GLUCOSE METABOLISM IN CRITICAL ILLNESS

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INTRODUCTION

The pathophysiology of glucose metabolism in critical illness is a complex spectrum ranging from protein calorie malnutrition and starvation of the one hand, to a hypermetabolic response engendered by injury, inflammation and infection on the other. In their pure state, the two can exhibit almost diametrically opposite pathophysiological changes. An understanding of the hormonal, cytokine and growth factor changes occurring in these two states is crucial for the appropriate assessment and management of the patient with a critical illness. The continuum from one to the other is a dynamic flux so that a patient may present acutely, usually with a hypermetabolic stress response and evolve into starvation and malnutrition if and when the acute stress is overcome. Similarly a malnourished patient may, by virtue of a catastrophic event, be thrown into a hypermetabolic state and have few or no reserves to deal with the acute decompensation.

PROTEIN CALORIE MALNUTRITION (STARVATION)

Simple starvation results in physiological changes that are all geared to protect and preserve the body and especially its protein integrity and stores. Thus, hormonal change occurs to mobilize alternative sources of fuel. Insulin levels fall, and contra-insulin hormones like cortisol and growth hormone increase, so that adipose tissue stores are primarily mobilized to act as the fuel.

In simple starvation, there is a relatively clear cascade of events. In the face of a lack of nutrient supply, to meet nutrient demands, the body activates specific adaptive responses to preserve lean body mass. There is a relative immediate decrease in energy expenditure and thus a lowering of the basal metabolic rate. This is accomplished by changes in thyroid hormone metabolism mainly by an increased conversion of T4 to reverse T3, rather than T3, as well as a changed activity of the sympathetic nervous system.

Alternative fuel sources are mobilized and utilized and there is a reduction in protein wasting. Initially, stored glycogen is utilized as the fuel source and is able to, on an average, yield about 1200 kcal (in a 70-kg subject). Since glycogen stores are obviously limited, the next important fuel source is glucose synthesis from amino acids by gluconeogenesis. At the same time, the body begins to mobilize and oxidize fat stores, which have the capability of providing 1,60,000 Kcal in a 70kg subject. By 72 hours of onset of starvation, the adaptive response is fully functional and all except obligate glucose dependent tissues (like brain and red blood cells) utilize fatty acids, glycerol and ketones as the primary fuel source. This is reflected in a decrease in the respiratory quotient to 0.6-0.7 in the starved patient. It is important to note that while there is reduced protein synthesis there is a significant decrease in protein catabolism because of reduced utilization of gluconeogenetic protein substrate so that there is net preservation of protein stores and decreased ureagenesis. Obviously, if this state is further prolonged, adipose tissue reserves can be depleted to the point where skeletal muscle can no longer be protected. The average time total starvation can be sustained by humans, at standard body weight, seems to be 60-70 days, with an average loss of about 33% of standard body weight prior to demise, as shown in individuals who opt for hunger strikes. As a corollary, death usually ensues because of pneumonia occurring secondary to weak respiratory effort, heart failure, liver failure and Wernicke's encephalopathy with an oculogyric crisis.

STRESS HYPERMETABOLISM

Stress hypermetabolism represents the other end of the spectrum from starvation. Physiologically, there is a generalized response of the body to mobilize energy and substrate to support the inflammatory response, immune function and tissue repair. There is no attempt to preserve lean body mass; as well resources are mobilized to deal with the acute stress.

Carbohydrate metabolism continues apace and characteristically there is increased glucose oxidation as indicated by a respiratory quotient of 0.8-0.9, thus reflecting a very mixed fuel source. Gluconeogenesis is accelerated in the face of stress hypermetabolism and it cannot be adequately suppressed by exogenous glucose or insulin infusions. Furthermore, there is increased activity of the Cori cycle, which synthesizes glucose from

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lactate. The total system is geared to produce glucose and maintain it as the primary fuel source. Thus, the hyperglycemia seen in the stressed individual is secondary to more than simple insulin resistance engendered by an excess of contra-insulin hormones. While insulin resistance usually occurs because of decreased cellular glucose uptake, the hyperglycemia of the non-diabetic septic patient occurs in the face of maximal glucose oxidation, indicating a relatively healthy influx of glucose into cells. Thus, the hyperglycemia of the hypermetabolic patient is secondary to increased glucose synthesis by gluconeogenesis and Cori cycle activity.

