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Eur J Vasc Endovasc Surg **24**, 535–539 (2002)
doi:10.1053/ejvs.2002.1755, available online at http://www.idealibrary.com on IDEAL®

Patients with Chronic Critical Limb Ischaemia have Reduced Total Antioxidant Capacity and Impaired Nutritional Status

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Introduction: *it has previously been demonstrated that total antioxidant capacity (TAC) can help predict which patients undergoing femoro-distal reconstruction are susceptible to postoperative infections*
Aims: *the aims of this study were to examine if TAC is influenced by the nutritional state of the patient and the degree of ischaemia.*
Patients and Methods: *thirty patients with rest pain (21 men and 9 women), with a median age of 69 years and fifteen controls (9 men and 6 women), median age of 66 years, were studied. Nutritional status was assessed using serum albumin, body mass index (BMI), maximum voluntary contraction using a hand grip dynamometer and bioelectrical impedance to determine lean body mass. Blood was also taken for total antioxidant capacity (TAC).*
Results: *patients with chronic critical limb ischaemia (CCLI) had a lower TAC than controls (752 vs 1130 μmol/l, $p < 0.05$ Mann–Whitney U-test). There was no difference in serum albumin concentration between the CCLI group compared with controls (31 mmol/L vs 35 mmol/L, $p > 0.05$ Mann–Whitney U-test). There was also no difference in BMI (23 vs 27, $p > 0.05$ U-test) between the two groups. The other markers of nutrition including, maximum voluntary contractions (28.6 kg/m^2 vs 37.4 kg/m^2, $p < 0.05$ M–W U-test), and lean body mass (3.0 vs 3.8 M–W U-test), showed a significant reduction in the vascular patients.*
Conclusion: *TAC is significantly reduced in patients with CCLI and this may, in part, be explained by their impaired nutritional status.*

Key Words: Total antioxidant capacity; Nutrition; Bioimpedance; Peripheral vascular disease.

Introduction

It has previously been shown that a reduction in the total antioxidant capacity (TAC) in patients undergoing femoro-distal surgery is associated with an increased risk of postoperative infections, including the development of the systemic inflammatory response syndrome (SIRS) and sepsis.[1] The aims of this study were to determine if this reduction in TAC could, at least in part, be explained by the patients nutritional status.

More than twenty years have passed since the high incidence of protein energy malnutrition in surgical patients was first shown, and adverse changes in nutritional status during hospitalisation have also been reported.[2] Nutritional status has also been shown to have important effects on health in recovery from illness or surgery. Experimental semi-starvation of normal volunteers that caused a 25% loss of body weight (to a body mass index [BMI] of 17.5) was associated with apathy, depression, fatigue and loss of will to recover.[3] Consequent loss of muscle power affects respiratory function, increasing susceptibility to chest infections,[4] and reduces cardiac function.[5] Impaired immune function also increases the risk of infection.[6] Such complications result in increased morbidity and mortality and a longer hospital stay.

Several authors have shown that episodes of ischaemia-reperfusion can reduce the TAC,[7,8] it is possible, therefore, that the longer or more severe the bouts of ischaemia the greater the reduction in the TAC and subsequent increase in the risk of developing infective complications. If these patients have an unimpaired nutritional status with low TAC, then they may benefit from antioxidant supplementation. If their nutritional status is impaired, then nutritional supplementation will also be required.

Financial Support: Yorkshire Vascular and Surgical Research Fund.
Presented in part at the Surgical Research Society Meeting, January 1998.
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The techniques available for nutritional assessment have significant limitations. Plasma proteins reflect nutritional status, although, they are insensitive markers during the early stages of malnutrition. Tissue necrosis and ulceration may produce an acute inflammatory response, which may also affect the plasma protein concentrations.

Body composition analysis allows measurement of varying components of the body according to physical properties. Bioelectrical impedance analysis (BIA) allows assessment of body composition by measurement of the impedance of the human body to the passage of a small AC electric current. It allows measurement of total body water, fat and lean body mass. It is a simple technique, allowing quick, safe, non-invasive measurement and is thus suited to clinical practice. Its portable nature makes it suitable for use in critically ill patients. More complex techniques, such as dual-energy x-ray absorptiometry (DEXA), allow more detailed and accurate assessments of body composition but are limited in availability, costly and unsuitable for ill patients, being more suited to research.

Patients and Methods

The protocol used in the study was approved by the local ethics committee. Thirty non-diabetic patients, 21 men and nine women with chronic critical limb ischaemia[9] were studied prospectively. Fifteen age and sex matched controls were obtained from general surgery outpatients, none of these patients suffered from peripheral vascular disease. Patients who were self-prescribing vitamin supplementation were excluded.

Peripheral venous blood samples were taken pre-operatively, collected into sterile bottles containing EDTA as an anticoagulant and immediately centrifuged with the plasma frozen and stored at −70°C for subsequent analysis of total antioxidant capacity (TAC).

