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Editorial Article

Metabolic abnormalities in acute renal failure, influence on nutritional management

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Running title: Metabolic changes in acute renal failure

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Introduction

Acute renal failure (ARF) occurs when there is a rapid loss of the clearance capacity of the kidney. This leads to an abrupt accumulation of unexcreted waste products. Even though the specificity of uremic toxins is debated, it is clear that accumulated waste products lead to anorexia, lethargy, nausea, vomiting and other symptoms associated with uremia. ARF also causes accumulation of sodium, water and electrolytes which can cause life-threatening problems from extracellular volume overload, hyperkalemia, etc.

In patients with ARF, the mortality rate has not changed substantially in spite of the intensive use of dialysis. For example, the mortality rate of wounded soldiers with ARF in the Korean and Viet Nam wars was scarcely different in spite of the wide-spread availability of dialysis in Viet Nam compared to the Korean War [1]. Even patients who develop ARF from other causes have a poor prognosis with a mortality rate of 50-60%. The rate is even higher in elderly patients and those with failure of other organs [2].

Why the mortality rate is so high if dialysis can replace the function of the kidney as it does for patients with chronic renal failure (CRF)? There is no simple answer but one reason is the catabolism associated with ARF or diseases causing ARF.

Secondly, ARF develops rapidly, so metabolic defects are more dramatic and the ability of a patient to respond to metabolic abnormalities is more limited than in CRF patients. Consequently, principles guiding the therapy of metabolic abnormalities associated with CRF may not apply to patients with ARF.

It is important to recognize this difference because it changes the dietary prescription, including the amounts of protein and calories (fat and carbohydrates), as well as minerals and vitamins.

Metabolic abnormalities in ARF

Energy metabolism

In rats with experimental ARF but without sepsis, trauma, etc. there is decreased oxygen consumption (i.e. "uremic hypometabolism") even when hypothermia and acidosis are corrected, suggesting impairment of oxidative phosphorylation [3,4]. In adults with ARF or advanced CRF, energy expenditure is normal unless there is a complicating disease [5,6]. These results indicate that acute uremia exerts little influence on energy metabolism and decreases rather than augments energy expenditure. This observation is consistent with the grossly abnormal pattern of substrate oxidation in ARF. Carbohydrate oxidation is slightly reduced and lipid oxidation slightly increased in subjects with ARF after an overnight fast.

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Carbohydrate metabolism

ARF is commonly associated with hyperglycemia because of insulin resistance. In experimental ARF, the plasma insulin concentration is elevated, maximal insulin-stimulated glucose uptake by skeletal muscle is 50% lower and glycogen synthesis in muscle is impaired [7,8]. Since the dose-response relationship between insulin concentration and glucose uptake reveals that the insulin concentration causing a half-maximal stimulation of glucose uptake is normal, there must be a postreceptor defect in insulin action rather than impaired insulin sensitivity in ARF. In support of this conclusion, the maximal rate of insulin-stimulated glycogen synthesis in muscle is abnormally low [8].

A second abnormality in glucose metabolism in ARF is accelerated hepatic gluconeogenesis mainly from amino acids released during muscle protein catabolism. Hepatic extraction of amino acids, their conversion to glucose and urea production are all increased by ARF [9,10].

The abnormality in muscle glucose and protein metabolism caused by ARF were shown to be interrelated: the impaired uptake of glucose and its conversion to energy in muscle are highly correlated with the accelerated rate of protein catabolism [7,8].

In healthy subjects, hepatic gluconeogenesis from amino acids is readily and completely suppressed by an exogenous infusion of glucose which stimulates release of insulin. However, in conditions such as sepsis or ARF, hepatic glucose formation is diminished but not halted by infusing glucose. This has important implications for prescribing a regimen of nutritional support for an ARF patient because it means that protein catabolism cannot be suppressed simply by providing increased amounts of nutritional substrates [11]. To improve therapy of ARF patients and preserve lean body mass, strategies that successfully block protein catabolism must be developed.

