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Energy metabolism in cancer and human immunodeficiency virus infection

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WEIGHT CHANGE IN CANCER AND HUMAN IMMUNODEFICIENCY VIRUS (HIV) INFECTION

Cancer and HIV infection are often considered to be synonymous with the profound weight loss which is characterized as cachexia. Undoubtedly many patients do experience periods of weight loss, but by generalizing we may lose some of the important heterogeneity which exists in both diseases. The paper of Warren (1931) has been extensively cited as showing that the most common cause of death in patients with cancer (accounting for 114 of 500 cases) was cachexia. However, Warren (1931) also remarked on the ‘startling’ number of cases in which ‘excellent nutrition and not infrequently obesity are maintained to the end’. Studies of the prevalence of weight deficits at diagnosis have also been widely used to support the notion that patients lose weight, but these give no indication of the weight change associated with disease progression (Dewys et al. 1980). By focusing on weight loss alone, perhaps in association with intermittent periods of treatment, it is easy to disregard important periods of weight gain between treatment cycles in which nutritional status may be restored.

There are undoubtedly differences in patterns of weight change associated with cancer at different sites and not surprisingly gastrointestinal cancers are associated with some of the most marked weight loss. There may also be a secular effect on the weight change experienced by patients with cancer, linked to recent improvements in symptom control and the introduction of less-toxic treatment regimens for some cancers. Unfortunately, too few clinics keep detailed records of weight change to allow a comprehensive analysis of these factors to be possible. A retrospective analysis of weight change in patients with lung cancer showed that virtually all patients lost weight as their disease progressed (Costa et al. 1980), whereas a recent prospective study of sixty patients with lung cancer showed great variability in the pattern of weight change measured at five 6-week intervals following a diagnosis of advanced disease (Sarna et al. 1994). Self-reported changes in weight at diagnosis, compared with ‘healthy’ weight, ranged from $-31\%$ to $+32\%$, and the range of weight change over the following 6 months was $-24$ to $+28\%$. On average there was no significant weight change across the group at any time, but this conceals the substantial inter-individual variability; 46-9\% of patients lost weight, 15-6\% had no change and 37-5\% gained weight. Only 6\% of patients had chronic unremitting weight loss, with a...
reduction in the weight at each assessment. Although this study may be biased towards subjects with less-aggressive disease, since it was they who completed the 6-month study, it clearly demonstrates that weight loss is not inevitable. Among patients with small-cell lung cancer (SCLC) at Addenbrooke’s Hospital, Cambridge, we have observed great variability in the weight course of individuals (Jebb, unpublished results). Fig. 1 illustrates longitudinal data from four individuals in a series of forty patients, who all received chemotherapy for 12 weeks following diagnosis. Here we can see an example of weight stability, progressive weight loss, treatment-related weight loss followed by regain and excessive weight gain.

Similar diversity exists in patients with HIV infection. A retrospective analysis of weight records in patients at St George’s Hospital, London, identified the clinical correlates of typical patterns of weight change (Macallan et al. 1993). Weight changes were measured in thirty patients with stage IV HIV infection over a period of 9–49 months. Two distinct patterns of weight loss were observed: (1) episodes of acute weight loss of which 82% were associated with non-gastrointestinal opportunistic infections; (2) chronic weight loss of which 65% of episodes were associated with gastrointestinal disease. Of the 30 patients, 43% experienced at least one period of weight stability (median 10 months, range 4–33 months) and 75% of patients experienced a period of weight gain (median 9.4 kg, range 4–25 kg).

A number of patients with cancer and HIV infection experience problems of excessive weight gain. There may be a number of reasons for this, including some drugs (particularly corticosteroids), changes in lifestyle (e.g. giving up work or active leisure pursuits), or a reduction in habitual dietary restraint. More detailed studies of weight change in larger groups of patients will allow the identification of factors which predict weight change. This may allow nutritional interventions to be more precisely targeted at patients at high risk of weight loss or excessive weight gain.

