# Metabolic Changes in Protein Malnutrition

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ONE OF THE MAJOR CONCERNS in the world today is the adequacy of food supply in relation to population growth. The prevalance of protein malnutrition and its serious consequences are well recognised today in many of the developing countries. For man, the most important changes are those due to insufficient intake of protein or intake of protein of poor quality. Among the more general signs of protein malnutrition in human beings are poor growth, lack of resistance to infection and a high mortality rate.

Individuals who have a marginal nutrient intake may have a low level of vitality and health and these may eventually result in subclinical nutritional deficiency symptoms. Often, the severe deficiency state will become obvious only when they have prevailed for a long period of time. It is important to identify these conditions in the early stages before the tissue changes have advanced to a point where they cause irreversible damage.

One of the objectives in studying the metabolic changes in protein malnutrition is to be able to detect the existence and also to measure the extent of protein deficiency. Persons who have subsisted on insufficient intakes of protein undergo progressive biochemical changes which precede the clinical manifestations of malnutrition. The present paper will consider some changes which may be detected in vivo and which can serve as methods for evaluating protein nutrition in population groups.

The sequence of biochemical changes expected to occur in the organism when it is subjected to conditions of protein lack or protein restriction are (a) reduction in the metabolic expenditure of body proteins which can be considered as a process of metabolic adaptation; (b) decrease in the so-called protein reserves with some tissues suffering more than others; and (c) decrease in protein moieties with key metabolic functions such as enzymes, resulting in highly abnormal biochemical and physiological function.

Biochemical methods may be employed to test three aspects of protein nutrition:-

1) The relative adequacy of dietary intake
2) Metabolic changes due to tissue malnutrition
3) Depletion of body stores of protein

The biochemical methods used for the above purposes involve quantitative determination of nutrients or related metabolites in such tissues as blood and urine. The interpretation of results requires a knowledge of the metabolism of amino acids and protein, including their storage in the body, the possibility of synthesis and the mode of excretion.

The primary function of proteins in diets is to supply amino acids. The quality of a protein depends upon its amini acid composition. In adult animals only amino acids are absorbed, there being no appreciable transfer of proteins across the intestinal wall. There is intimate mixing of nitrogen derived from the food with that derived from the catabolism of tissue proteins and the plasma amino acid pattern represents

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the resultant of the two processes. Calorie intake has a substantial influence on protein utilisation, in that calorie restriction results in substantial increase in nitrogen excretion due to utilisation of tissue proteins for energy. Conversely, addition of carbohydrates or fat to calorically inadequate diets produces increased nitrogen retention.

**Adaptive enzyme changes**

It is known that in man as well as in the rat, the level of protein intake influences the activity of some enzymes concerned with amino acid metabolism. These changes may reasonably be regarded as adaptive and part of a compensating mechanism, since their effect must be to economise on amino acids when supplies are short.

In rats on a low protein diet, there is an increase in the activity of the amino acid activating enzymes and a decrease in the activity of the urea cycle enzymes in the liver. The effect of these two changes in rats would presumably be that, on a low protein diet, an amino acid entering the liver would have a greater chance of being incorporated into protein and a smaller chance of being degraded to urea than in those on a normal protein intake. Thus the organism adjusts to a low protein intake not by a reduction of overall nitrogen turnover, but by an alteration or diversion of metablic pathways such that a smaller proportion of the available nitrogen is excreted and a larger proportion is used for protein synthesis.

We must visualise that a large proportion of the amino acids liberated by catabolism may be resynthesized to proteins in the same cell, without ever entering the blood stream. In the ideal state, there would be complete re-utilisation with no loss or wastage at all.

**Reduction in metabolic expenditure of nitrogen**

The output of nitrogenous substances in the urine has long been know to vary with the nitrogen intake. Nitrogen excretion in urine is high when protein intake has been high and vice versa. In normal subjects, urea may account for 80 – 90% of the total urinary nitrogen. Changes in urea excretion account for the observed changes in urinary excretion of nitrogen, since other urinary nitrogen constituents remain stable for all practical purposes under these conditions. The excretion of endogenous urea fluctuates with the size of the nitrogen metabolic pool, so that in general urea excretion is high when the reserves are maximum and low whn they are depleted. When individuals live on chronically sub-optimal intakes of protein, their metabolic expenditure of body proteins is reduced.

In malnourished subjects, total urinary nitrogen is low and the amount of urea nitrogen both absolute and relative is reduced. A low proportion of urea nitrogen might be regarded as evidence of protein depletion. Changes in the ratio of urinary urea to total nitrogen or creatinine essentially reflect variations in urea excretion, since the relative amounts of other urinary nitrogenous compounds are not altered significantly in malnutrition. Platt (1954) measured the urinary excretion of urea of children and lactating women of different nutritional and socio-economic conditions and found the ratio of urea nitrogen to total nitrogen to be markedly lower in the groups with poorer nutrition.

