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Relationship between weight loss, reduction of body cell mass and inflammatory response in patients with cancer

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Reduced food intake is a major cause of continuing weight loss in patients with cancer. Previous work has suggested that an ongoing inflammatory response may also contribute to weight loss and alter the nature of body tissue loss. To examine this, body cell mass was estimated using measurements of total body potassium (TBK) in 31 patients with gastrointestinal cancer and weight loss with or without an inflammatory response (C-reactive protein level above 5 mg/l). Albumin levels, total body water and 24-h urinary creatinine clearance were also measured. When measured TBK was expressed as a percentage of predicted normal values there was a significant reduction in TBK for patients with an inflammatory response compared with that of those without ($P = 0{\cdot}04$). However, when a different prediction equation for TBK was used this difference was not significant ($P = 0{\cdot}29$). Therefore, it remains uncertain whether an ongoing inflammatory response in patients with cancer and weight loss contributes to loss of body cell mass.

It has long been recognized that weight loss (cachexia) is the single most common cause of death in patients with cancer[1,2]. Reduced food intake is a major factor in continuing weight loss of the cachectic cancer host. However, there can be significant changes in carbohydrate, fat and protein metabolism that may contribute to the negative energy balance. It has been hypothesized that these metabolic changes are part of a tumour–host inflammatory response[3]. However, not all patients with cancer develop systemic signs of an ongoing inflammatory response such as an acute-phase protein reaction. Nevertheless, if the metabolic changes associated with inflammation are ongoing and contribute to weight loss it would be expected that body composition of patients with cancer would differ between those with or without an inflammatory response.

The body can be compartmentalized into body fat and lean body mass, estimated by isotope dilution using tritiated water[4]. Lean body mass has been further divided into an extracellular component and body cell mass. In metabolic terms body cell mass is considered of primary importance because it is 'that component of body composition containing the oxygen-exchanging, potassium rich, glucose oxidising, work performing tissue'[5]. Body cell mass can be estimated by measuring total body potassium (TBK)[5]. Such body composition measurements can be expressed as a percentage of the normal value predicted from equations (derived from a large number of subjects) to allow an accurate comparison of measurements from small groups of patients.

It has been reported that in patients with cancer the estimated body cell mass is below that predicted from studies on normal individuals[6]. Furthermore, Moley *et al.*[7] found that the body cell mass of weight-losing patients with cancer is reduced compared with that of weight-losing patients without malignancy. In contrast, Macfie and Burkinshaw[8] reported no difference in body cell mass between weight-losing patients with benign disease and those with cancer. Watson and Sammon[9] suggested that lean body mass, which includes body cell mass, is less well conserved in weight-losing patients without cancer who have inflammatory disorders compared with that in weight-losing patients with cancer. Therefore, it is not clear whether the loss of body cell mass that accompanies weight loss is different in patients with and without cancer. Such conflicting results might be explained by heterogeneity of the groups examined. None of the studies assessed whether patients had an inflammatory response. To do so might allow clearer separation of weight-losing patients with cancer into those who have a 'metabolic' component to weight loss compared with those with simple starvation.

Inflammation results in the production of a number of acute-phase proteins. Of these, an increase in serum C-reactive protein (CRP) concentration has been most commonly used as a marker of the magnitude of the inflammatory response in humans[10,11]. It has been reported that in a proportion of patients with malignancy circulating CRP levels are raised and gradually increase with disease progression[12]. The fact that not all patients with cancer and weight loss have increased concentrations of CRP[13] may allow assessment of the relationship between the inflammatory response and body cell mass. The aim of this study was to determine, in a group of patients with advanced gastrointestinal cancer and documented weight loss, whether an inflammatory response was associated with an alteration in body cell mass.

Patients and methods

Study design

Thirty-one patients with histologically proven cancer of the gastrointestinal tract and documented weight loss of 10–43 per cent underwent measurement of total body water (TBW), TBK, and serum CRP and albumin concentrations. On the morning of the body composition measurements, blood samples were taken and the patient's height and weight recorded. Urine had been collected over

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the previous 24 h for measurement of creatinine excretion. Each patient was questioned carefully about his or her weight before illness and weight loss. None had undergone surgery, radiotherapy or chemotherapy in the previous 2 months. No patient complained of moderate or severe dysphagia and none had an obvious functional obstruction to food intake or abnormal liver function. The study was approved by the local hospital ethics committee; all patients gave written informed consent.

Analytical methods

For measurement of TBW, tritium-labelled water (3·7 MBq) was taken orally and allowed to equilibrate for 4 h before blood samples were obtained. Corrections were made for the fraction of the dose excreted in the urine.

