Pathophysiology of Cancer Cachexia: Current Understanding and Areas for Future Research

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Abstract

Weight loss and failure to gain weight normally in cancer patients are attributable to negative energy balance and altered metabolism. Energy balance is negative because of decreased intake, increased expenditure, or both. Changes in carbohydrate metabolism include glucose uptake and lactate production by tumor, relative hypoinsulinemia, and relative insulin resistance. Alterations in protein metabolism include preferential uptake of amino acids by the tumor, decreased synthesis of some host tissue proteins such as muscle tissue, and increased synthesis of other host proteins. Lipid metabolism is seemingly less affected. These metabolic changes result in muscle wasting in adult cancer patients and growth failure in pediatric cancer patients. Host tissues are catabolized to meet the nutritional demands of the tumor, and nutritional death may ensue.

Weight loss in adult patients and weight loss or failure to gain weight normally in children are frequent adverse effects of cancer (15). Weight loss or the failure to gain weight normally must represent disturbed coupling between energy intake and energy expenditure. In the normal coupling of these 2 processes, if energy expenditure is increased (such as by increased activity), energy intake increases. Conversely, if energy intake is decreased (such as in a voluntary reduction of caloric intake), homeostatic processes, such as a lowering of metabolic rate, result in reduced caloric expenditure.

In cancer patients, either reduced caloric intake or increased caloric expenditure or a combination of the 2 results in negative energy balance, cessation of growth, and weight loss. In some patients, factors causing reduced intake such as interference with normal gastrointestinal function may be apparent, but in many patients no apparent cause of decreased intake can be discerned. In some patients, such as in a patient with fever, increased energy expenditure may be obvious, but in most patients, increased expenditure escapes clinical detection.

In this paper, I will review current understanding of energy balance in cancer patients. However, negative energy balance is only one determinant of cancer cachexia; therefore, I will also review alterations in metabolism in cancer patients which contribute to our understanding of cancer cachexia.

Energy Balance

The role of insufficient food consumption as a cause of weight loss or growth failure in a cancer patient seems indisputable. However, evidence suggests that increased energy use may also be an important variable (32). Food consumption may be considered to be insufficient either in absolute terms or in terms relative to an increased energy use. Also to be considered when evaluating the relative adequacy of food intake are individual variations in caloric requirements for weight gain (27) and homeostatic adjustment to reduced caloric intake. In normal subjects, a forced reduction in caloric intake leads to a reduction in caloric expenditure; but in cancer patients, this normal adaptation may be blunted or blocked (3)

There are relatively few studies of energy balance in cancer patients and no detailed studies of energy balance in children with cancer. In adults, a report by Warnold et al. (32) is probably the best available study. They estimated caloric intake and expenditure over a 24-hr period and compared the results with controls having roughly comparable activity. They found both decreased energy intake and increased energy expenditure in the cancer patients compared with controls. The energy expenditure averaged 1980 kcal/24 hr, well within the range of normal caloric intake, while energy intake averaged 1340 kcal/24 hr. One illustrative case from that series was a patient who was studied while his tumor was present and again after its surgical removal. When the tumor was present, his energy intake was 1390 kcal/day, and his expenditure was 3330 kcal/day. During the second study, 20 weeks after surgery, he was in caloric balance with an intake of 2270 kcal/day and an expenditure of 2190 kcal/day. If we consider the second study as representative of his normal metabolic state, then the initial study showed both reduced intake and increased expenditure.

Many studies of caloric expenditure are deficient due to technical or other considerations. Patients have been studied by indirect calorimetry (O2 consumption and CO2 production) often for only limited periods of time, and the data obtained have then been extrapolated to 24 hr of expenditure. Errors in sampling and analyses and the magnification of these errors by extrapolation must be considered when interpreting the results from indirect calorimetry. Energy expenditure in cancer patients should be studied using direct calorimetry (measuring body heat production) for periods of at least 24 hr to encompass the usual diurnal cyclic variations in metabolism. Also patients should be studied at a caloric intake of their choice and at a caloric intake commensurate with their energy expenditure. The latter would evaluate whether increasing the energy intake results in a further increase in energy expenditure. These studies would resolve the question of whether energy balance is easily obtainable or is elusive. This kind of study would also provide a clue as to whether patients have reduced their caloric intake as a means of reducing their caloric expenditure (see below).

