postulated that in kwashiorkor there is impairment in the detoxification, excretion and metabolism of aflatoxins (**Hendrickse , 1991**). At least 12 aflatoxins have been identified. The pathological changes are scattered areas of hepatic necrosis and biliary hyperplasia , rather than fatty liver development. (**Srikantia , 1982**)

- Clinical Features of kwashiorkor :

Early clinical evidences of kwashiorkor are vague but do include lethargy , apathy and irritability (**Barltrop , 1992**). When well advanced the features are divided into 3 groups (**Jelliffe and Jelliffe , 1992**)

(1) constant features :

Edema , growth retardation in weight and height , muscle wasting with some retardation of subcutaneous fat and psychological changes .

(2) Usual features :

Hair changes , moderate anemia , light coloured skin , loose stools and moon face .

(3) Occasional features :

Flaky paint dermatitis , hepatomegaly , skin ulcers , fissures and blisters , associated vitamin deficiencies and associated infection .

[I] Constant Features

1- Edema

Soft , pitting , painless edema , usually starts in the feet and legs , and extending to the perineum , upper extremities and face . the trunk is the least affected part in the body (**Jelliffe and Jelliffe, 1992**) . Ascites is uncommon , except with complications as tuberculous peritonitis , septic peritonitis or hepatic failure (**Hendrickse , 1984**)

- The edema may be due to :

- Hypoalbuminemia (**Khar and Alleyne , 1973**) .
- Kidney malfunction due to hypokalemia leading to sodium and water retention (**Walter and Share , 1988**) .
- Stimulation of posterior pituitary to produce ADH (**Srikantia and Mohanhams , 1970**) .
- Inadequate function of sodium pump due to energy deficiency (**Golden , 1982**) .
- Leakiness of cell membranes due to injury by free radicals (**Golden et al , 1990**) .

- Disruption of adaptive endocrinal mechanism due to excess carbohydrate intake (**Torun and Chew , 1994**) .
- Zinc and vanadium deficiency , both elements normally have some inhibitory effects on sodium reabsorption (**Patrick , 1980**) .
- Decreased interstitial pressure from loss of muscle and fat (**Waterlow , 1984**) .

2- Growth retardation :

The first manifestation is failure to gain weight , which may be masked by edema and good amount of subcutaneous fat , then there are slowing of linear growth, decrease in mid-arm circumference , delayed bone growth and delayed motor and mental development (**McGregor , 1993**).

Growth failure may be acute as after infections such as measles or gastroenteritis , this will diminish the weight / height ratio , or may be chronic which leads over a period of months or years to failure of weight and height gain with little or no changes in weight / height ratio (**Castiglia, 1996**)

3- Muscle wasting with some retention of subcutaneous fat :

as evidenced by measurement of arm circumference and overlying skin fold thickness (**Jelliffe , 1966**) .

4- Psychological changes :

Udani (1992) reported that longer the PEM , younger the child , poorer the maternal health and literacy , more the adverse effects of PEM on the nervous system . PEM adversely affects gross motor activities , skilled fine motor activities , perception , cognitive , memory , attention , language development and intersocial relationship , all of which will affect the total child development and its future in different fields of life particularly academic performance. **Liu et al (2003)** found that malnutrition at age 3 years is associated with poor cognition at age 11 years independent of psychosocial adversity.

DeLong (1993) reported that apathy , inactivity , fearfulness , anorexia and lack of spontaniety are the main psychological features of kwashiorkor .

Behavioral abnormalities are transient and rapidly return to normal in contrast to the developmental levels that remains low for many years (**McGregor , 1993**) .

The psychological changes in kwashiorkor may be due to damage of cerebrum due to lack of its class proteins (**Marsden, 1990**) or may be due to deficiency of essential aminoacids , serotonin , nicotinic acid and zinc together with high level of lead (**Badr et al , 1992**)

Househam (1991) found a CT picture of cerebral shrinkage , while **Gunston et al (1992)** reported that MRI image suggestive of cerebral atrophy , mainly of frontal horns of lateral ventricles.

[II] Usual features.

(1) Hair changes

The hair shows a wide range of abnormalities , especially in prolonged cases of malnutrition (**Alleyne et al , 1981**) .

The hair becomes brittle , sparse , discolored , silky , easily pickable , dry , lusterless and may become light red brown in color , it may be prematurely grey or show a pepper and salt appearance (**Champion et al , 1992**) .

These changes are probably due to deficiency of sulphur – containing aminoacids which are necessary for melanin synthesis. Vitamin A , nicotinic acid, copper, zinc and essential fatty acids deficiencies also contribute to these changes (**Jelliffe , 1966**)

The “flag sign” refers to alternating bands of normal and deficient pigmentation , and this reflects alternating periods of normal and deficient protein intake. (**Mclaren et al , 1967**)

(2) Anemia :

Children with kwashiorkor frequently have a moderate to severe degree of anemia which may be:

a- Normocytic anemia :

In PEM , there are abnormalities of red cell membrane lipids (**Brown et al , 1978**) and increased adenosin triphosphate (ATP) activity (**Kaplay , 1978**) resulting in altered membrane permeability that is compensated for by an increase in glycolytic activity . Acidosis and hypoglycemia which are common

accompaniments of severe infection , diarrhea and hepatic dysfunction associated with PEM , all these metabolic changes inhibit red cell glycolysis resulting in hemolysis (**MacDaugall et al , 1982**)

b- Microcytic anemia

Which may be due to:

- Impaired erythropoietin production or diminished bone marrow response to erythropoietin (**Wickramasinghe et al, 1985**)
- Decreased iron and iron binding capacities and increased levels of lead in blood (**Badr et al , 1992**)

c- Macrocytic anemia :

Secondary to folic acid and possibly vitamin E deficiency (**MacDaugall et al , 1982**) .

It has been pointed up that anemia of kwashiorkor is an adaptive phenomenon , the red cell mass is determined by the oxygen demands of actively metabolizing tissues and since lean body mass is reduced in severe malnutrition a compensatory reduction in oxygen transport capacity (circulating Hb) is appropriate to spare amino acids for other synthetic functions (**Caballero et al , 1985**) . In severely malnourished patients,

hematinics will not induce a hemopoietic response until dietary treatment produces an increase in lean body mass with subsequent rise in oxygen demand calling for accentuated hemopoiesis . If at this stage iron , vitamin B12 and folic acid are not given in sufficient amounts , functional anemia will result (**Torun and Chew , 1994**)

(3) Diarrhea

Diarrhea may be due to infection by different bacterial , viral. fungal and parasitic agents (**Hassan et al , 1989**)

Lactose intolerance , due to intestinal mucosal injury in the form of severe villous atrophy and lactase enzyme deficiency , was suggested to be one of the most important causes of diarrhea in PEM (**Romer et al ,1983**)

III - Occasional Features :

(1) Skin changes :

These have been described as mosaic and flaky paint dermatosis (**Latham, 1991**). The lesions are at first erythematous, then purple and reddish brown in colour with marked exfoliation, there is darkening of the skin over pressure areas (**Abiodum , 1991**) . Mucosal lesions such as cheilosis , xerophthalmia and vulvovaginitis are also found. The cause of skin changes is attributed to deficiency of aminoacids “especially sulphur containing aminoacids”, essential fatty acids, vitamin A ,

nicotinic acid and zinc (**Latham ,1991**) . Hypopigmented patches is perhaps the result of phenyl alanine deficiency and post inflammatory hypopigmentation (**Champion et al ,1992**) .

(2) Hepatomegaly :

Hepatomegaly results from fatty infiltration which is attributed to the reduction in hepatic synthesis of B- lipoprotein which normally transports triglycerides from the liver , as well as the synthesis of large amount of triglycerides from excess dietary carbohydrates (**Hansen et al , 1976**) .

Fatty liver is a characteristic feature of kwashiorkor. Although this is one of the criteria by which marasmus is differentiated from kwashiorkor, the condition can occur in both syndromes. Microscopically, fat appears first in the peripheral areas and spread to the central vein area of the liver lobules and distends the liver cells (**Khalil et al , 1977**) .

In acute stages of kwashiorkor the liver is enlarged , soft with rounded edges due to marked fatty change starting in the peripheral areas and spreading progressively to the central vein . The intracytoplasmic fat vacuole , when large , can cause atrophy of pre-existing cellular components . These changes are reversible with treatment (**Manson and Apted , 1982**) . Cirrhotic changes were found to occur only in cases complicated by aflatoxins ingestion, schistosomiasis and other hepatic parasitic infestations (**Conn, 1982**) .

(3) Associated vitamin deficiencies :

A variety of signs possibly due to associated vitamin deficiencies may be found . Keratomalacia and xerophthalmia are

the most serious complications of vitamin A deficiency , while angular stomatitis is the most common complication of riboflavin deficiency. The frequency of vitamin deficiencies vary with diet, geographical location and season (**Hansen and Peltifor ,1992**) .

A positive correlation has been shown between the incidence and severity of xerophthalmia and severity of PEM (**Bluhm and Summers, 1993**)

Vitamin deficiencies in PEM may caused by diarrhea that aggrevates malabsorption, and also by alterations in transport proteins e.g. retinol-binding protein (**Torun and Chew,1994**).

(4) Associated Infections :

In PEM , there is a greater predisposition to infections and to severe complications of otherwise less important infectious diseases. Pneumonia is one of the leading causes of death in kwashiorkor (**Talboom et al , 1986**). Measles is the most severe viral infection associated with kwashiorkor (**Wharton,1991**) . While nosocomial infections pose a major threat to these children. Gastroenteritis and dehydration are responsible for 11 to 50% of mortalities in uncompensated cases of kwashiorkor (**Matta, 1992**). Bacteremia is 3.5 times more common in children with kwashiorkor than in marasmic children , and gram negative enteric aerobes were isolated 2.6 times more frequently from malnourished than from well nourished children (**Friedland, 1992**). Tuberculosis may be difficult to diagnose because of anergy induced by malnutrition (**Wharton and Weaver,1998**) .

In malnutrition, the immune system can not function optimally. Malnutrition also produces adverse effects on antigenically non specific mechanisms of host defense. The end result is “Nutritionally Acquired Immune Deficiency syndrome” which is known to afflict millions of people in the third world (**Beisel, 1991**)

- Other features include :

- Bone changes :

Bone of malnourished children are short but their width appears to be in proportion to their length , usually there are reduction in bone density and thickness. The degree of depression of bone turnover in malnourished children may be related to the severity of the illness (**Branca et al, 1992**).

Despite the similarity in bone histology between pre kwashiorkor and rickets, radiology does not show epiphyseal rachitic changes and the serum alkaline phosphatase levels are not raised in kwashiorkor . This suggests the existence of rickets at a histological level only. Resumption of growth in such children is likely to cause further mineral depletion , rendering them susceptible to rickets (**Mukherjee et al , 1991**) .

- Gastrointestinal changes :

Cracking of lips, angular stomatitis and smooth tongue are common . These changes are mainly due to atrophy of the

mucosal lining of the upper alimentary system (**Fagundes - Neto, 1981**)

The lack of peristalsis , achlorhydria , poor secretion of immunoglobulin A and bile salts combine to allow fecal bacteria and fungi to overgrow in the small intestine and stomach (**Golden , 1988**) .

Anorexia is an early manifestation of kwashiorkor. It may be severe as to necessitate tube feeding (**Fayad et al , 1980**). Vomiting is frequent . Abdominal distension may occur with diarrhea due to hypokalemia , malabsorption and hypotonia (**Brewster et al,1997b**). The stool are bulky , semisolid , with low pH and may contain excess lactic acid and unabsorbed sugars (**Lifshitz , 1980**)

- Cardiac changes :

Cardiac evaluation of kwashiorkor patients revealed reduced cardiac mass in all cases. Reduced left ventricular systolic and diastolic dimensions and right ventricular posterior wall thickness was detected (**Mahmoud et al , 1992**) .

The rate of capillary filtration in the forearm to a given increment in cuff pressure is significantly reduced in kwashiorkor patients, which may be due to reduced capillary surface area secondary to a relative decrease in capillary density resulting from the edema (**Richardson and Iputs, 1992**).

- Renal changes :

There are reduction in the renal plasma flow , glomerular filtration rate and renal tubular functions with production of small volume of diluted urine (**Barness, 1987**). The electron microscopy showed glomerular basement membrane thickness with varying degree of epithelial cell edema (**Garg et al , 1989**) .

- Pathological changes in Kwashiorker :

The main features of kwashiorkor are atrophy of the pancreas and small intestinal mucosa (**Sullivan et al., 1991**) , in addition to some functional and biochemical abnormalities. The enteropathy and atrophic pancreas lead to malabsorption , steatorrhea, poor absorption and deficiencies of the fat-soluble vitamins. Small intestinal disaccharidase activity is depressed and the very ill child may also be intolerant of monosaccharides . Plasma protein concentrations are reduced. The plasma concentration of all substances normally carried by B – lipoprotein , such as cholesterol , triglyceride and the fat soluble vitamins , is reduced also . The extracellular fluid is hypotonic and hyponatremia may occur as a result of overhydration rather than a total body deficit of sodium. Circulating cortisol concentrations are high, contributing to the fluid retention and hyponatremia. The protein deficiency results in hypoplasia of the bone marrow despite adequate amount of erythropoietin (**Wharton and Weaver,1998**)

Marasmus

Marasmus is a clinical syndrome of severe PEM characterized by extreme growth failure , with weight of 60% or less than that expected for age and wasted muscles and subcutaneous fat (**Jelliffe and Jelliffe , 1991**).

Nutritional marasmus is due primarily to eating very little of an well-balanced diet . i.e. a deficiency of all food components. When marasmus presents during infancy it is usually due to lactational failure , low birth weight or multiple birth, commonly in association with recurrent infection , particularly gastro enteritis . Later , it may indicate a local famine or social disruption . The combination of nutritional marasmus and gastro enteritis contributes to the very high prevalence of infant and childhood malnutrition found in many developing countries (**Wharton , 1991**)

Marasmus is more frequent in infants than in older children, this is due to 2 main factors: first, the rapidly growing infant ,

with very high energy requirements , can develop the extreme wasting that leads to marasmus in a relatively short period of time, usually in a matter of few weeks, when the dietary restriction is severe. The other factor is that for cultural reasons , infants are more likely to be subject to the marasmus producing type of diet . The effects of this diet and early weaning also increase the incidence of diarrhea in infants (**Behar and Viteri , 1978**).

- Clinical Features of Marasmus :

Initially , there is failure to gain weight followed by progressive loss of weight until emaciation results . There is loss of subcutaneous fat , this is lost first from the abdominal wall, then the limbs and finally the buccal pad of fat with loss of turgor in skin that becomes wrinkled and loose. The abdomen may be distended or flat, and the intestinal pattern may be readily visible . There is muscle wasting with resultant hypotonia (**Shamir and Wilschanski , 1998**)

The temperature is usually subnormal , the pulse may be slow, and the basal metabolic rate tends to be reduced . There is irritability with an anxious appearance . The infant is hungry and is usually constipated , but the so-called starvation type of diarrhea may appear , with frequent small stools containing mucous (**Curran and Barness , 2000**). Associated features of vitamin deficiencies or infection may be present.

Marasmic Kwashiorkor

Sometimes defined as atrophic kwashiorkor. It results from inadequate caloric supply and deficient protein intake. Edema is constant and body weight is less than 60% of the expected weight for age (**Benjamin and Fernando, 1988**). So, the manifestation of kwashiorkor appears in a child who already has advanced degree of energy deficiency.

Biochemical Abnormalities in PEM

In PEM , the decrease in concentration of serum albumin is the most characteristic change (**Golden , 1982**). Alpha-1 and-2 globulins are reduced , while gamma globulin synthesis and turnover are not affected and may even increase in the presence of infection (**O'Brien and Chase , 1980**).

Prealbumin, ceruloplasmin, retinol-binding protein, erythrocyte glutathione , fructosamine and fibronectin are reduced in kwashiorkor patients (**Benjamin , 1989 and Mayatepeck et al, 1993**). Transferrin is decreased in PEM, but if iron deficiency anemia coexists it is increased due to lack of iron (**Delpeuch et al, 1980**).

Plasma values of essential amino acids may be decreased in relation to nonessential ones, and there may be increased aminoaciduria.

Reduction in the intestinal absorption of different fat fractions is observed in PEM leading to reduced concentrations of serum lipoproteins and lipids (**Viteri et al , 1973**). Plasma lecithin-cholesterol acyl transferase , the main plasma cholesterol-esterfying enzyme , is decreased , probably due to reduced enzyme mass secondary to impaired hepatic synthesis (**Dhansay et al , 1991**). The serum cholesterol level is low, but it returns to normal after a few days of treatment.

Ketonuria is common in the early stage , but frequently disappears in the later stages. Blood glucose values are low , but glucose tolerance curves may be diabetic in type. The decrease in the blood glucose level is attributed to decreased glucose absorption as a result of disaccharidase deficiency and decreased glycogenolysis (**Metcoff et al , 1960**). Blood insulin levels are reduced and unresponsive to glucose (**Hansen et al , 1976**) possibly due to B-cell insufficiency, peripheral insulin resistance (**Garg et al , 1989**) or elevated plasma free cortisol levels, leading to glucose intolerance (**Hansen et al , 1976**) , especially in the sever forms of malnutrition. Insulin response to dietary carbohydrate returns to normal when serum albumin is restored to normal levels.

Potassium and magnesium deficiencies are frequent. Severe hypophosphatemia ($< 0.32 \text{ mmol / L}$) is associated with increased mortality.

The serum values of amylase , esterase , cholinesterase , transaminase, lipase and alkaline phosphatase are decreased. There is diminished activity of pancreatic anzymes, but the values return to normal after few days of treatment.

Signs of vitamins (Particularly Vitamin A) and mineral deficiencies are usually evident.

Bone growth is usually delayed. Growth hormone secretion may be increased (**Curran and Barness , 2000**).

Complications of PEM

Complications of acute stage

(1) Infection

Protein energy malnutrition is one of the most frequent causes of secondary immune deficiency states. Alterations either in cellular or humoral immune mechanisms increase the susceptibility to infections in malnourished children (**Ozkan et al, 1993**).

Children with PEM showed high dranged cellular immunity as evidenced by impairment of lymphocyte transformation after stimulation by phytohaemagglutination (**Chowdhury et al , 1993**).

Decreased bactericidal activity of neutrophils may be one of the mechanisms responsible for infection (**Nayak et al , 1989 and Forte et al, 1999**) .

Hoffman et al (1985) reported that the derangement in cellular immunity include impaired T cell mitogenesis, alloreactive cytotoxic T- lymphocytes and selective depletion of T-cell subsets.

(2) Diarrhea and Dehydration

Matta (1992) reported that gastroenteritis and dehydration are responsible for 11% to 50% of mortalities in uncompensated cases of kwashiorkor. The classic signs of dehydration such as sunken eyeballs and decreased skin turgor are not apparent. Useful signs are : Low urinary output , weak rapid pulse , cool moist extremities , low blood pressure , dry mouth and tongue and a declining state of consciousness (**Torun and Viteri , 1988**).

(3) Hypothermia

Body temperature below 35.5 °c may occur due to impaired thermoregulatory mechanisms and severe infections (**Torun and Chew, 1994**)

(4) Heart Failure

Acute congestive heart failure occurs in PEM due to excess sodium intake. Moreover, heart affection in kwashiorkor, anemia or arrhythmias (hypokalemia) , vigorous refeeding and volume overload may also be involved (**Wharton, 1991**) .

(5) Metabolic Complications

In PEM , the water and electrolyte changes include :

- Hypoosmolarity and moderate hyponatremia :

despite the increase in total body water in kwashiorkor, there is maldistribution of this water which results in expansion of the extracellular fluid at the expense of the intracellular compartment (**Zetterstrom , 1991**) .

- Hypocalcemia and hypophosphatemia (**Soriano, 1991**) .

- Decreased body potassium without hypokalemia due to decreased muscle protein and loss of intracellular potassium (**Torun and Chew , 1994**) .

(6) Haematological Complications

Purpura is commonly encountered in PEM . Functional platelets abnormalities , depressed prothrombin and other vitamin K dependent factors have been reported (**Hassenein and Tankovsky, 1972**) . Decreased fibrinogen level with an increase in fibrin degradation products have also been reported (**El-Sokkary et al, 1984**) .

Long Term Complications

A - chromosomal changes

Chromosomal abnormalities appear to be more frequent in children with PEM (**Armendares et al, 1971**) . In Egypt , the frequency of chromosomal aberrations was found to be nine times greater than in normal population (**El- Ghazali et al, 1990**) . **Osman et al (1995)** found that malnutrition rendered the

chromosomes more liable to structural damage either spontaneously or as an exaggerated response to mutagenic agent (bleomycin) . However , the effect of protein deficiency in the pathogenesis of chromosomal damage could not be conducted. The study speculated that other factors contributing to the pathogenesis of kwashiorkor as energy deficiency , vitamin deficiency especially vitamin A,E,B complex and trace elements as zinc and selenium might play a role in the process of chromosomal damage .

(2) Effect on growth and development

Some permanent defect in stature may occur if growth is arrested by malnutrition below the age of two years. This stunting may affect his maximal working capacity as an adult . Study of the effects of malnutrition on neurodevelopment suggests that mild retardation occurs in some malnourished children , reflecting as much the associated social deprivation (**McGregor et al , 1991**) .

Prognosis of PEM

Mortality rate varies from 10% to 60% , averaging 15% in those sufficiently ill to be admitted to hospital (**Wharton and Weaver , 1998**) . The features that are associated with poor prognosis include:

- Age less than 6 months .
- Deficit in weight for height greater than 30% or in weight for age greater than 40% .
- Stupor , coma or other alterations in mental status and consciousness .
- Infections , particularly bronchopneumonia or measles .
- Petechiae or hemorrhagic tendencies (Purpura is usually associated with septicemia or viral infection) .
- Dehydration and electrolyte disturbances , particularly hypokalemia and severe acidosis .
- Persistent tachycardia , signs of heart failure or respiratory difficulty .
- Total serum protein below 30 g / l .
- severe anemia with clinical signs of hypoxia .
- clinical jaundice or elevated serum bilirubin .
- Extensive exudative or exfoliative cutaneous lesions or deep decubitus ulcerations .
- Hypoglycemia or hypothermia (**Torun and Chew , 1994**).

Prevention of PEM

Prevention of PEM requires provision of a good supply of food and prompt treatment of gastroenteritis with oral rehydration therapy (**Weaver , 1994**) . Prolonged breast feeding up to two years should be encouraged along with the use of locally available protein foods. Early refeeding after episodes of diarrhea is recommended (**Brown and McLaren , 1984**) , as renourishment is as important as control of gastroenteritis in preventing undernutrition and reversing weight loss and growth failure (**Briend , 1990**).

Promotion of health education , immunization programs and family planning , regular supervision of child's progress and recording growth at a child health clinic are important tools in the early detection of moderate deficiency , allowing advice and treatment to be given well before occurrence of severe malnutrition (**Wharton and Weaver , 1998 & Ojofeitimi et al., 2003**) .

Treatment of PEM

Immediate management of any problems such as those of severe diarrhea , renal failure and shock and replacement of missing nutrients are essential .

(A) Emergency Treatment for :

(1) Dehydration and electrolyte imbalance

For correction of dehydration and electrolyte imbalance , the main consideration is that dehydration is generally hypotonic , there is severe potassium depletion , some renal function alterations are usually present, large amount of fluids are abnormally accumulated and the cardiac reserve being diminished and may be insufficient to manage a large and sudden mobilization of fluids into the intravascular space (**Vis , 1985**)

For mild to moderate dehydration , feeding are administered orally or by nasogastric tube to prevent aspiration . Intravenous (I.v.) fluids are necessary for the treatment of severe dehydration. If I.v. fluids can not be given , an intraosseous (marrow) or intraperitoneal infusion of 70 ml/kg of half- strength Ringer's lactate solution may be life saving .

(2) Anemia

Blood transfusion may be indicated as life saving measure when there is severe anemia (hemoglobin less than 6 gm /100 ml) or shock (**Brown, 1991**)

(3) Hypoglycemia

Hypoglycemic children are hypothermic with a slow pulse and poor peripheral circulation . The main fasting blood glucose is 55 mg / dl. Treatment includes early institution of adequate dietary carbohydrate and search for treatment of infection (**Brewester et al, 1997a**)

(4) Cardiac Failure

It may develop when there is severe anemia, during or after administration of I.v. fluids , or shortly after the introduction of high protein and high energy feedings (**Torun and Viteri, 1988**) . Moreover , hyponatremia and hypokalemia may also contribute to cardiac failure in patients with PEM (**Erinoso et al , 1993**) . Treatment in the form of diuretics and digoxin (0.03 mg/ kg every 6-8 hours) (**Torun and Chew , 1994**).

(B) Dietetic Treatment

Breast feeding should continue during the period of rehydration , approximately every half hour. In fact , breast feeding should be a basic component of treatment because of its excellent nutritional qualities and the protection it provides against infection (**Brown , 1991**) .