Lipid metabolism

There are profound alterations in lipid metabolism in patients with ARF. The triglyceride content of plasma lipoproteins, especially VLDL and LDL, is increased but total cholesterol, and in particular, HDL-cholesterol are decreased [5]. The protein component of lipoproteins also is abnormal with low concentra-tions of apoproteins A-I and A-II [12]. The major cause of these lipid abnormalities is impaired lipol-ysis. In ARF patients, the activities of both lipolytic pathways (peripheral lipoprotein lipase and hepatic triglyceride lipase), are decreased by ~ 50%.

These findings are important for the design of nutritional regimens. For example, lipids contained in the lipid emulsions used in parenteral nutrition regimens are degraded in the same fashion as the endogenous VLDL lipid particles. Consequently, the impaired lipolysis caused by ARF delays the elimination of intravenously infused lipid emulsions; the elimination half-life is doubled and the clearance of conventional fat emulsions is reduced by more than 50% [12].

Lipid emulsions used in parenteral nutrition usually contain triglycerides with long-chain fatty acids, mostly derived from soybean oil, but there are fat emulsions with a mixture of long-and medium-chain triglycerides. The proposed advantages of infusing medium-chain triglycerides include:

- A more rapid elimination of lipids from the plasma due to a higher affinity of the medium-chain triglycerides for lipoprotein lipase.
- A carnitine-independent metabolism of fatty acids.

However, the impaired lipolysis caused by ARF cannot be bypassed simply by using medium-chain triglycerides; the clearance of this type of fat emulsion is equally retarded in ARF patients [12]. In contrast, the oxidation of fatty acids is not impaired by ARF.

The abnormalities in lipid metabolism associated with ARF are not due to carnitine deficiency. In contrast to patients with CRF, plasma carnitine levels are increased in ARF due to an increased release of carnitine from muscle plus activated carnitine synthesis in the liver.

Protein-and amino acid metabolism

A major problem of ARF is the rapid accumulation of nitrogen-containing waste products. A major cause of this problem is excessive protein catabolism with sustained negative nitrogen balance [5]. The import-ance of abnormal protein metabolism caused by ARF is highlighted by considering normal values of protein turnover in adults (Figure 1). In a 70 kg man eating 1 g protein/kg/day (protein is 16% nitrogen), the nitrogen excretion is 11.2 g/day if the patient is in neutral nitrogen balance. The amount of protein being synthesized and degraded each day is about 280 g protein/day [11].

In fact, it is about 10-fold higher than the amounts of plasma proteins being synthesized and degraded each day. These results emphasize why a small, but persistent decrease in the rate of protein synthesis or increase in the rate of protein degradation cause large losses of lean body mass. Experimentally, it has been shown that ARF causes muscle protein catabolism by reducing the rate of protein synthesis and increasing the rate of protein degradation. The abnormalities in protein synthesis and breakdown in muscle cause excessive release of amino acids from muscle which

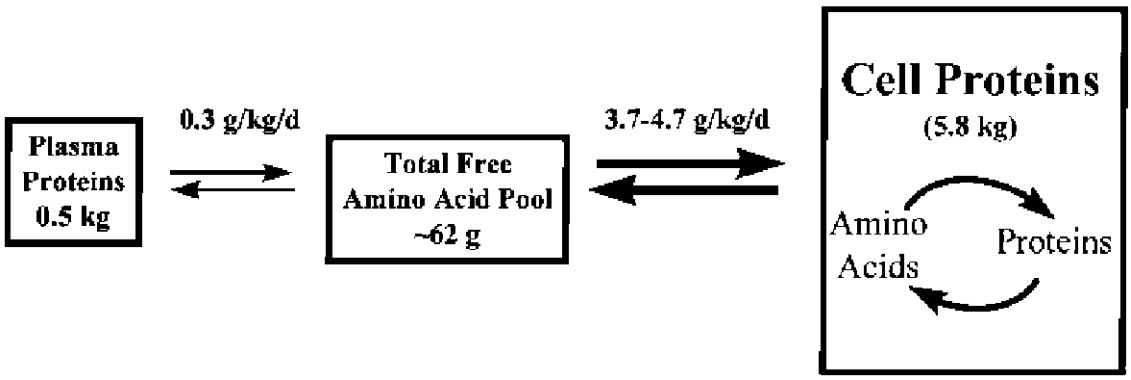

Fig. 1. Rate of protein turnover in a normal 70 kg man eating 1 g protein / kg / day.

are metabolized to urea and other nitrogen-containing waste products [7,13].

