CHAPTER 75

Carbohydrates and Lipids

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OBJECTIVES

This chapter will:

1. Describe the main alterations in carbohydrate and lipid metabolism in isolated and complicated acute renal failure.
2. Elucidate the mechanisms of carbohydrate and lipid metabolic dysfunctions.
3. Highlight the therapeutic implications of the metabolic alterations.

Patients with acute renal failure (ARF) may present with a widely varying hormonal and metabolic status. The isolated acute loss of excretory renal function causes metabolic alterations that are similar to those encountered in chronic renal failure. More often, however, ARF is associated with conditions such as sepsis, trauma, and multiple-organ failure and is seen in about 36% of patients in the intensive care unit (ICU).[1] These latter patients usually sustain profound hormonal dysfunction, which results in impairment of protein, carbohydrate, and lipid metabolisms.

The metabolic response to stress in critically ill patients is characterized by the increased production of stress mediators, such as counterregulatory hormones (catecholamines, cortisol, glucagon, growth hormone), cytokines (interleukin-1, interleukin-6, tumor necrosis factor-alpha), and other immune mediators (thromboxane A2, prostaglandins). These stress mediators upregulate, in critical illness, membrane expression of glucose transporters (GLUT), allowing glucose to enter cells with consequent intracellular glucose levels higher than extracellular levels leading to glucose overload in several tissues; they are responsible for insulin resistance, enhanced proteolysis, glycogenolysis, gluconeogenesis, and lipolysis and ultimately lead to negative nitrogen balance, hyperglycemia, and hypertriglyceridemia.

CARBOHYDRATE METABOLISM

Hyperglycemia is the most significant manifestation of altered carbohydrate metabolism in critically ill patients with ARF. Poor glucose control may result in significant complications in critically ill patients, with an increment of mortality up to 20% per each millimole of increase of plasma glucose,[2] and hyperglycemia has been found to be an independent predictor of death in patients admitted to ICUs with ARF.[3] Although some randomized prospective studies have demonstrated that the administration of intensive insulin therapy may play an important role in reducing morbidity and mortality in surgical and medical ICU patients,[4,5] more recent trials and meta-analyses in adult patients do not confirm these data and observe an increase of mortality and a higher risk of hypoglycemia.[6,7] Moreover, a U-shaped curve relationship between glucose levels and mortality has been observed.[8] In fact, more recent guidelines suggest glycemic targets are higher than they were before[9,10]; data in ARF patients are limited and further studies are needed, but it seems reasonable to suggest higher levels of glycemia are also in critically ill patients with ARF. There are four major causes of elevated blood glucose concentrations in this condition: insulin resistance, augmented hepatic glucose output, inadequate insulin secretion, and impaired metabolic clearance of insulin.

Elevated plasma insulin levels have been reported in acutely uremic patients,[11,12] anephric subjects,[13] and in rats induced with acute uremia.[14–16] The importance of the kidney in removing insulin from the bloodstream has been shown in humans and in experimental animals[17,18] and, in fact, many patients with diabetes, once they develop renal insufficiency, register a decreased requirement for exogenous insulin.[19] The lack of renal tissue, however, is not the only mechanism responsible for the decrease in insulin degradation. Cianciaruso et al.[20] studied endogenous insulin production and degradation in a model of acutely uremic dogs. Conscious, and with catheters in the portal vein, the femoral artery, and the main left hepatic vein, the animals were studied in the postabsorptive state and during a combined hyperinsulinemic and hyperglycemic state induced by the exogenous infusion of insulin and glucose. The study showed that, in the basal (fasting) state, the endogenous production and hepatic removal of insulin in uremic dogs were not different from those in controls. Thus the hyperinsulinemia observed in the postabsorptive state in ARF is not related to altered splanchnic insulin

kinetics; rather, other factors (extrasplanchnic), such as decreased degradation of insulin by the kidney and the muscle, appear to be responsible for the higher insulin levels in this condition. These findings are in accordance with in vitro data, in which, in nephrectomized rats, a decreased degradation of insulin by the muscle has been observed.[21] During the combined infusion of insulin and glucose, plasma insulin levels rose much higher in uremic dogs than in controls, as was expected because of the lack of renal tissue, but also observed was the consistently reduced insulin removal by uremic dogs' livers. This study[20] also found a lower endogenous secretion in acute uremia, probably because the markedly higher plasma insulin concentration in the uremic animals prevented endogenous insulin production from being activated by hyperglycemia. Thus reduced hepatic insulin degradation contributes to the hyperinsulinemia observed in acutely uremic patients after exogenous insulin infusion.