Cow's milk is widely accepted as an effective , economic and convenient basis of dietary therapy , and lactose intolerance is relatively uncommon . Sugar and vegetable oils are often added to increase the energy content of feeds and casein can be used in severe cases to augment the protein content (**Weaver et al, 1995**).

Dried skimmed milk is usually used as base , but full cream milk powder in any form is fully acceptable . Using these foods it is possible to formulate a diet which will provides 96-155 Kcal , 2-4 g milk protein , 4-6 mmol potassium, 1-3 mmol magnesium and less than 2 mmol sodium / kg / day (**Wharton and Weaver , 1998**)

Symptoms of hypocalcemia should be treated by both calcium and magnesium parenterally . Oral supplementation should start when serum concentrations of both ions rise to normal levels or symptoms disappear (**Torun and Chew , 1994**).

Vitamins and minerals , especially vitamin A, potassium and magnesium are necessary . Bacterial infection should be treated concomitantly with the dietary therapy .

After treatment has been initiated , the patient may lose weight for a few weeks owing to loss of apparent or inapparent edema . Serum and intestinal enzymes return to normal , and intestinal absorption of fat and protein improves . When high calorie and high protein diets are given too early and too rapidly , the liver may become enlarged , the abdomen becomes markedly distended , and the child improves more slowly (**Curran and Barness , 2000**)

The insulin like growth factors (IGF_S) , also called somatomedins, are defined as polypeptide growth factors secreted by the liver and other tissues in response to stimulation by growth hormone (GH) (**Guyton , 1996**). They mediate the anabolic and mitogenic actions of GH (**Reiter and Rosenfeld , 1998**).

Many of the somatomedin effects on the growth are similar to the effects of insulin , moreover , these factors are structurally similar or closely related to proinsulin , therefor , they are called IGF_S (**Nyomba et al , 1997**).

In the late 1950's , many researchers observed that GH administration to hypophysectomized rats, resulted in increased incorporation of sulphate and thymidine into cartilage in vivo. In subsequent experiments , GH itself did not produce these effects in vitro , whereas serum from GH- treated hypophysectomized rats did . They concluded that , the enhanced uptake of a sulphate and thymidine was due to a substance in serum which was GH-dependent and they called it sulphation factor . Subsequently , other names were given to this serum factor as, non suppressible insulin – like growth factor (NSIL) , somatomedin , and IGF (**King et al , 1985**).

In humans , there are two main forms of IGF_S : IGF₋₁ also called somatomedin – c and IGF₋₁₁ also called somatomedin – A (**Ganong , 1995**). **Daughaday et al (1987)** reported that there is a consensus that the term somatomedin should be used only when

referring to these peptides in a generic sense , and that IGF-₁ and IGF-₁₁ should be used when referring to the specific peptides .

The most important is IGF-₁ , which is GH dependent and its plasma levels are very sensitive to changes in GH availability (**Berne et al , 1998**) . It plays an important role in regulation , differentiation and proliferation of a number of cell types , acting as a major growth regulator (**Guler et al , 1989**) . While IGF-₁₁ is less GH dependent and more potent in assays for insulin like activity (**Underwood and VanWyk , 1992**) . It plays a predominant role during fetal life (**Underwood et al , 1991**) .

Synthesis of IGFs .

Somatomedins appears to be produced by liver , since somatomedins are produced by hepatocyte cultures (**John and Gareth, 1991**) , moreover , somatomedin content is found to be high in hepatic than in portal blood veins , and serum concentrations of somatomedins were reduced by hepatectomy or hepatocellular diseases (**Goodman et al, 1994**) .

Somatomedins are not stored in liver , but they are released into plasma , which is the best source for its isolation . Liver is not the only organ involved in somatomedins production, since other tissues have been found to produce somatomedins including fibroblasts , myoblasts , chondrocytes , osteoblasts , bone , brain , gastrointestinal epithelium , Kidney and lung (**Herington , 1991**) .

Hills et al (1996) reported that the main production sites for IGF₋₁ are fibroblasts or other cells of mesenchymal origin . IGF₋₁₁ and IGF₋₁₁ m RNA_s can be demonstrated by insitu hybridization to be localized in mesenchymal and fibroblast-like cells in interstitial and perivascular connective tissues and surrounding capsular tissues (**Han et al , 1987**) .

Structure of IGF_s

IGF₋₁ is a single basic polypeptide chain with three disulfide bridges. It is composed of 70 aminoacids (a a) , with a molecular mass of 7.64 K Da , while IGF₋₁₁ is a slightly acidic peptide of 67 a a , with a molecular mass of 7.47 k Da (**Daughaday and Rotwein , 1989**) .

IGF_s consists of A and B peptide domains (structurally homologous with insulin A and B chains) , they are connected to each other by c- domain , which in IGF₋₁ constitutes of 12 a a (with structural homology to c peptide of proinsulin) , while c-domain in IGF₋₁₁ constitutes of 8 a a . The IGF_s have an additional region called the D-domain , which is carboxy terminal extension that is not found in proinsulin . This extension consists of 8 a a in IGF₋₁ and 6 a a in IGF₋₁₁ (**Humbel , 1990**)

The sequence homology between IGF₋₁ and IGF₋₁₁ is 62% . Also , there is approximately 40% homology between IGF₋₁ and IGF₋₁₁ on one hand and the insulin on the other hand (**Honegger and Humbel , 1986**) . It is clear that this structural homology

explains the ability of both IGF_S to bind to the insulin receptor and of insulin to bind to the type₁ IGF receptor . On the other hand . Structural differences also explain the failure of insulin to bind to the IGF binding proteins (**Daughaday and Rotwein , 1989**).

In humans , a variant form of IGF₋₁ lacking 3 N- terminal a a residues has been found in the brain , and there are several variants of human IGF₋₁₁ (**Ganong , 1995**).

IGF Genes

Both IGFs are encoded by single copy genes . The human IGF₋₁ gene is located on the long arm of chromosome 12 (**Tricoli et al , 1984**) and the human IGF₋₁₁ gene is located on short arm of chromosome 11 adjacent to proinsulin gene (**Bell et al , 1985**) . The IGF₋₁ gene is a complex , multicomponent gene , with six exons , while IGF₋₁₁ gene contains nine exons .

The mechanisms involved in the regulation of IGF gene expression include the existence of multiple promoters , heterogeneous transcription initiation within each of the promoters , alternative splicing of various exons , differential RNA polyadenylation, and variable m RNA stability . Translation of IGF₋₁ genes may also be under complex control (**Reiter and Rosenfeld , 1998**) .

IGF Receptors

The overlapping biological effects of IGF_S and insulin were initially attributed to the structural homologies between the peptides themselves (**VanWyk et al , 1975**) . However , this interpretation proved overly simplistic when it was shown that the receptors for insulin and IGF-₁ are also structurally similar (**Massague and Czech , 1982**).

De Meyets (1994) suggested that the growth responses to IGF_S and insulin were mediated by IGF receptors, whereas acute metabolic responses such as glucose transport were mediated by the insulin receptors .

At least, two classes of IGF receptors exist . Structural characterization of these receptors documented the differences in the two forms of receptors :

Type ₁ IGF receptor

Type ₁ IGF receptor is closely related to the insulin receptor , both have heterometric structure composed of two extracellular α subunits and two intracellular B subunits . The α subunits contain the binding sites for IGF-₁ and are linked by disulfide bonds . The B subunits contain a transmembrane domain and an adenosin triphosphate – binding site and a tyrosin kinase domain . Binding of IGF-₁ to type ₁ receptors stimulates tyrosin kinase activity and autophosphorylation of tyrosin molecules on the receptor itself and tyrosin phosphorylation of other substrates

which produce cell differentiation or division or both (**Iterie et al, 1998**) .

Although the type ₁ receptor has been commonly termed the IGF-₁ receptor , it binds both IGF-₁ and IGF-₁₁ . Both of IGF peptides appear capable of activating tyrosin kinase by binding to this receptor . It has a highest affinity for IGF-₁ followed by IGF-₁₁ and the lowest affinity for insulin (**Froesch et al, 1997**) .

Amoui et al (2001) found that , despite the high degree of homology between type ₁ IGF receptor and insulin receptor , the recent evidence suggests that the two receptors have distinct biological roles . The cytoplasmic domain of type ₁ IGF receptor and insulin receptor have differences in their intrinsic signalling potentials .

Type 2 IGF receptor

Type 2 IGF receptor bears no structural homology to either the insulin or type ₁ IGF receptors . It has no tyrosin kinase activity . It is a single chain glycosylated transmembrane protein and is identical to the cation – independent mannose – 6 – phosphate (M6P) receptor (**Oshima et al , 1988**) .

Type 2 IGF receptor binds IGF-₁₁ with high affinity , IGF-₁ with lower affinity and it does not bind insulin (**Rosenfeld et al , 1987**) .

The mitogenic and metabolic actions of both IGF-₁ and IGF-₁₁ appear to be mediated through type ₁ IGF receptor

(**Adashi et al , 1989**). Monoclonal antibodies directed against the IGF₋₁ – binding site on the type 1 IGF receptor inhibit the ability of both IGF₋₁ and IGF₋₁₁ to stimulate thymidin incorporation and cell replication.

At least one function of the M6P / IGF₋₁₁ receptor is to act as an intracellular shuttle by transporting acid hydrolases and other mannosylated proteins to the lysosomal compartment .

Type ₁ IGF receptors are distributed throughout the body and are down- regulated by increased IGF₋₁ concentration and vice verse (**Lowe et al., 1989**). While type ₂ IGF receptors are particularly abundant in the brain and C.S.F (**Froesch et al, 1997**), also it has been found to be present at the basolateral membrane of the proximal tubular renal cells (**Rogers and Hammerman , 1988**).

Insulin – like Growth Factors Binding Proteins (IGFBP_s)

The IGF_s circulates in Plasma in complex with a family of binding proteins that extend the serum half life of the IGF peptides , transport the IGF_s to target cells . and modulate the interaction of the IGF_s with the surface membrane receptors . At least six distinct classes of IGF- BP_s (IGFBP₋₁ through IGFBP₋₆) have been identified . They are designated on the basis of their a sequence (**Zapf et al , 1990**). They all bind both IGF₋₁ and IGF₋₁₁, but not insulin . they differ in terms of function , tissue distribution and regulation (**Jun et al , 1996**).

The identification and characterization of IGFBP_s in body fluids and in conditioned media from cultured cells has been facilitated by the development of a number of biochemical and assay techniques , including gel chromatography , radio receptor assays , affinity cross- linking , western ligand blotting , immunoblotting and specific radioimmunoassays. However, study of the molecular biologic characteristics of the IGFBP_s has provided the most information concerning their structural interrelationship (**Reiter and Rosenfeld , 1998**) .

IGFBP-1

IGFBP-₁ is a 28 KDa plasma protein that binds IGF-₁ and IGF-₁₁ with high affinity (**Lee et al , 1997**) . It consists of 259 a a . It was initially purified from amniotic fluid (**Drop et al , 1979**) . Its gene is 5.2 Kb long located on the short arm of chromosome 7 and composed of 4 exons .

The liver , kidney and brain appear to be the major sites of production . It is also found in serum , lymph , C.S.F and culture media from a variety of cell types . IGFBP-₁ is not GH dependent. Its serum concentrations are increased by conditions in which insulin secretion or responsiveness is diminished , including fasting , insulin resistance , pregnancy and hypopituitarism . Values are decreased by hyperinsulinism whether caused by feeding , glucose infusion , GH or glucocorticoids. The

concentration fluctuate markedly throughout a 24 hours (**Underwood and VanWyk , 1992**).

Lee et al (1997) reported that the insulin is the most important single regulator of IGFBP₋₁ . Within minutes after exposure to insulin , the hepatocytes down-regulate the synthesis and secretion of IGFBP₋₁ .

In serum from normal subject , the major part of IGFBP₋₁ (90%) is highly phosphorylated , whereas the remnant 10% is represented by non – Phosphorylated isoforms (**Frystyk , 2000**) . The factors controlling the state of phosphorylation remain to be determined , but they appear to be under hormonal control (**Westwood et al , 1995**) . Highly phosphorylated IGFBP₋₁ has a six fold higher affinity for IGF₋₁ than non- phosphorylated form , and it is likely that IGF₋₁ action is stimulated by dephosphorylated IGFBP₋₁ and inhibited by phosphorylated IGFBP₋₁ (**Jones et al , 1991**) .

IGFBP₋₁ may be involved in reproductive functions , including endometrial cycling (**Giudice et al , 1994**), oocyte maturation (**Adashi, 1994**) and fetal growth (**Giudice et al , 1995**) .

It is the major IGFBP in fetal serum in early gestation . In the newborn serum , levels of IGFBP₋₁ are inversely correlated with birth weight , which is consistent with an inhibitory role on fetal IGF action (**Reiter and Rosenfeld, 1998**).

Zapf et al (1990) reported that IGFBP-₁ apparently serves as a shuttle transporter of IGF-₁ from serum to the interstitial fluid , and it also controls the concentrations of free IGF-₁ at its site of action.

IGFBP-₁ also appears to have an important metabolic role because its gene expression is enhanced in catabolic states (**Thissen et al , 1994**) and serum levels undergo diurnal variation (**Reiter and Rosenfeld, 1998**). Insulin suppresses and glucocorticoids enhance IGFBP-₁ mRNA levels (**Lee et al, 1993**)

IGFBP-₁ inhibits IGF-₁ mediated effects , most likely by blocking the interaction between free IGF-₁ and the IGF-₁ receptor (**Frystyk, 2000**). However in some experimental situations IGFBP-₁ has been shown to stimulate rather than inhibit IGF-₁ action (**Baxter , 2000**) . The background for the heterogenous effects of IGFBP-₁ still remains to be fully clarified, but it may depend on post translational modifications of IGFBP-₁, such as phosphorylation , which appears to enhance IGFBP-₁ affinity for IGF-₁ and thereby inhibit IGF action .

IGFBP-₂

The IGFBP-₂ is a 33 K Da protein (**Styne , 1994**) . Consisting of 270 a a . The IGFBP-₂ gene is located on the long arm of chromosome 2 (**Binkert et al , 1992**) It presents in high concentrations in fetal tissues , particularly in CNS (**Lamson et**

al, 1989) and is present in a variety of tissues . IGFBP-₂ level fluctuate less than IGFBP-₁ . IGFBP-₂ is expressed in secretory endometrium and endometrial tumors (**Giudice et al , 1994**) , and is the major IGFBP in seminal fluid (**Rosenfeld et al , 1990**).

IGFBP-₂ concentrations are increased by hypophysectomy and decreased by administration of GH and glucocorticoids (**Brown et al , 1989**) and insulin administration like IGFBP-₁ (**Ooi et al , 1990**).

IGFBP-₃

IGFBP-₃ is the major circulating form of IGFBP_s , is GH dependent but with a longer halflife than GH and does not exhibit pulsatility (**Paramo et al , 2001**) . It is a 264 a. a. long cysteine rich protein and it was first isolated from human plasma by **Martin and Baxter (1986)**.

the IGFBP-₃ gene is located on chromosome 7 in proximity to the gene for IGFBP-₁ (**Cubbage et al , 1990**) . it contains four exons homologous to those of IGFBP-₁ and-2 and a fifth exon . the mature IGFBP-₃ protein has a molecular weight of approximately 29 K Da , but because it is N- glycosylated , it normally migrates as a doublet – triplet of 40 to 46 K Da (**Baxter , 1994**) .

In circulation , almost all the IGF_s are present as 150 K Da ternary complexes, which consists of IGF₁ or ₁₁ linked to IGFBP-₃ and an acid labile subunit (ALS) (**Baxter 1994**) . This complex

is synthesized by the liver , IGFBP-₃ appears to be synthesized in hepatic endothelia (Portal venous and sinusoidal) and kupffer's cells , whereas ALS is synthesized in hepatocytes (**Arany et al , 1994**). It is regulated by GH and nutritional status , the levels are reduced by GH deficiency and nutrients restriction , due to the reduction in ALS m RNA and ALS nuclear transcription (**Ooi et al , 1990**).

Unlike free IGF_s and IGF_s bound to the binary complexes , which can cross the vascular endothelium , formation of the ternary complexes restricts the IGF_s to the circulation , prolongs their half-lives and allows them to be stored at high concentration in plasma to facilitate their endocrine actions and to minimize their local effects due to their intrinsic insulin- like activities such as hypoglycaemia (**Zapf et al , 1995**) . In this complex , the IGF_s have a half – life in humans of around 16 hours , while the half life of IGF bound to BP-₃ , BP-₁ and BP-₂ is approximately 20 minutes and the half life of free IGF-₁ is a few minutes (**Guler et al , 1989**) .

Serum level of IGFBP-₃ is constant over the 24 hours . It has been found that IGFBP-₃ undergo partial proteolysis under certain conditions (**Giudice et al, 1990**) , and this is believed to increase the circulating free IGF_s , thus increasing their availability to tissues .

The serum level of IGFBP-₃ is regulated by age , nutrition and GH. IGFBP-₃ concentrations are low in patients with GH

deficiency and increase following GH treatment (**Blum et al , 1993**).

Bar et al (1990) reported that IGFBP-₃ plays an important role as a serum carrier protein for IGF_s due to its highest serum concentration . On the other hand , the concentrations of IGFBP-₁ and -₂ are higher in lymph than in serum . However , IGFBP-₃ is more than just a passive carrier of IGF_s in the circulation. IGFBP₃ has multiple growth regulatory functions at the cellular level (**Conover et al , 1994**) . IGFBP-₃ can be a potent inhibitor of cell growth by virtue of its ability to bind IGF with high affinity , thereby preventing its interaction with membrane receptors (**De Mellow and Baxter, 1988**). IGFBP-₃ can also function as a direct cell growth inhibitor , independent of its IGF binding activity (**Oh et al , 1993**) . Furthermore IGFBP₃ can potentiate IGF action in a number of cell systems (**De Mellow and Baxter , 1988 & Michell et al , 1997**) .

IGFBP-4

The IGFBP-₄ is the smallest of the IGFBP_s , with a 237 a a . Its gene is located on chromosome 17 (**Gao et al , 1993**) . It is N-glycosylated and therefor migrates with molecular masses of 28 KDa in the glycosylated form and 24 KDa in the nonglycosylated form (**Bautista et al , 1991**) , IGFBP-₄ seems to be the only

IGFBP with no potential to enhance the mitogenic action of the IGF_S (**Chelius et al , 2001**) .

IGFBP-5

Mature IGFBP-₅ contains 252 a a . It is most closely related in sequence to IGFBP-₃ . It has been isolated from rat ovary and human placenta and from a human osteosarcoma (**Shimasaki et al, 1991**) . It is encoded by a gene located on chromosome 5. When IGFBP-₅ adheres to fibroblast extracellular matrix, it potentiates the growth stimulatory effects of IGF on DNA synthesis (**Jones et al, 1993**).

IGFBP-6

The mature peptide contains 216aa and has a molecular weight of approximately 23 KDa . It is encoded by a gene located on chromosome 12 (**Kiefen et al , 1991**) . It has a high affinity for IGF-₂ compared to IGF-₁ (**Martin et al , 1990**) . IGFBP-₆ is found in relatively high levels in CSF. It may also has a role in regulating ovarian activity , by functioning as antigonadotropin (**Rohan et al , 1993**).

Biological Actions of IGF_s

The IGF_s modulate an extraordinarily wide variety of biological actions in addition to mediating the growth promoting effect of GH (**Jones and Clemmons , 1995**). IGF_s stimulate proliferation and differentiation of numerous cell types and promote anabolic functions in numerous tissues , such as increased production of protein , RNA and DNA (**Sara and Hall, 1990 & Cohick and Clemmons , 1993Williams et al , 1990 & Gao et al, 2001**) , in the regulation of pituitary GH secretion and in facilitating the actions of other hormones and factors (**Tannenbaum et al , 1983**) .

(1)Mitogenic Action

The IGF_s have been extensively studied for their capacity to stimulate DNA synthesis and / or cellular proliferation . Cells shown to respond to IGF_s include fibroblasts , myoblasts , smooth muscle cells and mesenchymal cells. (**VanWyk , 1984**). Evidence of the importance of IGF₋₁ to the proliferation of cultured fibroblasts comes from studies demonstrating that a monoclonal antibodies to IGF₋₁ can block the growth stimulatory action of plasma on these cells (**VanWyk and Pledger , 1984**).

Pledger et al (1981) found that there are other growth factors that facilitate expression of mitogenic activity of IGF_s such as

platelet derived growth factor (PDGF) and fibroblast growth factor (FGF) .

The balance between proliferation and differentiation varies from tissue to tissue and may vary in the same tissue depending on the developmental status and the rest of hormonal milieu (**Underwood and VanWyk , 1992**).

(2) Incorporation of sulphate into the proteoglycan molecule of cartilage that leads to linear growth (Salmon and Daughaday, 1957) . In bone cells , locally produced IGF_S may act as a potential endogenous mediator of Parathyroid hormone (PTH) and calcitrol . The key role of IGF system for bone formation is demonstrated by the finding that approximately 50% of basal bone cell proliferation can be blocked by inhibiting the actions of endogenously produced IGF_S by bone cells in serum free culture (**Mohan , 1993**).

(3) Effect on endocrine tissues

The IGF_S are synthesized in the adrenals and gonads in response to stimulation by their respective trophic hormones and then interact with the same trophic hormone in regulating cell proliferation and the specialized functions of the gland . IGF_S potentiate the steroidogenic action of ACTH and angiotensin I I in the adrenals (**Penhoat et al , 1989**) and of LH on androgen production by theca- interstitial cells in the overy (**Magoffin et**

al, 1990) and leydig cells in the testis (**Kasson and Hsueh , 1987**) and FSH in ovarian granulosa cells (**Adashi et al, 1988**).

(4) Role in fetal growth

IGF_S appear to play a central role in regulating embryonic and fetal growth and differentiation (**Gluckman , 1997**) . m RNA have been identified in humans for IGF-₁₁ from as early as 18 days (**Han et al , 1987**) and for IGF-₁ from at least 12- 14 weeks of gestation . Both peptides are present in human fetal blood at least by as the second trimester (**D'Ercole , 1987**) .

(5) Effect on Muscles

IGF_S stimulate the proliferation of myoblasts and the differentiation into myotubes (**Florini et al , 1986**) .

(6) Effect on hematopoiesis in bone marrow

Erythrocyte mass is closely coupled to the total body mass during the growth of mammals . Although erythropoietin is the regulator of the red blood cell mass , the coupling of red blood cell mass to growth is controlled by GH and IGF-₁ (**Merchav et al, 1988**)

(7) Effect on differentiation of lens epithelium

Somatomedins also appear to be involved in proliferation and differentiation of lens epithelium . Cell proliferation of the lens is GH dependent and can be stimulated in vivo by administration of GH or IGF-₁ (**Rothstein et al , 1980**).

(8) Rapid effects of IGF_s

These effects are the same as elicited by insulin. IGF_s stimulate glucose and amino acid uptake and increase glycogen synthesis of muscle in the same way as insulin and inhibit lipolysis of the fat cells . These insulin like effects are mediated through the insulin receptors (**Froesch et al , 1997**).

Regulation of IGFs

(1) Hormonal

GH is the primary regulator of post natal somatomedin production (**Clemmons , 2001**). IGF-₁ levels are more GH dependent than IGF-₁₁ levels. IGF-₁ concentrations are elevated in conditions of GH excess (e.g. acromegaly) (**Underwood et al , 1994**) , and decreased in states of GH deficiency (**Kandemir et al , 1997**) . In a response to a bolus injection of GH , there is a lag of 6 hours before a significant increase in plasma concentrations of IGF-₁ is observed in hypopituitary patients (**Copeland et al , 1984**) . GH stimulates IGF-₁ gene expression in all tissues. In most tissues , this IGF-₁ has local “autocrine” and “paracrine” actions , but the liver actively secretes IGF-₁ (and its binding proteins) into the circulation . Until recently , it was thought that this hormonally secreted IGF-₁ produced by the liver was responsible for many of GH in vivo actions. **Sonksen (2001)** reported that the recent data from hepato-specific IGF-₁ knock – out mice have shed serious doubt on this, since their growth and metabolism appear to be quite normal despite very low circulating IGF-₁ levels, therefore, circulating IGF-₁ should now be considered more as a “ marker” of GH action on the liver than as the mechanism by which GH exerts its effects .

Sirotkin et al (2001) demonstrate the involvement of GH and IGF-₁ in the control of porcine ovarian secretory activity and the ability of GH to regulate IGF-₁ production and reception.

They suggested that IGF-₁ despite its dependence on GH , do not mediate GH action on ovarian cells.