The importance of maintaining body weight and good nutritional status in patients with disease is becoming increasingly apparent. In healthy volunteers experimental semi-starvation with a 25% loss of body weight was associated with apathy, depression and fatigue, which were reversible on re-feeding (Keys et al. 1950). In patients with co-existing weight loss and weight gain...
injury or disease there are additional effects on morbidity and mortality which have recently been reviewed (British Association for Parenteral and Enteral Nutrition, 1994). The literature shows clearly that malnutrition delays recovery, increases the incidence of serious complications, increases treatment costs and impairs quality of life.

Studies of energy metabolism in cancer and HIV infection can help to explain the fluctuations in energy balance. Ultimately, body weight represents the sum of the body’s macronutrient stores and the end result of the cumulative balance between energy intake and energy expenditure. It is necessary, therefore, to examine each of the components of this energy balance equation to identify the mechanisms which perturb the body’s natural homeostatic mechanisms of weight control. A more-detailed understanding of the disruption in physiological regulatory processes will provide a more rational basis for appropriate nutritional care.

ENERGY EXPENDITURE

Until relatively recently measures of energy expenditure in patients with cancer or HIV infection have been limited to the measurement of resting energy expenditure (REE). In both conditions there have been reports that REE is increased, decreased or the same as that of control subjects. Although some of this variance may be due to the heterogeneity of the diseases which may exhibit varying metabolic effects, it is also a consequence of a number of methodological factors. For the most part studies have been cross-sectional, which poses the problem of choosing an appropriate control group for comparison, and few studies have adequately accounted for differences in body composition. Moreover, few studies rigorously apply the strict measurement criteria demanded for the assessment of BMR. Instead, measurements of resting metabolic rate (RMR) are made under a variety of conditions, which in general tend to be biased towards an overestimate of REE in clinical conditions compared with the procedures used for generating ‘control’ data from healthy subjects. Examples of these factors are the use of mouth pieces or ventilated hoods which stress the patient, or inadequate correction for the effects of diet-induced thermogenesis, particularly in patients receiving prolonged periods of artificial nutrition. Measurements may be made whilst the patient is hospitalized, at a time of acute illness, and this value taken as an approximation of day-to-day expenditure even when in periods of remission (Elia & Jebb, 1992).

Interpreting the measured RMR is also difficult. Patients losing weight would be expected to have a suppression of RMR, over and above that due to a decrease in fat-free mass (FFM; Keys et al. 1950), so even a ‘normal’ value may represent hypermetabolism. There may also be other changes in body composition which have an important impact on metabolic rate. Heymsfield & McManus (1985) have demonstrated that patients with cancer show disproportionately large losses of skeletal muscle, with a relative preservation of visceral organs. In the resting state, skeletal muscle makes only a small contribution to energy requirements, whilst liver, kidney, spleen and brain which represent only 5% of body weight account for over 60% of RMR (Elia, 1992). A change in the proportional mass of these organs relative to total FFM, therefore, has the potential to cause apparent increases in energy expenditure, when referenced to total FFM.

In an attempt to overcome some of these difficulties we measured REE in twenty-eight patients with SCLC (Jebb et al. 1994). Mean RMR at diagnosis was 108% of predicted RMR (range 96–151%). Patients experiencing a partial or complete remission (n 18) maintained their weight and had a significant decrease in RMR of 15·7 (SD 11·7) kJ/kg FFM (P < 0·0001), whilst in the non-responders (n 10) weight decreased by −4·33 (SD
Fig. 2. Changes in resting energy expenditure at diagnosis and following treatment of small-cell lung cancer. RMR, resting metabolic rate; FFM, fat-free mass. (a) Responders, (n 18), (b) non-responders (n 10). Values post-treatment were significantly different from those at diagnosis for responders (P < 0.0001), but not significant for non-responders.

5.4) kg (P < 0.05) but RMR was unchanged (Fig. 2). Changes in organ size, measured by computed tomography, were not significant in either group. In patients with SCLC, the elevation of RMR associated with active disease is unlikely to be a direct effect of the tumour itself since its mass is extremely small; rather it is more probable that it represents a host response, perhaps mediated via the action of cytokines and acute-phase proteins.