Energy balance should also be studied under conditions of an activity level of the patient's choice and at an increased activity level.
level. It will be of interest to know whether the increase in caloric expenditure with exercise is similar in cancer patients and in normal controls. The pattern of decreased activity in cancer patients is not well understood. A possible explanation is that cancer patients may decrease their activity to reduce their energy expenditure and thus diminish their energy deficit.

Increased Energy Expenditure

The increased energy expenditure of cancer patients includes energy expenditure within the tumor and energy demands placed on the host by the presence of the tumor. The energy requirements within the tumor will be discussed below in terms of carbohydrate and protein metabolism. The energy requirements of a tumor affect energy expenditure by host organ systems. If increased amounts of food need to be ingested and digested, this may increase energy utilization within the digestive system. Circulation of blood through the tumor may increase energy utilization by the heart. Increased energy expenditure results in increased oxygen consumption and increased carbon dioxide production, and this may increase the work of breathing.

Reduced Energy Intake

The reduced caloric intake in cancer patients is not well understood. Alterations in taste and smell sensation have been documented in cancer patients (6, 7, 23), but the relationship between these alterations and reduced caloric intake is not clear-cut. In several studies, reduced caloric intake seemed to correlate with these sensory abnormalities (5); but in a multi-variable analysis currently in progress, the association is of borderline statistical significance.2

Hypothalamic food intake control centers have been studied with the general conclusion that these centers are not abnormal in the cancer-bearing host (21). Bernstein (2) has recently drawn attention to learned aversions related to chemotherapy as a possible factor in reduced intake. It is likely that learning processes play a large role in controlling food intake. People learn to prefer certain foods because of pleasant tastes, smells, etc., during eating and because of pleasant internal feelings which follow eating of these foods. If eating of specific foods is followed by unpleasant sensations, one learns to avoid those foods. Normally, there is a slight increase in body heat production following eating, and this is perceived as pleasant. However, excessive body heat production is unpleasant, and if eating a certain amount of food resulted in an unpleasant degree of heat production, a learned reduction in food intake might result. I postulate that the increased energy expenditure in cancer patients includes an increased energy expenditure in response to energy intake and that intake of a normal-sized meal results in an unpleasant amount of body heat production. The patient then learns to eat less in order to avoid this unpleasant sequela of eating. This hypothesis is testable using continuous calorimetry to study the heat produced following a meal of the patient’s choice or a high-calorie meal.

Biochemical changes following eating might also lead to learned alterations in eating behavior. Lactate production is increased in cancer patients (see below) and Holroyde (11)3 has shown that increased carbohydrate intake results in a further increase in lactate production. It is known that infusion of lactate into normal volunteers elicits sensations of nausea. Thus, it is possible that, if a cancer patient eats a normal-sized meal, lactate production may increase, a feeling of nausea may ensue, and the learned response may be to eat less to avoid this sequence. Psychophysical studies in cancer patients can elucidate this possibility.

Mobilization of Energy Stores

When energy expenditure exceeds energy intake, energy stores must be utilized in accordance with principles of thermodynamics. Short-term deficits are met by mobilization of glycogen to form glucose, but glycogen stores are limited and are soon depleted. Body fat and body protein are then mobilized to meet energy requirements. In simple starvation, most of the energy requirements are drawn from body fat, and critical organs adapt to use of lipids and lipid metabolites as an energy source (3). However, in cancer cachexia, there is an increased need for glucose for use by the tumor (see below), and muscle protein is broken down to provide the carbon skeletons for gluconeogenesis.