- Other hormones that influence IGF-₁ expression includes :

- Sex hormones

The pubertal rise in serum IGF-₁ levels reflect the effects of gonadal steroids on IGF-₁ transcription , some of which results from the pubertal rise in GH secretion and some is due to the direct effect of gonadal steroids on IGF synthesis or secretion , since a pubertal rise in serum IGF levels is also observed in patients with GH receptor deficiency (**Vaccarello et al , 1993**) . In rhesus monkey uteri and human breast tissues , the IGF-₁ and IGF-₁ mRNA levels have been shown to be up- regulated by estradiol (**Clark et al , 1997**). **Ren et al (2001)** found that there are existing evidences that estrogen regulates expression of the IGF system in vitro and in vivo.

- Insulin

There is a positive correlation between plasma IGF-₁ and insulin level . Insulin also affects production and circulating levels of IGFBP₅ which is thought to influence IGF-₁ binding and activity (**Smith et al , 1989**). In untreated diabetes , there is reduction in the secretion of somatomedin , which is restored to normal after treatment by insulin (**Bereket et al , 1995**)

- Thyroxin

It has a weak stimulatory effect on IGF₋₁. Plasma IGF₋₁ concentrations are low in thyroid hormone deficiency and increased after thyroxin replacement (**Underwood and VanWyk,1992**)

- Prolactin

It has a weak stimulatory effect on IGF₋₁ . The IGF₋₁ concentrations were normal in GH deficient patients with prolactin secreting tumors (**Clemmons et al , 1981b**)

- Glucocorticoids

They reduce plasma somatomedin activity (**Ganong , 1995**) . The expression and secretion of IGFBP₋₁ is regulated by ACTH (**Fottner et al , 2001**). Administration of glucocorticoids increases IGFBP₋₁ , presumably by a direct effect on IGFBP₋₁ gene transcription (**Powell et al, 1993**) .

(2) Nutritional Status

The second major regulator of IGF₋₁ is the nutritional status (**Clemmons et al , 1985**) . So , IGF₋₁ can be used as a useful indicator of nutritional insufficiency (**Uterman et al , 1985**) . An adequate caloric and protein intake has to be maintained to maintain an adequate serum IGF₋₁ (**Phillips and Unterman , 1984**). Fasting for 3 days results in substantial reduction in total serum IGF₋₁ (**Merimee et al , 1982**) . Following a five days fast , values decline by 53% , and subjects must be refed for at least 8

days for values to return to normal . During fasting and refeeding, the change in IGF-₁ correlates with the change in nitrogen balance (**Isley et al , 1983**) , the change is due to both energy and protein deficiency , since low energy or protein intake leads to diminished liver production of IGF_s and to a decrease in their plasma levels , despite increases in GH secretion . In fact , in these pathophysiological states , the lack of somatomedin is the likely cause of the elevated GH levels through negative feed back. Decreased IGF-₁ level in nutritional restriction despite normal or elevated GH levels is caused by resistance to GH , defects in IGF-₁ gene transcription and translation and m RNA instability (**Rabkin , 1997**) . Because IGF-₁ production is sensitive to protein and energy deficiencies , serum IGF-₁ level may be valuable in assessment of the nutritional status (**Numata et al , 1999 & Weisstaub and Araya, 2003**).

Owens et al (1994) found that the serum concentration of IGF-₁ have been shown to correlate directly with fetal weight .

Boyne et al (2003) found that maternal IGF-₁ levels positively influence birth weight.

Brennan et al (1999) found that IGF-₁ is low in children who are malnourished .

(3) Age

The age is an important determinant of normal serum IGF-₁ concentration . Plasma concentrations rise from very low levels , 20 to 60 ng / ml at birth , to peak values between 600 and 1100 ng / ml at puberty (**Underwood and VanWyk, 1992**). The

concentrations fall rapidly in the second decade , reaching mean values of 350 ng / ml by age 20 , and then decline more slowly over each decade. They are 50% of the 20-year – old values by age 60 years (**Rudman et al . 1981**).

(4) Sex

Average plasma IGF-₁ levels are slightly higher in females at each age (**Clemmons and VanWyk , 1984**) . Maternal plasma levels increase during pregnancy (**Daughaday and Rotwein , 1989**).

(5) Genetic

IGF-₁ concentrations are more highly correlated in monozygotic twins than in the same sex dizygotic twins , indicating a gene effect upon IGF-₁regulation (**Styne , 1997**).

There is a very close correlation between IGF-₁ concentrations and height in many different types of populations , and these appear to be due to genetic factor . This genetic determinant is independent of intrinsic GH secretion (**Clemmons, 2001**).

(6) IGFBP

Serum concentrations and actions of IGF_S are also regulated by IGFBP_S . The affinity of these binding proteins for IGF_S can be reduced by increased phosphorylation of the binding proteins , by protease cleavage or by binding of the protein to the cell surfaces (**Blat and Villaudy , 1994**).

Therapeutic uses of IGF_s

Human IGF₋₁ can now be produced in unlimited amounts using recombinant DNA technology , and the number of studies of its possible application is rapidly growing (**Arbet et al , 1999**), Thus IGF₋₁ may prove useful in treatment of various clinical conditions from pathologic short stature to catabolic states including the postoperative period (**Hayes et al , 2001**) .

Patients with insulin- dependent diabetes mellitus have reduced endogenous IGF₋₁ production . **Usala et al (1992)** found that diabetic patients with extreme insulin resistance had substantial improvement in metabolic control during administration of IGF₋₁ . **Fisher et al (2001)** suggested that at supraphysiological levels, IGF₋₁ bypasses some forms of insulin resistance and has been proposed as a therapeutic agent in the treatment of diabetes , but the side effects of high dose of IGF₋₁ (100-250 ug/kg) have precluded its clinical use . They found that low doses of IGF₋₁ (40-80 ug/kg) has no selective advantage over additional insulin in regulating glucose metabolism in hyperglycemic depancreatized dogs .

Prealbumin

Transthyretin (TTR) (Previously Known as Prealbumin) a protein of approximately 55 KDa that circulates in the serum of a wide range of vertebrates, is a tetramer consisting of four identical polypeptide chains held together by noncovalent bonds (**Stockigt , 2001**).

Each monomer is a 127 a a chain regulated by a single gene on chromosome 18. The tetramer is symmetric about a central cavity, which completely penetrates the molecule and contains Two T₄ binding sites, one at each end of the central cavity (**Robinson et al, 1978**).

It is so named because it migrates a head of albumin in the customary electrophoresis of serum or plasma protein (**Spiekerman 2000**). It binds and transports approximately 10% of both the serum thyroxin and triiodothyronin (T₃) , the latter with greater affinity. It has two binding sites, but because of negative cooperativity, interaction with the first hormone molecule decreases the binding affinity of the second and only one site is normally occupied (**Irace and Edelhoch, 1978**).

The liver is the primary site of synthesis of TTR, but the choroids plexus (**Schreiber et al, 1990**), and the pancreatic islets (**Jacobsson et al, 1990**) are additional sites of TTR synthesis. TTR expression, an early event in the embryonic development, first occurs in the choroids plexus and later in the liver (**Thomas et al , 1988**).

In the plasma, TTR forms a complex with the low molecular weight retinol binding protein (RBP) helping to prevent glomerular filtration and subsequent loss of RBP and retinol (**Veldee , 1999**). TTR and RBP are considered the major transport proteins for thyroxin and vitamin A respectively, the TTR and RBP complex circulates in the plasma in a ratio of 1 : 1 mol / L (**Spiekerman , 2000**).

The normal adult levels of TTR ranges from 160 to 400 mg / L (**Storiko, 1968**). The serum TTR concentration is age dependent. The levels in healthy neonates approximately half those found in adults. TTR increases at puberty, with a larger increase in boys than girls, and decrease in both sexes after the age of 50 years (**Ingenbleek and Young, 1994**).

TTR has a relatively short half life of 1 to 2 days, making it a rapid responder to nutritional adequacy. The high tryptophan content (**Smith et al, 1973**) and the high ratio of essential to non essential a a (**Gofferje, 1978**) comprising TTR make its plasma concentration sensitive to the quality of protein provided.

TTR is a negative acute phase reactant, the serum level fall in inflammation and malignancy, as well as in liver cirrhosis and protein – wasting diseases of the gut or kidneys, because of decreased synthesis and, to lesser extent, increased degradation (**Johnson et al, 1999**). Elevated TTR concentrations are associated with renal insufficiency (reduced catabolism) , steroid

administration, and alcoholism (**Kindmark and Laurell, 1972 & Alper, 1974**).

The circulating level of TTR is reflected by the availability of its transport ligand , thyroxin (mainly T3). Consequently, in conditions in which the circulating level of T3 is decreased, e.g. in hypothyroidism, the use of TTR as a nutritional marker may be compromised (**Veldee, 1999**) .

Transthyretin can be measured by a variety of methods, including radial immunodiffusion, turbidimetry and nephelometric immunoassay (**Veldee , 1994**).

Several studies prefer the use of TTR over other serum proteins as an indicator of nutritional status, since the half life of albumin is approximately 20 days, and it does not reflect the recent changes in nutritional status. Transferrin has a half life of only 8.8 days and so can reflect more recent changes in nutritional status. However, transferrin levels are increased in iron deficiency, reducing the specificity of this measurement for nutritional status. TTR has a short half life and can be used to reflect changes in nutritional status over the short term as in patients receive nutritional support to assess response to therapy (**Heber, 2001**). Nutritional support can cause a daily increase in TTR up to 10mg / L (**Spiekerman et al, 1993**).

Church and Hill (1987) compared the ability of TTR, RBP, transferrin and albumin to predict nitrogen balance in patients

requiring parenteral nutrition for two weeks. A positive nitrogen balance was reflected by a rise in TTR in 88% of cases compared with 65, 67 and 61% for RBP, transferrin and albumin, respectively. Similar correlations were found for negative nitrogen balance, where a fall in TTR occurred in 70% of cases compared with 25, 55 and 45% for RBP, transferrin, and albumin.

Transthyretin concentration do not appear to be significantly influenced by fluctuations in the hydration state. Although end-stage liver disease appears to affect all protein levels in the body, liver disease does not affect TTR as early or to the same extent as it affects other serum protein markers, particularly RBP (**Spiekerman, 2000**).

Bourry et al (1982) found that TTR is the most sensitive and helpful indicator when looking at the nutritional status of the very ill patients.

Transthyretin has been shown in both the pediatric and neonate population to be a highly accurate and relatively inexpensive marker for nutritional status (**Georgieff et al, 1987**).

Kurugol et al (1997) reported that TTR is a reliable and sensitive indicator for detection of mild and marginal malnutrition.

Amino Terminal Procollagen - 1

Collagen is the most abundant single protein in most vertebrates. In large animals, it may make up a third of the total protein mass. Collagen fibers form the matrix, or cement, material in bone, on which the mineral constituents precipitate, these fibers constitute the major portion of tendons, and a network of collagen fibers is an important constituent of skin (**Mathews and Van Holde, 1996**).

Collagen is an inert rigid protein forming the major structural component of the bone. It is the most abundant protein in the human body, constituting approximately 30% of the body protein, with up to 40% in the skin, and 50% of bone.

Each collagen polypeptide, designated α chain, has a repeating sequence Glyc – X – Y that is about 1000 residues long. Every third residue is glycine, about one – third of the X positions are occupied by proline and a similar number of Y positions are 4-hydroxyproline. Glycine is essential as its small size is needed to fit into the center of the helix. Proline and hydroxyproline residues give a considerable rigidity to the structure. A collagen molecule includes three α chains interwined in a collagen triple helix in which the glycine residues occupy the center of the structure (**Brownie and Kernohan, 1999**).

Several types of collagen are formed by different polypeptide chains, the sequence of each is controlled by a separate gene (**Krane, 1988**). At least 32 genes encode the α peptide chains of vertebrate collagen. These chains are assembled into the 19

known types of collagen. Alternative splicing of the mRNAs provides additional isoforms (**Metzler , 2001**). Collagen genes contain many exons (about 40). Various genes span from 20 to 40 kilobases. The genes are dispersed among nine chromosomes (**Roskoski, 1996**).

Collagen is synthesized in the cells as a single polypeptide chain in a precursor form carrying at the N-terminal and at the C-terminal additional procollagen peptides. They are then subjected to a series of posttranslational modification, including hydroxylation of certain proline and lysine residues by specific hydroxylases, and glycosylation by specific galactosyl and glucosyl transferases (**Adelmann , 1982**). Then formation of triple helix takes place within the endoplasmic reticulum (**Martinez – Hernandez and Miller, 1985**). The completed triple – helical procollagen molecule is transferred to the Golgi apparatus for packaging into vesicles and secreted into the extracellular space. The procollagen peptides are then cleaved by specific proteases. Concurrently, the triple helices assemble into fibrils and the collagen is stabilized by extensive cross – linking (**Raisz et al , 1998**).

Collagens are classified on the basis of their size and mode of self – assembly as fibrillar or non-fibrillar : The fibrillar collagens include types I , II , III , V and XI and occur in almost all connective tissues. The non-fibrillar collagens form a diverse group and can be subdivided into basement membrane collagens

(types IV and VII), found mainly in the extracellular matrix & short chain collagens (types VIII and X) found mainly in vascular and corneal endothelium, and fibril-associated collagens (types IX , XII and XIV) found attached to existing fibrillar collagens (**Gillham et al, 1997**).

Type I collagen is the most abundant collagen type in the human body. Most of it present in bone, where it accounts for about 90% of the organic matrix, but it also serves as the main structural protein in soft tissues, together with other collagen types (**Risteli and Risteli, 1999**). It is synthesized by a variety of specialized cells, such as fibroblasts, chondrocytes, and osteoplasts, and is secreted as a procollagen molecule contains globular amino and carboxy terminals (**Risteli et al , 1993**).

Type I collagen is a heterotrimer of two $\alpha_1(1)$ and one $\alpha_2(1)$ chain. Each chain contains about 1500 aa residues and the molecule is a cylinder 1.4 nm in diameter and 300 nm in length (**Gillham et al , 1997**).

Collagen Turnover :

Skletal growth comprises two continous parallel processes : bone formation by osteoblasts and bone resorption by osteoclasts, Jointly called bone modeling (**Monolagas , 2000**). Bone formation involves the synthesis, and bone resorption involves the degradation of type 1 collagen, the combination of which is defined as collagen turnover (**Risteli and Risteli , 1999**).

The turnover of collagen , both synthesis and degradation, is more abundant during growth and involves the production of specific by-products useful as markers of turnover rate. For type 1 collagen, markers of synthesis include the carboxy-terminal and amino-terminal propeptides of type 1 procollagen (PICP and PINP respectively). Type 1 collagen degradation can be specifically detected by analysis of either cross-linked carboxy – or amino-terminal telopeptides or by cross-links themselves liberated during the degradation process (**Risteli and Risteli, 1997**). While synthesis of type III collagen is reflected by the amino-terminal propeptide of type III procollagen (PIIINP) (**Risteli and Risteli, 1999**).

The concentrations of markers of type 1 and III collagen turnover decrease from the fetal period to adulthood, reflecting changes in growth velocity. Their concentrations in cord serum are about 50-fold higher than those in adults. The decrease in type 1 and III collagen turnover by age is manifested already in the fetus, markers of collagen turnover in cord blood decrease with increasing gestational age (**Seibold-Weiger et al, 2000**).

Procollagen I

Collagen is first synthesized as a longer molecule, procollagen, that contain additional “Propeptides”. All the known procollagen contain peptide extensions at both ends of their three polypeptide chains. The polypeptides of procollagen are called pro α chains. In the case of type 1 collagen, the two polypeptides are referred to as pro α_1 and pro α_2 . The amino terminal propeptide of the pro α_1 chain has a molecular weight of about 20.000 dalton and contains three distinct structural domain : a globular amino terminal domain, a central collagen like domain, and another short globular domain (**Engel et al, 1977**). The pro α_2 chain also contain an amino-terminal propeptide with a collagen like domain that matches the collagen like region of the pro α_1 amino-terminal propeptide. The carboxy-terminal propeptide of both the pro α_1 and pro α_2 chains have a molecular weights of 30.000 to 35.000 dalton and globular confirmation without any collagen like domain “ Fig. 1 ” .

Both the PINP and PICP contain cystein, which is not found in type 1 collagen. In the PINP, the cystein forms only interchain disulfide bonds, whereas in PICP, the cystein is involved in both intrachain and interchain disulfide bonds (**Miyahara et al, 1982**).

The PINP and PICP are produced principally in a molar ratio of 1 : 1. However, in clinical situations, altered behaviour can be found, the reasons for which may be altered clearance or even the

existence of variant forms of type 1 collagen (**Risteli and Risteli, 1997**).

Fig. (1) schematic presentation of type 1 procollagen

The molecule is composed of two identical pro α_1 chains (solid lines) and one pro α_2 chain (dashed line). In addition to the central triple-helical region that gives rise to the collagen molecule, the precursor contains amino-and carboxy terminal non-triple-helical domains. The amino-terminal domain is composed of a presumably globular region, a short collagen like segment, and a non-triple-helical region in which cleavages by the amino-terminal protease occur. Interchain disulfide bonds are limited to the carboxy-terminal domain (**Metzler , 2001**).

The biochemical structure and metabolism of PINP and PICP are different. The PICP is cleaved shortly after synthesis, whereas part of the PINP can still be found on the surface of collagen fibers. It is possible that the removal of PINP regulates

the further growth of the fibers. In mineralized bone no PINP can be found, in contrast to the soft connective tissues, where some PINP is present in newly synthesized matrix. The two propeptides are cleaved from the circulation via separate receptors of the liver endothelial cells. PICP is endocytosed by mannose receptors (**Smedsrod et al, 1990**), and PINP by scavenger receptors. The mannose receptors seem to be hormone sensitive, whereas the scavenger receptors are apparently not affected by the hormones (**Melkko et al, 1994**). These biochemical and physiological differences partially explain the different behaviour of the PICP and PINP antigens in the blood.

Changes in the concentration of PINP are found, for example, during growth. However, since bone is the major collageneous organ and also metabolically active throughout life, the PINP, as an indicator of type 1 collagen turnover is useful as a biochemical marker of metabolic bone diseases. **Jensen et al (1997)** reported that PINP might be used as a marker for evaluating increased bone turnover in patients with chronic renal failure. **Saarto et al (1998)** found that PINP is a sensitive marker of bone turnover rate, and the changes in PINP level significantly predicted changes in bone marrow density (BMD). **Diaz-Martin et al (1999 & De la Piedra et al., 2003)** found that PINP is an adequate biochemical marker of bone formation to be used in the detection of bone metastases in patients with prostatic carcinoma. **Kajantie et al (2001)** found that PINP is one of the biochemical markers that can reflect postnatal growth velocity in very low birth

weight (VLBW) infants. They reported that PINP showed a significant positive correlation with lower leg growth velocity and with weight growth in those infants.

The intact PINP shows greater dynamics than PICP assay, for example, serum PINP was found to be significantly higher in breast cancer patients with bone metastases, while serum PICP in those patients did not differ significantly from that of controls (**Tahtela and Tholix, 1996**). In osteoporosis, PINP was found to be more sensitive marker of bone turnover than PICP (**Garnero et al , 1997**). **Tahtela et al (1997)** suggested that both PINP and PICP serum levels reflect the rate of bone formation, but because the clearance of PINP is probably less sensitive to the hormonal changes, PINP may prove to be superior to PICP as a marker of bone formation.

Patients and Methods

Patients and Methods

The present study was carried out on 75 Egyptian infants and children suffering from malnutrition. They were 46 males and 29 females. They were selected from children attending the gastroenterology unit of pediatric Department at Tanta university over a period from September 2000 to October 2002. All malnourished children due to non nutritional causes were not included in this study. According to their ages, they were classified into four groups with 20 children in each age period 6 mo – < 1 yr , 1 – < 2 yr and 2 – < 3 ys , with 15 children from 3 – 4 years. According to wellcome's classification (Wellcome, 1970), they were 20 (26.7%) children with marasmus, 17 (22.7%) children with kwashiorkor, 13 (17.3%) with marasmic kwashiorkor and 25 (33.3%) were underweight.

Seventy five age and sex matched healthy children with no signs of malnutrition were used as controls.

- All children were subjected to :

A- Careful history taking and thorough clinical examination

Including the presence of edema, muscle wasting, subcutaneous fat loss, skin changes, hair changes, hepatomegaly and mental apathy, and to exclude any organic disease.

B- Anthropometric Measurements :

1- Weight

Wight (kg.) is measured by calibrated beam balance scale for children below 2 years, and with electric balance for children above 2 years.

2- Height

Height (cm.) was measured in standing position for children above 3 years on stadiometers, while in children below 3 years, the length was taken in the lying supine position with legs fully extended. The distance from the vertex to the base of the heel was recorded.

3- Mid-upper arm circumference (MUAC)

It was measured (cm.) with flexible non stretchable measuring tape. While the left arm of the child was completely relaxed and extended by

child's side, a mark was drawn on the lateral side of the upper arm midway between the acromion and olecranon processes. The tape was then passed around the arm in a plane perpendicular to the long axis of the arm. It must be just touching the skin but not compressing the tissue.

4- Triceps skin-fold thickness (TSF) (mm.)

The child was standing with his back to the measurer and his arm relaxed with palm facing the lateral thigh. The skin-fold was picked up over the posterior surface of the triceps muscle just below the mark (which is midway between the acromion and olecranon processes), and the caliper jaws are applied at the marked level. The thumb and forefinger of the left hand pick up a fold of skin and subcutaneous tissue and pinch it away from the underlying muscle. This fold is firmly maintained throughout the course of the measuring operation. The calipers are applied to the fold a little below the pinch point and the right hand is allowed to fully relax its grip on the trigger so that the jaws can exert full pressure.

C- Laboratory investigations :

Including :

- 1- Routine investigations in the form of urine analysis, complete blood picture, total serum proteins and random blood sugar.
- 2- Estimation of serum IGF₋₁ , IGFBP₋₁ , IGFBP₋₃ , prealbumin, and amino terminal procollagen₋₁.

(a) Estimation of IGF₋₁

Serum IGF₋₁ was estimated by Radioimmunoassay using the MEDGENIX IGF-1-D-RIA-CT kit (Kit of Biosource Europe SA. Belgium), which allowed the direct determination of IGF-1 in serum.

Neither extraction, nor pre-treatment step was needed to measure the IGF-1 in samples. Strong and specific decoupling agents were used during incubation step to remove IGF-1 from binding protein.

A fixed amount of ¹²⁵I-labelled IGF-1 competes with the IGF-1 to be measured in the sample or in the standard for a fixed amount of antibody sites being immobilized to the lower inner surface of a plastic tube. After an incubation allowing this competition reaction, tubes were emptied and washed to remove the excess unbound IGF-1 – 125.

(b) Estimation of IGFBP-1

Serum IGFBP-1 was estimated by Radioimmunoassay using the DSL-7800 Active TM total IGFBP-1 coated-tube immunoradiometric Assay kit (Diagnostic systems Laboratories, Inc. Texas USA.).

The procedure employs a two-site immunoradiometric assay (IRMA). The IRMA is a non-competitive assay in which the analyte to be measured is “sandwiched” between two antibodies. The first antibody was immobilized to the inside walls of the tubes. The other antibody was radiolabelled for detection. The analyte present in the unknowns, standards and control was bound by both of the antibodies to form a “sandwich” complex. Unbound materials were removed by decanting and washing the tubes.

(c) Estimation of IGFBP-3

Serum IGFBP-3 was estimated by immunoradiometric assay (IRMA) using IGFBP-3 IRMA CT (KIPB 1014) (Kit of Biosource Europe SA. Belgium).

The sensitive IGFBP-3 IRMA is a solid phase immunoradiometric assay. A first monoclonal anti-IGFBP-3 antibody bound to a polystyrene tube will capture the IGFBP-3 of the sample in the presence of a second ¹²⁵I- Labelled monoclonal anti-IGFBP-3 antibody.

Following the incubation and the one step formation of the solid phase – IGFBP-3 labelled monoclonal antibody sandwich, the tube was washed to remove excess of unbound labelled antibody. The radioactivity of the sandwich was directly proportional to the amount of IGFBP-3 present in the sample.

(d) Estimation of Prealbumin.

A quantitative determination of prealbumin by immunoprecipitin analysis using kit provided by Diasorin Inc. Minnesota USA.

The SPQ Antibody Reagent set 11 for prealbumin permits the quantitative determination of prealbumin in human serum by automated immunoprecipitin analysis.

Standards, control and patient samples were pipetted undiluted into sample cups. Microvolumes of these samples and polymer diluent are automatically pipetted into individual cuvettes.

Following an initial incubation and measurement of sample blank, undiluted antiserum is added to the cuvettes. The sample (antigen) solution and antiserum are then mixed in the reaction cuvettes.

Insoluble antigen-antibody complexes begin to form immediately, producing turbidity in the mixture and thus increasing the amount of light scattered by the solution. Following an incubation period lasting approximately 5 minutes, the absorbance of the solution is measured at the analytical wavelength.

