

Impact of disease on markers of macronutrient status

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In trying to define the scope of the present review, definition of some of the terms will be helpful.

First, what is a marker? The relevant definition from the Chambers English Dictionary is that a marker is 'something which indicates or records a position'. From this it follows that a marker should be such that a clear record of the position can be made (e.g. in a patient's case notes), so that any change in that position can also be recorded.

What is nutritional status? One satisfactory definition is that nutritional status is the state or condition of the body produced by the process by which the organism obtains and utilizes the nutrients in food. It results from the balance between the supply and assimilation of nutrients on the one hand, and the expenditure by the organism on the other (modified from McLaren & Meguid, 1988). The important feature here is that the nutritional status is the net result of intake and output and, although it is often desirable to have a more detailed breakdown of this, it is not necessary to have further information regarding the intake and output individually.

When trying to evaluate different markers of nutritional status and, hence, define which markers should be used in a particular situation, the next question is what use will be made of the results of the nutritional assessment. For example, results may be used:

- (1) to indicate adequacy of long-term nutrition;
- (2) to indicate adequacy of recent nutrition;
- (3) to indicate the need for nutritional supplements;
- (4) if repeated, to indicate efficacy of nutritional intervention;
- (5) to indicate prognosis.

For each of these possible uses, the value of a particular marker will depend on the clinical or research setting for the measurement; for example:

will it be used to study a group of patients or an individual?

is it for use in the community or in hospital?

is it for use in research or for treatment?

is there a need to understand the mechanism of any abnormality, e.g. reduced intake and/or absorption and/or utilization and/or increased expenditure?

is this understanding only of academic interest, or would it be helpful in planning nutritional intervention?

how available is it for routine use in terms of ease of analysis, turn-around time, or cost?

Having defined these purposes to which the marker will be put, it then becomes possible to review each marker in terms of the four features normally used to assess the value of a particular laboratory indicator; these are:

accuracy: how well can it be measured in relation to the true value?

precision: how repeatable is the measurement?

sensitivity: how well does it identify individuals with the condition, or how many individuals with the condition would be classified as not having it (false negatives)?

specificity: how well does it identify individuals without the condition, or how many without the condition would be classified as having it (false positives)?

It is apparent that these features fall into two groups: how well the measurement can be made (precision and accuracy), and how well the result can be interpreted (sensitivity and specificity).

Thus, the key question now becomes whether disease affects the measurement itself, which is uncommon (except for certain measurements of body composition where the disease process may reduce precision), or whether the disease process alters the interpretation of the result. This question can be more clearly stated as: (1) does the disease process alter the sensitivity, i.e. making it less likely to detect only a mild degree of protein–energy malnutrition, so that some patients with protein–energy malnutrition would be regarded as not being malnourished, or (2) does the disease process affect the measurement to make it more likely to diagnose malnutrition where it is not present?

The disease process may alter sensitivity and specificity in either or both of two ways. First, the disease state will have a direct effect on nutritional status, usually by increasing the nutritional requirement for both protein and energy as part of the metabolic response to serious illness (Cuthbertson, 1932; Wilmore, 1991), whilst at the same time causing a reduction in appetite, and possibly also a reduction in intake due to the clinical circumstances of the patient, e.g. dysphagia, malabsorption, nausea and vomiting. Such a disease process, therefore, would lead to a reduced nutritional status, making it more likely that it will be detected using appropriate markers.

However, second, and the essence of the problem, is that many of the markers which are used are themselves directly affected by the disease process. That is, they change in relation to disease independently of the changes related to nutritional status. Hence, a marker might be valid in some circumstances, such as where the population to be studied has a low prevalence of disease (e.g. in population screening), but the same marker may be invalid in a population with a high prevalence of acute or chronic disease.

In the following discussion, therefore, the markers which are commonly used will be critically reviewed in terms of how their measurement may be of value in assessing nutritional status, and how interpretation of the measurement may be affected by disease. In the space available, the techniques involved and their rationale are only described in outline, but attention should be drawn to a recent detailed review commissioned by the International Federation of Clinical Chemistry (Shenkin *et al.* 1996).