Besides abnormalities in protein turnover, uremia can blunt the transport of amino acids into muscle and increase the degradation of amino acids in muscle. In rats with ARF, there is depressed transport of amino acids into skeletal muscle because the activity of the System A transporter is blunted[14]. The abnormality in amino acid transport is linked to insulin resistance and to impaired cellular ion transport processes, including depressed sodium-coupled amino acid transport. This problem is linked to impaired NaK-ATPase activity [15,16]. We found that both the activity and receptor density of NaK-ATPase are abnormal in adipose cells and muscle from uremic rats apparently because there is a circulating inhibitor since there is no consistent abnormality in expression of NaK-ATPase in muscle or adipose cells [16,17].

ARF patients with metabolic acidosis also exhibit accelerated degradation of amino acids [18,19]. One mechanism for this abnormality was shown to be an increase in the activity of the rate-limiting enzyme in branched-chain amino acid (BCAA) metabolism, branched-chain ketoacid dehydrogenase or BCKAD [20,21]. When accelerated amino acid catabolism is combined with reduced amino acid uptake and impaired protein synthesis, the pools of amino acids in plasma and in the intracellular compartment become imbalanced and this leads to changes in plasma amino acids. Any change in plasma amino acids will be aggravated when there is an inadequate intake of protein or amino acids because of ARF. The major consequence of abnormalities in amino acid metabolism is that amino acids are redistributed to the liver: hepatic extraction of amino acids from blood, with resulting gluconeogenesis, ureagenesis and protein synthesis (acute phase protein secretion) all are increased in the liver of rats with ARF [9,10]. In summary, there are multiple abnormalities of protein and amino acid metabolism in uremia.

Causes of muscle catabolism in ARF

In ARF, there are stimuli that could accelerate protein and amino acid catabolism, including defects in hormonal responses and metabolic acidosis. For example, a major catabolic stimulus in ARF is the resistance of muscle to the anabolic effects of insulin. In experimental ARF, it was found that the maximal rate of insulin-stimulated protein synthesis in muscle is depressed while the rate of protein degradation in muscle is increased even in the presence of insulin [7]. As noted, ARF-induced abnormalities in protein and energy metabolism in muscle are linked; the rate of protein catabolism was found to be closely related to the decrease in glucose uptake and its conversion to lactate in muscle [7,8].

Besides insulin resistance in ARF, there are high circulating levels of catabolic hormones (glucocorticoids, catecholamines, glucagon) in blood and hyperparathyroidism may be present [5]. Each of these could stimulate protein breakdown. For example, increased glucocorticoids will reduce protein synthesis and increase protein degradation in muscle [22,23]. It also is possible that release of inflammatory mediators (e.g., tumor necrosis factor and interleukins) because of sepsis or other diseases causing ARF act to stimulate muscle hypercatabolism [11]. Inadequate nutritional support in the presence of these stimuli will potentiate the loss of lean body mass.

Metabolic acidosis also stimulates protein breakdown in muscle [24,25]. In adults with uncomplicated metabolic acidosis or with the acidosis of uremia,

there is increased catabolism of protein and BCAA [18,19]. Other reports document that acidosis stimulates protein catabolism in children and adults, including dialysis patients [26,27]. It is important to emphasize that the catabolism caused by metabolic acidosis will be most dramatic in patients with anorexia or those eating a low-protein diet.This occurs because metabolic acidosis impairs the normal responses to eating a low-protein diet (Figure 2).

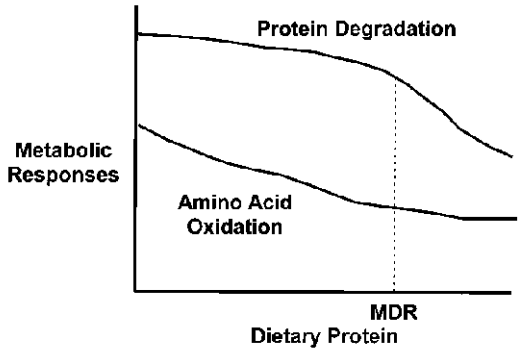

Fig. 2. The metabolic responses to changes in dietary protein are a progressive decrease in amino acid oxidation until the minimum daily requirement (MDR) of ~ 0.6 g protein/kg/day is reached. At this level, protein degradation becomes lower.