In the patient with diabetes, especially Type 2 diabetes, where insulin resistance is already present in the premorbid condition, the excess mobilization of glucose synthesis caused by the hypermetabolic state continues apace, since there does not seem to be any feedback by glucose on any of the glucogensis pathways stimulated by the hypermetabolic state. If anything, at least theoretically, any defect in insulin action would further augment the gluconeogenesis pathways. Glucose oxidation remains at or close to maximal in such patients and exogenous insulin is therefore unlikely to adequately control the hyperglycemia, just as it has been shown in the individual without diabetes.

In the hypermetabolic state there is increased oxidation of all chain lengths of fatty acids. Concomitantly, there develops an essential fatty acid deficiency characterized by decrease in levels of linoleic and arachidonic acids and an increase in oleic acid. This is thought to be secondary to hyperinsulinema, which inhibits mobilization of fatty acids from adipose tissue. This deficiency may manifest within the first two weeks of the hypermetabolic syndrome and is worsened by the occurrence of decreased triglyceride clearance especially if liver and other organ failure is associated with the hypermetabolic stress syndrome.

Protein catabolism is significantly increased in the hypermetabolic stress syndrome and the rate of protein synthesis is markedly less than the rate of catabolism. Thus, there is a significant and constant loss of lean body mass as shown by an increased ureagenesis and urinary nitrogen losses, if the kidney is healthy. Amino acids needed for wound healing and maintaining the adequacy of the protective cellular inflammatory response as well as for gluconeogenesis, are mobilized from the skeletal muscles, connective tissue and the gut and in extreme cases, visceral organs like the liver, heart and kidneys. Amino acids can also be used as an oxidative fuel source at extra hepatic sites.

Almost all of the changes outlined above in carbohydrates, fat and protein metabolism are initiated and modulated by changes in the balance of insulin and the changes induced in the neuroendocrine and cytokine axis by this stress. Thus, there is an increase in aldosterone and antidiuretic hormone which causes the retention of salt and water and an increase in glucagon, cortisol and growth hormones, as well as catecholamines, the classical contra-insulin hormones. The increase in plasma catecholamines leads to the increase in the basal metabolic rate. There is little doubt that in the stressed hypermetabolic individual, the control of the basal metabolic rate shifts from thyroid hormone to catecholamines. Bio-chemically, catecholamines stimulate gluconeogenesis, glycogenolysis and accelerates lipolysis, which is controlled dynamically by the presence of hyperinsulinemia, which in turn slows down lipolysis. In stress hypermetabolism, the different effects of insulin manifest differently. Thus, while insulin, even in pharmacologic exogenous doses, is ineffective in further increasing the membrane transport and intracellular metabolism of glucose in the hypermetabolic patient, it is able to suppress lipolysis and protein breakdown. However, the latter are modulated by the push-pull response of insulin on the one hand and glucagon, catecholamines and growth hormones on the one hand and glucagon, catecholamines and growth hormones on the other hand. Glucagon promotes gluconeogenesis and hepatic amino acids extraction and working with cortisol accelerates protein breakdown characterized by increased ureagenesis, to provide amino acids for gluconeogenesis and direct amino acid oxidation utilization. Cortisol further promotes gluconeogenesis. The role of thyroid hormones in this situation is still unclear.

The cytokines, or inflammation mediators, are classically increased in the Hypermetabolic State and play a significant role in modulating the effect of hormones in the maintainence of energy and nutrient supply during the hypermetabolic Stress State. Cytokines are proteins secreted by activated monocytes and phagocytes and are either produced locally at the sites of injury or systemically in response to injury or shock. One of the main factors is the tumor necrosis factor (TNM) which accelerates protein catabolism. Working in concert with interleukin 1 (IL-1), TNF accelerates muscle Proteolysis, while at the same time increasing insulin and glucagon levels. IL-1 independently contributes to hyperglycemia by increasing