TBK was determined by measuring the amount of the naturally occurring potassium radioisotope (^{40}K) in each patient using a shielded-room scanning whole-body counter (Department of Nuclear Medicine, Southern General Hospital, Glasgow, UK)[14].

Serum albumin was analysed by immunoturbidometric methods using an Encore centrifugal analyser (Baker Instruments, California, USA). Antisera for the albumin were obtained from the Scottish Antibody Production Unit (Carluke, UK).

Serum CRP concentrations were measured by fluorescence polarization immunoassay using an Abbott TDX analyser and Abbott reagents (California, USA). The limit of detection of this assay is a CRP concentration of 5 mg/l.

Urinary creatinine clearance was analysed on a Hitachi 704 discrete analyser (Boehringer Mannheim, Lewes, UK) based on the standard endpoint Jaffe reaction.

Calculations

Body-weight and its components vary systematically with age, sex and height in healthy subjects and also with body habitus[15]. To correct for such variation between the two groups, measured TBW and TBK were also expressed as a percentage of predicted normal values.

For each patient, predicted values for TBW (litres) were calculated based on the formulae of Watson *et al.*[16] using age (years), height (centimetres) and measured weight (kilograms):

Predicted TBW for
male patients = 2·447 − 0·09516 × age
+ 0·1074 × height + 0·3362 × weight

Predicted TBW for
female patients = −2·097 + 0·1069 × height + 0·2466 × weight

From each patient's sex, age and height, predicted values for normal TBK (millimoles) were calculated using formulae from the authors' laboratories, as TBK_B (Boddy *et al.*[17]) and TBK_W (W. S. Watson, unpublished data) based on 116 normal subjects. These predictive formulae are based on TBK measurements using normal subjects in the same geographical area.

Predicted TBK_B for
male patients = 53·02 × height − 9·74 × age − 5305

Predicted TBK_B for
female patients = 33·63 × height − 7·73 × age − 2727

Predicted TBK_W for
male patients = 35·76 × height − 4·51 × age − 2483

Predicted TBK_W for
female patients = 35·76 × height − 4·51 × age − 3211

Body cell mass (grams) was determined from measured TBK using the formula derived by Moore *et al.*[5]:

Body cell mass = TBK × 8·33

Statistical analysis

Data are presented as median (range). Where appropriate, data were tested for statistical significance using the Mann–Whitney *U* test.

Results

Clinical and biochemical characteristics of the weight-losing patients with cancer are shown in *Table 1*. Male and female patients were grouped according to the presence (CRP level above 5 mg/l) or absence (concentration less than 5 mg/l) of an inflammatory response. In the male patients, the two groups were not significantly different with regard to height, body-weight (before illness and measured) and percentage weight loss. However, the median serum albumin concentration of male patients with an inflammatory response was significantly lower than that of those who did not have an inflammatory response ($P < 0·05$).

Body composition measurements of the patients with cancer are shown in *Table 2*. When the male and female groups were considered separately there was no statistical difference between patients with or without an inflammatory response in measured and predicted TBW or measured and predicted TBK. However, when the male and female patients were considered, median predicted TBK for those with an inflammatory response was either significantly lower ($P = 0·04$, TBK_B) or no different ($P = 0·29$, TBK_W) compared with those who did not have an inflammatory response.

There was no statistical difference in creatinine clearance between patients with and without an inflammatory response.

Table 1 Clinical and biochemical details of weight-losing patients with cancer

	Age (years)	Height (cm)	Body-weight (kg)		Weight loss (%)	Serum albumin (g/l)	Serum C-reactive protein (mg/l)
			Before illness	Measured			
Inflammatory response							
Men ($n = 15$)	64 (55–76)	170 (154–181)	69 (60–85)	54 (40–72)	18 (10–38)	38 (29–44)	29 (12–170)
Women ($n = 7$)	74 (63–75)	154 (146–168)	63 (50–64)	42 (37–53)	29 (15–34)	36 (32–41)	34 (22–68)
No inflammatory response							
Men ($n = 6$)	72 (66–76)	167 (153–173)	67 (63–95)	55 (45–62)	21 (11–43)	43 (39–45)*	
Women ($n = 3$)	74 (72–77)	153 (150–154)	54 (51–66)	45 (44–50)	18 (11–24)	41 (40–42)	

Values are median (range). * $P < 0·05$ (*versus* men with inflammatory response, Mann–Whitney *U* test)