With spot samples of urine, the total nitrogen or urea nitrogen may be related to creatinine. The urea nitrogen/creatinine nitrogen ratio is an approximate index of dietary protein related to muscle protein stores. An index of 30 or lower in a random sample is indicative of malnutrition. Arroyave (1965) found the urea/creatinine ratio to be from 8 – 9 in preschool children of low socio-economic status and around 15 in children of the same age group belonging to the upper socio-economic group.

**Serum Albumin**

One of the immediate consequences of a reduced protein intake is a decrease in protein turnover. When protein intake is altered, changes in the fractional and absolute rates of albumin catabolism may occur without corresponding changes in serum albumin concentration. In malnourished infants, the fractional catabolic rate of plasma albumin is decreased. The synthetic rate is closely dependent on the protein intake. When the protein intake is reduced, there is an immediate fall in the rate of albumin synthesis, followed after a lag period of several days, by a fall in the rate of catabolism. There is also a transfer of albumin from the extravascular to the intravascular pool. These are mechanisms which tend to preserve the constancy of intravascular mass when the synthetic rate is reduced by a low protein diet.

The simple measurement of serum or plasma total protein concentrations will not reveal early stages of protein deficiency. Serum albumin is synthesised at the expense of other tissue proteins. When the deficiency is severe, there is detectable drop in total protein concentration. It appears that although a distinct fall in albumin concentration occurs only when the clinical picture ensues, some less evident decreases occur earlier. A fall in albumin concentration might be regarded as a sign of incipient exhaustion of protein reserves. It is to be appreciated that the possibility of plasma volume changes makes the interpreta-

tion of plasma protein concentration a difficult question.

In addition to albumin, other plasma protein fractions may also be reduced in malnutrition. Lack of transport protein in the plasma causes a marked depression in levels of plasma vitamin A. The concentration of growth hormone has been shown to respond rapidly to changes in dietary protein intake. Growth hormone produces a fall in the catabolic rate of albumin. Children recovering from malnutrition show decreasing levels of growth hormone 1 – 2 weeks after refeeding.

**Muscle proteins and Creatinine**

The body's ability to synthesise serum albumin is affected relatively late and the primary effect of protein lack is depletion of muscle tissue. When the amino aicd supply of the diet is inadequate, the body utilises proteins of some tissues to maintain the amino acid pool at a minimum, but yet compatible with the synthesis of other proteins of key metabolic importance.

Skeletal muscle proteins are a significant endogenous source of essential nitrogen under conditions of dietary protein restriction. Skeletal muscle forms only about 25% of the body weight in infants against 45% in adults. Muscle forms the largest protein reservoir of the body (20% protein). This reservoir is rather easily depleted and other tissues are spared at its expense. Although the overall calculated turnover rate of muscle proteins is slow, muscle is composed of many kinds of protein, covering a whole range of metabolic activities, some of which undoubtedly have a faster turnover than others. It is known that glucocorticoids exert a catabolic effect on the muscle and an anabolic effect on the viscera. This would make muscle a source of amino acids for enriching the amino acid pool and promoting protein synthesis in organs such as the liver (Waterlow, 1969).

Decreased muscle mass is a characteristic of children suffering from long-term protein malnutrition. Biochemically, restricted protein intake is reflected by a low urinary excretion of creatinine per unit of time. The muscle mass can be estimated by measuring the urinary excretion of creatinine. Estimation of the decrease in muscle mass is necessary for evaluating loss of reserve body proteins as maintenance of skeletal muscle mass is compatible only with adequate protein intake. Standard, Wills and Waterlow (1959) showed a statistical correlation between changes in creatinine excretion and muscle mass as estimated from skinfold thickness and limb circumference. Creatinine excretion is roughly proportional to body muscle mass in man and the daily excretion varies almost linealy with the body weight.

Borsook and Dubnoff (1947) demonstrated that 98% of the body creatine, the precursor of body creatinine, is in muscle. The rate of creatinine excretion must depend upon the amount or concentration of creatine in muscle and the rate at which it is irreversibly converted to creatinine. Creatinine for practical purposes is not affected directly by variations in protein intake.

The measurement of creatinine output is, in fact, of great value in the assessment of protein nutrition. It gives information about one of the most important reservoirs of protein in the body. According to Clark et al (1951), the creatinine coefficient (mg. creatinine/24 hrs/Kg body weight) is 22 (range 14.2 – 32.0) from birth to 24 months of age and 25 (range 16.3 – 36.2) in subjects aged between 2 years and 18 years. Arroyave and Wilson (1961) proposed that to relate creatinine excretion to body length, rather than weight provides a more sensitive index of the loss of muscle mass as the former index is unaffected by adipose tissue.