Several studies have shown that sensitivity to the action of insulin, with respect to glucose metabolism, is impaired markedly in patients with renal failure[22] and in critically ill patients.[23,24] Insulin resistance is a condition characterized by impaired glucose disposal in the presence of either normal or elevated serum insulin concentrations. The clinical manifestation of insulin resistance is often a state of hyperglycemia in the setting of hyperinsulinemia. The major glycoregulatory functions are impaired, including stimulation of glucose transport, inhibition of gluconeogenesis, and stimulation of net glycogen synthesis and glucose oxidation.[25] Along with alterations in glucose metabolism, the antilipolytic effect of insulin is impaired in these conditions, with fatty acids being the major oxidative fuel for energy requirements. The metabolic changes induced by insulin resistance, however, may be a natural response to starvation or injury. In fact, in a condition of lack of food, insulin resistance may ensure that the limited stores of carbohydrates are used for glucose-dependent and insulin-insensitive tissues such as the brain. Insulin-sensitive tissues will use fat instead of glucose as a source for energy.

The presence of insulin resistance can be detected and quantified by the technique of hyperinsulinemic euglycemic clamp,[26] by which exogenous insulin is infused at a fixed rate to increase plasma insulin concentration and maintain it at a constant level. Variable amounts of glucose are delivered, with an infusion pump, to avoid hypoglycemia and maintain euglycemia. Therefore, in this condition, glucose disposal depends primarily on the dose of exogenous insulin administered, and dose-response curves may be constructed between glucose disposal and plasma insulin concentration. The severity of insulin resistance in patients with ARF has never been tested with this technique; however, data are available in critically ill medical patients, studied with the hyperinsulinemic euglycemic clamp, 1 day after their admission to a medical ICU.[27] Admission diagnoses of these patients included respiratory insufficiency, sepsis, primary multiple-organ failure, neurologic disorders, and cardiogenic shock. These data show that, in critically ill patients, insulin sensitivity is reduced by 70% compared to healthy controls, indicating severe impairment of insulin-mediated glucose uptake by all body tissues. In this study, the development of insulin resistance and its severity were not related to the underlying causes for ICU admission but to the severity of illness as assessed by the Acute Physiology and Chronic Health Evaluation (APACHE) score, thereby indicating that insulin resistance is mainly a response to critical illness.

Basi et al.[3] studied insulin resistance in 90 critically ill patients with ARF. These patients were participants in the Program to Improve Care in Acute Renal Disease (PICARD),[28] an observational study of 618 adult ICU patients with ARF. In this study, the homeostasis model of insulin resistance (HOMA-R) index was used as a measure of insulin resistance,[29] wherein

$$\text{HOMA-R index} = \text{serum insulin (mIU/mL)} \times \text{plasma glucose (mmol/L)}/22.5$$

normal value is assumed 1.0 in healthy subjects, aged 35 or younger, with normal body weight. The median value of HOMA-R in the population studied was 9.47 (interquartile range 4.10 to 18.81), indicating that insulin resistance was, in fact, highly prevalent in ARF.