Table 2 Body composition of weight-losing patients with cancer

	TBW (litres)	TBW/TBW_P (%)	TBK (mmol)	TBK/TBK_H (%)	TBK/TBK_W (%)	Body cell mass (kg)	Creatinine excretion (mmol per 24 h)
Inflammatory response							
Men ($n=15$)	34·8 (27·2–47·6)	107 (91–122)	2249 (1570–3113)	76 (52–95)	72 (48–91)	18·7 (13·1–25·9)	8·0 (2·3–14·4)
Women ($n=7$)	23·3 (21·5–29·2)	92 (86–111)	1519 (1120–2065)	74 (66–114)	72 (63–110)	12·7 (9·3–17·2)	4·8 (3·6–6·5)
No inflammatory response							
Men ($n=6$)	32·7 (24·8–41·5)	103 (89–117)	2114 (1822–2657)	84 (67–86)	71 (63–79)	17·6 (15·2–22·1)	6·7 (3·7–8·9)
Women ($n=3$)	24·9 (22·6–28·8)	100 (89–108)	1778 (1500–1780)	94 (87–96)	90 (83–92)	14·8 (12·5–14·8)	7·8 (4·9–8·0)

Values are median (range). TBW, total body water; TBW_P, predicted total body water[16]; TBK, total body potassium; TBK_H, predicted total body potassium according to Boddy *et al.*[17]; TBK_W, predicted total body potassium according to W. S. Watson (unpublished data)

Discussion

By studying patients with cancer with similar weight loss and type of malignancy, this study attempted to determine whether the presence of an inflammatory response, characterized by an increased serum CRP concentration, is associated with changes in TBK. Approximately 70 per cent of the patients with cancer in this study had detectable circulating CRP (level above 5 mg/l). This proportion is similar to that reported for patients with lung and colorectal cancer[13]. The significant reduction in albumin concentration in the male patients with an inflammatory response is consistent with an ongoing acute-phase response in these[18]. The basis of the inflammatory response in patients with gastrointestinal cancer is not known; the effect may be the result of a specific host–tumour immune response or a non-specific inflammatory response secondary to tissue damage induced by the tumour.

The ages of the male patients with an inflammatory response tended to be lower than those of the male patients with no such response (*Table 1*). Given this trend, direct comparison of the measured TBK in the two groups may be in error because body potassium is known to decline with age[5,15,17]. Therefore, the measured TBK values were also expressed as a percentage of predicted normal TBK values (*Table 2*).

TBW has been reported as increased in patients with cancer[9,19]. In the present study, however, measured TBW was within 5 per cent of the predicted value in all patients. Therefore it is unlikely that there were major fluid changes in these patients.

It has been suggested previously[20] that TBK and urinary creatinine clearance measurements can be used to resolve body cell mass into non-muscle and muscle components, which may be particularly useful in studies of wasting disease and to allow normalization of metabolic measurements to non-muscle (i.e. visceral) cell mass. The relationship between muscle potassium and creatinine excretion was derived using *in vivo* neutron activation analysis to measure total body nitrogen, and compartmental analysis to estimate muscle and non-muscle mass from TBK and total body nitrogen data[21]. It was argued that errors in estimating creatinine excretion would limit this approach to comparative studies in groups of patients. In the present study, creatinine was measured in an attempt to estimate the degree of muscle wasting. No significant difference was demonstrated between male groups or between all patients with an inflammatory response compared with those without. However, there was considerable variability in the creatinine excretion estimates, which would have obscured any small differences. Furthermore, measured creatinine excretion was low (all men: median 7·6 mmol per 24 h; all women: median 4·9 mmol per 24 h) compared with published data[22], suggesting that skeletal muscle was the major site of body cell mass loss in all patients.

There was no statistically significant difference between the male groups when measured TBK was expressed as a percentage of the predicted value (*Table 2*). However, when male and female groups were combined ($n=31$) there was a statistically significant difference when the prediction equation of Boddy *et al.*[17] was used. This finding was not observed when another prediction equation (W. S. Watson, unpublished data) for TBK was used. Given that both equations are based on data from normal subjects drawn from the same area of Scotland the basis for such a difference is not clear. It may be that measurements from a larger number of patients would resolve this problem. Nevertheless, the effect – if real – of the inflammatory response on the greater loss of TBK and consequently body cell mass is likely to be small (approximately 1–2 kg). However, given the importance of the body cell mass any loss may be detrimental.

A recent report suggests that anorexia and weight loss (which contribute to mortality) in an animal model of cancer cachexia can be attenuated by reducing the inflammatory response[23]. In this context it is of considerable importance to establish whether there are alterations in body composition of the weight-losing patient with cancer and an inflammatory response. Further studies of larger homogeneous groups of weight-losing patients with cancer are therefore warranted.

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