Results depicted in Figure 2 show that when dietary protein is restricted, the principal compensatory response is a dramatic reduction in amino acid oxidation resulting in more efficient utilization of dietary essential amino acids. If protein intake is adequate, production of metabolic waste products is decreased and nitrogen balance is neutral. This response permits the body to retain enough amino acids to replace the protein lost in normal turnover without changing the levels of amino acids in plasma and cells [11]. If, however, dietary protein is below the minimum daily amount (~ 0.6 g protein/kg/day), another response is activated and the rate of protein degradation falls. Fortunately, renal failure alone, in the absence of metabolic acidosis, does not block these responses [28,29]. Metabolic acidosis, however, stimulates both the degradation of BCAA by activating BCKAD and the rate of protein degradation in muscle [18-21,24,25]. Consequently, metabolic acidosis would block the ability of the patient to respond to a low-protein diet by reducing the rate of degradation of amino acids and protein. This would lead to negative nitrogen balance and loss of lean body mass.

Another stimulus for catabolism is dialysis. Protein catabolism during dialysis is due in part to losses of nutritional substrates [30]. There is also evidence that the dialytic process stimulates protein degradation in muscle, even in normal subjects [31]. In these experiments, normal adults were given a "sham-dialysis" by passing their blood through a dialysis filter while the rate of protein degradation was measured in leg muscles. Muscle proteolysis was found to be significantly increased.

Pathways activated to degrade protein

Recent evidence indicates that the bulk of protein in all cells, including muscle, is degraded by the ubiquitin-proteasome pathway which requires ATP [11]. Membrane proteins, transcription factors as well as structural proteins are all degraded by this proteolytic pathway. Fortunately, the rate of degradation in this pathway is highly regulated. The first type of regulation is that protein that will be degraded is conjugated to ubiquitin (Figure 3).

Ubiquitin is a member of the heat-shock protein family that is present in all cells and serves to identify which protein should be degraded in the proteasome. A second level of regulation occurs at the proteasome, a multisubunit complex of proteins forming a ringed complex with a central "tunnel"; inside this tunnel, proteolysis occurs. The proteasome unfolds the substrate protein, removes ubiquitin and directs the protein into the central tunnel where it is clipped into small peptides of 7-12 amino acids. These small peptides are degraded by cytoplasmic peptidases and the amino acids are released from the cell.

Experimentally, the ubiquitin-proteasome pathway in muscle has been found to be activated in a number of catabolic states including metabolic acidosis, uremia, starvation, diabetes, cancer, sepsis, trauma and denervation [11]. In each of these conditions, the increased activity of the pathway is accompanied by high levels of mRNAs encoding ubiquitin and at least some subunits of the large proteasome complex. The increase in levels of mRNAs is due in part to stimulation of transcription of the genes, at least in uremia and diabetes [11]. Because the ubiquitin-proteasome pathway is activated in many illnesses, the signal stimulating the transcription of these genes is under intensive investigation.

Regarding therapy of ARF, there are inhibitors of the ubiquitin-proteasome pathway that can block the excessive muscle protein degradation in isolated muscle of rats with ARF. The usefulness of these inhibitors in blocking the excessive protein degradation in muscle of animals or patients with catabolic conditions have not been tested [11].

Nutritional therapy of ARF patients

The consequences of these metabolic alterations plus those from diseases causing ARF determine the type and optimal composition of nutritional support therapy. The stable patient with uncomplicated ARF

and minimal to moderate hypercatabolism generally does not require any nutritional intervention while hypercatabolic patients with dysfunction of organs besides the kidney will require nutritional support to prevent the loss of lean body mass. Some points deserve special consideration:

First; at what level of renal failure do the various metabolic defects become clinically important? Clinical studies indicate that changes in lipid and carbohydrate metabolism can be measured in virtually all patients when the creatinine clearance is below 30 ml/min (corresponding to a serum creatinine > 3.0 mg/dl). Likewise, protein balance is abnormal (i.e. muscle protein catabolism is high and there is impaired protein synthesis when creatinine clearance is below 25 ml/min), especially if there is acidosis.