A calibration curve was generated by assaying a series of 5 standards with known concentrations of prealbumin and using the instrument's data reduction capability or manually plotting the change in absorbance versus concentration. Concentrations for the control and patient samples were interpolated from the calibration curve.

(e) Estimation of Aminoterminal propeptide of type 1 procollagen.

Aminoterminal propeptide of type 1 procollagen (PINP) was measured by Radioimmunoassay method using Type 1 procollagen (PINP intact Radioimmunoassay Kit from Orion Diagnostica. Finland).

The INTACT PINP assay Kit is based on the widely used radioimmunoassay technique. A sample containing an unknown amount of the substance to be assayed is mixed with a standard amount of a radioactively labelled derivative of the

same substance. The labelled and unlabelled antigens are then allowed to compete for the limited number of high affinity binding sites of the antibody.

The amount of radioactive antigen in the antigen-antibody complex is reversely proportional to the amount of unlabelled antigen in the reaction mixture.

After separating the free antigen from the antibody-antigen complex, the residual radioactivity is counted and the actual concentration is calculated with the aid of a standard curve based on known amounts of unlabelled antigen analysed in parallel with the unknown.

Specifically in this kit, 50 ul of sample serum was mixed with 200 ul of PINP antiserum and 200 ul of ^{125}I -labelled PINP. After a 2-hour incubation at 37°C , separation reagent was added, tubes were allowed to stand for a short while and then centrifuged. The supernatant was then removed and the sediment containing the precipitated antibody-antigen complex is counted in a gamma counter. A standard curve was produced by calculating the binding of six standards as a percentage of the maximum possible binding and plotting these values. The results for unknowns were then expressed in terms of bound radioactivity. PINP values might be read directly from the standard curve.

- Statistical analysis :

The data of this study were computerized and analyzed using SPSS program version 10.0.

All the data of the present work were presented by means $(\bar{X}) \pm$ standard deviation (SD). They were subjected to the following tests of significance :-

To test the significance between two means, independent t-test between means was done. Where one way anova test was used to determine the significance between three or more means, with Donette test to localize the difference if it is present. Chi² test was used for comparing categorical data.

A probability (P) value of < 0.05 was considered statistically significant, while that > 0.05 was considered statistically insignificant.

Results

Results

The study was carried out on 75 malnourished children and 75 normal controls.

They were divided according to age into 4 groups :

The first group (under 1 year) included 20 malnourished children (marasmus = 11 & Kwo = 3 & MKwo = 4 & underweight = 2) and 20 normal control with matching sex.

The second group (from 1 – 2 years) included 20 malnourished children (marasmus = 7 & Kwo = 6 & M Kwo = 7) and 20 normal control.

The third group (from 2 – 3 years) included 20 malnourished children (marasmus = 2 & Kwo = 8 & M Kwo = 2 & underweight = 8) and 20 normal control.

The fourth group (from 3 – 4 years) included 15 malnourished children (all were underweight) and 15 normal control.

Anthropometric and laboratory data of the 4 groups are summarized in Tables (1 , 2 , 3 and 4). Data are presented as range, means and SD.

Table (1) . Anthropometric and laboratory measurements in the infants under 1 year.

		Marasmus n = 11	KWO n = 3	M KWO n = 4	underweight n = 2	control n = 20
Age (months)	Range	8 – 12	10 – 12	9 – 12	6 – 9	6 – 12
	Mean ± SD	10.18 ± 1.66	11.00 ± 1.00	10.75 ± 1.50	7.5 ± 2.12	8.70 ± 1.66
Weight (kg)	Range	4.50 – 5.50	6.20 – 6.50	5.00 – 5.40	4.50 – 6.20	6.40 – 10.00
	Mean ± SD	5.00 ± .35	6.40 ± .17	5.17 ± .17	5.35 ± 1.20	8.03 ± .96
Length (cm)	Range	60.00 – 65.00	67.00 – 69.00	62.00 – 64.00	67.00 – 69.00	60.50 – 76.00
	Mean ± SD	62.36 ± 2.01	68.00 ± 1.00	62.75 ± .95	68.00 ± 1.41	66.67 ± 14.46
WAM	Range	49.10 – 57.89	60.78 – 67.70	50.98 – 56.84	62.50 – 67.39	81.92 – 103.65
	Mean ± SD	53.60 ± 2.74	64.93 ± 3.66	54.70 ± 2.56	64.94 ± 3.45	91.34 ± 6.34
HAM	Range	78.94 – 88.43	47 – 92.00	81.57 – 88.88	95.83 – 101.51	94.20 – 102.12
	Mean ± SD	85.46 ± 3.20	77.54 ± 24.31	85.43 ± 3.35	98.67 ± 4.01	97.75 ± 2.12
MUAC (cm)	Range	8.00 – 10.50	8.00 – 9.50	9.50 – 10.50	10.00 – 12.00	13.00 – 15.00
	Mean ± SD	9.04 ± .75	8.83 ± .76	9.75 ± .50	11.00 ± 1.41	13.77 ± .49
TSFT (mm)	Range	3.50 – 5.00	4.00 – 4.50	4.00 – 5.00	5.50 – 6.00	6.50 – 8.00
	Mean ± SD	4.18 ± .46	4.33 ± .28	4.50 ± .40	5.75 ± .35	7.20 ± .41
IGF-1 (ng/ml)	Range	10.30 – 63.00	9.30 – 35.70	12.50 – 33.60	33.10 – 51.50	45.50 – 169.70
	Mean ± SD	27.43 ± 15.34	19.66 ± 14.08	21.25 ± 10.43	42.30 ± 13.01	84.28 ± 33.91
IGFBP-1 (ng/ml)	Range	31.60 – 97.90	38.00 – 45.70	35.10 – 64.30	44.00 – 62.30	13.40 – 54.90
	Mean ± SD	62.04 ± 23.23	40.83 ± 4.23	47.60 ± 13.44	53.15 ± 12.94	30.19 ± 10.46
IGFBP-3 (ng/ml)	Range	615.00 – 1170.00	485.00 – 780.00	495.00 – 835.00	1010.00 – 1025.00	600.00 – 1610.00
	Mean ± SD	844.09 ± 175.75	611.66 ± 151.84	677.50 ± 147.90	1017.50 ± 10.60	1062.25 ± 323.11
Prealbumin (mg/L)	Range	34.00 – 122.00	64.60 – 85.50	85.10 – 94.00	115.50 – 122.70	93.00 – 242.50
	Mean ± SD	91.20 ± 26.85	72.70 ± 11.21	89.52 ± 4.88	119.10 ± 5.09	166.98 ± 36.62
PINP (ug / L)	Range	79.60 – 139.50	65.00 – 93.40	54.50 – 106.00	123.50 – 182.00	87.50 – 253.20
	Mean ± SD	102.85 ± 17.92	80.86 ± 14.49	71.65 ± 23.54	152.75 ± 41.36	156.78 ± 47.57

WAM = Weight for age median.

HAM = Height for age median.

MUAC = Mid upper arm circumference.

TSFT = Triceps skin fold thickness.

IGF-1 = Insulin – like growth factor-1.

IGFBP-1 = Insulin – like growth factor binding protein-1.

IGFBP-3 = Insulin – like growth factor binding protein-3.

PINP = Amino terminal procollagen-1.

Table (2) . Anthropometric and laboratory measurements in the children from 1 to 2 years.

		Marasmus n = 7	KWO n = 6	M KWO n = 7	control n = 20
Child age (m)	Range	15 – 24	12.5 – 18	13 – 24	14 – 24
	Mean ± SD	18.86 ± 2.73	15.33 ± 1.97	18.71 ± 4.54	18.55 ± 3.55
Weight (kg)	Range	5.50 – 6.50	6.20 – 7.60	5.40 – 7.10	9.50 – 12.50
	Mean ± SD	5.95 ± .38	7.05 ± .63	6.18 ± .64	11.02 ± .78
Length (cm)	Range	63.00 – 76.00	69.00 – 74.00	64.00 – 77.00	75.00 – 87.00
	Mean ± SD	67.42 ± 4.46	71.66 ± 1.75	70.42 ± 4.85	81.50 ± 3.18
WAM	Range	47.41 – 55.55	60.78 – 70.37	48.24 – 59.66	83.33 – 105.12
	Mean ± SD	52.77 ± 3.18	65.99 ± 4.03	55.35 ± 3.61	98.34 ± 5.02
HAM	Range	76.19 – 93.82	88.19 – 92.90	81.70 – 89.01	94.42 – 102.43
	Mean ± SD	81.92 ± 5.83	90.63 ± 2.03	85.91 ± 2.38	99.21 ± 2.16
MUAC (cm)	Range	8.50 – 10.00	9.00 – 10.50	9.00 – 11.00	14.50 – 16.00
	Mean ± SD	9.42 ± .60	9.91 ± .73	10.28 ± .75	15.20 ± .52
TSFT (mm)	Range	3.50 – 4.50	3.50 – 5.00	4.50 – 6.50	6.50 – 8.00
	Mean ± SD	3.85 ± .37	4.58 ± .58	5.42 ± .78	7.27 ± .41
IGF-1 (ng/ml)	Range	8.00 – 59.50	12.00 – 36.50	7.20 – 38.00	32.40 – 166.00
	Mean ± SD	32.61 ± 18.10	26.48 ± 11.09	21.92 ± 12.78	85.90 ± 41.61
IGFBP-1 (ng/ml)	Range	28.00 – 94.00	60.70 – 103.00	26.80 – 89.40	7.20 – 65.20
	Mean ± SD	67.97 ± 22.45	74.36 ± 15.49	60.08 ± 20.02	32.74 ± 14.72
IGFBP-3 (ng/ml)	Range	600.00 – 1120.00	395.00 – 935.00	485.00 – 820.00	620.00 – 1970.00
	Mean ± SD	840.00 ± 186.79	650.83 ± 182.68	656.42 ± 123.88	1218.75 ± 356.78
Prealbumin (mg/L)	Range	54.00 – 132.20	63.00 – 105.10	44.00 – 109.00	97.00 – 293.80
	Mean ± SD	101.97 ± 27.55	72.00 ± 28.03	76.97 ± 21.63	171.82 ± 45.15
PINP (ug / L)	Range	32.20 – 135.30	5.50 – 92.00	56.30 – 116.50	66.90 – 215.50
	Mean ± SD	99.28 ± 32.01	52.51 ± 32.94	81.84 ± 20.30	147.65 ± 38.72

Table (3). Anthropometric and laboratory measurements in the children from 2 to 3 years.

		Marasmus n = 2	KWO n = 8	M KWO n = 2	underweight n = 8	control n = 20
Child age (m)	Range	25 – 29	25 – 29	26 – 28	25 – 36	25 – 36
	Mean ± SD	27.00 ± 2.83	26.25 ± 1.49	27.00 ± 1.41	31.00 ± 4.93	28.90 ± 3.06
Weight (kg)	Range	7.20 – 7.50	7.90 – 9.20	7.30 – 7.50	8.20 – 11.00	11.00 – 15.50
	Mean ± SD	7.35 ± .21	8.42 ± .41	7.40 ± .14	9.50 ± 1.11	12.45 ± 1.08
Length (cm)	Range	72.00 – 79.00	75.00 – 82.00	79.00 – 80.00	75.00 – 91.00	82.00 – 96.00
	Mean ± SD	75.50 ± 4.94	77.62 ± 2.50	79.50 ± .70	83.25 ± 6.29	89.15 ± 3.45
WAM	Range	58.59 – 59.50	62.69 – 75.40	54.88 – 57.69	63.07 – 77.20	83.94 – 106.87
	Mean ± SD	59.04 ± .64	66.20 ± 4.08	56.28 ± 1.98	70.07 ± 4.88	94.63 ± 6.03
HAM	Range	82.28 – 87.29	84.26 – 90.90	87.29 – 89.88	85.22 – 95.78	93.18 – 102.85
	Mean ± SD	84.78 ± 3.54	87.39 ± 2.44	88.58 ± 1.83	90.19 ± 3.77	98.17 ± 2.71
MUAC (cm)	Range	9.50 – 10.00	11.50 – 12.30	10.00 – 10.00	10.50 – 12.50	14.00 – 16.00
	Mean ± SD	9.75 ± .35	11.87 ± .35	10.00 ± .00	11.68 ± .70	15.22 ± .61
TSFT (mm)	Range	4.00 – 4.50	4.00 – 6.00	5.50 – 5.50	5.50 – 7.00	7.00 – 8.50
	Mean ± SD	4.25 ± .35	5.00 ± .80	5.50 ± .00	6.25 ± .46	7.77 ± .41
IGF-1 (ng/ml)	Range	17.40 – 39.00	10.00 – 39.00	13.40 – 31.50	19.50 – 107.90	14.20 – 142.50
	Mean ± SD	28.20 ± 15.27	24.77 ± 12.57	22.45 ± 12.79	59.55 ± 27.97	88.96 ± 29.03
IGFBP-1 (ng/ml)	Range	31.40 – 59.40	35.30 – 89.50	36.50 – 43.90	13.80 – 46.20	15.50 – 69.50
	Mean ± SD	45.40 ± 19.79	51.81 ± 17.50	40.20 ± 5.23	28.71 ± 9.98	33.49 ± 13.37
IGFBP-3 (ng/ml)	Range	570.00 – 790.00	465.00 – 1210.00	660.00 – 995.00	790.00 – 1680.00	960.00 – 2350.00
	Mean ± SD	680.00 ± 155.56	805.62 ± 247.32	827.50 ± 236.88	1130.63 ± 303.81	1666.50 ± 419.61
Prealbumin (mg/L)	Range	97.50 – 137.00	23.50 – 118.00	68.00 – 124.00	77.00 – 153.20	87.00 – 281.50
	Mean ± SD	117.25 ± 27.93	85.72 ± 30.14	96.00 ± 39.59	110.17 ± 23.47	174.53 ± 41.47
PINP (ug / L)	Range	69.50 – 101.00	10.70 – 94.00	46.40 – 75.00	87.10 – 172.00	42.50 – 220.80
	Mean ± SD	85.25 ± 22.27	58.21 ± 31.63	60.70 ± 20.22	116.60 ± 32.24	133.92 ± 45.94

Table (4). Anthropometric and laboratory measurements in the children from 3 to 4 years.

		Underweight n = 15	Control n = 15
Child age (m)	Range	37 – 48	38 – 48
	Mean ± SD	40.07 ± 3.65	40.93 ± 3.06
Weight (kg)	Range	8.70 – 12.50	14.00 – 16.50
	Mean ± SD	10.78 ± 1.04	15.18 ± .72
Length (cm)	Range	85.00 – 98.00	88.00 – 105.00
	Mean ± SD	90.66 ± 3.51	98.33 ± 4.27
WAM	Range	60.81 – 77.46	93.33 – 105.76
	Mean ± SD	72.18 ± 5.46	100.94 ± 3.20
HAM	Range	89.00 – 96.93	89.79 – 107.69
	Mean ± SD	92.65 ± 2.37	100.02 ± 4.10
MUAC (cm)	Range	11.50 – 13.50	15.00 – 16.00
	Mean ± SD	12.50 ± .56	15.43 ± .41
TSFT (mm)	Range	6.00 – 8.00	7.00 – 8.50
	Mean ± SD	6.86 ± .51	7.86 ± .48
IGF-1 (ng/ml)	Range	28.50 – 118.70	43.50 – 136.50
	Mean ± SD	56.97 ± 26.62	93.25 ± 26.67
IGFBP-1 (ng/ml)	Range	22.00 – 56.50	5.50 – 65.30
	Mean ± SD	37.84 ± 11.07	22.13 ± 15.98
IGFBP-3 (ng/ml)	Range	690.00 – 1435.00	1090.00 – 2410.00
	Mean ± SD	1105.33 ± 233.33	1733.00 ± 336.40
Prealbumin (mg/L)	Range	81.50 – 224.00	93.00 – 261.20
	Mean ± SD	137.49 ± 38.76	184.60 ± 44.19
PINP (ug / L)	Range	34.20 – 172.30	85.50 – 181.80
	Mean ± SD	94.60 ± 32.71	123.90 ± 26.36

Table (5). The means of age (month) in the malnourished children and control among the 4 age groups.

Age group	Malnourished Mean ± SD	Control Mean ± SD		
			t	P value
Under 1 year (n = 20)	10.15 + 1.76	8.70 + 1.66	2.68	.011*
From 1 to 2 years (n = 20)	17.75 + 3.54	18.55 + 3.55	- .714	.479
From 2 to 3 years (n = 20)	28.30 + 3.93	28.90 + 3.06	- .538	.593
From 3 to 4 years (n = 15)	40.07 + 3.65	40.93 + 3.06	-.704	.487

P < 0.05* Significant

Table (5) Shows that no significant difference between the malnourished children and controls as regards age, with the exception of the first age group (under 1 year) in which the mean age of malnourished children was significantly higher than that of controls. (P < 0.05)

Table (6). The sex distribution of the malnourished children and control in the 4 age groups.

Age group	Malnourished		Control		Pearson chi-square	Sig.
	Male n %	Female n %	Male n %	Female n %		
Under 1 year (n = 20)	13 (65%)	7 (35%)	13 (65%)	7 (35%)	000 ^b	1.000
From 1 to 2 years (n = 20)	11 (55%)	9 (45%)	11 (55%)	9 (45%)	000 ^b	1.000
From 2 to 3 years (n = 20)	12 (60%)	8 (40%)	12 (60%)	8 (40%)	000 ^b	1.000
From 3 to 4 years (n = 15)	10 (66.7%)	5 (33.4%)	10 (66.7%)	5 (33.3%)	000 ^b	1.000

P < 0.05 Significant

Table (6) shows that there is no statistical difference between the malnourished children and controls as regards sex among the 4 age groups.

Table (7). The weight (kg) in the malnourished children and controls among the 4 age groups.

Age group	Malnourished	Control		
	Range Mean \pm SD	Range Mean \pm SD	t	P value
Under 1 year (n = 20)	4.50 – 6.50 5.28 \pm .62	6.40 – 10.00 8.03 \pm .96	-10.68	.000
From 1 to 2 years (n = 20)	5.40 – 7.60 6.36 \pm .70	9.50 – 12.50 11.02 \pm .78	-19.7	.000
From 2 to 3 years (n = 20)	7.20 – 11.00 8.64 \pm 1.09	11.00 – 15.50 12.45 \pm 1.08	-11.08	.000
From 3 to 4 years (n = 15)	8.70 – 12.50 10.78 \pm 1.04	14.00 – 16.50 15.18 \pm .72	-13.42	.000

P < 0.05 Significant

Table (7) Shows that there is statistical significant reduction in weight among the malnourished children when compared to the controls in the 4 age groups.(P < 0.05)

Table (8). The mean length (cm) in the malnourished children and controls among the 4 age groups.

Age group	Malnourished	Control		
	Range Mean \pm SD	Range Mean \pm SD	t	P value
Under 1 year (n = 20)	60.00 – 69.00 63.85 \pm 2.92	60.50 – 76.00 66.67 \pm 14.46	-0.856	.397
From 1 to 2 years (n = 20)	63.00 – 77.00 69.75 \pm 4.22	75.00 – 87.00 81.50 \pm 3.18	-9.92	.000
From 2 to 3 years (n = 20)	72.00 – 91.00 79.85 \pm 5.21	82.00 – 96.00 89.15 \pm 3.45	-6.650	.000
From 3 to 4 years (n = 15)	85.00 – 98.00 90.66 \pm 3.51	88.00 – 105.00 98.33 \pm 4.27	-5.36	.000

P < 0.05 Significant

Table (8) Shows that there is no significant difference between malnourished children and controls as regards length in the first age group (Under 1 year) (P > 0.05) & while there are significant decrease in the malnourished children in the other age groups (P < 0.05).

Table (9). The weight for age median (WAM) in the malnourished children and controls among the 4 age groups.

Age group	Malnourished Range Mean \pm SD	Control Range Mean \pm SD		
			t	P value
Under 1 year (n = 20)	49.10 – 67.70 56.65 \pm 5.59	81.92 – 103.65 91.34 \pm 6.34	-18.34	.000
From 1 to 2 years (n = 20)	47.41 – 70.37 57.64 \pm 6.65	83.33 – 105.12 98.34 \pm 5.02	-12.8	.000
From 2 to 3 years (n = 20)	54.88 – 77.20 66.04 \pm 6.09	83.94 – 106.87 94.63 \pm 6.03	-14.89	.000
From 3 to 4 years (n = 15)	60.81 – 77.46 72.18 \pm 5.46	93.33 – 105.76 100.94 \pm 3.20	-17.58	.000

P < 0.05 Significant

Table (9) Shows that there is significant decrease in the WAM for all age groups of malnourished children when compared to their controls (P < 0.05).

Table (10). The height for age median (HAM) in the malnourished children and controls among the 4 age groups.

Age group	Malnourished	Control		
	Range Mean \pm SD	Range Mean \pm SD	t	P value
Under 1 year (n = 20)	78.94 – 101.51 85.59 \pm 9.92	94.20 – 102.12 97.75 \pm 2.12	-5.35	.000
From 1 to 2 years (n = 20)	76.19 – 93.82 85.93 \pm 5.14	94.42 – 102.43 99.21 \pm 2.16	-10.6	.000
From 2 to 3 years (n = 20)	82.28 – 95.78 88.37 \pm 3.38	93.18 – 102.85 98.17 \pm 2.71	-10.10	.000
From 3 to 4 years (n = 15)	89.00 – 96.93 92.65 \pm 2.37	89.79 – 107.69 100.02 \pm 4.10	-6.01	.000

P < 0.05 Significant

Table (10) Shows that there is significant decrease in the all age groups of malnourished children as regards HAM when compared to their controls (P < 0.05).

Table (11). The mid upper arm circumference (MUAC) (cm) in the malnourished children and controls among the 4 age groups.

Age group	Malnourished Range Mean \pm SD	Control Range Mean \pm SD		
			t	P value
Under 1 year (n = 20)	8.00 – 12.00 9.35 \pm .96	13.00 – 15.00 13.77 \pm .49	-18.27	.000
From 1 to 2 years (n = 20)	8.50 – 11.00 9.87 \pm .75	14.50 – 16.00 15.20 \pm .52	-25.8	.000
From 2 to 3 years (n = 20)	9.50 – 12.50 11.40 \pm .92	14.00 – 16.00 15.22 \pm .61	-15.36	.000
From 3 to 4 years (n = 15)	11.50 – 13.50 12.50 \pm .56	15.00 – 16.00 15.43 \pm .41	-16.14	.000

P < 0.05 Significant

Table (11) Shows that there is significant decrease in the MUAC in the malnourished children of the 4 age groups when compared to their controls (P < 0.05).

Table (12). The triceps skin fold thickness (TSFT) (mm) in the malnourished children and controls among the 4 age groups.

Age group	Malnourished	Control		
	Range Mean \pm SD	Range Mean \pm SD	t	P value
Under 1 year (n = 20)	3.50 – 6.00 4.42 \pm .61	6.50 – 8.00 7.20 \pm .41	-16.82	.000
From 1 to 2 years (n = 20)	3.50 – 6.50 4.62 \pm .88	6.50 – 8.00 7.27 \pm .41	-12.1	.000
From 2 to 3 years (n = 20)	4.00 – 7.00 5.47 \pm .91	7.00 – 8.50 7.77 \pm .41	-10.29	.000
From 3 to 4 years (n = 15)	6.00 – 8.00 6.86 \pm .51	7.00 – 8.50 7.86 \pm .48	-5.49	.000

P < 0.05 Significant

Table (12) Shows that there is significant decrease in the TSFT for malnourished children in the 4 age groups when compared to their controls (P < 0.05).

Table (13). The insulin-like growth factor-1 (IGF-1) (ng/ml) in the malnourished children and controls among the 4 age groups.

Age group	Malnourished Range Mean \pm SD	Control Range Mean \pm SD		
			t	P value
Under 1 year (n = 20)	9.30 – 63.00 26.52 \pm 14.51	45.50 – 169.70 84.28 \pm 33.91	-7.00	.000
From 1 to 2 years (n = 20)	7.20 – 59.50 27.03 \pm 14.44	32.40 – 166.00 85.90 \pm 41.61	-5.98	.000
From 2 to 3 years (n = 20)	10.00 – 107.90 38.79 \pm 25.91	14.20 – 142.50 88.96 \pm 29.03	-5.76	.000
From 3 to 4 years (n = 15)	28.50 – 118.70 56.97 \pm 26.62	43.50 – 136.50 93.25 \pm 26.67	-3.72	.001

P < 0.05 Significant

Table (13) Shows that there is significant decrease in the IGF-1 among the malnourished children in the all age groups when compared to controls (P < 0.05).

Table (14). The insulin-like growth factor binding protein-1 (IGFBP-1) (ng/ml) in the malnourished children and controls among the 4 age groups.