MARKERS USED TO ASSESS NUTRITIONAL STATUS

Markers commonly used must either directly indicate the net balance of intake and output, or by making two separate measurements, it must be possible to estimate separately the intake and the output, so that the net balance can then be calculated.

Tests which indicate adequacy of long-term nutrition

The adequacy of nutrition over a fairly prolonged period is best assessed by measuring body composition, usually by non-laboratory methods. However, since these require fairly sophisticated equipment to provide adequate accuracy and precision, other tests have been introduced, either of tissue function, particularly skeletal muscle function, or measurement of certain laboratory analytes, which are thought to reflect some aspects of body composition. The effects of illness on these various measurements will be reviewed (p. 435).

Tests of body composition. The most-frequently-used method of assessing body composition is measurement of body weight. Where this can be measured in a relatively stable situation without recent changes in fluid balance, it is best interpreted in relation to the usual weight of the individual in health, or in population studies in relation to the ideal weight for an individual of that particular height and build (Frisancho, 1990). For some clinical purposes, and for population studies, anthropometry, including mid-arm muscle circumference and triceps skinfold thickness (or measurement of up to four skinfold thicknesses, as proposed by Durnin & Womersley, 1974), allows a fairly accurate estimate of body skeletal muscle and fat compartments (Frisancho, 1990). These measurements, however, are subject to significant inter-observer error, and also are subject to variations in fluid balance (Green *et al.* 1990).

A somewhat more complex measurement is bioelectrical impedance analysis which has been intensively studied recently (Lukaski *et al.* 1986). Although it provides useful data in quantitative terms for many patients, those with acute fluid changes, and especially with collections of fluid, are not suitable for analysis (Elia, 1992).

Of greatest value, but requiring the most sophisticated equipment and, therefore, requiring more mobility on the part of the patient, are measurements of total body K, dual-energy X-ray absorptiometry, and *in vivo* neutron-activation analysis (for review, see Shenkin *et al.* 1996).

The effects on analytical accuracy and precision of these measurements, and on sensitivity and specificity of classification of the results during a chronic illness, which is relatively stable and, therefore, not producing acute fluid changes, or during an acute illness with fairly marked short-term fluid shifts, are shown in Tables 1 and 2 respectively. It is apparent that although most of the tests are of value in chronic illness, probably only *in vivo* neutron-activation analysis, and to a lesser extent total body K, may be of value in acute illness.

Functional tests of body composition. The main functional tests which have been studied are tests of muscle power, whether voluntary, as measured by hand-grip dynamometry (Martin *et al.* 1985) or after electrical stimulation, or aspects of immune function, particularly delayed hypersensitivity reaction (Twomey *et al.* 1982). As is shown in Table 3, the main problems with these tests are the lack of accuracy and precision in chronic illness since the disease process directly affects the measurement and, moreover, the lack of specificity of these tests. Although of some value in population studies, these tests are of little value in the sick patient in hospital.

Laboratory markers of body composition. Certain laboratory markers have been suggested to reflect body composition.

Table 1. *Tests of body composition in chronic illness*

	Accuracy*	Precision*	Sensitivity†	Specificity†
Body wt (% ideal or usual wt)	+	+	+	+
Anthropometry	±	±	●	+
Bioelectrical impedance	+	+	+	+
Total body K	++	++	++	+
DEXA	++	++	++	++
Neutron activation	++	++	++	++

DEXA, dual-energy X-ray absorptiometry; ±, fair; +, good; ++, excellent.

*Relates to the measurement of the variables.

†Relates to the identification of malnutrition.