Carbohydrate Metabolism

Carbohydrates provide a major source of the energy requirements for tumor metabolism. The magnitude of glucose uptake by a tumor-bearing limb has been studied in perfusion experiments and averaged 160 mg/min in patients with soft-tissue sarcoma (24). If this level of uptake were constant over 24 hr, the average tumor would take up 230 g of glucose. Glucose uptake was proportionate to tumor size and was approximately 1.4 g/24 hr/g of tumor (24). This level of glucose uptake (230 g/24 hr) by tumor agrees quite well with the increased glucose turnover of 170 g/24 hr observed by Holroyde (11) in studies of whole-body glucose metabolism in weight-losing cancer patients. Holroyde, however, did not find glucose turnover to be proportionate to tumor size, perhaps reflecting greater heterogeneity in his study population.

Glucose is metabolized in tumor tissue predominantly via anaerobic glycolysis (31). This predominance of anaerobic metabolism over aerobic metabolism persists even if tumor cells are well oxygenated in tissue culture, and it is explained by concentrations of enzymes which control cellular metabolism.

One consequence of this anaerobic metabolism is the release into the circulation of lactate by tumor cells. Lactate is transported via the circulation and is metabolized by the liver and kidney to produce glucose in an energy-requiring process. This cycle from glucose to lactate back to glucose, known as the Cori cycle, has been estimated to account for a 10% increase in energy expenditure in the tumor-bearing host (34).

Arterial blood levels of lactate increase only slightly in the presence of a tumor,2 reflecting the considerable ability of the liver and kidney to metabolize lactate. However, in the presence of extensive liver damage, such as with extensive liver metastases, lactic acidosis may develop. As discussed above, a question for future study is the role of lactate production in producing anorexia.

Another aspect of carbohydrate metabolism which may be
relevant to cachexia is abnormality of glucose tolerance (28). In this study by Smith et al., cancer patients had a mean blood glucose in excess of 160 mg/100 ml 2 hr after a standard p.o. glucose load. Over the interval from 1 to 4 hr after glucose p.o., cancer patients had statistically elevated blood glucose values compared to controls. Plasma insulin rose at a slower rate in cancer patients, but the eventual maximum concentrations were identical. However, the insulin:glucose ratio was lower in cancer patients, suggesting a relative hyporesponsiveness of insulin release by islet cells.

There is also evidence for insulin resistance in cancer patients. In a study of glucose loading p.o. (5 g every 15 min), the steady-state level of glucose was higher in cancer patients than in controls, while both groups had comparable insulin levels (26, 28). Also, in a study in which exogenous insulin was administered while endogenous insulin production was blocked, blood glucose was approximately twice as high in cancer patients as in controls, while comparable steady-state insulin levels were achieved providing further evidence for insulin resistance (27).

Future studies should include further evaluation of insulin resistance using the recently developed glucose clamp and insulin clamp techniques. The mechanism(s) of insulin resistance should be a focus of future research.

Protein Metabolism

Abnormalities in protein metabolism in cancer patients include the flow of amino acids into the tumor for synthesis of protein, reduction of synthesis of some host proteins, and an increased synthesis of other host proteins. The flow of amino acids into tumors has been documented in animal models (8) and in humans (24). The human studies measured arteriovenous differences in a tumor-bearing limb in the postabsorptive state. In the tumor-free limb of these patients, there was release of all amino acids. The tumor-bearing limb released less of every amino acid and, overall, released less than one-half of the quantity of amino acids released by the control limb. This reduced release from the tumor-bearing limb reflects the net effect of amino acid uptake by tumor tissue and amino acid release by normal tissue in that limb (24).

Synthesis of muscle proteins is generally depressed in cancer patients. Plasma amino acids in cancer patients are altered with decreases in some amino acids (4). However, decreased muscle protein synthesis is not simply due to alterations in the precursor pool. When protein synthesis is measured in cultures of tissues taken from cancer patients, the depressed synthesis is only partially corrected by an addition of an excess of amino acids (16) or insulin (19).