Age group	Malnourished Range Mean \pm SD	Control Range Mean \pm SD		
			t	P value
Under 1 year (n = 20)	31.60 – 97.90 55.08 \pm 19.89	13.40 – 54.90 30.19 \pm 10.46	4.95	.000
From 1 to 2 years (n = 20)	26.80 – 103.00 67.13 \pm 19.59	7.20 – 65.20 32.74 \pm 14.72	6.27	.000
From 2 to 3 years (n = 20)	13.80 – 89.50 40.77 \pm 16.92	15.50 – 69.50 33.49 \pm 13.37	1.50	.140
From 3 to 4 years (n = 15)	22.00 – 56.50 37.84 \pm 11.07	5.50 – 65.30 22.13 \pm 15.98	3.12	.004

P < 0.05 Significant

Table (14) Shows that there is IGFBP-1 increase in the all age groups of malnourished children when compared to their controls. This increase was insignificant in the third age groups (children from 2 to 3 years) (P > 0.05), while it was statistically significant in the other age groups (P < 0.05).

Table (15). The insulin-like growth factor binding protein-3 (IGFBP-3) (ng/ml) in the malnourished children and controls among the 4 age groups.

Age group	Malnourished Range Mean \pm SD	Control Range Mean \pm SD		
			t	P value
Under 1 year (n = 20)	485.00 – 1170.00 793.25 \pm 192.25	600.00 – 1610.00 1062.25 \pm 323.11	-3.20	.003
From 1 to 2 years (n = 20)	395.00 – 1120.00 719.00 \pm 181.52	620.00 – 1970.00 1218.75 \pm 356.78	-5.58	.000
From 2 to 3 years (n = 20)	465.00 – 1680.00 925.25 \pm 303.13	960.00 – 2350.00 1666.50 \pm 419.61	-6.40	.000
From 3 to 4 years (n = 15)	690.00 – 1435.00 1105.33 \pm 233.33	1090.00 – 2410.00 1733.00 \pm 336.40	-5.93	.000

P < 0.05 Significant

Table (15) Shows that there is significant decrease in the IGFBP-3 among the malnourished children in all age groups when compared to controls (P < 0.05).

Table (16). The values of prealbumin (mg/L) in the malnourished children and controls among the 4 age groups.

Age group	Malnourished Range Mean \pm SD	Control Range Mean \pm SD		
			t	P value
Under 1 year (n = 20)	34.00 – 122.70 90.88 \pm 23.12	93.00 – 242.50 166.98 \pm 36.62	-7.85	.000
From 1 to 2 years (n = 20)	44.00 – 132.20 84.23 \pm 27.87	97.00 – 293.80 171.82 \pm 45.15	-7.38	.000
From 2 to 3 years (n = 20)	23.50 – 153.20 99.68 \pm 28.70	87.00 – 281.50 174.53 \pm 41.47	-6.63	.000
From 3 to 4 years (n = 15)	81.50 – 224.00 137.49 \pm 38.76	93.00 – 261.20 184.60 \pm 44.19	-3.10	.004

P < 0.05 Significant

Table (16) Shows that there is significant decrease in the mean values of prealbumin in the all age groups of malnourished children when compared to their controls (P < 0.05).

Table (17). The values of aminoterminal propeptide of type-1 procollagen (PINP) (ug/L) in the malnourished children and controls among the 4 age groups.

Age group	Malnourished Range Mean \pm SD	Control Range Mean \pm SD		
			t	P value
Under 1 year (n = 20)	54.50 – 182.00 98.30 \pm 29.83	87.50 – 253.20 156.78 \pm 47.57	-4.65	.000
From 1 to 2 years (n = 20)	5.50 – 135.30 79.15 \pm 33.39	66.90 – 215.50 147.65 \pm 38.72	-5.99	.000
From 2 to 3 years (n = 20)	10.70 – 172.00 84.52 \pm 39.79	42.50 – 220.80 133.92 \pm 45.94	-3.63	.001
From 3 to 4 years (n = 15)	34.20 – 172.30 94.60 \pm 32.71	85.50 – 181.80 123.90 \pm 26.36	-2.70	.012

P < 0.05 Significant

Table (17) Shows that there is significant decrease in the mean values of PINP in the all age groups of malnourished children when compared to their controls (P < 0.05).

As regards type of malnutrition, the malnourished children were classified into marasmus (M) & Kwashiorkor (Kwo) & marasmic Kwashiorkor (MKWO) and underweight. The anthropometric and laboratory data for each type of malnutrition were summarized in Tables (18 , 19)

Table (18). The mean values of the anthropometric measurements for each type of malnutrition and for controls :

		Marasmus n = 20	KWO n = 17	M KWO n = 13	underweight n = 25	control n = 75
* Child age (m.)	Range	8 – 29	10 – 29	9 – 28	6 – 48	6 – 48
	Mean ± SD	14.90 ± 6.19	19.71 ± 6.72	17.54 ± 6.49	34.56 ± 9.96	23.16 ± 11.97
P value VS control		.006	.589	.235	.000	
*Child weight (kg)	Range	4.50 – 7.50	6.20 – 9.20	5.00 – 7.50	4.50 – 12.50	6.40 – 16.50
	Mean ± SD	5.57 ± .83	7.58 ± .96	6.06 ± .88	9.93 ± 1.82	11.43 ± 2.66
P value VS control		.000	.000	.000	.009	
*Child length (cm)	Range	60.00 – 79.00	67.00 – 82.00	62.00 – 80.00	67.00 – 98.00	60.50– 105.00
	Mean ± SD	65.45 ± 5.22	73.82 ± 4.37	69.46 ± 6.66	86.48 ± 7.85	82.95 ± 13.90
P value VS control		.000	.008	.000	.492	
* WAM	Range	47.41 – 59.50	60.78 – 75.40	48.24 – 59.66	60.81 – 77.46	81.92 – 106.87
	Mean ± SD	53.85 ± 3.24	65.90 ± 3.77	55.29 ± 2.96	70.92 ± 5.39	96.00 ± 6.39
P value VS control		.000	.000	.000	.000	
* HAM	Range	76.19 – 93.82	49.47 – 92.90	81.57 – 89.88	85.22 – 101.51	89.79 – 107.69
	Mean ± SD	84.16 ± 4.43	86.80 ± 9.97	86.17 ± 2.66	92.35 ± 3.61	98.71 ± 2.86
P value VS control		.000	.000	.000	.000	
* MUAC (cm)	Range	8.00 – 10.50	8.00 – 12.50	9.00 – 11.00	10.00 – 13.50	13.00 – 16.00
	Mean ± SD	9.25 ± .69	10.64 ± 1.36	10.07 ± .64	12.12 ± .82	14.87 ± .84
P value VS control		.000	.000	.000	.000	
* TSFT (mm)	Range	3.50 – 5.00	3.50 – 6.00	4.00 – 6.50	5.50 – 8.00	6.50 – 8.50
	Mean ± SD	4.07 ± .43	4.73 ± .68	5.15 ± .74	6.58 ± .60	7.50 ± .51
P value VS control		.000	.000	.000	.000	

P < 0.05 significant.

Table (18) Shows that, as regards children age, there is decrease in the mean ages of the marasmic, KWO and MKWO groups when compared to controls. This decrease was statistically significant in marasmic groups ($P < 0.05$), while in KWO and MKWO the decrease was statistically insignificant ($P > 0.05$). On the other hand, there is a significant increase in the mean age of the underweight group when compared to controls ($P < 0.05$).

The anthropometric measurements (Weight, length, WAM, HAM, MUAC and TSFT) all showing statistical significant decrease in the malnourished children of all groups when compared to controls, with the exception of length in the underweight group who showing insignificant increase when compared to the controls.

Table (19). The mean values of the laboratory measurements for each type of malnutrition and for controls :

		Marasmus n = 20	KWO n = 17	M KWO n = 13	underweight n = 25	control n = 75
IGF-1 (ng/ml)	Range	8.00 – 63.00	9.30 – 39.00	7.20 – 38.00	19.50 – 118.70	14.20 – 169.70
	Mean ± SD	29.32 ± 15.67	24.47 ± 11.76	21.80 ± 11.08	56.62 ± 25.86	87.75 ± 33.19
P value VS control		.000	.000	.000	.000	
IGFBP-1 (ng/ml)	Range	28.00 – 97.90	35.30 – 103.00	26.80 – 89.40	13.80 – 62.30	5.50 – 69.50
	Mean ± SD	62.45 ± 22.49	57.83 ± 19.64	53.18 ± 17.7	36.14 ± 12.32	30.14 ± 13.99
P value VS control		.000	.000	.000	.358	
IGFBP-3 (ng/ml)	Range	570.00 – 1170.00	395.00 – 1210.00	485.00 – 995.00	690.00 – 1680.00	600.00 – 2410.00
	Mean ± SD	826.25 ± 176.22	716.76 ± 218.45	689.23 ± 147.23	1106.40 ± 244.00	1399.27 ± 455.51
P value VS control		.000	.000	.000	.002	
Prealbumin (mg/L)	Range	34.00 – 137.00	23.50 – 118.00	44.00 – 124.00	77.00 – 224.00	87.00 – 293.80
	Mean ± SD	97.57 ± 27.05	78.58 ± 26.59	83.76 ± 20.82	127.28 ± 34.73	173.81 ± 41.43
P value VS control		.000	.000	.000	.000	
PINP (ug/L)	Range	32.20 – 139.50	5.50 – 94.00	46.40 – 116.50	34.20 – 182.00	42.50 – 253.20
	Mean ± SD	99.84 ± 23.37	60.20 ± 30.12	75.45 ± 21.06	106.29 ± 36.04	141.67 ± 42.32
P value VS control		.000	.000	.000	.000	

P < 0.05 significant.

Table (19) shows that there is significant decrease in the IGF-1 & IGFBP-3 & Prealbumin and PINP in all malnourished groups when compared to controls. On the other hand, IGFBP-1 shows an increase in all malnourished groups when compared to controls, this increase was statistically significant in the marasmic, KWO and MKWO groups, while in the underweight group the increase was statistically insignificant.

Table (20) . The mean values of the anthropometric and laboratory measurements in the malnourished children and controls.

		Malnourished	Control		
		n = 75	n = 75	t	P value
Child age (m)	Range	6 – 48	6 – 48	-.227	.821
	Mean ± SD	23.00 ± 11.37	23.16 ± 11.97		
Weight (kg)	Range	4.50 – 12.50	6.40 – 16.50	-9.661	.000
	Mean ± SD	7.56 ± 2.22	11.43 ± 2.66		
Length (cm)	Range	60.00 – 98.00	60.50 – 105.00	-3.907	.000
	Mean ± SD	75.05 ± 10.64	82.95 ± 13.90		
WAM	Range	47.41 – 77.46	81.92 – 106.87	-27.210	.000
	Mean ± SD	62.52 ± 8.52	96.00 ± 6.39		
HAM	Range	76.19 – 101.51	89.79 – 107.69	-13.131	.000
	Mean ± SD	87.83 ± 6.57	98.71 ± 2.86		
MUAC (cm)	Range	8.00 – 13.50	13.00 – 16.00	-21.589	.000
	Mean ± SD	10.66 ± 1.45	14.87 ± .84		
TSFT (mm)	Range	3.50 – 8.00	6.50 – 8.50	-15.216	.000
	Mean ± SD	5.24 ± 1.18	7.50 ± .51		
IGF-1 (ng/ml)	Range	7.20 – 118.70	14.20 – 169.70	-11.019	.000
	Mean ± SD	36.02 ± 23.48	87.75 ± 33.19		
IGFBP-1 (ng/ml)	Range	13.80 – 103.00	5.50 – 69.50	7.202	.000
	Mean ± SD	51.03 ± 20.86	30.14 ± 13.99		
IGFBP-3 (ng/ml)	Range	395.00 – 1680.00	600.00 – 2410.00	-8.658	.000
	Mean ± SD	871.06 ± 267.67	1399.26 ± 455.51		
Prealbumin (mg/L)	Range	23.50 – 224.00	87.00 – 293.80	-11.698	.000
	Mean ± SD	100.77 ± 34.73	173.81 ± 41.43		
PINP (ug / L)	Range	5.50 – 182.00	42.50 – 253.20	-8.396	.000
	Mean ± SD	88.78 ± 34.43	141.67 ± 42.32		

Table (20) Shows that there is no significant difference between the malnourished children and controls as regards age ($P > 0.05$). The anthropometric measurements (Weight, Length , WAM , HAM , MUAC and TSFT) all showing significant decrease in the malnourished children in relation to controls. As regards laboratory measurements , the IGF₋₁ & IGFBP-3 & prealbumin and PINP showing significant decrease while the IGFBP₋₁ showing a significant increase in the malnourished children when compared to controls ($P < 0.05$).

Table (21). Simple Pearson correlation studies in all malnourished children (75 cases) as one group.

	IGF-1 (ng/ml)	IGF BP-1 (ng/ml)	IGFB P-3 (ng/ml)	Prealbu Min (mg/L)	PINP (ug/L)
IGF₁ (ng/ml)					
Pearson correlation		-.368**	.481**	.323**	.105
Sign (2-tailed)		.001	.000	.005	.369
IGFBP₁ (ng/ml)					
Pearson correlation	-.368**		-.201	-.328**	-.186
Sign (2-tailed)	.001		.084	.004	.110
IGFBP_{.3} (ng/ml)					
Pearson correlation	.481**	-.201		.433**	.169
Sign (2-tailed)	.000	.084		.000	.148
Prealbumin (mg/ml)					
Pearson correlation	.323**	-.328**	.433**		.317**
Sign (2-tailed)	.005	.004	.000		.006
PINP (ug / L)					
Pearson correlation	.105	-.186	.196	.317**	
Sign (2-tailed)	.369	.110	.148	.006	

** Correlation is significant at the 0.01 level (2 – tailed).

Table (21) Shows that IGF-1 & IGFBP-3 and prealbumin have a positive significant correlation with each other.

The IGFBP-1 shows a significant negative correlation with IGF-1 & IGFBP-3 and prealbumin.

The PINP shows a significant positive correlation with prealbumin.

Discussion

Discussion

Protein energy malnutrition (PEM) is an important nutritional deficiency worldwide. It constitutes a major pediatric problem in most of developing countries because it stands as a major threat to infant's health, growth, and development. PEM covers not only the clinical spectrum, ranging from kwashiorkor to severe marasmus, but also the milder forms which manifest themselves in varying degrees of growth retardation and functional impairment in millions of poor children of the developing countries (**Waterlow, 1992**).

The assessment of infants with failure to thrive always demands a very careful history, physical examination and laboratory work-up to rule out organic disease and to assess possible nutrition alteration (**Lifshitz and Maggioni, 1995**).

In our study, the mean weight for age in the malnourished children (53.85 ± 3.24 in marasmus, 65.90 ± 3.77 in kwashiorkor, 55.29 ± 2.96 in marasmic kwashiorkor and 70.92 ± 5.39 in underweight) was significantly lower ($P < 0.05$) than in control (96.00 ± 6.39). These results were consistent with the definition of PEM according to Wellcome's classification (**Wellcome, 1970**). In all our malnourished children, the weight for age median was lower than the cut off (80%) of the median.

In our study, the mean values of height for age median in the malnourished children (84.16 ± 4.43 in marasmus, 86.80 ± 9.97 in kwashiorkor, 86.17 ± 2.66 in marasmic kwashiorkor and 92.35 ± 3.61 in underweight) was significantly lower than in control (98.71 ± 2.86) with $P < 0.05$. There is also significant reduction of height for age median in the marasmus, kwashiorkor, and marasmic kwashiorkor children when compared to underweight group. This in agreement with **Waterlow (1988)** who suggested that decreased height for age indicates that the child has, at some period, been chronically malnourished.

Mid upper arm circumference (MUAC) is a method that currently widely used for detecting malnutrition. Taking 12.5 cm as cut off point in children < 5 years, below which the child is identified as malnourished.

In this study, MUAC measurement demonstrated significant reduction in all malnourished groups when compared to control. The mean values of MUAC were lower than 12.5 cm in all malnourished groups and were ($9.25 \pm .69$) in marasmus, (10.64 ± 1.36) in kwashiorkor, ($10.07 \pm .64$) in marasmic kwashiorkor, and ($12.12 \pm .82$) in underweight children, while it was ($14.87 \pm .84$) in the control group.

The MUAC is an indicator of muscle status and muscle atrophy is a common finding in all types of PEM. Meanwhile it is also an indicator of subcutaneous fat status, and subcutaneous fat

is lost in cases of marasmus and marasmic kwashiorkor as represented by **Bhatia et al (1999)**.

Triceps skin fold thickness (TSF) is the most sensitive skin fold measurement for energy reserves (**Waston and Dako, 1977**).

In our study, the TSF (mm) in the malnourished children ($4.07 \pm .43$ in marasmus, $4.73 \pm .68$ in kwashiorkor, $5.15 \pm .74$ in marasmic kwashiorkor, and $6.58 \pm .60$ in underweight) was significantly lower than in control ($7.50 \pm .51$) with $P < 0.05$.

The insulin – like growth factors (IGF_S) are polypeptides that are chemically related to insulin. They are synthesized in the liver and also produced at multiple sites. IGF_S may act locally or at a distance and they exhibit diverse biological actions, including effects on differentiated cell functions as well as on growth.

The plasma levels of IGF₋₁ are regulated by growth hormone (GH), consistent with its proposed role as mediator of GH action, while IGF₋₁₁ has been shown to be less dependent on GH.

In our study IGF₋₁ was concerned because the effects of malnutrition on circulating IGF₋₁ levels are sufficiently pronounced. **Clemmons et al (1985)** proposed that plasma IGF₋₁ levels can be used to assess nutritional status and gauge the response to nutritional support regimns.

Malnutrition induces a state of GH resistance. The mechanism involved depends on the severity, duration and time of onset, postulated to be due to down – regulation of GH receptors or defects at the post – receptor level (**Maes et al., 1991**). However, as the growth promoting effect of GH is mediated in part by IGF₁ (**Teale and Macks, 1986**), the low levels of this growth factor and its carrier protein, IGFBP₃, during nutritional deprivation have also been implicated as contributing factors for GH insensitivity (**Thissen et al., 1990 & Maes et al., 1991**).

Bier (1991) reported that GH concentrations are elevated in various forms of malnutrition and shown to be accompanied by a reduction in circulating IGF₁ level. The decreased IGF₁ level is due to reduced IGF₁ gene expression which is a consequence of both GH receptor and post receptor defects. The latter, which can be induced by dietary protein restriction alone, appears to predominate during protein malnutrition and are magnified by the insulin insufficiency which often accompanies reduced dietary intake. Additionally, restricted nutritional intake causes an increase in low molecular weight IGFBP₁, and a decline in the high molecular weight IGFBP₃. Infusion of IGF₁ is capable of inducing IGFBP₃ synthesis during dietary protein restriction and both insulin and IGF₁ can augment IGFBP synthesis in cultured fibroblasts.

Emler and Schlach (1987) found that changes in rat serum IGF₁ during fasting and refeeding are paralleled by changes in the liver IGF₁ mRNAs. This suggests that one post – receptor mechanism for decreased IGF₁ is impaired IGF₁ transcription or decreased IGF₁ mRNA stability. There may also be a translational block, indicating that IGF₁ biosynthesis may be controlled at multiple levels.

In our study, the serum levels of IGF-1 were significantly decreased in all malnourished children (29.32 ± 15.67 in marasmus, 24.47 ± 11.76 in kwashiorkor, 21.80 ± 11.08 in marasmic kwashiorkor, and 56.62 ± 25.86 in underweight) when compared to controls (87.75 ± 33.19) (P < 0.05). Similar results were obtained by **Hintz et al (1978)**, **Soliman et al (1986)**, **Tirapegui et al (1990)** and **Zamboni et al (1996)**.

Isley et al., (1984) reported that dietary protein and energy intake contribute significantly to alterations in plasma IGF₁, but during the recovery phase while intake level are still low, energy rather than protein deficiency is a more important determinant of plasma IGF₁ restoration.

IGFBP₁ has been shown to inhibit the mitogenic and cellular metabolic actions mediated by IGF₁ by limiting the availability of free IGF₁ (**Lee et al, 1997**). Insulin, on the other hand has been

shown to inhibit the IGFBP – gene promotor and thus IGFBP₋₁ production in the liver (**Suwanickul et al, 1994**).

IGFBP₋₁ is the only IGFBP that displays rapid dynamic regulation in vivo, with serum levels varying as much as 10-fold in relation to meals (**Busky et al, 1988**). Because of this unique property, IGFBP₋₁ is thought to play an important role in acute regulation of IGF₋₁ availability. The fasting induced increase in the concentration of IGFBP₋₁ would result in decreased levels of free/ dissociable IGF₋₁ in serum (**Bereket et al, 1996**).

In this study the mean levels of serum IGFBP₋₁ were significantly increased in marasmus (62.45 ± 22.49), kwashiorkor (57.83 ± 19.64) and marasmic kwashiorkor (53.18 ± 17.7) when compared to control group (30.14 ± 13.99) ($P < 0.05$). While there is insignificant increase in the mean serum level of IGFBP-1 in the underweight group (36.14 ± 12.32) when compared to control group. This was consistent with the result obtained by **Phillip et al (1998)**. Also **Palacio et al (2002)** reported a significant increase of the IGFBP₋₁ in the malnourished children in comparison to control group, and the level of serum IGFBP₋₁ was significantly decreased after 10% weight gain among the PEM patients.

Katz et al (2002) reported that the decline in the level of IGF₋₁ during fasting appears to be the result of the steady rise in IGFBP₋₁ that occurs as insulin declines and speculated that this

decline in IGF levels which is controlled by the rise in IGFBP₁ serves to protect against possible insulin – like activity of the IGF_S during fasting.

In our study, we found a significant negative correlation between IGF₁ and IGFBP₁ in malnourished children. This is similar to result obtained by **Shinobe et al (1997)** who reported that serum IGF₁ / IGFBP₁ ratio is useful not only as a nutritional marker but also as a predicting index of responsiveness to r-hGH.

IGFBP₃ is not only the most abundant but has the highest affinity for IGF₁ and IGF₁₁. Most circulating IGF₁ is held in a ternary complex comprising IGF₁, IGFBP₃, and an acid labile subunit. Serum concentration of IGF₁ are significantly correlated to serum IGFBP₃ and GH, with nutrition being a further major regulator of IGF₁ (**Grant et al, 1973 & Clemmons et al, 1981a**). The relation between IGF₁ and IGFBP₃ can be modified further by specific IGFBP proteases which degrade IGFBP₃ into smaller fragments that have a decreased affinity for IGF₁ and hence increase IGF₁ bioavailability. **Osler et al (1995)** predicted that IGFBP₃ proteases would be more active in severe PEM.

In our study, the serum levels of IGFBP₃ (ng/ml) were significantly decreased in all malnourished children (826.25 ±

176.22 in marasmus, 716.76 ± 218.45 in kwashiorkor, 689.23 ± 147.23 in marasmic kwashiorkor, and 1106.40 ± 244.00 in underweight) when compared to controls (1399.27 ± 455.51) ($P < 0.05$). This result was consistent with the previous studies that reported a significant reduction of serum IGFBP₃ in the malnourished children (**Hernandez et al, 1992 & Counts et al, 1992 & Smith et al, 1995 & Wan Nazaimoon et al, 1997 and Palacio et al, 2002**).

On the other hand. **Zamboni et al (1996)** found that IGFBP₃ was reduced in the marasmic group but not in kwashiorkor group when compared to control. They suggested that the low IGFBP₃ level in marasmus is due to increased adaptive proteolysis of IGFBP₃, in contrast, in kwashiorkor the IGFBP₃ proteolytic activity was very low, probably because of inhibition by aflatoxins.

As reported by **Blum et al (1993)** IGF₁ and IGFBP₃ levels of the normal children were significantly correlated. In this study, however, IGF₁ levels of the malnourished children were found to be positively and significantly correlated to IGFBP₃ levels, indicating that both IGF₁ and IGFBP₃ were equally affected in cases of malnutrition. In addition, we have also observed that in spite of malnutrition, there was still significant age related increase of IGFBP₃ similar to that seen in normal children.

Wan Nazaimoon et al (1996) demonstrated a strong positive correlation between IGF₁ and IGFBP₃ in the malnourished children. They suggested that these biochemical measurements are indeed useful indicators of growth and nutritional status in children.

Phillip et al (1998) found that serum levels of IGF₁ was highly correlated to serum IGFBP₃ in the malnourished children, but on the other hand, they found that IGF₁ and IGFBP₃ are not useful for the evaluation of nutritional status of children under the age of 2 years.

In this study, the serum levels of prealbumin (mg/L) were significantly decreased in all malnourished children (97.57 ± 27.05 in marasmus, 78.58 ± 26.59 in kwashiorkor, 83.76 ± 20.82 in marasmic kwashiorkor, and 127.28 ± 34.73 in underweight) when compared to controls (173.81 ± 41.43) $P < 0.05$. This is in accord with other reported studies (**Ingenbleek et al, 1975 & Ogushina and Hussain, 1980 & Sliverman and Christenson, 1994 and Kurugol et al, 1997**) who reported that prealbumin is a sensitive indicator for detecting various grades of PEM.