gluconeogenesis, most likely as a result of stimulation of the hypothalamic pituitary axis (HPA) and ACTH. TNF alpha, IL-1 beta and IL-2, all inhibit lipoprotein lipase, causing poor triglyceride breakdown and impairing lipid uptake, with IL-2 further activating some lipolysis. Cytokines are initially very beneficial, providing help to fight bacteria, promoting wound healing and mobilizing energy and substrate stores. But, their prolonged or excessive production aids and abets depletion of protein and energy stores and enhances morbidity. Specifically IL-1 and TNF down regulate the albumin gene by decreasing the rate of synthesis of albumin messenger RNA translator. Thus, albumin is specifically decreased because of reduced synthesis. In the face of increased catabolism and a shift of albumin from the intravascular to the extravascular space at the site of injury of inflammation, the decreased synthesis contributes to the hypoalbuminemia, seen in the hypermetabolic stress syndrome. It is, therefore, important to note that while the extent of hypoalbuminemia may predict the injury and inflammatory response, It is a poor marker for assessing the nutritional state of the hypermetabolic patient.

A large number of growth factors like platelet-derived growth factor, transforming growth factor, colony stimulation growth factor, epidermal growth factor, as well as IGF I, have been shown to be increased in the Hypermetabolic State. Because of their ability to regulate cell growth, division and repair, growth factors are no doubt involved in the development and maintenance state; which is after all, an attempt by the body to deal with an overwhelming stress and overcome it.

NUTRITIONAL ASSESSMENT

Obviously assessment and support of the hypermetabolic patient includes more than just calorie and protein evaluations followed by prescriptions. However, keeping within the scope of this paper, we will limit ourselves to these factors.

Nutritional support is designed on the basis of a nutritional assessment, which includes a number of important factors. The premorbid clinical state is important. Premorbid weight loss puts the patients at higher risk for having a compromised status and stores. Hypermetabolic stress in this situation is further magnified. Weight per se, is also misleading, in that total body water and salt are increased in the Hypermetabolic State.

Hypoalbuminemia is another important factor in the assessment. However, because cytokines like IL-1, TNF or endotoxin induce anorexia and hypoalbuminemia, albumin levels are not necessarily a good indicator of nutrition in this setting. Furthermore, albumin bound elements are therefore difficult to interpret, as are levels of albumin bound drugs.

The status of the premorbid Glucose State is important in that this presence of diabetes becomes an important element. However, hyperglycemia is multifactorial and not necessarily only due to impaired insulin action.

Age remains a critical factor. Aging changes the body composition and most formulae for nutritional assessment, do not take this change into consideration. Aging decreases the lean body mass and since ureagenesis and urine nitrogen excretion is dependent on lean body mass, the lower lean body mass in the elderly generates less urea and urinary nitrogen and therefore underestimates the level of stress that the elderly patient may be under. It also underestimates their stores. Thus, earlier nutritional support is necessary, but this is not usually evident in the common calculations done for the hypermetabolic stress syndrome.

Keeping these caveats in mind, the goal of nutritional support is to preserve essential organ structure and function. Nutritional requirements therefore must include the provision of non-protein and protein calories. These caloric requirements of the hypermetabolic patient are based on the resting energy expenditure and the level of metabolic stress. During high metabolic stress, nearly one-third of the energy expenditure is amino acid derived another third come form glucose, and the final third from fat. Thus, it is logical to provide a parallel level of exogenous support.

To determine the energy requirements, the gold standard is indirect, or in research situations, the more cumbersome, direct calorimetry. However, numerous studies have shown that the Harris Benedict equation, with some stress factor correction, correlates well with indirect calorimetry in most patients. In special circumstance, like very severely stressed patients, volume overload patients (in whom weight assessment to very difficult), morbidly obese or severely malnourished patients or in patients with hepatic and renal dysfunction, as well as the nutritionally supported individual proving difficult to wean off a ventilator and possibly, the premorbid patient with uncontrolled diabetes, the Harris Benedict equation is significantly inaccurate and indirect calorimetry is necessary to assess requirements.

Carbohydrate requirement guidelines have been established and these recommend that the maximum glucose administered should not exceed 5 gm/kg/day within the context that total calories should not exceed 25-30 kcal/kg/day. The maximal rate of glucose oxidation is about 5 mg/kg/min. In the hypermetabolic stress syndrome, the glucogenic pathways are so significantly stimulated that a large part of the substrate needed to get maximal glucose oxidation is endogenously provided (up to 4 mg/kg/min.). Thus, excessively high exogenous glucose loads only contribute to circulating hyperglycemia, since cellular uptake is already maximized, glucose oxidation is maximal and endogenous insulin levels are already high and therefore insulin action is also maximized. Thus, high exogenous glucose loads may only contribute to circulating hyperglycemia, excess carbon dioxide production and therefore ventilatory difficulties, hyperosmolar states and fatty infiltrates of the liver. "Restricting" the carbohydrates administered and providing the rest of the needed calories as fat and protein has been shown to be more advantageous.