However, RMR is only part of the total energy expenditure (TEE) of an individual. Changes in voluntary physical activity have the potential to exert a much greater influence on TEE. Anecdotally, it appears that sick patients reduce their habitual activity and this may counterbalance the increase in RMR. In recent years the development of isotopic-tracer techniques has facilitated the measurement of TEE in free-living individuals. The energy cost of physical activity (and a small component of thermogenesis) can be calculated by subtracting RMR (Coward, 1988).

We have recently measured TEE in patients with SCLC using the novel labelled-bicarbonate–urea technique over 1 d in five patients and the mean over 2 d in a further three patients (Gibney et al. 1997). The method was validated against the measurement of energy expenditure in a whole-body calorimeter in five patients and shown to predict CO2 production to 102.1 (SD 3.4) %. REE, measured by indirect calorimetry was 106 (SD 11) % of predicted values (P < 0.05). Free-living energy expenditure averaged 8.73 (SD 2.34) MJ/d. TEE : RMR, which represents the physical activity level (PAL) of the subjects, and is normalized for differences in body size, was 1.36 (SD 0.22) with a range of 1.15–1.75, but all subjects except one had a PAL < 1.4 (Fig. 3). The exceptional subject was in remission and was consciously trying to maintain his very active lifestyle, walking or jogging several
miles each day, which is atypical for the majority of patients with cancer. In comparison with reference data from healthy individuals the measured energy expenditure of these subjects is very low, despite the modest increase in their RMR. Recent estimates suggest that the PAL of the healthy population with moderate activity is 1.5–1.7 (Department of Health, 1991) and a recent analysis of the world doubly-labelled water (DLW) literature suggests a mean PAL of 1.6 for age- and sex-matched controls (Black et al. 1996). The low level of TEE measured in our patients suggests that their energy requirements are unlikely to be higher than their pre-illness levels. In general, it appears that the increase which is observed in RMR is more than counterbalanced by a decrease in spontaneous physical activity.

We have also measured TEE in a much-larger group of patients with HIV infection using DLW (n 52; Macallan et al. 1995). The mean REE was 7.11 (SD 1.05) MJ/d, TEE
averaged 11.5 (SD 2.8), giving a PAL value of 1.6. Individual data are illustrated in Fig. 4 which also demonstrates the strong association of TEE with the weight status of the patients. The difference between TEE and REE represents the energy expended on physical activity. In the patients losing the greatest amount of weight, expenditure on physical activity was very low, with TEE only slightly higher than REE, whilst in those who were weight-stable or gaining weight TEE was almost twice REE. Contrary to the widespread belief that weight loss may be driven by high energy requirements secondary to hypermetabolism, the sickest patients actually had the lowest energy requirements. These patients, who in general had acute opportunistic infections, were often hospitalized with minimal voluntary physical activity. Conversely, patients who were weight-stable or gaining weight were at home, in a quiescent phase of the disease and able to go about their usual activities. In these subjects TEE was not significantly different from control subjects. Similar results have been obtained in a smaller group of patients (n 10) using the labelled-bicarbonate-urea method; TEE was 10.69 MJ/d, with a PAL value of 1.42 (Paton et al. 1996).

To date these remain the only studies of TEE in free-living individuals with cancer and HIV infection. Future studies need to address the changes in TEE during the progression of the disease and the inter-individual variability. Ultimately changes in physical activity may be used to assess patient well-being as a comparable but more objective assessment of performance status than clinical impression.

ENERGY INTAKE

Healthy individuals are able to adapt to periods of increased or decreased energy needs by changes in energy intake, maintaining a relatively-stable body weight. However, pathological processes frequently disrupt these regulatory processes. Furthermore, since energy expenditure is unchanged or decreased in patients with cancer or HIV infection, it follows that the major determinant of weight loss must be energy intake. In some cases, there may be a clear indication of the underlying cause of the poor energy intake. This may include physical symptoms such as nausea, vomiting or pain, social causes such as isolation or economic hardship, and behavioural or psychiatric causes such as anxiety or depression. For patients who experience prolonged periods in hospital or who are unable to prepare food themselves at home, the available food may simply be inadequate for their needs. Elderly patients in a psychiatric hospital were observed to be losing weight, despite eating all the food offered to them (Prentice et al. 1989). Their measured energy expenditure was only 6-1 (SD 1.4) MJ/d, which implies that the hospital food provided less than this and was insufficient to meet their energy requirements. In other patients, food intake may be poor due to physical handicaps, e.g. patients who are dysphagic following a stroke or those with motor neurone disease. Malabsorption may reduce intake both as a consequence of gastrointestinal losses and an apparent diminution of subsequent intake. A twofold reduction in gastric emptying rate has been reported in patients with head injuries and this limits the amount of energy the patients can digest even from enteral tube feeding (Weekes & Elia, 1995).