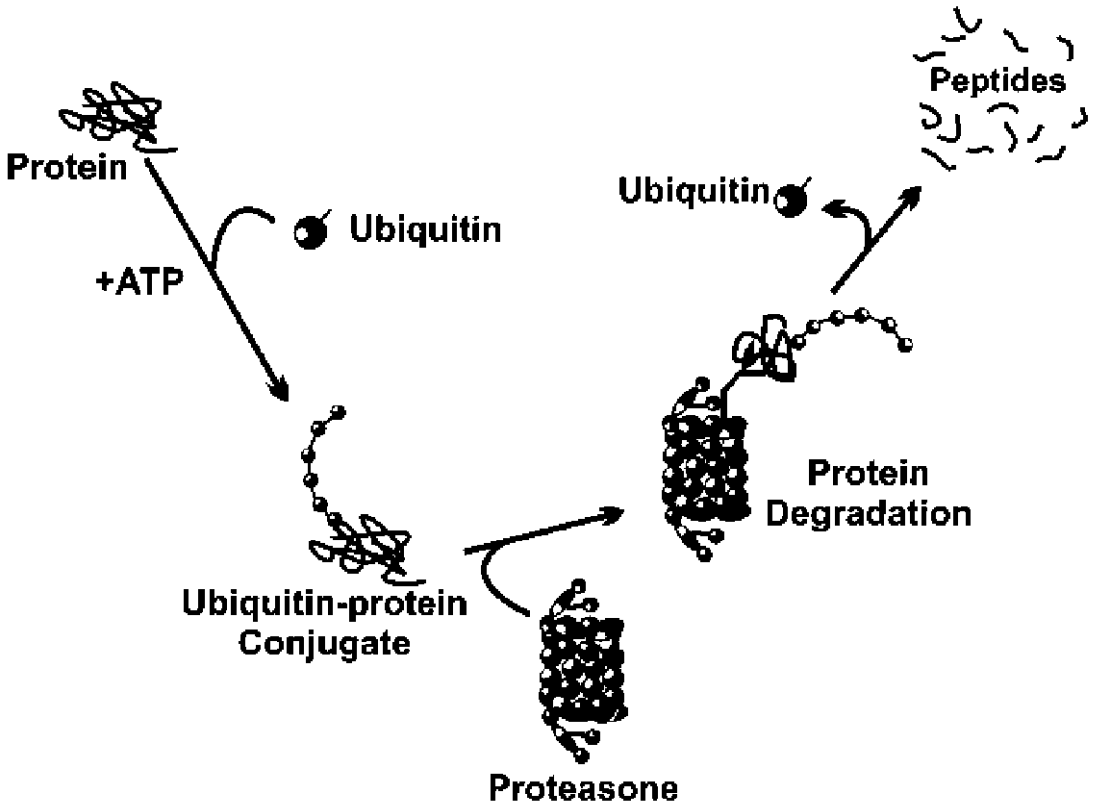

Fig. 3. Schematic drawing of the ubiquitin-proteasome pathway showing that proteins degraded in this pathway are first conjugated with ubiquitin in an ATP-dependent reaction. The conjugated protein is recognized, unfolded and degraded to small peptides by the proteasome.

A second question; is should nutrients be given enterally or parenterally? Whenever possible, enteral nutrition is preferred. Even if parenteral nutrition is needed, some nutrients should be given by the enteral route since even small amounts can improve intestinal functions, especially the barrier against translocation of bacteria through the intestinal wall and hence, sepsis [5].

The third question; is when should nutritional support be initiated? During the acute phase of injury (i.e. within the first 24 hours after trauma or surgery - known as the "ebb phase") nutrients should be withheld. Provision of amino acids or glucose during this phase increase oxygen requirements in damaged organs, including the kidney, but oxygen supply is often limited leading to more tissue injury and further impairment of renal function [32]. It is recommended that nutritional support should be withheld for 24 hours after the injury and then given at a low rate to ensure optimal nutrient utilization while avoiding metabolic derangements.