As indicated, about a third of non-protein calories can be provided as fat and using long chain omega 3 fatty acids (between 1-1.5 gm/kg/day) is recommended. The omega 6 fatty acids form metabolities like prostaglandins, leukotriences and platelet activating factor, which are very metabolically active in continuation of the hypermetabolic stress syndrome. The omega 3 fatty acids give rise to less active metabolites.

Protein needs in hypermetabolic stress syndrome are significantly increased, but it must be remembered that exogenous protein does not inhibit catabolism; it only stimulates the synthetic rate. Thus, the lean body mass continues to be catabolized to provide amino acids for hepatic acute phase reactants, gluconeogenic substrate, and maintenance of the cellular inflammatory response and fuels for direct oxidation. Exogenous protein supports synthesis and in a way, provides more protein for catabolism should the hypermetabolic state continue, thereby allowing for longer survival of the patient. The recommendations are that protein and/or amino acids should be administered between 1.2-2gm/kg/day and this is geared to promote a positive nitrogen balance. Administrations beyond these levels have no benefit and may predispose to azotemia. It is important to remember, that in the stress hypermetabolic state, the ratio of non-protein calorie to nitrogen ratio is optimized closer to 80:1 or 100:1 rather than in the usual total parenteral nutrition, which contain 150:1 ratio. Individualization for each hypermetabolic individual is mandatory.

Routes of providing nutrition have various pros and cons, but the route does not seem to play a significant role in modulating glucose kinetics or the nutritional state; while it does seem to have a significant role to play in protection of the gut and of immune function. Thus, the route of administration does not need a detailed discussion.

Monitoring the response to nutritional support is very important, so that therapy for each individual with hyper- metabolic stress syndrome can be individualised. Besides monitoring weight, which as explained above can be misleading in the face of increased salt and water retention, and upper arm circumference, which again can be very misleading (not only prior to, but within one or two days of starting refeeding, because of the edema evoked). It would seem that an-early 24 hours urine for urea nitrogen, to assess the catabolic state, is probably ideal. This not only shows the degree of catabolism, but also the degree of metabolic stress. While it can be inaccurate in the premorbid starved individual, it still gives a significant window into the nutritional state of the individual. Subsequently, another 24 hour urinary urea nitrogen performed within a week of starting nutritional support provides a good index for the efficiency of the nutrition, at least as far as nitrogen balance is concerned. Of course, if indirect calorimetry is available, it can be used on 2-3 day basis to assess energy requirements and further titration of the nutritional support, with the fractions of protein; carbohydrate and fat administered being more appropriately calculated. While some authorities claim that while testing for energy and showing subsequent recovery may also be of some use, such testing has fallen by the way side, partly because it is Cumbersome and partly because it does not remain as exact as one would like it to be. Measures of muscle strength and bio-impedance methods for determining total body water can be used, but again they are cumbersome and not exact. It would seem that the 24 hours urea nitrogen excretion is probably the best method of assessing the efficacy of the nutritional support.

SUMMARY

Hyperglycemia is a common feature seen it most intensive care situations. It is crucial to difference this hyperglycemia from others, since all hyperglycemias are not created alike. Even in the individual who had Type 2 diabetes and becomes catastrophically ill, the contribution of the diabetes and its hyperglycemia is not the only factor causing

the hyperglycemia. In other words, in the critically ill, the hypermetabolic syndrome that evolves, in of itself induces hyperglycemia and it is simplistic to say that such hyperglycemia is because of insulin resistance. In fact, in the hypermetabolic stress syndrome, cellular glucose uptake is already maximized and insulin-which is already endogenously high, is unlikely to further cause cellular glucose uptake. Glucose oxidation is maximized as well. Because of these factors, the nutritional support of such an individual with large numbers of calories in the form of dextrose or carbohydrate are not only not beneficial, but may prove of some risk. A clearer understanding of the cascade of events and the pathophysiological basis of stress hypermetabolism, allows for a better prescription of nutritional support and augurs a more advantageous outcome to the hypermetabolic stress syndrome in any one individual

Reference for further reading

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