Table 2. *Tests of body composition in acute illness*

	Accuracy*	Precision*	Sensitivity†	Specificity†
Body wt (% ideal or usual wt)	+	±	±	±
Anthropometry	±	-	-	-
Bioelectrical impedance	±	±	±	-
Total body K	++	+	+	+
DEXA	+	+	±	±
Neutron activation	++	+	++	++

DEXA, dual-energy X-ray absorptiometry; -, poor; ±, fair; +, good; ++, excellent.

* Relates to the measurement of variables.

† Relates to the identification of malnutrition.

Table 3. *Functional tests of body composition*

	Accuracy*	Precision*	Sensitivity†	Specificity†
In chronic illness				
Muscle power				
Voluntary	±	±	+	-
Stimulated	+	+	+	±
Delayed hypersensitivity	±	±	+	-
In acute illness				
Muscle power				
Voluntary	±	-	+	-
Stimulated	?	?	?	?
Delayed hypersensitivity	±	-	+	-

-Poor; ±, fair; +, good; ++, excellent; ? unknown.

* Relates to the measurement of variables.

† Relates to the identification of malnutrition.

Serum albumin has a relatively long half-life and has been widely used in studies of nutritional status, but its use is inappropriate as a marker of body composition. Although in prolonged protein-energy malnutrition, serum albumin does eventually fall, in short-term starvation or even in patients with anorexia nervosa, serum albumin is usually normal (Broom *et al.* 1986). However, many studies have demonstrated that a low serum albumin is associated with severe illness, and since severe illness itself may be associated with malnutrition, low serum albumin, therefore, is often associated with patients who are malnourished (Doweiko & Nompleggi, 1991). It is, however, not a marker of malnutrition, nor of nutritional status.

Urinary creatinine is a better marker of body muscle mass, since the turnover of creatine in skeletal muscles is usually kept within fairly narrow limits and, hence, the excretion of creatinine reflects the total skeletal muscle mass (Forbes & Bruining, 1976). However, excretion may vary by 20% from day-to-day as part of normal intra-individual variation and, therefore, the average of a number of specimens is required. Moreover, patients with fluctuating renal function will clearly have changes in urinary creatinine. A third laboratory marker which is sometimes used is the total lymphocyte count and, although a measurement of less than 1500 cells/mm³ may indicate protein-energy malnutrition, many non-specific factors can also alter the lymphocyte count; this is not

Table 4. *Laboratory markers of body composition*

	Accuracy*	Precision*	Sensitivity†	Specificity†
		Chronic illness		
Serum albumin	++	++	±	±
Urine creatinine	+	±	±	±
Total lymphocytes	+	+	+	●
		Acute illness		
Serum albumin	++	++	+	-
Urine creatinine	±	-	-	-
Total lymphocytes	+	±	±	-

-, Poor; ±, fair; +, good; ++, excellent.

*Relates to the measurement of variables.

†Relates to the identification of malnutrition.

widely used, therefore, in serious illness. A summary of the effect of illness on these markers is shown in Table 4.

Tests which indicate adequacy of recent nutrition

There are a number of tests which can be used to assess the adequacy of nutrition over a relatively short time period before the assessment. Such tests are of special value, since if they are repeated they indicate the efficacy of any nutritional intervention and, therefore, whether this requires to be changed to improve the response to nutritional therapy.

Calculation of nutrient balance. The accurate assessment of nutrient balance requires two different assessments to be made, first of dietary intake and second of utilization. Dietary intake is often difficult, since not only is the amount of diet actually consumed problematical, but its composition is variable, and the amount absorbed from the gastrointestinal tract is usually unknown. The accuracy of this part of the balance increases dramatically when intravenous nutrition is used, since the amount and composition are accurately known, and absorption is, of course, 100 %.

Measurement of utilization may be difficult with regard to energy utilization, since this requires indirect calorimetry which, although widely used in research circumstances, is rarely part of a routine investigation (Elia & Livesey, 1992). The cornerstone of most balance measurements is, therefore, N balance. The accuracy and precision of N balance depend on the type of nutrition being used, the completeness of urine collections and the type of analytical technique used to measure N in urine. Urea-N as a percentage of total N may vary from 59 to 96 %, with a mean of about 85 % (Fuller & Elia, 1990). Greater accuracy can be achieved by measuring both urea plus NH₃-N or, of course, by measuring total urine N, using appropriate techniques (Grimble, 1990).