**Plasma amino acid pattern**

Children maintained experimentally for even a few days on a nitrogen free diet, show alternations in concentration of plasma-free amino acids – particularly valine, leucine, isoleucine and cysteine, this change being accompanied by an increase of some of the non-essential amino acids. There is good correlation between plasma amino acid levels and proportionate weight dificits, if this is not more than 30%. As body protein deficits are made good, fasting amino acid nitrogen increases.

In protein malnutrition, there is usually a fall in total amino nitrogen and most of the essential amino acids, particularly the branched chain amino acids. However, phenylalanine and lysine are much less affected. There is also a fall in some of the non-essential amino acids, particularly tyrosine. The concentration of most of the non-essential amino acids, notably glycine, alanine, proline, histidine, serine and aspartic acid, are well maintained or even increased.

In laboratory practice, a one dimensional chromatography is done on a fasting sample of serum, and it is usual to express the plasma amino acid pattern as a ratio of the non-essential to the essential amino acids. (Whitehead's ratio).

$$\text{Whitehead's ratio} = \frac{\text{glycine, serine, glutamic acid, taurine}}{\text{leucine, isoleucine, valine, methionine}}$$

According to Whitehead (1964) the ratio in healthy

children is less than 2. The ratio is increased in protein malnutrition and is high in kwashiorkor.

**Mechanism of changes**

Levels of non-essential amino acids are maintained simply because their carbon skeletons can be manufactured in the body. They compete with the dwindling amounts of essential amino acids for nitrogen made available by transamination. The concentration of lysine is maintained because it is not involved in transamination. The altered pattern of amino acids in plasma may lead to a distortion of the intracellular amino acid pattern and this, in turn, may affect the rate of protein synthesis.

**Enzymes in protein malnutrition**

The lack of amino acids is expected to interfere also with enzyme synthesis as a primary factor. Definite and consistent decreases in some enzymes have been found in severe protein malnutrition and alterations in amino acid metabolism have been demonstrated in kwashiorkor. They are probably due both to widespread metabolic changes, possibly caused by enzyme defects and to immediate inadequacy of dietary protein.

**Hydroxyproline excretion**

The results obtained by Widdowson and Whitehead (1966) in rats undergoing protein depletion suggested that significant rises in amino acid ratio did not occur as early as changes in hydroxyproline excretion.

Hydroxyproline peptides are excreted in the urine as a by-product of collagen metabolism. The amount of hydroxyproline excreted is closely related to the rate of growth. During growth, there is not only an increase in the amount of collagen, but also, as in bone, a continuous remodelling, so that catabolism of collagen accompanies synthesis. The measure of hydroxyproline excretion is a measure of the turnover rate of collagen. Increased excretion of hydroxyproline during growth results from the presence of increased amounts of metabolically active soluble collagen in tissues. Determination of hydroxyproline excretion is particularly valuable, since it is a dynamic measurement, which gives information about rates rather than absolute amounts and it is an estimate of growth rate.

Picou, Alleyne and Seakins (1965) showed that hydroxyproline excretion was generally reduced in undernourished children. Malnourished children excreted 14.6 mg/24 hours and normal children 32.7 mg/24 hours. This may be a useful index of growth failure, before there are significant changes in body weight. In the absence of growth, there is a reduction in the size of the soluble collagen pool. In malnutrition, the amount of collagen in the body is relatively increased and that of the cellular protein decreased. Collagen is stable in some tissues than in others and it does not share in the general depletion of body proteins.

Whitehead (1965) related the amount of hydroxyproline to that of creatinine in random specimens of urine. In normal children, the rate of hydroxyproline excretion decreases with increasing age, as the rate of growth falls off, while that of creatinine increases. Whitehead found that the reduction in the hydroxyproline index in malnourished children was statistically related to the weight deficit. He showed that the measurement of total urinary hydroxyproline was of value in assessing the nutritional status of communities of children. Those living on diets deficient in either protein or in the total calories excreted subnormal amounts of hydroxyproline.

$$\text{Hydroxyproline Index} = \frac{\text{mM hydroxyproline}}{\text{mM Creatinine/1/kg body wt}}$$

The index for normal children is between 2.0 and 5.0 (mean 3). Clinically malnourished children have indices between 0.5 – 1.5 (mean 1) and in marginally undernourished children, the index ranges between 1.0 and 2.0 (mean 1.5). Abnormal values are found in children deficient in both protein and total calories.

It is evident from the above that an understanding of the metabolic changes in protein malnutrition can contribute significantly to the assessment of nutritional status during the early stages of protein deficiency.

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