In many cases, individual patient assessments can detect these primary effects and with appropriate management food intake can be restored. However, in a subgroup of patients, notoriously those with cancer or HIV infection, energy intake remains inadequate despite the availability of food and the capacity for digestion and absorption of nutrients. This is characterized as the ‘anorexia of disease’ and represents a failure of the normal homeostatic mechanisms which regulate body weight. Many patients recognize the
consequences of their failure to eat and yet despite their motivation are still unable to overcome this profound anorexia. This has been clearly demonstrated in the HIV population. The 7d weighed dietary records showed that in the sickest patients energy intake amounted to only 5.6 (SD 2.6) MJ/d, despite access to food, nutritional supplements and dietetic counselling (Macallan et al. 1995). Fig. 5 shows TEE and energy intake, such that the difference between the two represents net energy balance. It is clear that the major determinant of weight change was energy intake which varied threefold across the group and greatly exceeded the changes in TEE.

These observations raise important questions about the control of appetite. We know little about the normal physiological process which maintain energy balance, and even less about how they are perturbed by pathological states. Numerous theories of appetite control are based on the effects of sensory influences (Booth, 1990), gastrointestinal factors (Read et al. 1994), neuroendocrine mediators (Rohner-Jeanrenaud, 1995) and oxidative feedback processes (Langhans & Scharrer, 1992). There is little doubt that the release of cytokines and acute-phase proteins during pathological processes is part of the anorectic response, but the mechanism of their action is not at all clear (Plata-Salaman, 1995).

The most fundamental method to reverse the anorexia of disease would be to treat the underlying disease and to control the symptoms. Our inadequate understanding of the aetiology of anorexia means that other more-specific interventions are largely empirical and focus on maximizing energy intake in the face of anorexia. For patients with cancer and HIV infection, nutritional supplements or sip feeds are the most-widely-used interventions and have been the subject of numerous clinical trials. Not all studies have achieved weight gain, or even a reduction in the rate of weight loss, but some of the negative findings may be because patients did not always consume the prescribed supplement. In a trial involving patients with head and neck cancer, only 30% of patients consumed at least 80% of the prescribed volume (Arnold & Richter, 1988). Palatability is a key issue, particularly in patients with cancer who may also suffer taste disturbances. Bolton et al. (1992) found that one-third of patients declined a range of sip-feed supplements because they were considered unpalatable.
Ultimately the net effect of supplementation programmes depends on the concomitant effects on a patient's voluntary intake of their normal diet. This is often poorly documented. An important study by Rana et al. (1992) in post-surgical patients carefully recorded energy intake from a sip feed and from the hospital diet. The sip feed not only supplemented the food intake but stimulated the consumption of other foods by an average of 1.05 MJ/d. This study is particularly important since it suggests that supplements may help to reverse the anorectic process. This may be via a disinhibition of intake once a threshold of energy intake has been reached, a phenomenon which has also been described in relation to enteral nutrition (Bastow et al. 1985; Allison, 1995). Similar studies need to be performed in patients with cancer and HIV infection.

It is probable that interventions designed to reduce the production and release of pro-inflammatory mediators may ultimately be of the greatest benefit since they may be able to reverse the anorexia itself. Recent research has shown the powerful effect that nutritional factors may have on the cytokine response; for example, feeding with fish oil diminishes the anorectic effect of interleukin-1 and tumour necrosis factor (Hellerstein et al. 1990). Other non-nutritional cytokine inhibitors may also be used. Appetite stimulants such as megestrol acetate may be able to override the anorectic response. Although the precise mechanism of action of megestrol acetate is unclear, recent evidence has implicated the neuropeptide, neuropeptide Y, which is a powerful feeding stimulant (McCarthy et al. 1994). Other nutritional and pharmacological strategies used in the treatment of anorexia have been reviewed recently and this is an area of much current research (Jebb, 1997a).