A gradually decreasing level of serum prealbumin concentration with increasing severity of PEM found in the present study was also in agreement with the result obtained by

Ingenbleek et al (1975) who reported doubling and tripling of plasma prealbumin values after the 1st and 2nd week of treatment of severe PEM cases with appropriate high protein diet in children.

Decreased liver synthesis of prealbumin due to limited supply of substrate and very high turnover rate of prealbumin have been supposed to be responsible for its rapid fall in response to protein deprivation (**Ogunshina and Hussain, 1980**). The lower prealbumin concentration in kwashiorkor than those of marasmus was probably due to more liver injury and thus lesser ability of the liver to synthesize prealbumin and more severe dietary protein deprivation. Similarly, slightly higher prealbumin concentration in marasmic kwashiorkor cases perhaps indicate a slightly lesser amount of liver injury than those of kwashiorkor ones.

Type 1 collagen is the most abundant collagen type in the body. It accounts for more than 90% of the organic matrix of bone. Type 1 collagen is derived from a larger protein, type 1 procollagen, which has propeptide extensions at both ends of the molecule. These propeptides are removed by specific proteinases before the collagen molecules are assembled into fibres. Both propeptides, aminoterminal propeptide of type 1 procollagen (PINP) and carboxyterminal propeptide of type 1 procollagen (PICP), can be found in the circulation, where their concentration in principle reflects the synthesis rate of type 1 collagen (**Kajantie et al, 2001**).

Doherty et al (2002) reported that severe malnutrition was associated with low rates of bone and collagen synthesis and high rates of collagen degradation.

In our study, PINP was concerned. **Tahtela et al (1997)** reported that PINP may prove to be superior to PICP as a marker of bone formation, because the clearance of PINP is probably less sensitive to the hormonal changes.

In our study, the serum levels of PINP (ug/L) were significantly decreased in all malnourished children (99.84 ± 23.37 in marasmus, 60.20 ± 30.12 in kwashiorkor, 75.45 ± 12.06 in marasmic kwashiorkor and 106.29 ± 36.04 in underweight) when compared to controls (141.67 ± 42.32) ($P < 0.05$). This is in accord with **kajantie et al (2001)** who reported that PINP concentration is likely to reflect type 1 collagen synthesis in both the skeleton and soft tissues, which is supported by its positive relationship with both lower leg and weight growth velocities.

Klinger et al (1996) found that serum procollagen may serve as a marker to reflect some of the biochemical changes induced by IGF₋₁ in connective tissue in the initial periods of treatment. They found that IGF₋₁ raises serum procollagen levels in children with Laron syndrome.

Doherty et al (2002) reported that early weight gain and subsequent linear growth were associated with early increments in IGF₋₁, IGFBP₋₃ and markers of bone and collagen formation.

Summary and Conclusions

Summary and Conclusions

Protein energy malnutrition still represents a major health problem among infants and children in the developing countries.

The aim of this work was to study the serum levels of IGF₁, IGFBP₁, IGFBP₃, prealbumin and aminoterminal propeptide of type 1 procollagen (PINP) in infants and children with PEM.

Seventy five malnourished egyptian infants and children aged between 6 month and 4 years were the subject of this study were divided as follow : 20 children with marasmus , 17 children with kwo, 13 children with mkwo, and 25 children with underweight.

The children were picked up from those attending Gastroenterology Unit of Pediatric Department at Tanta University Hospital, Tanta, Egypt.

Seventy five age and sex matched normal children were picked up from surgical ward and outpatient clinic of Tanta University Hospital and served as a control group.

All children were subjected to thorough clinical appraisal, anthropometric measurements that included weight, length, mid upper arm circumference (MUAC) and triceps skin fold thickness (TSF).

Determination of serum levels of IGF₁, IGFBP₁, IGFBP₃, prealbumin and PINP was done.

As regards anthropometric measurements, the mean weight for age was found to be significantly decreased in all

malnourished groups when compared to controls. The mean height for age was significantly decreased in all malnourished children when compared to controls. Also, MUAC and TSF were found significantly decreased in all malnourished groups when compared to controls.

The results of the study demonstrated that the mean levels of serum IGF₁, IGFBP₃, Prealbumin and PINP were significantly lower in all malnourished children than in controls.

On the other hand, the mean level of serum IGFBP₁ was found significantly increased in the marasmas, Kwo and m Kwo groups, but insignificantly increased in underweight group when compared to controls.

From this study; we concluded :

- Still PEM cases are found in developing countries, despite the efforts done to improve the socioeconomic standards and hygienic measures in these communities.
- Anthropometric measures still represents the corner stones in diagnosis of PEM cases especially before the full blown picture of the disease appear.
- The biochemical parameters IGF₁, IGFBP₁, IGFBP₃, prealbumin and PINP correlate significantly with anthropometric measurements in cases of PEM. these biochemical parameters were found to be sensitive indicators for nutritional status and can be used for diagnosis of subclinical cases of PEM.

- The IGF₁ , IGFBP₃ and PINP have a significant positive correlation with prealbumin, while IGFBP₁ has a significant negative correlation with prealbumin in PEM cases.

Recommendations :

We recommend :

- All children attending the outpatient clinic should be thoroughly examined for signs of malnutrition especially in developing countries.
- Anthropometric measurements should be done as a routine in sick children.
- The use of these biochemical markers in pediatrics is likely to continue to increase because these measurements are non invasive, generally available, capable of measuring changes in PEM over short intervals. Their increased use has the potential to result in better selection of patients for therapy and better monitoring of the effectiveness of therapies. The only difficulties for its use as indicator for nutritional status are the need for special laboratory for its determination and also its expensive price for those patients in the developing countries.
- Other studies to be done on a wide scale or a big numbers of children in multicenters to evaluate the benefit of these laboratory investigations for diagnosis and follow up of PEM cases.
- promotion of health education, immunization programs and family planning in the developing countries.

References

Abiodun PO (1991)

Use of Soya beans for the dietary prevention and management of malnutrition in Nigeria.

Acta Paediatr Scand Suppl, 374 : 175 – 85

Adashi EY (1994)

Regulation of intrafollicular IGFBP_s possible relevance to ovarian follicular selection. In : Baxter RC, Gluckman PD and Rosenfeld RG (eds.) The insulin- like growth factors and their regulatory proteins. Elsevier : 341– 50 .

Adashi EY, Resnick CE and Hernandez JV (1988)

IGF₁ as an amplifier of follicle stimulating hormone action : studies on mechanisms and site of action in cultured rat granulosa cells .

Endocrinology , 122 : 1583 – 91

Adashi EY, Resnick CE and Rosenfeld RG (1989)

IGF₁ hormonal action in cultured rat granulosa cells : Mediation Via type-1 but not type – 2 IGF receptors .

Endocrinology , 126 : 216 – 22

Adelmann (1982)

collagen degradation. In : Gerlach V, Pott G, Routerberg J and Voss BP (eds.) Connective Tissue of the normal and fibrotic human liver.

George Thieme Stuttgart : 18 – 20

Alexander JW (1986)

Nutrition and infection

Arch Surg , 121 : 966 – 72

Alleyne GA, Hay RW, Picon PJ, Stanfield JP and Whitehead R (1981).

“ Protein Energy Malnutrition “

Gastroenterology, 30 : 95 – 103

Alper CA (1974)

Plasma Protein measurements as a diagnostic aid .

N Engl J Med., 291 : 287 .

Amoui M, Craddock BP and Miller WT (2001)

Differential phosphorylation of IRS₋₁ by insulin and IGF₋₁ receptors in Chinese hamster ovary cells.

J Endocrinol, 171 : 153 – 62

Arany E, Afford S and Strain AJ et al (1994)

Different cellular synthesis of IGFBP₋₁ and IGFBP₋₃ within human liver

J Clin Endocrinol Metab., 79 : 1871 – 76

Arbet EC, Janknecht RD and Eckhart WB (1999).

Role of focal adhesion Kinase and MAP Kinase activation by IGF₋₁ or insulin

FEBS (letter), 454(3) : 252 – 56

Armendares S, Salamanca F and Frenk S (1971).

Chromosome abnormalities in severe PCM

Nature,232 : 271 – 73

Badr MA, EL-shafie NA, Hassan GA, Omar NF and EL-safty VR (1992)

Blood lead and protoporphyrin level in infants with
PEM Egypt J pediatr, 9 (1-2) : 35 – 44

Ballabriga A (1985)

The problem of malnutrition , an introduction .

Ann Nestle “ Malnutrition” , 43 (1) : 1 – 4

Bar RS , Clemmons DR and Boes M et al (1990)

Transcapillary Permeability and subendothelial
distribution of endothelial and amniotic fluid IGFBP_s
in rat heart .

Endocrinol , 127 : 1078 – 86

Barltrop D (1992)

Nutrition . In : Campbell AG and McIntoch N (eds.).

Forfar and Arneil’s Textbook of pediatrics. 4th ed.

Churchill Livingstone New York London : 1257- 98 .

Barness LA (1987)

Nutrition and nutritional disorders, In : Behrman RE and Vaughan VC (eds.) Nelson Textbook of pediatrics, 13^{ed} ed.

WB SAUNDERS Co., Philadelphia London : 138 – 50

Barness LA (1992)

Nutritional Disorders. In : Behrman RE, Nelson WE and Vaughan V C (eds.) Nelson Textbook of pediatrics, 14th ed.

WB SAUNDERS Co. Philadelphia London : 130

Bautista CM, Baylink DJ and Mohan S (1991)

Isolation of a novel IGFBP from human bone .

Biochem Biophys Res Commun , 176 : 756

Baxter RC (1994)

IGFBP_s in the human circulation : A review .

Horm Res, 42 : 140 – 44

Baxter RC (2000)

IGFBP_s interactions with IGF_s and intrinsic bioactivities

Am J physiol, 278 : 967 – 76

Behar M and Viteri FE (1978)

Disturbance of nutrition in PEM, In: Jelliffe DB and Stanfield JP (eds.) Diseases of children in subtropics and tropics, 3^{ed} ed.

English language Book Society and Edward Arnold Ltd. London : 196 – 205

Beisel WR (1991).

The history of nutritional immunology

J Nutr Immunol, 1 : 1 – 12

Bell GI, Gerhard DS and Fong NM et al (1985)

Isolation of the human IGF genes : IGF₋₁₁ and insulin genes are contiguous.

Proc Natl Acad Sci, USA, 82 : 6450

Benjamin DR (1989)

Laboratory tests and nutritional assessment in PEM

Ped Clin North Am., 193 : 61

Benjamin T and Fernando E (1988)

PEM. In : Marvice ES and Vernon RY (eds.) , Modern nutrition in health and disease, 7th ed.

WB Saunders Edinburgh Philadelphia : 446 – 50

Bereket A , Lang GH and Blethen SL et al (1995)

IGFBP₋₂ and insulin : Studies in children with type₋₁ diabetes mellitus and maturity – onset diabetes of the young.

J Clin Endocrinol Metab., 80 : 3647

Bereket A, Wilson TA, Blethen SL, Fan J, Frost RA, Celato MC and Lang CH (1996)

Effect of short term fasting on free / dissociable IGF-1 concentration in normal human serum.

J Clin Endocrinol Metab, 81 : 4379 – 84.

Berne RM, Levy MN, Koeppen BM and Stanton BA (1998)

The hypothalamus and pituitary gland. In : Physiology, 4th ed.

Mosby, Baltimore, Boston : 896.

Bhatia RC, Pooni PA, Singh H and Singh D (1999)

MUAC for detecting malnutrition during infancy.

Indian J Pediatr, 66 (6) : 834 – 38.

Bier DM (1991)

Growth hormone and IGF₁ : Nutrition, Pathophysiology and therapeutic Potential.

Acta Pediatr Scand Suppl, 374 : 119 – 28.

Binkert C , Margot JB and Landwehr J et al (1992)

Structure of the human IGFBP-2 gene.

Mol Endocrinol, 6 : 826 – 36.

Blat C and Villaudy T (1994)

In vivo proteolysis of serum IGFBP₃ results in increased availability of IGF to target cells.

J Clin Invest., 93 : 2286 – 90

Bluhm DP and Summers RS (1993)

Plasma Vitamin A levels in measles and malnourished pediatric Patients and their implications in therapeutics

J. Trop . Pediatr., 39 (3) : 179 – 82

Blum WF, Albertsson Wikland K, Rosberg S and Ranke MB (1993)

Serum levels of IGF-1 and IGFBP-3 reflect spontaneous GH secretion.

J Clin Endocrinol Metab, 76 : 1610 – 16.

Boisclair Y R , Rhoads RP , Ueki I , Wang J and Ooi GT (2001)

The acid – labile subunit of the 150 KDa IGF binding protein complex : an important but forgotten component of the circulating IGF system.

J Endocrinol, 170 : 63 – 70.

Bourry J, Milano G and Caldani C (1982)

Assessment of nutritional proteins during the parenteral nutrition of cancer patients.

Ann Clin Lab Sci, 12 : 158

Boyne MS, Thame M, Bennett FI , Osmond C, Miell JP and Forrester TE (2003)

The relationship among circulating IGF₋₁ , IGFBP₋₁ and ₋₁₁ and birth anthropometry : a prospective study.

J Clin Endocrinol Metab ; 88 (4) : 1687 – 91.

Branca F , Robin SP, Luzzi AF and Golden MHN (1992)

Bone turnover in malnourished children .

Lancet, 340 : 1493 – 96

Brasseur D, Hennort P, Dramaix M, Bahwere P, Donnen P , Tonglet R, Deverecker T and Duchateau J (1994)

Biological risk factors for fatal PEM in hospitalized children in Zaire.

J pediatr Gastroenterol. Nutr., 18 (2) : 220 – 24.

Brennan BM, Gill M , Pennells L, Eden OB, Thomas AG and Clayton PE (1999)

IGF₋₁ , IGFBP₋₃ and IGFBP protease activity : relation to anthropometric indices in solid tumors or leukaemia.

Arch Dis . Childhood, 80 (3) : 226 – 30

Brewster DR, Morary MJ and Graham MS (1997a)

Case management of Kwo, An intervention project at seven nutrition rehabilitation centers in Malawi

Eur J clin Nutr, 51 (3) : 139 – 47

Brewster DR, Morary MJ, Menzies IS, Loughlin EV and Henry RL (1997 b)

Intestinal permeability in Kwo

Arch Dis child , 76 (30) : 236 – 41

Briend AI (1990)

Is diarrhea a major cause of malnutrition among the under fives in developing countries ? A review of available evidence

Eur J Clin Nutr, 44 : 611 – 28

Brown AL, chariotti L and Orłowski C et al (1989)

Nucleotide sequences and expression of a cDNA Clone encoding a fetal rat binding protein for IGFs.

J Biol Chem, 264 : 5148 – 54

Brown KH (1991)

Appropriate diets for the rehabilitation of malnourished children in the community setting .

Acta paediatr Scand, 347 : 151 – 59

Brown KH and McLaren WC (1984)

Nutritional management of acute diarrhea : an appraisal of alternatives.

pediatrics, 73 : 119 – 25

Brown KH, Suskind RM, Lubin B et al (1978)

Changes in red blood cell membrane in protein calorie malnutrition.

Am J Clin Nutr, 31 : 574 – 84.

Brownie AC and Kernohan JC (1999)

Proteins. In : Biochemistry : A core text with self assessment.

Churchill Livingstone Philadelphia London : 12 – 25

Busky WH, Snyder DK and Clemmons DR (1988)

Radioimmunoassay of a 26.000 dalton plasma IGFBP : control by nutritional variables

J Clin Endocrinol Metab, 67 : 1225 – 30.

Buzina R (1980)

Classification of PEM

Excer Med. Pediatr and Pediatr surg., 43 (3)

Caballero B, Solomon NW, Baster R and Torun B (1985)

Haemostatic mechanisms in utilization of exogenous iron in children recovering from severe malnutrition .

J pediatr. Gastroenterol . Nutr., 4 : 96 – 102

Castiglia PT (1996)

PEM (Kwo and marasmus)

J pediatr Health care, 10 (1) : 28 – 30

Champion RH, Burton JL and Ebling EJ (1992)

Metabolic and nutritional disorders. In : Rook WE (ed.) Textbook of dermatology 9th ed.

Raven Press New York : 225 – 29

Chelius D, Baldwin MA, Lu X and Spencer EM (2001)

Expression, purification and characterization of the structure and disulfide linkages of IGFBP₄

J Endocrinol., 168 : 283 – 96

Chowdhury FA , Miah RA, Begum B and Rahman KM (1993)

The transformation in vitro of Peripheral lymphocytes of malnourished children .

Bangladesh Med Res Counc Bull, 19 (2) : 67 – 70 .

Church JM and Hill GL (1987)

Assessing the efficacy of intravenous nutrition in general surgical patients : Dynamic nutritional assessment with plasma proteins

J Parenteral Enteral Nutr., 11 : 135 – 39

Clark B (1998)

Dietary nutritional assessment. In : Campbell AG and McIntosh N (eds.), Forfar and Arneil's Textbook of pediatrics 5th ed .

Churchill Livingstone New York London : 1187 .

Clark B, Howell A and Anderson E (1997)

Type 1 IGF receptor gene expression in normal human breast tissue treated with Oestrogen and progesterone .

Br J Cancer , 75 : 251 – 57

Clemmons DR (2001)

IGF₁ and its binding proteins. In : DeGRoot LJ and Jameson JL (eds.) Endocrinology 4th ed.

WB saunders Co Philadelphia London : 439 – 60

Clemmons DR and VanWyk JJ (1984)

Factors Controlling blood concentration of somatomedin- c Clin Endocrinol Metab , 13 (1) : 133

Clemmons DR, Klibanski A and Underwood LE (1981a)

Reduction of plasma immunoreactive somatomedin-c during fasting in humans.

J Clin Endocrinol Metab, 53 : 1247 – 50.

Clemmons DR, Underwood LE and Ridgway EC (1981b)

Hyperprolactinemia is associated with increased immunoreactive somatomedin – c in hypopituitarism

J Clin Endocrinol Metab, 52 : 731 – 35

Clemmons DR, Underwood LE, and Maes RN (1985)

Use of somatomedin - C/ IGF₁ measurement to monitor the response to nutritional repletion in malnourished patients.

Am J Clin Nutr, 41 : 191 – 98.

Cohick WS and Clemmons DR (1993)

The IGFs

Ann Rev Physiol ., 55 : 131 – 53

Conn H (1982)

Cirrhosis. In : Conn H and George KL (eds.) Diseases of liver, 5th ed.

J.B. Lippincot Co., Philadelphia Toronto : 835 – 65

Conover CA Clarkson JT, Durham SK and Bale LK (1994)

Cellular actions of IGFBP₃

Adv Exp Med Biol , 343 : 255 – 66

Copeland KC, Johnson DM, Kuehl RJ et al (1984).

Estrogen Stimulates GH and Somatomedin-c in castrate and intact female baboons.

J Clin Endocrinol Metab, 58 : 698.

Counts DR, Owirtsman H, Cdrilsson MS and Cutler GB (1992)

The effect of anorexia nervosa and refeeding on GH binding protein, the IGFs and the IGFBPs.

J Clin Endocrinol Metab, 75 : 762 – 67.

Cabbage ML, Suwanichkal A and Powell DR (1990)

IGFBP-3. Organization of the human chromosomal gene and demonstration of promotor activity

J Biol Chem , 265 : 12642 – 49

Curran J S and Barness LA (2000)

Nutrition. In : Behrman RE, Kliegman RM and Jenson HB (eds). Nelson Textbook of pediatrics, 16th ed .

WB SAUNDERS Co., Philadelphia London : 138.

D'Ercole AJ (1987)

Somatomedin, IGF_s and fetal development

J Dev physiol, 9 : 481 – 95

Daughaday WH and Rotwein P (1989)

IGF₋₁ and ₋₁₁ peptide, messenger ribonucleic acid and gene structures, serum and tissue concentrations.
Endocrinol Rev., 10 : 68 – 91

Daughaday WH , Hall K and Salmon WD et al (1987)

On the nomenclature of the somatomedins and IGFs
(Letter)
J Clin Endocrinol Metab., 65 : 1075 – 76

De la Piedra C, Castro – Errecaborde NA , Traba ML, Mendez – Davila C, Garcia – Moreno C, Rodriguez de Acuna L and Rodriguez – Molina J (2003).

Bone remodeling markers in the detection of bone metastases in prostatic cancer.
Clin Chim Acta ; 331 : 45 – 53.

Delong GR (1993)

Effects of nutrition on brain development in humans
Am J Clin Nutr, 57 : 286 – 90

Delpuech F, Cornu A and chevalier P (1980)

The effect of iron deficiency anemia on two indices of nutritional status. Prealbumin and transferrin
Br . J Nutr., 43 : 375 – 79

De Mellow JS and Baxter RC (1988)

GH dependent IGFBP both inhibits and potentiates IGF₋₁ stimulated DNA synthesis in human skin fibroblast

Biochem Biophys Res Commun, 156 : 199 – 204

De Meyets PD (1994)

The structural basis of insulin and IGF-1 receptor binding and negative cooperativity and its relevance to mitogenic versus metabolic signaling.

Diabetologia, 37 (supple 2) : s 135

Dhansay MA , Benad S and Donald PR (1991)

Plasma lecithin cholesterol acyl transferase activity and plasma lipoprotein composition and concentrations in Kwo Am J Clin Nutr, 53 : 517 – 19

Diaz – Martin MA, Traba ML, De la Piedra C, Guerrero R, Mendez – Davila C and De La Pena EG (1999)

Aminoterminal Propeptide of type 1 collagen and bone alkaline phosphatase in the study of bone metastases associated with prostatic carcinoma.

Scand J Clin Lab Invest. 59 (2) : 125 – 32.

Dickhaut SC, De Lee JC and Page CP (1984)

Nutrition status : Importance in predicting wound healing after amputation

J Bone Joint Surg Am, 66 : 7175

Doherty CP, Crofton PM, Sorker MA et al (2002)

Malnutrition, Zinc Supplementation and catch-up growth : changes in IGF-1, its binding proteins, bone formation and collagen turnover.

Clin Endocrinol, 75 (3) : 391 – 99.

Drop SL, Valiquette G and Guyda HJ et al (1979)

Partial purification and characterization of a binding protein for insulin – like activity in human amniotic fluid : a possible inhibitor of insulin like activity .

Acta Endocrinol (Copenh), 90 : 505 – 18

EL – Ghazali S , Mikhail M , Awadallah M and Shatla HM (1990)

Significant increase of chromosomal damage in PEM .

J trop Med Hyg , 93 : 372 – 76

EL – Mougny M (1999)

Basic Pediatrics

Cairo : 101 – 12

EL – Sokkary SA , Abdel Khalik KA, Farid MM , Abdel Fattah S, Aboel Magd L and Shatla HM (1984)

Fibrin and Fibrinogen degradation products in PEM in Egyptian children and infants .

Egypt J Pediatr , 1 : 102 – 27

Emler CA and Schlach DS (1987)

Nutritionally induced changes in hepatic IGF₁ gene expression in rats.

Endocrinology, 120 : 832 – 34.

Engel J , Bruckner P and Becker U (1977)

Physical Properties of the aminoterminal precursor specific protein type 1 procollagen.

Biochemistry , 16 : 4026 – 33.

Erinoso HO , Akinbami FO and Akinyinka OO (1993)

Prognostic factors in severly malnourished hospitalized Nigerian children.

Trop Geograph Med., 45 (6) : 290.

Fagundes –Neto N (1981)

Malnutrition and intestine. In : Lipshitz E (ed.)
Clinical disorders in pediatric gastroenterology and
nutrition . New York Basel : 249 .

Fayad JM , Ghali IM , Ghazi GH, Sharaf Eldin S and Dabach S (1980)

Gastrointestinal changes in PEM.

Egypt pediater Assoc , 28 : 225.

Fisher SJ , Shi ZO, Lickley HL, Efendic S, Varnic M and Giacca A (2001)

Low dose IGF₁ has no selective advantage over insulin in regulating glucose metabolism in hyperglycemic depancreatized dogs

J Endocrinol , 168 : 49 – 58

Florini JR , Ewton DZ and Falen SL (1986)

Biphasic concentration dependency of the stimulation of myoblast differentiation by somatomedins.

Am J physiol, 250 : 771 – 78.

Fong Y , Moldawer L and Marano MA (1989)

Starvation leads to decreased levels of m RNA for myofibrillar proteins.

J Surg Res, 46 : 457 – 61.

Forte WC, Gonzales CC, Carignani S and Mimica I (1999)

Evaluation of polymorphonuclear neutrophils in moderate malnutrition.

Rev Assoc Med Bras , 45 (2) : 147 – 51.

Fottner C , Engelhardt D and weber MM (2001)

Identification, characterization of IGFBP expression and secretion by adult human adrenocortical cells

J Endocrinol , 168 : 465 – 74

Friedland IR (1992)

Bacteremia in severely malnourished children.