Nutritional status was determined from anthropometric data; body mass index, handgrip dynamometry and bioelectrical impedance. Venous blood was also collected into standard heparinised tubes for measurement of albumin levels. Height and weight were used to determine body mass index (weight (kg)/height (m^2)). Muscle function as measured by maximum voluntary grip strength has been used as an indicator of pre-operative nutritional status capable of detecting the likelihood of complications after gastrointestinal surgery.[10] Functional status was measured with a Harpenden handgrip dynamometer (kg/m^2) (CMS Weighing equipment Ltd, London, U.K.): patients were asked to grip the dynamometer three times with their non-dominant hand, and the highest reading recorded.

Body composition indexes were measured by a bio-electrical impedance plethysmograph (model BIA 101; RJL Systems, Detroit, MI, U.S.A.).[11] The technique consisted of placing electrodes on the dorsal surfaces of the hands and feet at the distal metacarpals and metatarsals, respectively, and between the distal prominence of the radius and ulna, and between the medial and lateral malleoli of the ankle. An excitation current of 800 amp at a signal frequency of 50 kHz at the distal electrodes on the dorsal surfaces of the hand and foot were introduced and the voltage drop was measured at the proximal electrodes. Resistance and reactance were measured in triplicate and the mean was used for computerised calculation of lean body mass and body fat, with the result expressed as lean/fat ratio.

The circulating levels of plasma proteins depend on the rate of synthesis, the volume of distribution and the rate of catabolism. Many of the plasma proteins are also negative acute phase reactants, so it is clear that their levels reflect more than just nutritional factors. However, decreased protein intake produces a decease in plasma protein level, thus providing a good nutritional marker. The most commonly measured proteins measured in nutritional assessment are albumin, transferrin and prealbumin.

The enhanced chemiluminescent assay for TAC in body fluids has been described elsewhere.[1]

Statistical Analysis

The data were recorded on a proforma and transferred to Microsoft Excel version 7.0. Statistics were performed using the Excel add-in, Astute (University of Leeds, U.K.) and C-Stat for Windows (Cherwell Scientific, Oxford, U.K.).

As the data were skewed, non-parametric analyses were employed. The results are expressed as medians and interquartile ranges. The Mann–Whitney *U*-test of significance was used to examine the difference between results in two groups. Bivariate correlation was with Pearson's correlation coefficient.

Results

Thirty patients, 21 men and nine women with a median age of 69 years were compared to 15 control subjects (Table 1).

Table 1. Patient demographics. Results shown as medians and interquartile range in brackets.

	Rest Pain	Controls
N	30	15
M/F	21/9	9/6
Age	69 (62–78)	66 (52–74)
Smoker	23	6
IHD	17	4
Pulmonary disease	13	4
Renal disease	12	1
ABPI	0.2 (0–0.3)	0.95 (0.8–1.12)
Height (cm)	162.7 (150.3–175.2)	167.5 (151.1–174)
Weight (kg)	65.7 (59.0–84.1)	70.2 (64.2–99.4)
Body Mass Index (kg/m^2)	23 (18–31)	27 (21–33)

Table 2. A comparison of nutritional characteristics between patients with chronic critical ischaemia and controls (medians and interquartile ranges).

	Rest pain	Controls
Albumin (mmol/l)	31 (21–42)	35 (29–41)
MVC (kg/m^2)	28.6 (24.2–35.3)	37.4 (32.1–40.8) $p < 0.05$
Lean body mass (kg)	49.3 (45.1–62.0)	57.3 (52.4–75.1) $p < 0.05$
Fat (kg)	16.8 (14.4–22.4)	15.6 (14.1–23.8)
Lean/Fat ratio	3.0 (2.8–3.6)	3.8 (3.4–4.3) $p < 0.05$

The TAC in the patients with chronic critical lower limb ischaemia was significantly lower than the control group (752 μmol/l (625–812) vs 1130 μmol/l (945–1189), $p < 0.05$ Mann–Whitney *U*-test). There was no difference in albumin levels between vascular patients and the control group, although the interquartile ranges were much larger in the vascular group (31 mmol/l [21–42 mmol/l] vs 35 mmol/l [29–41 mmol/l] $p > 0.05$ Mann–Whitney *U*-test) (Table 2). There was no significant difference in BMI between the vascular patients and the control group (23 [18–31] vs 27 [21–33] $p > 0.05$ Mann–Whitney *U*-test) (Table 1).

Maximum voluntary contractions (MVC) also showed a significant reduction in patients with CCLI (28.6 kg/m^2 [24.2–35.3] vs 37.4 kg/m^2 [32.1–40.8] $p < 0.05$ Mann–Whitney *U*-test).

Lean body mass, expressed as lean/fat ratio, also showed a significant reduction in the vascular patients compared with the control group (3.0 [2.8–3.6] vs 3.8 [3.4–4.3], $p < 0.05$ Mann–Whitney *U*-test). The lean body mass was reduced in those with CCLLI compared to the controls (49.3 kg [45.1–62 kg] vs 57.3 [52.4–75.1 kg] $p < 0.05$ Mann–Whitney *U*-test). There was no significant differences in body fat between the two groups (16.8 kg [14.6–22.4 kg] vs 15.6 kg [14.1–23.8 kg]) (Table 2). There was also a positive correlation between TAC and lean body weight, suggesting that the patients with the lower lean/fat ratio have the lower TAC ($r = 0.78$, $p = 0.037$ Pearson's correlation coefficient). (Fig. 1).