The development of insulin resistance with renal failure has two main causes: the loss of the homeostatic and metabolic functions of the kidney and the metabolic conditions caused by the critical illness. Studies employing a combination of isotopic and net balance techniques[30] have shown in conscious dogs and in healthy, postabsorptive (overnight fasted state) humans[31] that renal glucose release accounts for about 25% of all glucose released into the circulation and its uptake of glucose accounts for almost 20% of all glucose removed from the circulation. Because the normal human kidney does not contain appreciable glycogen stores, it is likely that the release of glucose by the kidney is due to gluconeogenesis exclusively. Renal glucose production is regulated by hormonal influence, with insulin inhibiting and catecholamines stimulating this process. Observations in humans have shown that, during euglycemic hyperinsulinemic clamp experiments, systemic glucose (i.e., the sum of hepatic and renal glucose) appearance decreases to zero[32] and that renal glucose production in humans is not irrelevant; therefore the loss of a major target organ for insulin could result in insulin resistance.

Site and possible mechanisms of insulin resistance in renal failure have been studied extensively. However, most of the research conducted in humans refers to chronic rather than acute renal failure,[22] whereas ARF has been studied in experimental models, in vitro and in vivo.[33] Using a combined technique (the hyperinsulinemic euglycemic clamp with the arterial-venous femoral catheterization for the measurement of leg glucose exchange), De Fronzo et al.[34] found that the major site of insulin resistance in chronic renal failure resides in peripheral tissues. Because muscle tissue accounts for more than 90% of the disposal of the infused glucose load, the authors conclude that skeletal muscle is the primary site of insulin resistance in uremia.

Data on peripheral glucose uptake in ARF have been obtained in conscious dogs, studied 24 to 30 hours after bilateral nephrectomy and undergoing a mild hyperglycemic (160 to 180 mg/dL) glucose clamp.[33] The results (Fig. 75.1) indicate that the rate of nonhepatic glucose uptake was significantly reduced in uremic dogs as compared with sham-operated normal dogs. The average values were 737 ± 341 mmol/min in the acutely uremic dogs and 1337 ± 393 mmol/min in the control animals ($p < .01$). The data suggest that the ability of insulin to direct the disposal of glucose into oxidative metabolism or glycogen synthesis, in acute uremia, is markedly reduced, as is the ability of insulin to reduce the proteolysis and the release of lactate. These findings are consistent with the observations of other investigators that determined the responsiveness to insulin of skeletal muscle from acutely uremic rats.[35]

Studies conducted in patients with advanced chronic renal failure, using the hyperinsulinemic euglycemic clamp technique, in combination with hepatic vein catheterization

and H-3 glucose, have shown normal basal hepatic glucose production, normal splanchnic glucose balance, and normal splanchnic glucose uptake. In response to insulin infusion, glucose production was suppressed similarly in uremic and control subjects, whereas the splanchnic glucose uptake was unchanged.[34] In dogs experimentally induced with ARF,[33] in the basal period, the hepatic release of glucose was greater in the control dogs as compared with the uremic animals (Fig. 75.2). This result is likely the consequence of higher insulin levels in the uremic dogs. However, during the hyperglycemic clamp procedure (0 to 90 min), net hepatic uptake occurred in the control dogs, whereas in the uremic animals, hepatic glucose output fell but never switched to uptake. The response of hepatic lactate metabolism to the glucose and insulin infusion also was altered. The uremic dog liver continued to take up lactate, whereas in control dogs there was net hepatic output of lactate. This experiment indicates that, even during glucose infusion, there is persistent gluconeogenesis and an increased hepatic glucose output, mainly from conversion of amino acids released during protein catabolism.

The data confirm that in ARF the resistance to insulin-stimulated glucose uptake occurs mainly in peripheral tissues, but the liver contributes to glucose intolerance and insulin resistance, mainly during a glucose load as occurs with parenteral nutrition.