While synthesis of muscle proteins is depressed, synthesis of other host proteins may be increased. The liver seems to be protected from catabolic protein balance in the tumor-bearing host (17, 18, 30), and liver size remains normal or increases. The liver normally accounts for 20 to 25% of total oxygen consumption; therefore, continued hepatic protein synthesis may be an important factor in energy balance in cancer patients (34). When the characteristics of protein synthesis in the liver of tumor bearers are analyzed further, it is seen that synthesis of liver structural proteins is normal, while synthesis of secretory proteins such as acute-phase reactants is increased (22).

It is of interest to compare muscle metabolism in cancer-bearing hosts with that in pair-fed controls (imitating the decreased food intake of tumor bearers). Pair-fed controls show decreased muscle protein synthesis to the same level as do tumor bearers (29). However, pair-fed controls show decreased breakdown of muscle protein in contrast to increased breakdown of muscle protein in the cancer-bearing host tissues (16).

The pathophysiology of these alterations in muscle tissue can be in part explained by changes in muscle enzyme levels. Enzyme activities in muscle tissues of tumor-bearing animals and humans show depression of key enzymes of anabolism and increases in activity of catabolic enzymes, such as cathepsin D. The increased activity of catabolic enzymes in muscle tissue from cancer patients could be correlated with increased protein degradation compared to normal controls (15). Amino acids released from skeletal muscle are used for tumor protein synthesis and for gluconeogenesis to provide glucose for tumor metabolism (24). The result is progressive muscle wasting in the cancer patient.

Lipid Metabolism

Lipid metabolism is generally normal in cancer patients. Fasting free fatty acid levels are usually normal (11, 26), and they fall appropriately in response to insulin (19, 25). However, free fatty acid oxidation was suppressed to a lesser extent by glucose loading of cancer patients than that seen in normal controls (33). This decreased suppression of free fatty acid oxidation probably reflects utilization of glycerol for the accelerated gluconeogenesis in the cancer patient (25).

Seemingly at odds with these observations of Waterhouse which support increased utilization of free fatty acids are observations by Axelrod and Costa (1) which suggest decreased mobilization of fat in cancer patients. In Axelrod’s studies of the effect of a 4-day fast, controls show a progressive rise in free fatty acids during fasting, reflecting release from lipid stores. Cancer patients show a slower rise in fatty acids, suggesting decreased mobilization of lipid. A progressive rise in plasma ketones is noted in both groups with no difference between them.

In searching for an explanation for decreased lipid mobilization, Axelrod and Costa (1) have studied serial changes in hormones known to affect lipid metabolism. They have found that the cancer patients have decreased levels of triiodothyronine. During fasting, triiodothyronine levels fall in both controls and cancer patients, but differences between them continue for the duration of the fast. In interpreting these observations on plasma triiodothyronine levels, one must consider that a decrease in triiodothyronine levels is one of the homeostatic responses to reduced caloric intake. Thus, the low levels of triiodothyronine could reflect a response to antecedent hypocaloric intake rather than an effect of cancer. This area requires further study.

Body Composition

Observations on body composition, are relevant to this discussion of lipid metabolism. Cohn et al. (5), using neutron activation and whole-body counting, have estimated body fat and muscle compartments in cancer patients and age-matched
controls. They have noted relatively equal depletion of body fat and body muscle in cancer patients who have lost weight. If one thinks in terms of conservation of body function, mobilization of body fat and preservation of body muscle would be advantageous. However, in the cancer patients, the abnormalities of protein metabolism discussed above with normal or decreased lipid mobilization result in depletion of muscle reserves concurrent with relative preservation of body fat.