Ann Trop pediatr , 12 (4) : 433 – 40 .

Froesch ER, Hussain M , Schmid C and Zapf G (1997)

IGF_s . In : Port D and Sherwin RS (eds.) Ellenberg and Reifkin's Diabetes Mellitus, 5th ed.

Appleton and Lang, Stamford : 95 – 114

Frystyk J (2000)

Role of IGFBP₁ in glucose regulation.

Acta paediatr , 89 : 1025 – 31.

Ganong WF (1995)

The pituitary gland . In : Ganong WF (ed.) Review of medical physiology 7th ed.

Appleton and Lange Co. Norwalk , Connecticut, Los Altos , California : 368 – 78

Gao L, ling N and Shimasaki S (1993)

Structure of the rat IGFBP₄ gene

Biochem Biophys Res Commun, 190 : 1053 – 59

Gao Z , Matsuo H , Wang Y , Nokago S and Maruo T (2001)

Up-regulation by IGF₁ of Proliferating cell nuclear antigen and B cl₂ protein expression in human uterin leiomyoma cells.

J Clin Endocrinol Metab., 86 (11) : 5593 – 99

Garg SK , Marwaha PK, Gampathy V , Sialy R, Thapa BP, Walla BN and Dash RJ (1989)

Serum growth hormone , insulin and blood sugar responses to oral glucose in PEM

Trop J Med , 4 : 9 – 13

Garnero P , Vergnaud P and Delmas PD (1997)

Aminoterminal Propeptide of type 1 Collagen is a more sensitive marker of bone turnover than C-terminal propeptide in osteoporosis

J Bone Miner Res., 12 (1) : 579

Garrow JS (1966)

Classification of PEM

Arch Latin Am Nutr., 16 : 145

Georgieff MK , Sasanow SR and Pereira GR (1987)

Serum transthyretin levels and protein intake as a predictors of weight gain velocity in premature infants

J pediatr. Gastroenterol Nutr., 6 : 775

Gibson RS (1990)

Principles of nutritional assessment.

Oxford University Press . Oxford .

Gillham B , Papachristodoulou DK and Thomas JH (1997)

Will's Biochemical Basis of Medicine 3rd ed.

Bulterworth Heinemann Oxford : 279 – 88

Giudice LC, Farrell EM and Pham H et al (1990)

IGFBP_s in maternal serum throughout gestation and in the puerperium .

J Clin Endocrinol Metab., 71 : 806

Giudice LC , Irwin JC and Duspın BA et al (1994)

IGF_s & IGFBP_s and IGFBP protease in human uterine endometrium . In : Baxter RC , Gluckman PD and Rosenfeld RG (eds.) The IGF_s and Their regulatory proteins.

El sevier , Amesterdam : 351 – 61.

Giudice LC , deZegher F , Gargosky SE , Dsupın BA , de Las Fuentes L , Crystal RA , Hintz RL and Rosenfeld RG (1995)

IGF_s and their binding proteins in the term and preterm human fetus and neonate with normal and extremes of intrauterine growth

J Clin Endocrinol Metab , 80 (5) : 1548 – 55

Gluckman PD (1997)

Endocrine and nutritional regulation of prenatal growth

Acta paediatrica suppl, 423 : 153 – 57

Gofferje H (1978)

Prealbumin and retinol – binding protein = highly sensitive parameters for the nutritional state in respect to protein.

Med Lab ., 5 : 38.

Golden MH (1982)

Protein deficiency , energy deficiency and the edema of malnutrition

Lancet , 5 : 1 (8284) : 1261 – 65

Golden MH (1988)

The effect of malnutrition in the metabolism of children

Trans Roy Soc Trop Med Hyg , 82 : 3 – 6

Golden MH , Ramdath D and Golden BE (1990)

Free radicals and malnutrition , In : Dreosti I and clinton NJ (eds.) Trace elements, micronutrient and free radicals.

Humana Press : 87 – 89.

Gomez F , Garlvan RR , Frenk S and Cravioto JM (1956)

Mortality in second and third degree malnutrition

J Trop pediater , 2 : 77 – 83

Goodman J , Wachenberg BL , Liberman B , Nery M and Germek OA (1994)

IGF_s and their binding proteins .

J Clin Endocrinol Metab., 58 : 561 – 64

Gracey M (1996)

Diarrhea and malnutrition : a challenge to
paediatricians

J pediatr Gastroenterol Nutr., 22 : 6 – 16

Grant DB, Hambley J , Becker D and Pimstone BL (1973)

Reduced sulphation factor in undernourished children

Arch Dis Child, 48 : 596 – 600

**Guerrant RL, Schorling JB, McAuliffe JF and De Souza MA
(1992)**

Diarrhea as a cause and an effect of malnutrition.

Diarrhea prevents catchup growth and malnutrition
increases diarrhea frequency and duration.

Am J Trop Med Hyg , 47 (1) : 28

Guler HP , Zapf J , Schmid C and Froesch ER (1989)

IGF-1 & -11 in healthy man . Estimation of half lives
and production rates .

Acta Endocrinol., 121 : 753 – 58

Gunston GD , Burkinsher D , Malan H and Swe A (1992)

Reversible cerebral shrinkage in Kwo : An MRI study

Arch Dis child , 67 : 1030 – 32

Guyton AC (1996)

The Pituitary hormones and their control by the hypothalamus .In : Guyton HC and Hall JE (eds.) Textbook of Medical physiology 9th ed.
WB Saunders Co. : 936 – 40

Han VK , D’Ercole AJ and Lund PK (1987)

Cellular localization of somatomedin mRNA in the human fetus.
Science , 236 : 193 – 97

Hansen JD and Peltifor JM (1992)

PEM. In : McLaren DS and Burman D (eds.) Textbook of pediatric nutrition
Churchill Livingstone London Edinburgh New York :
118-22

Hansen JD , Buchman N and Peltifor JM (1976)

Nutrition in children. In : McLaren DS and Burman D (eds.) , Textbook of pediatric nutrition
Churchill Livingstone London Edinburgh New York :
250-53

Hassan EM , El-Meneza SA , EL- Rashidy Z , Rashad R , Rabie S and Fahmy SA (1989)

Detection of enteropathogens in diarrheal diseases among malnourished Egyptian infants and children
J Egypt Pub Health Assoc , 64 (5-6) : 461 – 74

Hassenein EA and Tankovsky I (1972)

Disturbances of coagulation mechanism in PEM
Trop and Geog. Med. : 152 – 62

Hayes VY , Urban RJ , Jiang J, Marcell TJ , Helgeston K and Mauras N (2001)

Recombinent human GH and recombinent human IGF.
₁ diminish the catabolic effects of hypogonadism in
man : Metabolic and molecular effects
J Clin Endocrinol Metab., 86 (5) : 2211 – 19

Heber D (2001)

Starvation and nutritional therapy. In : DeGroot LJ and
Jameson JL (eds.) Endocrinology, 4th ed.
WB Saunders Co., Philadelphia London : 642 – 53

Hendricks RG (1984)

The influence of aflatoxins on child heallh in the
tropics with particular reference to Kwo .
Trop Med Hyg , 78 : 427 – 35

Hendrickse RG (1991)

Kwo , the hypothesis that incriminates aflatoxins
Pediatrics , 88 (2) : 376 – 79

Hendrickse KM , Duggan C and Gallagher L (1995)

Malnutrition in hospitalized pediatric patients .
Arch pediater Adolesc Med , 149 : 1118 – 22

Herington AC (1991)

IGFs : Biochemistry and physiology. In : Robertson DM and Herington AC (eds.) Bailliere Clinical endocrinology and metabolism. Growth Factors in endocrinology, 5 (4) : 531

Hernandez M, Argente J , Navarro A, Caballo N, Buriso V and Polanco I (1992)

Growth in malnutrition related to gastrointestinal disease : Coeliac disease.

Horm Res, 38 (suppl 1) : 79 – 84.

Hills FA , English J and Chard T (1996)

Circulating levels of IGF₋₁ and IGFBP₋₁ throughout Pregnancy : Relation to birth weight and maternal weight

J Endocrinol , 148 : 303 – 09

Hintz RL, Suskind R, Amatayakul K, Thanangkul O and Olson R (1978)

Plasma somatomedin and GH Values in children with protein – calorie malnutrition.

J Pediatr, 92 : 153 – 56.

Hoffman L , Bell RC and Dier R (1985)

Effect of protein malnutrition and interleukin –1 on in vitro rabbit lymphocyte mitogenesis .

Nutr Res, 4 : 769 – 80.

Honegger A and Humbel RE (1986)

IGF₋₁ and ₋₁₁ in fetal and adult bovine serum :
purification, primary structures and immunological
cross – reactivities
J Biol chem. , 261 : 569

Househam KC (1991)

Computed tomography of the brain in Kwo : a follow
up study.
Arch Dis child , 66 : 623 – 26

Humbel RE (1990)

IGF₋₁ and ₋₁₁
Eur J Biochem., 190 : 445 – 62

Ingenbleek Y and Young V (1994)

Transthyretin (prealbumin) in health and disease :
Nutritional implications
Ann Rev Nutr., 14 : 495 – 533

**Ingenbleek Y, Van Den Shrieck HG, De Nayer P and De
Visscher M (1975)**

Albumin, transferrin and thyroxin binding prealbumin
/ retinol binding protein complex in assessment of
malnutrition.
Clin Chem Acta, 63 : 61.

Irace G and Edehoch H (1978)

Thyroxin induced conformational changes in
Prealbumin Biochemistry , 17 : 5729 – 33

Isley WL , Underwood LE and Clemmons DR (1983)

Dietary Components that regulate serum
somatomedin–c in humans .
J Clin Invest ., 71 : 175

Isley WL, Underwood LE, Clemmons DR (1984)

Changes in plasma somatomedin – c response to
ingestion of diets with variable proteins and energy
content.
J Parenteral Enteral Nutrition, 8 : 407 – 11.

Iterie N , Yoshino LL and Moses AC et al (1998)

Evidence that receptor aggregation may play a role in
transmembrane signaling through the IGF-1 receptor
Mol Endocrinol , 2 : 831

Jacobsson B , Carlstrom A and Plotz A (1990)

Transthyretin mRNA expression in the pancreas and in
endocrine tumors of the pancreas and gut .
J Clin Endocrinol Metab ., 71 : 875 – 80 .

Jeejeebhoy KN (1988)

The object of nutritional support
J Parenter . Enteral Nutr., 12 : 539 – 49

Jelliffe DB (1966)

Classification of PEM
WHO (monograph series) No. 29
Geneva WHO

Jelliffe D B (1968)

The assessment of the nutritional status of the
community
WHO (monograph series) no. 53
Geneva WHO

Jelliffe DB and Jelliffe EF (1991)

Protein energy malnutrition. In : Strickland GT (ed.)
Hunter's Tropical Medicine, 7th ed.
WB Saunders Co. Philadelphia : 914 – 22.

Jelliffe DB and Jelliffe EF (1992)

Causation of Kwo: Towards a multifactorial consensus
Pediatrics : 90 (1) : 110 – 13

Jensen PB, Rasmussen HB and Pedersen FB (1997)

Serum concentration of the aminopropeptide of type-1 procollagen in patients on haemo and peritoneal dialysis

APMIS, 105 (5) : 371 – 77

John CP and Gareth W (1991)

Genetics of non insulin dependent diabetes mellitus.

In: Textbook of diabetes . vol 1 : 172 – 80

Johnson AM, Rohlfes EM and Silverman LM (1999)

Proteins . In : Burtis CA and Ashwood ER (eds.) Tietz Textbook of clinical chemistry, 3rd ed.

WB Saunders Co. Philadelphia London : 477

Jones JI and Clemmons DR (1995)

IGF_s and their binding proteins : biological actions

Endocrinol Rev., 16 : 3 – 34

Jones JI , D’Ercole AG , Camacho Hubner C and Clemmons DR (1991)

Phosphorylation of IGFBP-1 in cell culture and in vivo

Proc Natl Acad Sci USA , 88 : 7481 – 85

Jones JI , Gockerman A and Busby WH et al (1993)

Extracellular matrix contains IGFBP_s : Potentiation of the effects of IGF₁

J cell Biol , 121 : 679 – 87

Jun LY, Tsushima T and Minel S (1996)

IGF_S and IGFBP_S (IGFBP₋₁ , ₋₂ and ₋₃) in diabetic pregnancy : relationship to macrosomia.

Endocrine J, 43 : 221 – 31.

Kajantie E , Dunkel L, Risteli J , Pohjavuori M and Andersson S (2001)

Markers of type 1 and 111 collagen turnover as indicators of growth velocity in very low birth weight infants.

J Clin Endocrinol Metab. , 86 (9) : 4299-306.

Kandemir N, Yordam N and Oguz H (1997)

Age related differences in serum IGF₋₁ and IGFBP₋₃ levels in congenital hypothyroidism

J Pediatr Endocrinol metab., 10 (4) : 379 – 85

Kaplay SS (1978)

Erythrocyte membrane Na⁺ and K⁺ activated adenosin triphosphatase in PEM

Am J Clin Nutr., 31 : 579

Kasson BG and Hsueh AJ (1987)

IGF₋₁ augments gonadotropin – stimulated androgen biosynthesis by cultured rat testicular Cells.

Mol cell Endocrinol, 52 : 27 – 34

Katz LE, De Leon DD, Zhao H and Jawad AF (2002)

Free and total IGF-1 levels decline during fasting

J Clin Endocrinol Metab, 87 (6) : 2978 – 83

Khalil M, Soliman SI, Hafez M, Mohareb SW, EL-Tahan H, Shaban N and Abdel-Aal A (1977)

Plasma lipoprotein lipase activity in relation to electron microscopic and biochemical changes in the fatty liver of Kwo.

Am J Clin Nutr., 27 : 260

Khar S and Alleyne GA (1973)

The effect of chronic calorie malnutrition on the kidneys .

J Int Med, 3 : 129

Kiefen MC, Masiarz FR and Bauer DM et al (1991)

Identification and molecular cloning of two new 30 kd IGFBP_s isolated from adult human serum

J Biol Chem., 266 : 9043 – 49

Kiju A, Teo B, hardin S and Ong F (1991)

Nutritional status of children in rural Sarawak Malaysia

Southeast Asian J Trop Med. Public Health, 22 (2) : 211 – 15

Kindmark CO and Laurell CB (1972)

Sequential changes of the plasma protein pattern in inoculation hepatitis.

Scand J Clin Lab Invest., 29 (Suppl 124) : 105.

King GL, Goodman AD and Buznay SN (1985)

Receptors and growth promoting effects of insulin and IGF_s on cells from bovine retinal capillary and aorta
J Clin Invest., 75 : 1028 – 36

Klinger B , Jensen LT, Silbergeld A and Laron Z (1996)

IGF₁ raises serum procollagen levels in children and adults with Laron syndrome.
Clin Endocrinol, 45 (4) : 423 – 29.

Konatey FI (1991)

Kwashiorkor
Br Med J, 302 : 180 – 81

Krane SM (1988)

Connective tissue structure and function. In :
Wagngaarden and Smith (eds.) Cecil Textbook of
medicine, 18th ed.
WB Saunders Co. Philadelphia : 1080.

**Kurugol Z, Egemen A , Cetingul N ,Kavakli K , Nisli G
and Oztop S (1997)**

Early determination of nutritional problems in
pediatric cancer patients .
Turkish J Pediatr., 39 (3) : 325 – 34.

Lamson G , Pham H and Oh Y et al (1989)

Exprpsion of the BRL_{-3A} IGFBP (r BP-30) in the rat
central nervous system.

Endocrinology , 123 : 1100-02.

Latham MC (1990)

PEM. It's epidemiology and control.

J Environ Pathol Toxicol , 10 (4 – 5) : 168 – 80.

Latham MC (1991)

The dermatosis of KWO in young children.

Semin. Dermatol , 10 (4) : 2702.

Lee PD, Conover GA and Powell DA (1993)

Regulation and function of IGFBP₋₁

Proc Soc Exp Biol Med., 204 : 4-29.

Lee PD , Giudice LC , Conover CA and Powell DA (1997)

IGFBP₋₁ : recent Findings and new directions.

Proc Soc Exp Biol Med., 216 : 319 – 57.

Lennard-Jones JE (1992)

A Positive approach to nutrition as treatment. In :
Lennard-Jones JE (ed.) King's Fund. Center. London
(Quoted from Reilly J. Forfar and Arneil's Text book
of Pediatrics. Campbell AG and McIntosh N (eds.) 5th
ed. : 1186.

Lifshitz F (1980)

Childhood diarrhea. An overview. In Lifshitz F (ed.)
clinical disorders in pediatric gastroenterology and
nutrition.

Marcel Dekker New York : 267-70.

Lifshitz F and Maggioni A (1995)

Nutritional management of failure to thrive. In : Gaull
GE (ed.) Pediatric nutrition.

Ped. Clin. North Am. Vol 42 (4) : 791 – 810.

Lin A and Santoro D (2002)

PEM. emedicine J / serial online

Available at [http // WWW emedicin. Com / dermatology /
topic 797 htm](http://www.emedicin.com/derm/topic/797.htm) (Full text).

**Liu J , Raine A , Venables PH , Dalais C and Mednick
SA (2003)**

Malnutrition at age 3 years and lower cognitive ability
at age 11 years : independence from psychosocial
adversity.

Arch Pediatr Adolesc Med : 157 (6) : 593 – 600.

Lowe WJ , Adam OM and Werner H et al (1989)

Regulation by fasting of IGF-1 and its receptor :
Effects on gene expression and binding.

J Clin Invest., 84 : 619.

**MacDaugall LG, Moodly G, Eyberg G and Guirk M
(1982)**

Mechanism of anemia in PEM in Johannesburg
Am J Clin Nutr., 35 (2) : 229 – 35

Maes M, Maiter D, Thissen JP, Underwood LE and Ketelslegers JM (1991)

Contribution of GH receptor and post-receptor defects to GH resistance in malnutrition.

Trends Endocrinol Metab, 2 : 92 – 97.

Magoffin DA, Kurtz KM and Erickson GF (1990)

IGF₁ selectively stimulates cholesterol side – chain cleavage expression in ovarian theca interstitial cells.

Mol Endocrinol., 4 : 489 – 96

Mahmoud E, Omran S , Fouad E and Salah Z (1992)

Evaluation of cardiac function in children with Kwo.

JAC, 1 : 32.

Manson PEC and Apter FIC (1982)

“ PCM ” In : Manson’s Tropical Diseases, 18th ed.

Baillier Tindau London : 513 – 19

Marsden PD (1990)

Kwashiorkor

Brit. Med. J, 301 : 1036 – 37

Martin JL and Baxter RC (1986)

IGFBP from human plasma. Purification and characterization

J Biol Chem , 162 : 8754

Martin JL, Willetts KE and Baxter RC (1990)

Purification and properties of a novel IGF₋₁₁ binding protein from transformed human fibroblast.

J Biol Chem, 265 : 4124.

Martina NA, Kim E, Chitkara U, Wathen NC, Chard T and Giudice LC (1997)

Early determination of nutritional problems in pediatric cancer patients.

Turkish J Pediatr. 39 (3) : 325 – 34.

Martinez – Hernandez AG and Miller E (1985)

Ultrastructural localization of type IV collagen in rat Kidney

J Cell Biology, 92 : 343 – 49.

Massague J and Czech MP (1982)

The subunit structures of two distinct receptors for IGF₋₁ and ₋₁₁ and their relationship to the insulin receptor

J Biol chem, 257 : 5036 – 45

Mathews CK and Van Holde KE (1996)

Biochemistry 2nd ed.

The Benjamin / Cummings Publishing Co., New York
Amsterdam : 165

Matta LJ (1978)

The children of santa Maria couque : a prospective field study of health and growth.

Cambridge, MA : MIT Press

Matta LJ (1992)

Diarrheal disease as a cause of malnutrition

Am J Trop Med Hyg, 47 (1) : 16 – 27

Maxwell SA, Apegyei F, de Uries HR, Mwanmut DD and Hendrickse RG (1989)

Aflatoxin in breast milk, neonatal cord blood and sera of pregnant women .

Toxicol Toxin Rev, 8 : 19 – 29

Mayatepeck E, Becker K, Gana L, Hoffman GF and Leichsenring M (1993)

Leukotrienes in pathophysiology of Kwo.

Lancet, 342 : 958 – 60

McGregor SG (1993)

Assessment of the effects of nutrition on mental development and behaviour in Jamaican studies

Am J Clin Nutr, 57 : 3035 – 45

McGregor SG , Powell. CA , Walker SP and Hines JH (1991)

Nutritional Supplementation. Psychological stimulation and mental development of stunted children.

Lancet , 338 : 1-5.

McLaren DS and Read WW (1975)

Weight / Length Classification

Lancet , 2 : 333.

McLaren DS, Pellett PL and Read WW (1967)

A Simple scoring system for classifying the severe forms of PEM in early childhood.

Lancet, : 533 – 35.

Megan S and Veldee MS (1999)

Nutritional assessment, therapy and monitoring. In : Burtis CA and Ashwood ER (eds.) Tietz Textbook of clinical chemistry , 3rd ed.

WB Saunders Co., Philadelphia London : 1359 – 94

Melkko J, Hellevik T, Risteli L, Risteli J and Smedsrod B (1994)

Clearance of the aminoterminal propeptides of type 1 and 111 procollagen is a physiological function of the scavenger receptor in liver endothelial cells .

J Exp Med., 79 : 405 – 12

Merchav S, Tatarsky I and Hochberg Z (1988)

Enhancement of erythropoiesis in vitro by human GH is mediated by IGF₁

Br J Haematol., 70 : 267 – 71

Merimee TJ, Zapf J and Froesch ER (1982)

IGF_s in fed and fasted states

J Clin Endocrinol Metab., 55 : 999

Metcoff J, Frank S, Antonowics I, Gordillo G and Lopez E (1960)

PEM

Pediatrics, 26 : 960

Metzler DE (2001)

The extracellular matrix and cell walls. In : Metzler DE, Metzler CM and Sauke DJ (eds.) Biochemistry: The chemical reactions of living cells, 2nd ed.

Harcourt Academic Press, Orlando : 427 – 44

Michell NP, Dent S, Langman MJ and Eggo MC (1997)

IGFBP_s as mediators of IGF₁ effects on colon cancer cell proliferation

Growth Factors, 14 : 269 – 77

Miyahara M, Njieha RK and Procop DJ (1982)

Formation of collagen fibrils by enzymic cleavage with procollagen proteinases.

J Biol Chem , 257 : 8442.

Mohan S (1993)

IGFBP_s in bone cell regulation

Growth Regulation, 3 : 67 – 70

Monolagas SC (2000)

Birth and death of bone cells

Endocrinol Rev., 21 : 115 – 37

Moy RJ, Smallman S and Booth IW (1990)

Malnutrition in a UK children's hospital

J Human Nutrition and Dietetics, 3 : 93 – 100

Mukherjee A, Bhattachazyya AK, Saiker PK and Mondal AK (1991)

Kwashiorkor – Marasmus syndrome and nutritional rickets. A bone biopsy study.

Trans Roy Soc Trop Med Hyg, 85 : 688 – 89

Nayak KC, Sethi AS, Aggarwal TD, Chadda VS and Fumar KK (1989)

Bactericidal power of neutrophils in PCM.

Indian J pediatr., 56 (3) : 371 – 77.

Numata M, Yamamoto H, Kawaguchi Y, Osaka N, Nakayama M, Kubo H, Shigematsu T and Hosoya T (1999)

A study of association between lean body mass and serum IGF₁ in continuous ambulatory peritoneal dialysis patients.

Japanese J Nephrol., 41 (1) : 8 – 13

Nyomba LG, Berard L and Murphy LG (1997)

Free IGF₁ in healthy subjects: relationship with IGFBP_s and insulin sensitivity

J Clin Endocrinol Metab., 82 (1) : 2177 – 81

O'Brien D and chase HP (1980)

Normal childhood nutrition and its disorders. In : Kampe CH, Silver HK and O'Brien D (eds.) Current Pediatric diagnosis and treatment, 6th ed.

Lange Medical Publication. Los Anglos California: 108

Ogushina SO and Hussain MA (1980)

Plasma thyroxin binding prealbumin as an index of mild PEM in Nigerian children.

American J Clin Nutr, 33 : 794 – 800.

Oh Y, Muller HL, Lamson G and Rosenfeld RG (1993)

IGF- independent action of IGFBP-3 in Hs 578 T human breast cancer cells. Cell surface binding and growth inhibition.

J Biol Chem., 268 : 14964 – 71

Ojofeitimi EO ; Owolabi OO, Aderonmu A, Esimai AO and Olasanmi SO (2003)

A study on under five nutritional status and its determinants in a semirural community of Ile-Ife, Osun State, Nigeria.

Nutr Health; 17 (1) : 21 – 27.

Ooi GT, Orlowski CC and Brown AL et al (1990)

Different tissue distribution and hormonal regulation of m RNA_s encoding rat IGFBP_s .