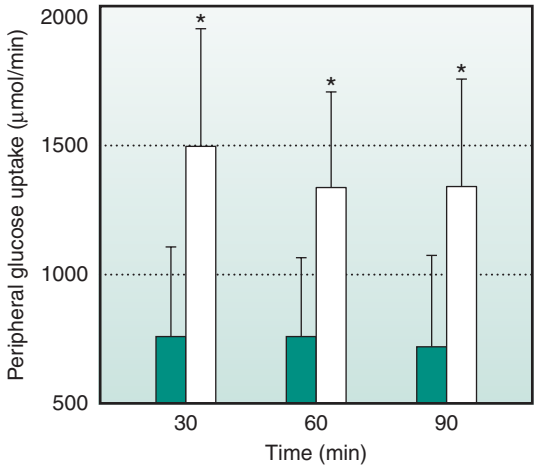

FIGURE 75.1 Calculated peripheral uptake of glucose after 30, 60, and 90 minutes of glucose and insulin infusion in acutely uremic dogs *(blue bars)* as compared with control dogs *(white bars).* (From Cianciaruso B, Bellizzi V, Napoli R, et al. Hepatic uptake and release of glucose, lactate, and amino acids in acutely uremic dogs. *Metabolism.* 1991;40[3]:261–269, with permission.)

LIPID METABOLISM

In contrast to the abundance of studies on chronic renal failure, few data are available on lipid metabolism in patients with ARF. The most frequent alterations of plasma lipids in ARF are hypertriglyceridemia and low cholesterol levels.[36] In fact, in ARF patients, the lipoprotein composition usually shows an increased triglycerides concentration, especially of low-density lipoprotein and very low–density lipoprotein, while total cholesterol and, in particular, high-density lipoprotein cholesterol levels are decreased. The leading cause of lipid abnormalities in ARF is impaired lipolysis. The enzyme that hydrolyzes triglycerides, contained in the circulating chylomicrons and very low–density lipoprotein, is lipoprotein lipase. In adipose tissue, the activity of lipoprotein lipase is increased by administration of insulin. When heparin is given intravenously, lipoprotein lipase activity is released into the blood plasma. This is a pharmacologic action of heparin, and heparin is not a physiologic cofactor of the enzyme. The lipolytic activity that is released is made up of two different enzymes that hydrolyze triglycerides. One of the lipases is derived from the liver and is resistant to inactivation by protamine. The second enzyme is of extrahepatic origin and is inhibited by protamine; it is primarily responsible for the hydrolysis of the triglycerides taken into the body in the form of chylomicrons. After heparin injection, from 45% to 95% of the lipolytic activity that appears in the blood plasma is protamine resistant; that is, it is the liver lipase. Maximal postheparin lipolytic activity, hepatic triglyceride lipase, and peripheral (protamine-inactivated) lipoprotein lipase were studied by Druml et al.[37] in 10 controls and 8 subjects with ARF. The activities of lipolytic systems, peripheral lipoprotein lipase and hepatic triglyceride lipase were both decreased in patients with ARF to less than 50% of normal values. [38] However, in contrast to this impairment of

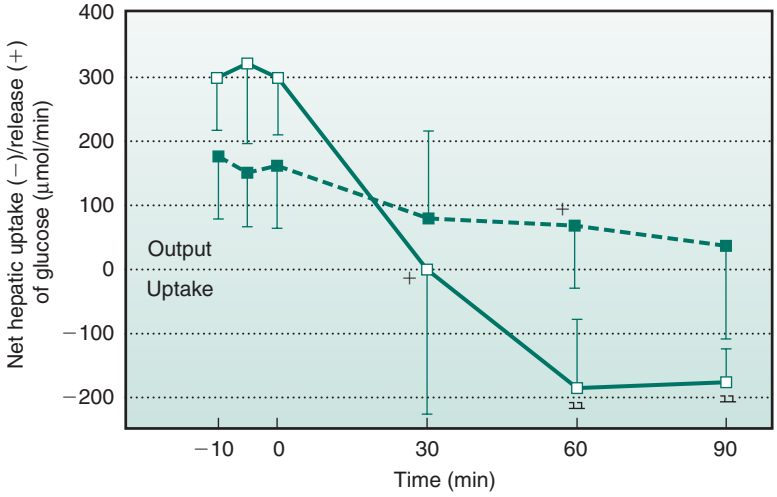

FIGURE 75.2 Net hepatic uptake or release of glucose during baseline and during a 90-minute infusion of glucose and insulin in acutely uremic dogs *(closed squares)* as compared with control dogs *(open squares).* (From Cianciaruso B, Bellizzi V, Napoli R, et al. Hepatic uptake and release of glucose, lactate, and amino acids in acutely uremic dogs. Metabolism. 1991;40[3]:261–269, with permission.)

lipolysis, oxidation of fatty acids was not affected by ARF. During infusion of labeled long-chain fatty acids, carbon dioxide production from lipids was comparable between healthy subjects and patients with ARF.[39] Metabolic acidosis can contribute to the impaired lipolysis of ARF by inhibiting lipoprotein lipase.