The most important feature of a well-conducted N balance study is that provided the measurements have been well performed, then the sensitivity and specificity of the data are high, and the efficacy of nutritional support can be deduced.

Measurement of a marker of recent nutrient balance. The most-widely-used plasma components which are thought to be markers of nutrient balance are certain short half-life plasma proteins. Serum transferrin, with a half-life of about 8 d, has been found to be more responsive to change in nutrition than albumin (Carpentier *et al.* 1982; Fletcher *et al.* 1987). However, serum prealbumin, with a half-life of less than 2 d, has been found to reflect more accurately the changes in protein-energy intake both in individuals without

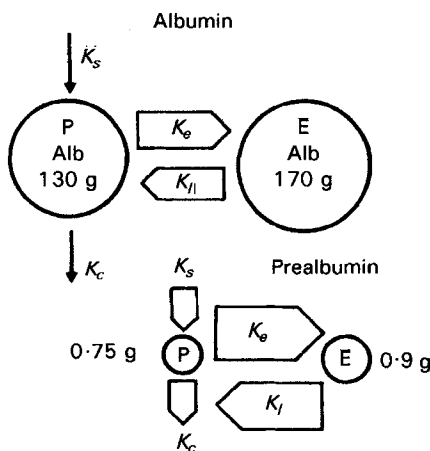


Fig. 1. The relationship of albumin (Alb) and pre-albumin exchange between blood and tissues to their synthesis and catabolism. K_i , fractional loss of protein to intravascular pool; K_e , fractional loss of protein to extravascular pool; E, extravascular pool; P, intravascular pool; K_s , rate of synthesis; K_c , rate of catabolism. (From Fleck, 1988; with permission.)

obvious disease processes, and also in those with chronic illness (Shetty *et al.* 1979; Thomas *et al.* 1988).

There are, however, many other factors which affect plasma protein concentration other than the supply of amino acids for protein synthesis. The most important of these factors is the redistribution of the protein between vascular and extravascular space (Fleck, 1988). The rate-constants for synthesis and catabolism of albumin are small in comparison with the rate-constants for exchange between intravascular and extravascular space (Fig. 1). By contrast, the rate-constants for synthesis and catabolism of prealbumin are significantly greater than for albumin and, hence, the serum concentration of prealbumin is a better marker of nutritional status than albumin, provided transcapillary exchange remains constant. It must be stressed, however, that in acute illness, the escape of both albumin and prealbumin to the interstitial fluid is markedly increased, leading to an acute reduction in plasma concentration of both these proteins. Moreover, in individuals with severe illness, changes in plasma volume may occur, changes in liver function which may alter protein synthetic rate are frequent and, furthermore, protein catabolic rate may be changed. Against this background the effect of nutritional adequacy on plasma protein concentrations in both chronic and acute illness is highly variable and may be extremely difficult to interpret (Table 5).

Table 5. Plasma proteins as markers of adequacy of recent nutrition

	Chronic illness		Acute illness	
	Sensitivity	Specificity	Sensitivity	Specificity
Transferrin	±	±	+	-
Pre-albumin	+	±	+	-
IGF-1	+	+	+	?

IGF-1, insulin-like growth factor 1; -, poor; ±, fair; +, good; ?, unknown.

A typical example of the lack of value of measurement of plasma proteins in the acutely-ill patient can be seen in a study of the effect of nutritional support in severely-traumatized patients, where aggressive nutritional support led to significantly improved N balance, but no significant difference in serum albumin, transferrin, prealbumin, or retinol-binding protein (Shenkin *et al.* 1980).