BODY COMPOSITION

Resolving anorexia is not an end in itself. Interventions must restore body weight, composition and functional performance. There is some evidence that HIV and cancer cachexia may be characterized by a disproportionate loss of lean tissue, suggesting a failure of normal regulatory processes which conserve skeletal muscle and visceral organs during periods of undernutrition, uncomplicated by disease. Therapies that simply overcome anorexia may not consistently restore an appropriate body composition.

There are numerous difficulties in accurately monitoring body composition and the changes associated with disease. Classical reference methods such as density, total body water and total body K are two-compartment models (fat and fat-free tissue) and assume a constant composition of fat-free tissue. Patients with cancer and HIV infection frequently experience an increase in hydration and changes in K concentration which invalidate these methods. We have described a method of analysis in which body water, bone mineral and fat are measured independently, leaving the remaining compartment, which is predominantly protein, to be calculated by difference from body weight (Fuller et al. 1992a). Although this requires access to a range of body-composition measurement facilities outside the provision of most hospitals, it does provide an accurate method for measurement of body composition with a precision of approximately 0.75 kg fat in a 'reference man' even under conditions of abnormal composition. The practical limitation to this approach has always been the measurement of body density, but with the advent of devices to measure body volume by air displacement rather than submergence underwater, this is now a viable method, at least for the purposes of clinical research (Dempster & Aitkens, 1995).

We have used this method as a 'gold standard' to evaluate the performance of other simpler techniques for routine clinical use (Fuller et al. 1992a). These have shown that skinfold thicknesses measured at four sites (Durnin & Womersley, 1974) give good...
agreement when measured by a single observer, although the validity is impaired by the inter-observer error associated with this technique (Fuller et al. 1991). The accuracy of impedance and resistance techniques depends entirely on the prediction equation employed. Moreover, in subjects with abnormal water status these measurements will be systematically biased. Newer multi-frequency impedance techniques offer greater potential since they make independent measures of extracellular and intracellular water (Cornish et al. 1996).

Unfortunately, the precision of indirect techniques for the measurement of changes in body composition is limited. Comparisons with balance studies show that multi-compartment models can measure the change in fat mass to ±0.77 kg in individual subjects (Jebb, 1993). Nonetheless, this still represents an error of ±29 MJ in net energy balance. Simpler methods based on a two-compartment analysis have larger errors, and this may be compounded by the use of prediction methods which carry their own inherent errors together with those of the method from which they were derived.

For the measurement of short-term changes in body composition the ultimate reference method is substrate balance. In a whole-body calorimeter it is possible to precisely measure dietary intake by the chemical analysis of duplicate food portions and collection of faeces to assess the digestibility. Protein oxidation is measured from the urinary losses of N, whilst fat and carbohydrate oxidation are calculated from O2 consumption and CO2 production data. These calculations are extremely sensitive to errors in respiratory gas exchange, but in our calorimeters with limits of precision of ±1%, the errors in fat oxidation are limited to ±9 g/d (Jebb et al. 1993).

We have studied the effect of undernutrition in healthy volunteers on the body’s macronutrient balance using whole-body calorimetry (Jebb et al. 1996). Three lean young healthy men (BMI 20–25 kg/m²) received 3.5 MJ/d for 12 d (containing (% energy) protein 31, fat 24, carbohydrate 45) and substrate flux was continuously measured. Changes in REE and TEE were small, amounting to only −8.3 and −10.5% respectively. However, there was a significant decrease in RQ, from 0.85 before underfeeding to 0.764 by day 12,