Nutritional Requirements for Growth

Nutritional requirements for growing children must include maintenance requirements, requirements for growth, and requirements for stress. Maintenance requirements for protein can be derived from nitrogen balance studies in which nitrogen balance is correlated with nitrogen intake. As one increases nitrogen intake from suboptimal to optimal, nitrogen balance changes from negative to positive. The nitrogen intake at which nitrogen balance crosses the zero intercept is taken as a measure of maintenance requirements. Several studies of this design lead to a suggestion of 140 mg/kg/day for maintenance for calculation of protein requirements for infants and children (9, 12-14). Losses through the skin, hair, and nails can be measured and, allowing for individual variation, one arrives at an estimate of 18 mg/kg for these losses (12). The protein requirements for growth can be calculated based on the protein content of normal weight gain and the efficiency of protein utilization (12). Protein for growth represents about 20 to 25% of the protein requirements of an infant. Finally, in a cancer patient, we must include a “stress allowance” for the requirements of the tumor and the stress effects of treatment. The magnitude of this stress allowance is entirely speculative (Table 1).

Caloric requirements can also be analyzed into component parts. Caloric requirements for basal metabolism can be calculated from the value suggested by Fleish of 53 kcal per sq m body surface area per hr or 1270 per sq m per 24 hr (Table 2) (10). Synthesis of protein is an energy-requiring process estimated at 3 to 8 kcal for each g of protein synthesized (20). If each g of growth is composed of 0.15 g protein, 0.6 g water, and 0.25 g fat, then each g growth would require 0.45 to 1.2 kcal/g growth. Based on a targeted weight gain of 0.9 g/kg/day, this converts to 0.4 to 1.1 kcal/kg body weight. In addition, one must allow for the metabolic requirements of activity which will be an addition of about 50% of basal metabolic requirements for moderate activity and a stress allowance for the requirements of the tumor and the effects of treatment.

If either the caloric or nitrogen requirements are not met in the cancer patient, the first effect will probably be interference with growth. Growth of soft tissue may be affected out of proportion to skeletal growth, and the weight/height ratio will fall below normal averages. With further decline in caloric intake, there may be insufficient energy for activity, and the child may become apathetic and listless. With decline in protein intake below growth requirements, the dynamic resynthesis of muscle may decline and further decrease activity. With continued inadequacies of caloric or nitrogen intake, host tissues will be catabolized to meet the needs of the tumor and the needs of vital host functions such as circulation and respiration. Eventually, these too may fail and nutritional death may ensue.