Alternatively to impaired lipolysis, there may be in ARF an increase in hepatic triglyceride secretion because of the elevated concentrations of insulin, free fatty acids, or both. Data obtained in studies of animals experimentally induced with ARF show increased, normal, or decreased plasma fatty acids and very low–density lipoprotein secretion.[40] In patients with ARF, plasma triglyceride levels do not correlate with triglyceride clearance or postheparin lipolytic activity; these results suggest that lipid secretion is increased in patients with ARF.[37]

However, data on incidence of hypertriglyceridemia and on the effects of lipids administration in ARF are scarce. The metabolism of lipids contained in commercial solutions used for parenteral nutrition is similar to endogen VLDLs; thus also the clearance of exogenous lipids administered as triglycerides or long- or medium-chain fatty acids may be altered in ARF.[41]

Changes in lipid metabolism develop rapidly in patients with ARF; impaired fat elimination is evident already at 48 to 96 hours from the start of renal failure, and the threshold below which these metabolic alterations are activated is a creatinine clearance of 50 to 30 mL/min.[40]

Changes in lipid metabolism in patients with ARF are characteristic of the metabolic response to severe stress and are promoted by catecholamines and inflammatory cytokines and exaggerated by the decreased insulin sensitivity of adipose tissue. The plasma cholesterol concentration is decreased in stress conditions, with decreased concentration of both low- and high-density lipoproteins. The mechanism for the hypocholesterolemia in acute illness is most likely multifactorial, where decreased synthesis and enhanced catabolism occur. Giovannini et al.[42] demonstrated that, in critically ill surgical patients, cholesterol levels correlate with decreased plasma proteins and hepatic protein synthesis, suggesting that hypocholesterolemia may be part of the negative acute phase response to acute illness. Several lines of evidence indicate that increased levels of proinflammatory cytokines may explain the hypocholesterolemia of acute illness. The parenteral administration of proinflammatory cytokines has been demonstrated to lower lipid levels[43,44] and show an inverse correlation between interleukin-6 and apolipoprotein A-1 levels in surgical ICU patients.[45]

The degree of hypocholesterolemia appears to correlate with the severity of the acute illness, morbidity, and mortality. Obialo et al.[46] reported that cholesterol levels below 150 mg/dL and serum albumin below 3.5 g/dL were independent predictors of mortality in patients with ARF. Emerging data show that tight glycemic control can result in an increase in high-density lipoprotein and low-density lipoprotein levels[47]; furthermore, a multivariate analysis of survival in surgical ICU patients by Van den Berghe et al.[48] suggests that the improvement in the lipid profile independently determined that insulin therapy contributed to a decrease in morbidity and mortality.

CONCLUSION

The main metabolic alterations of glucose metabolism in ARF are hyperglycemia and accelerated hepatic gluconeogenesis, mainly from conversion of amino acids released during protein catabolism, and hepatic gluconeogenesis cannot be suppressed by exogenous glucose infusions. Hyperglycemia in the critically ill may be an important determinant of complications and prognoses. Despite the altered lipid metabolism in ARF, lipids remain a fundamental energy source in these patients, and there are contrasting data on the benefits of intensive insulin therapy on this population.

Key Points

1. Critical illness leads to hyperglycemia—insulin resistance.
2. Critical illness causes accelerated gluconeogenesis.
3. Critical illness is responsible for low cholesterol and high-density lipoprotein levels.
4. Critical illness induces impaired lipolysis.
5. Critical illness determines increased triglycerides, low-density lipoprotein, and very low–density lipoprotein levels.

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A complete reference list can be found online at ExpertConsult.com.

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