![Fig. 6. Mean changes in macronutrient flux in healthy volunteers receiving 3.5 MJ/d for 12 d. (○), Intake; (●), oxidation; (■), balance. (From Jebb et al. 1996.)](https://www.cambridge.org/core/terms).
representing the increase in fat oxidation. Fig. 6 shows the changes in macronutrient flux throughout the study. Carbohydrate oxidation decreased sharply to closely match carbohydrate intake. The net loss of carbohydrate in the first few days represents the depletion of liver glycogen and the small persistent negative carbohydrate balance probably represents a gradual diminution of muscle glycogen stores. Protein oxidation was essentially unchanged, presumably protected by a proportionally-large protein intake. The remainder of the energy requirements were derived from fat and since dietary sources were inadequate the body fat stores were depleted. Accordingly losses of body fat can be calculated to be 60% of the total weight loss. This gives a useful indicator of the likely losses of fat and fat-free tissue by lean individuals during periods of acute undernutrition, uncomplicated by disease.

In studies of the composition of weight loss in cancer and HIV infection it is important that we compare the measured change with that predicted in a healthy individual of similar initial body composition, rather than using a single value, typically 75%, which has been derived from studies of voluntary weight loss in obese subjects. In a recent study of changes in body composition in patients with HIV infection we showed differences in the percentage of weight lost as fat-free tissue when measured using different techniques; dual-energy X-ray absorptiometry (DXA; 60% FFM), TBW (55% FFM) or skinfolds (57% FFM; Paton et al. 1997). Although the percentage of FFM lost seems high when compared with the 25% often assumed (from Garrow’s (Webster et al. 1984) studies in obese subjects), the composition was compatible with that predicted for uncomplicated undernutrition in initially-lean subjects and did not suggest the occurrence of disproportionate losses of FFM (Forbes, 1987).

In patients with cancer and HIV infection the accurate measurement of changes in body composition is generally of greater clinical importance than absolute measurements. Here the precision of the various techniques is of paramount importance. DXA is a novel technique which is now widely available in hospitals throughout the country. It allows the measurement of bone, fat and fat-free soft tissue in a simple and non-invasive manner which is suitable for all but the sickest of patients. The precision of measurements of fat-free tissue is approximately 2%. This will allow the detection of a change in composition of 2% in a group of only twenty-one patients (Jebb, 1997b). Moreover it is possible to measure regional changes in composition, e.g. in arms, legs or trunk. Methods have also been described to assess abdominal fat mass (Svendson et al. 1993) and appendicular muscle mass (Heymsfield et al. 1989; Fuller et al. 1992b). We have used DXA to measure the change in composition of patients with SCLC (Jebb et al. 1994). In patients who responded to treatment there was no significant change in body weight or composition. However, among patients with progressive disease who lost 7% of their body weight, 29% of the weight loss was fat and 71% FFM, of which 76% was lost from muscle. DXA undoubtedly represents a useful new tool for the measurement of changes in body composition in clinical practice, although reports of inter-machine differences in the measurement of soft tissue composition cast doubt on its absolute accuracy and suggest it is prudent to make repeat measures on a single machine (Paton et al. 1995).

CONCLUSIONS

The incidence, causes and consequences of weight change in patients with cancer and HIV infection remains a fertile area of research. The prospective identification of patients at high risk of weight loss will allow interventions to be more accurately targeted, whilst patients at risk of excessive weight gain may also need appropriate counselling.
It is now apparent that reductions in energy intake are the primary determinant of weight loss. However, we have yet to elucidate the reason why the body is unable to accurately regulate its intake to match its requirements, even though energy expenditure is often decreased due to reductions in physical activity as a consequence of ill-health. Until this becomes clear the strategies to restore energy intake will remain largely empirical and may do little to address the underlying anorexia.

Changes in body weight are a crude marker of the body’s energy imbalance, and more specific measurements of gross body compartments are required; lean tissue, water and fat are all of clinical interest. More practical reference methods are required and also more accurate tools to assess body composition at the bedside. Measurements of regional body composition, including appendicular muscle mass, abdominal fat and specific body organs are also important to document more precisely the effect of the disease and interventions designed to reverse these processes. Ultimately, this will allow the relationship between body composition and morbidity or mortality to be elucidated and, hence, optimize the nutritional management of patients with cancer and HIV infection.

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