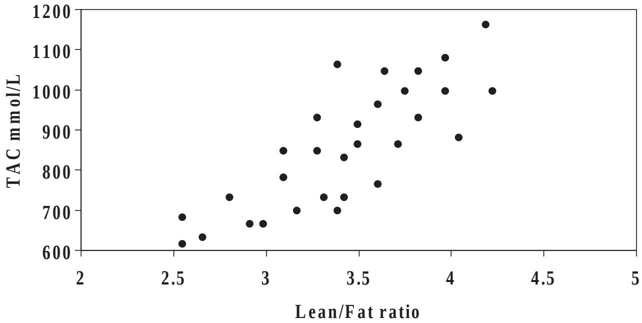

Fig. 1. Correlation between TAC and Lean/Fat ratio.

Discussion

Free radical activity and oxidative damage have now been implicated in a number of disease states. In particular, their role in vascular disease has received much attention.[12,13] Antioxidants provide the first line of defence against free radicals. Previous studies have shown that antioxidants in vascular patients are lower than age matched controls,[14,15] but there is no data on the state of nutrition of these vascular patients that may account in some part for this decrease.

The assessment of nutrition is of great clinical importance in the surgical patient. The decline in muscle strength and mass during ageing has been linked to functional decline and impaired mobility as well as impaired recovery from surgery.[16] Although many factors including chronic vascular illness, sedentary lifestyle, nutritional deficiencies and ageing itself may contribute to muscle weakness, and impaired recovery from surgery, only skeletal muscle disuse and undernutrion are potentially reversible with targeted interventions.[17]

Our results demonstrate the poor reliability of biochemical assessment of nutritional status. Only albumin concentrations were measured, though it is known that albumin concentrations respond slowly to protein restriction and are more a reflection of the illness of a patient than of nutrient intake. Transferrin is more sensitive, having a shorter half-life, but may be elevated during infection and stress and by concurrent iron deficiency. Thyroxin binding prealbumin and retinol binding protein both reflect nutritional intake but are also affected by inflammatory states.

BMI is also limited as a nutritional assessment index in that the specific compartments of the body contributing to the weight loss are not identified. For example, in unstressed starvation, significant depletion of fat stores occurs with relative preservation of lean body mass.[18,19] In trauma, however, the weight loss may represent primarily loss of lean body mass. Low body mass index measurements will also include some patients who normally weigh less than is usual for their height. Skeletal muscle function indices have been advocated for the assessment of nutritional status. Changes in muscle function such as contractility, relaxation rate and endurance may precede body composition changes and may help detect functional impairment at subclinical levels. The results of the present study suggest that MVC may help to identify patients with a chronic energy deficiency and possibly play a role in evaluating the prognosis of nutritionally depleted patients. A drawback in the testing of muscle strength with a dynamometer is the dependence on motivation of the subject to exert maximal effort. There were no large differences in the intravariability in MVC across the groups.

Lean body mass is a strong predictor of outcome in starvation and in a variety of acute and chronic illnesses.[20,21] It has been suggested that a reduction in lean body mass of more than 40% is incompatible with life, irrespective of the underlying cause. Although it is unclear to what extent protein depletion is simply a marker of severe illness, or whether it plays a direct causal role, evidence suggests that some complications such as reduced immunity and predisposition to sepsis may result from nutritional deficiency. Bioelectrical impedance appears to be a simple inexpensive, quick and reliable instrument that can be used to assess lean tissue and body composition. It has been used as part of the National Centre for Health Statistics survey on nutrition (National Health and Nutrition Examination Survey III) which provided reference ranges far 17 000 Americans aged over 12 years.[22] The results show that while body fat did not differ between the two groups, there was a significant reduction in lean body mass.

The study was not designed to identify a specific level of TAC or nutritional depletion that might predict those patients at risk from postoperative complications. It does, however, demonstrate that there are a number of vascular patients who have borderline nutrition that would not have been recognised using BMI or an isolated biochemical marker. Furthermore there was a positive correlation between lean/fat ratio and TAC. In previous work[1] we have shown that reduced TAC increases the risk of infective complications and thus identification of malnourished patients by bioelectrical impedance may prove a simple and effective method of predicting the risk of complications.

Although facilities to deal with nutritional problems exist in most hospitals the predicament of impaired nutrition is often not considered. This paper confirms that malnutrition is common in patients with critical limb ischaemia and is associated with changes in other markers which have previously been shown to predict an increase in complication. Furthermore the value of bioelectrical impedance as a simple method of identifying such patients is evident.

Techniques for the provision of artificial nutritional support are becoming increasingly sophisticated. There remains, however, a need for improved recognition and an appreciation of the treatment of nutrition related complications.

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Accepted 6 August 2002