References

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Discussion

Dr. Holroyde: We have been concerned, in collaboration with Dr. George Richard, with attempting to use isotope tracer methodology to assess overall carbohydrate metabolism in patients with cancer cachexia. Patients were not uniform as to cell type but were uniform in that all were losing weight, usually up to 15% of body weight, and none of the patients were considered to be terminal at the time of study. I'd like to give an overview of glucose and lactate metabolism in normal humans. The liver has glycogen stores and a supply of glucose through gluconeogenesis which supplies the central nervous system, muscle mass, and RBC. In RBC, lactate is produced which circulates to the liver and kidney where it is converted back to glucose, giving a return of glucose from lactate of approximately 35 g of glucose per day. This gives a total turnover, that is, net production plus utilization, of 200 g. This cycle, referred to as the Cori cycle, is energetically wasteful in that it requires energy to return lactate to glucose. In our view, however, no direct measurements of the effect on overall energy metabolism can be made, since I do not believe it is possible to calculate this given the present state of knowledge. In one of our patients the total production plus utilization of glucose was 365 g/day which is at least twice normal glucose turnover, an enormous elevation in the utilization of glucose. Assuming that the normal person would require 130 g for the central nervous system, 40 g for muscle, and 30 g for RBC, then we assume that the tumor requires on the order of 165 g/day. These data are consistent with the data both from animal models and from the work of Dr. Brennan using isolated limb perfusion (24). This is, in effect, an extraordinarily high recycling of lactic acid, that is, glucose to lactate by anaerobic metabolism and back to glucose as part of gluconeogenesis. We have now studied in the postabsorptive state approximately 80% either glucose or uniformly labeled lactic acid in order to measure Cori cycle in a cancer population. I'd like to preface any remarks by saying that nothing about the metabolic events we have seen is specific for neoplasia, and there is, in all instances, a rather remarkable spectrum of results. First of all, we looked at lactate production rates in 20 patients using [14C]-lactate, and roughly 50% of the patients had an increase in lactate production. This I think one would expect, both from in vitro data and from data on isolated tumors using arterio-venous differences. Thus, in a cancer patient population who are anorexic, lactate production is increased in about 50%. When I say increased, this is increased as compared to normal age-matched subjects, and it is important in all studies of metabolism to attempt to get appropriate controls. This is a very difficult thing to do. One thing that we must do is to forbear the use of healthy young men for controls because there are many known factors of metabolism which are very much dependent on the age of the subject. Carbohydrate tolerance is one such example, and it is also well known that many aspects of fat metabolism are affected by age even in normal people. So when I use controls for the purposes of this brief discussion, I'm referring to an elderly group of volunteers without evident disease. It is of no surprise that we found lactate production to be increased; what was surprising to us was that there was a lack of correlation with various clinical parameters. Specifically, even though lactate production tended to be increased as tumor burden tended to increase, a fact which I find very difficult to measure in adults with average solid tumors, this correlation was far from clear-cut. Equally, if we look at glucose turnover rates, and we now have in excess of 200 tumor studies, Cori cycle activity as measured was markedly elevated in about 30%, and these patients tend to be those that have the highest caloric expenditure and the highest O2 consumption, but this is not necessarily so. A further 30% of patients have moderately increased glucose turnover rates, and roughly 40% or so are normal. One can have enormous tumor burden and have totally normal glucose turnover rates. Equally, one can have normal rates of caloric expenditure. The difference in those patients who are normal versus those with elevated turnover is entirely attributable to increased glucose recycling through the Cori cycle in cancer patients. Therefore, its seems that we have some subjects with normal turnover and therefore with presumably normal requirements, and we have others with extraordinarily high requirements. It is of interest to us to compare these results with those in 7-day-fasted normals. During fasting, glucose turnover rate falls. If you look at cancer patients with anorexia or cachexia studied in the postabsorptive state, the glucose turnover may be normal or it may be markedly elevated, clearly different from controls who are starved but otherwise normal. It might, therefore, be attractive as a hypothesis to wonder whether even a normal glucose turnover in the face of reduced caloric intake is not inappropriately elevated.

I'd like to comment on Dr. DeWys' comments about carbohydrate intolerance. One thing which very rapidly will inhibit gluconeogenesis within the liver is insulin, so that the finding of elevated Cori cycle activity in some patients would make you think they probably would be insensitive to insulin, either through tissue insensitivity in the liver or through a reduced secretion of insulin by the pancreas. The first has been hypothesized, and the second I think has been reasonably proven. We have done some preliminary work and do find that, in patients with high Cori cycle activity, there is a degree of relative hypoinsulinemia relative to the prevailing glucose level at the time the study was performed. Why do people have high Cori cycle activity? I think one must assume that this is a mechanism by which enough glucose is supplied to the host, the cancer-bearing patient, and that without effective gluconeogenesis glucose homeostasis could not be maintained. One way of decreasing gluconeogenesis would be for the patient to eat more, that is, to increase carbohydrate intake; but through anorexia, whatever the mechanism for anorexia is, this does not seem to happen, and therefore one must assume that glycogen stores are probably depleted in such patients. Shapo, many years ago, using infusions of epinephrine, found that a very large percentage of weight-losing cancer patients appeared to be depleted of liver glycogen, and we have some ongoing studies using glucagon infusions which seem to support this contention. I would like to mention glucagon in passing since it is an extraordinarily catabolic, naturally-occurring hormone which also is antagonistic to the normal actions of insulin. Unfortunately, we do not fully understand the normal role of glucagon, and it has largely only been studied in normals and in patients with cancer.
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