Energy substrates

How many calories does the patient need? No patient with an acute disease should receive more calories than he or she can utilize because excess calories will

just be stored as fat. Lipogenesis occurs primarily in hepatocytes but unfortunately, the new lipid causes fatty infiltration of the liver and impairs hepatic function. An excess of calories increases oxygen consumption and body temperature ("substrate-induced thermogenesis") while stimulating catecholamine secretion ("nutritional stress"). Oxidation of carbohydrates is also associated with an exaggerated release of carbon dioxide that aggravates respiratory insufficiency [5]. Energy expenditure has been measured by indirect calorimetry or by dilution techniques using a right heart catheter and there is good evidence that the energy requirements of an ARF patient with sepsis and multiple organ dysfunction syndrome rarely exceeds 25 to 30% above basic requirements [5].

Thus, in 90% of the patients an energy supply of 130% of the Basal Energy Expenditure (BEE) as estimated by the Harris-Benedict equation will be sufficient.

Glucose: Should be the main energy substrate in a parenteral nutrition regimen. It should be supplied at a rate that does not exceed the rate of glucose oxidation and < 5 g/kg/day, because above this level the fraction of glucose converted to fat and the amount of CO2 generated increase sharply [33]. This occurs because of the glucose intolerance from ARF plus factors such as trauma or infections. Even though insulin will normalize the blood glucose, it will not augment the oxidation of glucose to energy. On the other hand, hyperglycemia can stimulate protein catabolism or non-enzymatic glycosylation of proteins and immunoglobulins [34]. For these reasons, at least a fraction of the energy requirement should be replaced by lipids.

Lipids: A combination of lipids and glucose as energy substrates increases the survival of uremic animals. This combination reflects the pattern of endogenous substrates oxidized more closely than glucose alone; the body oxidizes fatty acids to provide at least 60% of energy expenditure, even if glucose is given exclusively. In addition, lipids provide structural molecules (membrane components) and precursors of prostaglandin synthesis. Lipid emulsions also have a high specific energy content and a low osmolality. Medium-chain triglycerides do not offer specific advantages over emulsions containing long-chain triglycerides in patients with ARF [12]. Most agree that 10% fat emulsions should be avoided because the phospholipid/triglyceride ratio could result in liposome accumulation, especially in the presence of impaired lipolytic activity.

Amino acids and protein supply: Activation of protein catabolism in ARF along with enhanced hepatic conversion of amino acids to glucose is a metabolic response that is not suppressed by giving glucose or amino acids. Thus, it is impossible to achieve nitrogen balance simply by increasing energy intake in a catabolic patient with ARF. Moreover, any excess of nitrogen intake increases the production of urea and other nitrogenous waste products and more pronounced negative nitrogen balance.

The relationship between nitrogen intake and protein catabolism is "U-shaped": an insufficient amount stimulates endogenous protein catabolism but an excessive intake results in the surplus of amino acids being converted to urea and other waste products. Thus, the optimal intake should reduce endogenous protein breakdown and urea production to the minimum while stimulating protein synthesis. In non-catabolic patients during the recovery phase of ARF but not requiring dialysis therapy, protein requirements range from 0.6 - 0.8 g kg /day. In patients treated by regular renal replacement therapy (daily hemodialysis or continuous hemofiltration / hemodialysis) amino acid or protein intake should be adjusted to 1.2 g/kg/day [5]. In septic patients it was shown that an optimal intake was 1.4 g/kg/day so dietary protein or infused amino acids should be <1.5g protein/kg/day [11].

Since mortality in ARF is correlated with the degree of hypercatabolism and since protein catabolism cannot be suppressed by conventional nutritional strategies, future advances must include methods that inhibit protein catabolic pathways [11]. Possibilities include growth factors such as human growth hormone, epidermal growth factor or insulin-like growth factor-I. In rats with ischemic ARF, IGF-I improved nitrogen balance but also accelerated recovery from renal failure [35]. Preliminary clinical investigations have yielded less clear-cut results.

Conclusions

The objectives of nutritional support in patients with ARF do not differ from those in other clinical situations but there are multiple metabolic alterations that complicate the design of nutritional regimens. Current nutritional strategies do not correct or compensate for hypercatabolism. The identification of interventions that suppress the accelerated protein breakdown associated with ARF must be developed to improve nutritional support and ultimately, survival in patients. Since the pathways causing catabolism including the ubiquitin-proteasome pathway and BCKAD are known, there are targets for specific strategies. Growth factors such as human growth hormone or insulin-like growth factor-I and inhibitors of specific pathways of protein degradation present the most promising approach to the solution to hypercatabolism in ARF.

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