Mol Endocrinol., 4 : 321 – 28.

Oshima A, Nolan CM and Kyle JW (1988)

The human Cation – independent mannose – 6 – phosphate receptor. Cloning and sequence of the full length cDNA and expression of functional receptor.

J Biol Chem., 263 : 2553 – 62

Osler MH, Fiedler PJ, Levin N and Cronin MJ (1995)

Adaptation of the GH and IGF-1 axis to chronic and severe calorie or protein malnutrition.

J Clin Invest, 95 : 2258 – 65.

Osman GA, El-Mougi M, El-Badrawy F and El-mossalami MA (1978)

An epidemiological study of PEM in rural community in Egypt

J Egypt. Med. Assoc., 61 : 613

Osman GA, Hafez AS, Anwar WA and Mahmoud SA (1995)

Effects of chemical mutagenic agent on chromosomal pattern of Egyptian Kwo Infants

Gastroenterol., 34 : 145 – 49

Owen G and Lippman G (1977)

Nutritional Status of infants and young children .

USA Ped. Clin. North Am., 24 : 211

Owens JA, Kind KL, Carbone F, Robinson JS and Owens PC (1994)

Circulating IGF₁ and ₋₁₁ and substrates in fetal sheep following restriction of placental growth

J Endocrinol., 140 : 5 – 13

Ozkan H, Olgun N , Sasmaz E, Abacioglu H, Okuyan M and Cevik N (1993)

Nutrition, immunity and infections : T lymphocyte subpopulations in PEM.

J Trop Pediatr, 39 (4) : 257 – 60.

Palacio AC, Perez – Bravo F, Santos JL, Schlesinger L and Monckeberg F (2002)

Leptin levels and IGFBP_S in malnourished children : effect of weight gain .

Nutrition, 18 (1) : 17 – 19.

Paromo C, Fluiters E, de la Fuente J, Andrade A and Garcia – Mayor RV (2001)

Monitoring of treatment success in patients with acromegaly: The value of serum IGFBP₃ and serum leptin measurements in comparison to Plasma IGF₁ determination.

Metabolism, 50 (a) : 1117 – 21.

Patrick J (1980)

Nutritional edema

Lancet, 1 : 766 – 69

Penhoat A, Jaillard C and Saez JM (1989)

Synergistic effects of corticotrophin and IGF₁ on corticotrophin responsiveness in cultured bovine cortical cells

Biochem Biophys Res Commun., 165 : 355 – 59

Phillip M , HersHKovitz E , Rosenblum H, Savion I , Segev Y , Levy J and Frazer D (1998)

Serum IGF₁ and IGF₋₁₁ are not affected by undernutrition in children with non organic failure to thrive.

Horm Res, 49 (2) : 76 – 9.

Phillips LS and Unterman TG (1984)

Somatomedin activity in disorders of nutrition and metabolism

J Clin Endocrinol Metab., 13 : 145

Pledger WJ, Hart CA, Locatell KI and Scher CD (1981)

Platelet derived growth factor modulated proteins constitutive synthesis by a transformed cell line.

Proc Natl Acad Sci, USA, 78 : 4358 .

Pollack SV (1979)

Wound healing : A review : Nutrition factors affecting wound healing

J Dermatol surg Oncol., 5 : 615 – 19

Potter J, Klipstein K, Reilly JJ and Roberts MA (1995)

Nutritional status and Clinical course of acute admissions to a geriatric unit.

Age and Aging, 24 : 131-36

Powell DR, Lee PD and De Paolis LA et al (1993)

Dexamethason stimulates expression of IGFBP₁ gene expression in human hepatoma cells .

Growth Regulation, 3 : 11.

Procter RA (1927)

Kenya Med J , 3 : 284 (Quoted from Manson – Bahr PE and Apted FIC (eds.)

Manson's Tropical Diseases.

Puri S and Chandara RK (1985)

Nutritional regulation of host resistance and predictive value of immunologic tests in assessment of outcome.
Ped Clin North Am., 132 (2) : 499

Rabkin R (1997)

Nutrient regulation of IGF₁ (Review)
Mineral & Electrolyte Metab., 23 (3-6) : 157 – 60

Raisz LG, Kream BE and Lorenzo JA (1998)

Metabolic bone diseases. In : Wilson TD, Foster DW, Kronenberg HM and Larsen PR (eds.) Williams Textbook of Endocrinology.
WB Saunders Co. Philadelphia London : 1211 – 39

Reilly J (1998)

Anthropometric nutritional assessment . In : Campbell AG and McIntosh N (eds.) Forfar and Arneil's Textbook of pediatrics. 5th ed.
Churchill Livingstone New York London : 1186

Reiter EO and Rosenfeld RG (1998)

Normal and aberrant growth. In : Wilson JD, Foster DW, Kronenberg HM and Larsen PR (eds.) William's Textbook of Endocrinology, 9th ed.
WB Saunders Co. Philadelphia London : 1427 – 507

Ren M Q, Kuhn G, wegner J, Nurnberg G, Chen J and Ender K (2001)

Feeding daidzein to late pregnant sows influences the oestrogen receptor beta and type₁ IGF factor receptor mRNA expression in newborn Piglets

J Endocrinol., 170 : 129 – 35

Richardson D and Iputs J (1992)

Effects of Kwo malnutrition on measured capillary filtration rate in forearm

Am physiol Soc, 262 : 496 – 502

Risteli J and Risteli L (1997)

Assays of type₁ procollagen domains and collagen fragments

Scand J Clin Lab Invest suppl, 227 : 105 – 13

Risteli J and Risteli L (1999)

Products of bone collagen metabolism. In : Seibel MJ, Robins SP and Bilezikian JP (eds.) Dynamics of Bone and Cartilage Metabolism : Principles and clinical applications Academic Press London : 275 – 87

Risteli J, Elomaa I, Neimi S, Novamo A and Risteli L (1993)

Radioimmunoassay of the pyridinoline crosslinked carboxy terminal telopeptide of type₁ collagen

Clin Chem, 39 : 635 – 40

Roberts TI (1993)

Studies of human and murine giardiasis
Clin Inf Dis, 16 (2) : 98 – 104

Robinson P (1998)

Biochemical nutritional assessment. In: Campbell AG
and McIntoch N (eds.) Forfar and Arneil's Textbook
of Pediatrics. 5th ed.
Churchill Livingstone New York London: 1187

Robinson J, Cheng SY and Gershengorn E et al (1978)

Thyroxin transport proteins of plasma, molecular
properties and biosynthesis
Rec prog Horm Res., 34 : 477

Rogers SA and Hammerman MR (1988)

IGF₋₁₁ stimulates production of inositol triphosphate in
proximal tubular basolateral membranes from canine
Kidney
Proc Natl Acad Sci, USA, 85 : 4037

Rohan RM, Ricciarcelli E and Keifer MC (1993)

Rat ovarian IGFBP₋₆ , a hormonally regulated theca –
interstitial – selective spcciec with limited
antigonadotropic activity .
Endocrinology, 132 : 2507 – 12.

Romer H, Urbach R and Gomez MA (1983)

Moderate and severe PEM in childhood: effects on jejunal mucosal morphology and disaccharidase activities

J ped. Gastroenterol., 2 : 459 – 64

Rosenfeld RG, Conover CA, Hodges D, Lee PD, Misra P, Hintz RL and Li CH (1987)

Heterogeneity of IGF₋₁ affinity for the IGF₋₁₁ receptor. Comparison of natural, synthetic and recombinent DNA – derived IGF₋₁

Biochem Biophys Res Commun., 143 : 199 – 205

Rosenfeld RG, Pham H and Oh Y et al (1990)

Identification of IGFBP₋₂ and a low molecular weight IGFBP in human seminal Plasma

J Clin Endocrinol Metab., 70 : 551 – 53

Roskoski R (1996)

Biochemistry

WB Saunders Co, Philadelphia London : 475

Rothstein H, VanWyk JJ and Hayden JH (1980)

Somatomedin – c restoration of in vivo cycle traverse in GO/G₁ blocked cells of hypophysectomized animals,

Science, 208 : 410 – 12

Rudman DG, Kutner MH and Rogers CM (1981)

Impaired GH secretion in the adult population :
Relation to age and adiposity
J Clin Invest, 67 : 1361

Russel DM, Walker PM and Leiter LA (1984)

Metabolic and structural changes in skeletal muscle
during hypocaloric dieting.
Am J Clin Nutr, 39 : 503.

**Saarto T, Blomqvist C, Risteli J, Risteli L, Sarna S and
Elomaa I (1998)**

Aminoterminal propeptide of type₁ procollagen
correlates to bone loss and predicts the efficacy of
antiresorptive therapy in pre and post - menopausal
non metastatic breast cancer patients.
Br J Cancer, 78 (2) : 240 – 45

Salmon WD and Daughaday WH (1957)

A hormonally controlled serum factor which
stimulates sulphate incorporation by cartilage in vitro
J Lab Clin Med., 49 : 825

Sara VR and Hall K (1990)

IGF_s and their binding proteins
Physiology Rev., 70 : 591 – 614

Schreiber G, Aldred AR and Jaworowski A (1990)

Thyroxin transport from blood to brain via transthyretin synthesis in choroids Plexus

Am J physiol., 258 : 338 – 45

Seibold – weiger K, Wollmann HA, Ranke MB and Speer CP (2000)

Plasma concentrations of the carboxy terminal propeptide of type-1 procollagen in preterm neonates from birth to term

Pediatr Res., 48 : 104 – 08

Shamir R and Wilschanski M (1998)

Malnutrition. In : Altschuler SM and Liacouras CA (eds.) Clinical pediatric gastroentology

Churchill Livingstone philadephia London : 81-87

Shimasaki S, Shimonaka J and Zhang H P et al (1991)

Indentification of five different IGFBP_s from adult rat serum and molecular cloning of a novel IGFBP_{.5} in rat and human

J Biol Chem, 266 : 10646 – 53

Shinobe M, Sanaka T, Nihei H and Sugino N (1997)

IGF₋₁ / IGFBP₋₁ as an index of discrimination between. Nephron. 77 (1) : 29 – 36.

Shukry AS and Kamel LM (1974)

Classification of PEM according to length

Egypt gaz pediater Assoc, 22 (1) : 35

Silverman ML and Christenson RH (1994)

Amino acids and proteins. In : Burtic AC, Ashwood ER (eds.) Tietz Textbook of Clinical Chemistry. Philadelphia : 700.

Sirotkin AV, Makarevich AV, Kwon HB, Kotwica J and Bulla J (2001)

Do GH, IGF-1 and oxytocin interact by regulating the secretory activity of porcine ovarian cells?
J Endocrinol., 171 : 475 – 80

Smedsrod B, Melkko J, Rosteli L and Risteli J (1990)

Circulating carboxyterminal propeptide of type₁ procollagen is cleared mainly via the mannose receptor in liver endothelial cells
Biochem J., 271 : 345 – 50

Smith CP., Dunger DB and Williams AJ (1989)

Relationship between insulin, IGF₁ and dehydroepiandrosterone sulfate concentrations during childhood, puberty and adult life
J Clin Endocrinol Metab., 68 : 932

Smith FR, Goodman DS and Zaklama MS (1973)

Serum vitamin A, retinol – binding protein, and prealbumin concentrations in protein – calorie malnutrition
Am J Clin Nutr., 26 : 973

Smith WJ, Underwood LE and Clemmons DR (1995)

Effects of caloric or protein restriction on IGF-1 and IGFBP₅ in children and adults.

J Clin Endocrinol Metab, 80 : 443 – 49.

Soliman AT , Hassan AEHI, Aref MK, Hintz RL, Rosenfeld RG and Rogol AD (1986)

Serum IGF-1 and –11 Concentrations and GH and insulin responses to arginin infusion in children with PEM befor and after nutritional rehabilitation

Pediatr Res, 20 : 1122 – 30.

Sonksen PH (2001)

Insulin, GH and sport.

J Endocrinol., 170 : 13 – 25

Soriano JR (1991)

Electrolyte metabolism in PEM. In : 19th Nestle Nutrition workshop. The malnourished child : 21

Spiekerman AM (2000)

Vitamins and Nutritional assessment. In: Bishop ML, Duben – Engelkirk JL and Fody EP (eds.) Clinical chemistry : Principles, Procedures, Correlations, 4th ed. Lippincot Williams & Wilkins Philadelphia London 540-71

Spiekerman AM, Rudolph RA and Bernstein LH (1993)

Determination of malnutrition in hospitalized patients with the use of a group – based reference.

Arch Pathol Lab Med., 117 : 148.

Srikantia SG (1982)

An outbreak of aflatoxicosis in man. In: Jelliffe EF and Jelliffe DB (eds.) Adverse effects of food. Plenum Press New York.

Srikantia SG and Mohanrams S (1970)

Antidiuretic hormone values in plasma and urine of malnourished children
J Clin Endocrinol., 31 : 312 – 14

Stockigt JR (2001)

Transport protein variants. In: DeGroot LJ and Jameson JL (eds.) Endocrinology, 4th ed.
WB Saunders Co. Philadelphia London : 1603 – 08

Storiko K (1968)

Normal values for 23 different human plasma proteins determined by single radial immunodiffusion.
BLUT, 16 : 200 .

Styne DM (1994)

Growth. In: Greenspan FS and Baxter JD (eds.) Basic and Clinical Endocrinology, 4th ed.
Appleton and Lange Northwalk, Connecticut, San Mateo, California : 128 – 59

Styne DM (1997)

Growth. In : Greenspan FS and Stewler GJ (eds.) Basic and clinical Endocrinology, 5th ed.
Prentice – Hall Intern. Inc. London : 152

Sullivan PB, Marsh MN, Mirakian R, Hill SM, Millar PJ and Neale G (1991)

Chronic diarrhea and malnutrition. Histology of the small intestinal lesion

J pediatr Gastroenterol Nutr., 12 : 195 – 203

Suwanickul A, Allender SV, Morris SL and Powell DR (1994)

Corticosteroids and insulin regulates expression of the human gene for IGFBP₁ through proximal promotor elements.

J Biol Chem., 269 : 30835 – 41.

Tahtela R and Tholix E (1996)

Serum concentration of type₁ collagen carboxy terminal telopeptide (ICTP) and type₁ procollagen carboxy – and amino terminal propeptides (PICP, PINP) as markers of metastatic bone disease in breast cancer

Anticancer Res., 16 (4B) : 2289 – 93

Tahtela R, Turpeinen M, Sorva R and Koronen SL (1997)

The aminoterminal propeptide of type₁ procollagen : evaluation of commercial radioimmunoassay Kit and values in healthy subjects

Clin Biochem., 30 (1) : 35 – 40

Talboom JM, Maruping AP, Kabir H, Malatseli P and Anderson J (1986)

Severe PEM, death and survival in hospital, clinical finding

Trop Geogr Med., 38 : 351 – 58

Tannenbaum GS, Guyda HJ and Posner BI (1983)

IGF_s : a role in GH negative feedback and body weight regulation via brain.

Science, 220 : 77 – 79

Teale JD and Macks V (1986)

The measurement of IGF₋₁ : Clinical applications and significance

Ann Clin Biochem, 23 : 413 – 24

Thangkul O, Damrongsak D, vilhayasai V, and Olson ER (1980)

Clinical aspects of protein deficiency with special reference to PCM in children

J Nutr Sci., 26 : 189 – 208

Thissen JP, Ketelslegers JM and Underwood LE (1994)

Nutritional regulation of the IGF_s .

Endocrinal Rev., 15 : 80 – 101.

Thissen JP, Triest S, Underwood LE, Maes M and Ketelslegers JM (1990)

Divergent response of serum IGF-1 and liver GH receptors to exogenous GH in protein restricted rats.

Endocrinology, 126 : 908 – 13.

Thomas T, Power P, Schrieber G and Dziadex M (1988)

The expression of transthyretin mRNA in the developing rat brain

Dev Biol., 128 : 415 – 27

Torun B and Chew F (1994)

PEM. In: Shils ME, Olson JA and Shike M (eds.).
Modern nutrition in health and disease, 8th ed.
LEA and Febringer Philadelphia : 950 – 76

Torun B and Viteri FE (1988)

PEM. In: Shils ME and Young VR (eds.) Modern
nutrition in health and disease, 7th ed.
LEA and Febringer Philadelphia : 746

Triapegui JO, Cardose MA and Callegare MG (1990)

Somatomedin, growth and nutritional status
Gastroenterol, 27 (2) : 95 – 102.

Tricoli JV, Rall LB, Scott J, Bell GI and Shows TS (1984)

Localization of IGF gene to human chromosome 11
and 12
Nature, 310 : 784 – 86

Udani PM (1992)

Brain changes imaging in PEM
Indian J pediatr., 59 : 165 – 86

Underwood LE and VanWyk JJ (1992)

Normal and aberrant growth. In: Wilson JD and Foster DW (eds.) Williams Textbook of Endocrinology, 8th ed.

WB Saunders Co Philadelphia London : 1096 – 110

Underwood LE, Thissen JP, Lemozy S and Clemmons DR (1994)

Hormonal and nutritional regulation of IGF₋₁ and its binding protein

Horm Res., 42 : 145

Underwood LE, Thissen JP, Moats BM, Bruton E, Maes M and Ketelslegers JM (1991)

Nutritional regulation of IGF₋₁ and postnatal growth.

In : Spencer EM Elsevier, New York : 37.

United Nations Administrative Committee on Coordination, Subcommittee on Nutrition (UNACC / SCN) (1987)

First report on the world nutrition situation

Geneva : ACC / SCN, WHO

Usala AL, Madigan T, Buerguera B, Sinha MK, Caro JF and Cunningham P (1992)

Treatment of insulin resistant diabetic Ketoacidosis with IGF₋₁ in an adolescent with insulin dependent diabetes mellitus

N Engl J Med., 327 : 853 – 57

Uterman TG, Vazquez RM and Slas AJ (1985)

Nutrition and somatomedin. Usefulness of somatomedin – c in nutritional assessment
Am J Med., 78 : 228 – 34

Vaccarello MA , Diamond FB and Guevara AJ (1993)

Hormonal and metabolic effects and pharmacokinetics of recombinant human IGF₁ in GH receptor deficiency
J Clin Endocrinol Metab., 77 : 273 – 80

VanWyk JJ (1984)

The somatomedins ; Biological actions and physiologic control mechanisms. In: Li CH (ed.) Hormonal Proteins and peptides
Academic Press New York : 81 – 125

VanWyk JJ and Pledger WJ (1984)

Inhibition of the mitogenic effects of plasma by a monoclonal antibody to somatomedin – c
Proc Natl Acad Sci, USA, 81 : 2389 – 92

VanWyk JJ, Underwod LE and Hintz RL et al (1975)

Exploration of the insulin – like effects and growth promoting properties of somatomedin by membrane

receptor assays. In : Luft R and Hall K (eds.)
Advances in metabolic disorders
Academic Press New York : 127 – 50

Veldee SM (1994)

Nutrition. In : Tietz Textbook of Clinical Chemistry.
Burtis AC and Ashwood ER (eds.) Philadelphia : 1261
– 62.

Veldee MS (1999)

Nutritional assessment, therapy and monitoring. In:
Burtis CA and Ashwood ER (eds.) Tietz Textbook of
clinical chemistry, 3rd ed.
WB Saunders Co. Philadelphia London : 1359

Vis HL (1985)

On the treatment of certain forms of PEM in childhood
with respect to fatal complications
Ann Nestle., 43 : 19 – 23

Viteri FE (1991)

PEM. In: pediatric gastrointestinal diseases
BC Decker Inc. Philadelphia Toronto : 1596 – 610

Viteri F E, Flores JM, Alvarado J and Behar M (1973)

Intestinal malabsorption in malnourished children
befor and during recovery
Am J Dig Dis., 18 : 201 – 11

Walter SJ and Share AC (1988)

Effect of potassium depletion on renal tubular function
in the rat

Clin Sci, 75 : 621 – 28

Wan Nazaimoon WM, Osman A and Khalid BA (1996)

Effects of iodine deficiency on IGF₁, IGFBP₃ levels
and height attainment in malnourished children.

Clin. Endocrinol, 45 (1) : 79 – 83.

**Wan Nazaimoon WM, Rahmah R, Osman A, Khalid
BAK and Livesey J (1997)**

Effects of childhood malnutrition on IGF-1 and
IGFBP-3 levels : a Malaysian and New Zealand
analysis.

Asia pacific J Clin Nutr., 6 (4) : 273 – 76.

Waston JD and Dako DY (1977)

Anthropometric studies on african athletes who
participate in the 1st African University Games.

Brit J Nutr., 38 : 353 – 60.

Waterlow JC (1972)

Classification and definition of PEM

Br Med J, III : 566 – 71

Waterlow JC (1984)

Kwo, the pathogenesis of edema in Kwo and its
significance.

Trans Roy sco Trop Med Hyg., 71 : 436 – 41

Waterlow JC (1988)

Observations on the natural history of stunting. In :
Waterlow JC (ed.) : Linear growth retardation in less
developed countries.

Nestle Nutrition Workshop Series . Vol 14 , Raven
Press New York : 1 – 6.

Waterlow JC (1992)

Protein energy malnutrition

Asia pacific J Clin Nutr, 1 : 253 – 54

Waterlow JC (1994)

Childhood malnutrition in developing nations :
looking back and looking forward.

Ann Rev Nutr, 14 : 1 – 19

**Waterlow JC, Buzina R, Keller W, Lane JM, Nichman
MZ and Tanner JM (1977)**

The presentation and use of height and weight data for
comparing the nutritional status of groups of children
under the age of 10 years.

Bull WHO, 55 : 489 – 98.

Weaver LT (1994)

Feeding the weanling in the developing world :
problems and solutions .

International J. Food Sci Nutr., 45 : 127 – 34

Weaver L T (1998)

Clinical nutritional assessment. In: Campbell AG and McIntosh N (eds.) Forfar and Arneil's Textbook of pediatrics, 5th ed.

Churchill Livingstone New York London : 1188

Weaver LT, Dibba B, Sonko B, Bohane TD and Hoare S (1995)

Measurement of starch digestion of naturally ¹³C enriched foods before and after partial digestion with amylase rich flour using a ¹³C breath test.

Br J Nutr., 74: 531 – 37

Weisstaub SG and Araya M (2003)

Nutritional recovery , an unresolved challenge.

Rev Med Chil ; 13 (2) : 213 – 19.

Wellcome Trust Working Party (1970)

Classification of infantile malnutrition. Committee on nutrition

Lancet ii, 2 : 302 – 03

Westwood M, Gibson JM, Williams AC, Clayton PE, Hamberg O and Flyvbjerg A (1995)

Hormonal regulation of circulating IGFBP₁ phosphorylation status

J Clin Endocrinol Metab, 80 : 3520 – 27

Wharton BA (1991)

PEM: Problems and priorities.

Acta Paediatr Scand (suppl), 349: 5 – 14.

Wharton BA and Weaver LT (1998)

PEM. In: Campbell AG and McIntosh N (eds.) Forfar and Arneil's Textbook of pediatrics, 5th ed.

Churchill Livingstone New York London : 1191 – 94

Wickramasinghe SN, Gotes MP, Gill RG, Adenike GT and Akinyanju OO (1985)

Serum immune reactive erythropoietin and erythropoiesis in PEM

Br J Haematol., 60 : 515 – 24

Williams CD (1933)

A nutritional disease of childhood associated with a maize diet

Arch Dis child., 8 : 423 – 33

Williams GT, Smith CA, Sponser E, Dexter TM and Taylor DR (1990)

Haemopoietic colony stimulating factors promote cell survival by suppressing apoptosis

Nature, 343 : 76 – 79

World Health Organization (WHO) (1973)

Food and nutrition terminology

Terminology circular, no 27

World Health organization (WHO) (1983)

Measuring change in nutritional status
WHO. Geneva

World Health organization (WHO) (2000)

Dept of nutrition for health and development : a global
agenda for combating malnutrition.
Geneva WHO.

**Zamboni G, Duffillot D, Antoniazzi F, Valentini R,
Gendrel D and Tato L (1996)**

GH binding protein and IGFbps in PEM, before and
after nutritional rehabilitation
pediatr. Res., 39 (3) : 410 – 14.

**Zapf J, Hauri C, Futo E, Hussain M, Rutishauser J,
Maack CA and Froesch ER (1995)**

Intravenously injected IGF₁ / IGFbp₃ complex exerts
insulin like effects in hypophysectomized, but not in
normal rats
J Clin Invest., 95 : 179 – 86

**Zapf J, Schmid C, Guler HP, Waldvogel M, Hauri C and
Futo E (1990)**

Regulation of binding proteins for IGF_s in human :
Increased expression of IGFbp₂ during IGF₁
treatment of healthy adults and in patients with
extrapancreatic tumors
J Clin Invest, 86 : 952 – 61

Zetterstrom R (1991)

Salt and Fluid haemostasis in PEM

Acta pediatr Scand (suppl), 374 : 45 – 50