It would seem likely, therefore, that whenever the disease process activates a cytokine response, particularly interleukin-6, this stimulates production of the positive acute-phase proteins, such as C-reactive protein, and these short-half-life protein measurements become quite invalid (Carpentier *et al.* 1982; Fleck, 1988). It is worth noting that nutritional status itself does not appear to modify the cytokine response to trauma, although the magnitude of the C-reactive protein response may be somewhat attenuated (Curtis *et al.* 1995).

In view of this finding, other possible plasma markers of adequacy of nutrition have been examined. Plasma insulin-like growth factor 1 (IGF-1) has been found to relate to N balance (Counts *et al.* 1992), and some studies have suggested that plasma IGF-1 may be less affected by the presence of an acute-phase response than plasma prealbumin concentration (Burgess, 1992). This observation requires to be confirmed in patient groups with a variety of severe illnesses.

It is worth noting, however, that in patients who are fairly stable, and in those who are recovering from an acute illness, measurement of prealbumin may well be helpful in demonstrating the adequacy of nutritional support (Bastow *et al.* 1983).

Tests which indicate the need for nutritional supplements

Although tests may well be able to demonstrate the adequacy of either long-term or short-term nutrition, as indicated previously there are no tests which indicate whether an individual actually requires nutritional supplements. This assessment requires a much more complex analysis of many clinical factors, including the clinical history of the patient, the type, duration and severity of the disease process, and the clinician's expectation of the likely progress of the disease state. Although nutritional state has a bearing on this assessment, the decision to introduce nutritional support or nutritional supplements depends on clinical judgement rather than on laboratory assessment.

Tests which indicate efficacy of nutritional intervention

As summarized previously (p. 437), repeating those tests which indicate adequacy of recent nutrition, once or twice weekly, gives a good indication of the progress of the individual in response to nutritional therapy.

Tests which indicate prognosis

Indices have been developed which, by combining several measurements, can give an indication of the severity of the disease process and, therefore, the likely prognosis. Some of these indices include measurements which have a nutritional component and these have sometimes been called 'prognostic nutritional indices' (Mullen *et al.* 1979). One of the earliest of these included measurement of albumin, transferrin, triceps skinfold thickness and delayed hypersensitivity skin tests (Mullen *et al.* 1979), but since these are affected both by the severity of illness and by nutritional status this index should be used only to classify patients at risk of a poor outcome and not to indicate nutritional state.

In the Veterans Affairs Total Parenteral Nutrition Co-operative Study Group (1991) study patients at risk of a nutrition-related complication were identified either on the basis of having a nutrition index score less than 100 (i.e. $1.59 \times \text{serum albumin (g/l)} + 0.417 \times \text{usual weight/current weight} \times 100$), or any two of current weight less than 95 % ideal weight, serum albumin less than 39.2 g/l, and serum prealbumin less than 186 mg/l. As indicated from the previous discussion, it is apparent that many of these patients were introduced to the study on the basis of their illness-related effects, rather than their poor nutritional state. Despite this, provision of nutritional support to the most-severely-abnormal group of patients did reduce the risk of severe complications.

SUMMARY

It is apparent that illness, particularly acute illness, affects most tests which are used to assess macronutrient status. In acutely-ill patients, the best tests in terms of specificity for nutritional status are *in vivo* neutron-activation analysis for body composition and N balance as an assessment of recent intake. Changes in plasma protein concentration must be interpreted with great care, and this is best done in conjunction with changes in the acute-phase-protein response. Measurement of plasma IGF-1 may be helpful in the presence of an acute-phase response, but this requires further validation. In many such patients, the most important part of the assessment continues to be the clinical and dietary history, together with a careful physical examination.

However, the need for accurate measurement remains, so that nutritional status and its progress can be accurately quantified. This was best expressed many years ago by William Thompson, Lord Kelvin, when he stated '... when you can measure what you are speaking about and express it in numbers you know something about it... when you cannot express it in numbers your knowledge is of a meagre and unsatisfactory kind; it may be the beginning of knowledge, but you have scarcely, in your thoughts, advanced to the stage of science... '.

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