10. ACUTE COMPLICATIONS OF DIABETES MELLITUS

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1.1.   Hypoglycaemia

Hypoglycaemia is a lowered blood glucose level. It may be caused by exogenous, endogenous, or functional causes. In general, hypoglycaemia occurs when blood glucose levels are below 35 mg/dl (1.95 mmol/L) in the newborn for the first 48 hours of life, and 45-60 mg/dl (2.5-3.3 mmol/L) in children and adults. Evidence also indicates that some individuals may become symptomatic before glucose levels decrease to 50 mg/dl (2.78mmol/L), if the decrease is relatively rapid. Hypoglycaemia occurs most frequently in individuals with diabetes mellitus. It occurs in more than 90% of those with type I diabetes and limits the management of the disease. Hypoglycaemia in diabetes is sometimes called insulin shock or insulin reaction.

The symptoms of hypoglycaemia result from neurogenic reaction and from cellular malnutrition. Symptoms frequently vary among individuals but tend to be consistent for each person. Neurogenic reactions occur when the decrease in blood glucose is rapid with tachycardia, palpitations, diaphoresis, tremors, pallor, and arousal anxiety. The response is probably generated when the hypothalamus senses decreased glucose levels. The neuron receives inadequate supplies of carbohydrates to metabolize and is thus is unable to maintain normal function. Cellular malnutrition produces further symptoms including headache, dizziness, irritability, fatigue, poor judgement, confusion, visual changes, hunger, seizures, and coma. If an individual is receiving a b-blocking medication, the anatomic symptoms may be absent.

When hypoglycaemic symptoms are non-specific, the safest treatment is to provide some form of glucose, because failure to provide glucose may precipitate convulsions, coma, and death. If the hypoglycaemic individual is conscious, ingestion of fast-acting carbohydrate is preferred. If the individual is unconscious, intravenous glucose or subcutaneous glucagon administration will reverse the hypoglycaemia. After the crisis, the individual should be observed for a subsequent relapse, and an additional, longer-lasting source of carbohydrates should be provided. Prevention of episodes of hypoglycaemia through alternate therapeutic regimens and proper education should be the goal.

In Type I diabetes, most of the individuals lose the ability to secrete glucagon, and a major subset also lose their adrenergic response. The combined loss of both responses, but not loss of only one response, predisposes to severe hypoglycaemia. A small number of diabetic patients develop hypoglycaemia due to Addison's disease or growth hormone deficiency. Decreasing insulin requirement in a Type I diabetic can be the first manifestation of Addison's disease.

1.2.   Diabetic Ketoacidosis

Ketoacidosis, a serious complication of diabetes mellitus, is a common cause for hospital

admissions, and average mortality rates throughout the United States are 7-9%. Diabetic acidosis develops when there is an absolute or relative deficiency of insulin, and an increase in insulin counter-regulatory hormones: catecholamines, cortisol, glucagon, and growth hormone. Under these conditions, hepatic glucose production increases, peripheral glucose usage decreases, fat mobilization increases, and ketogenesis is stimulated. The most common precipitating factor is inter-current illness such as infection, trauma, surgery, or myocardial infarction. Interruption of insulin administration also may result in diabetic ketoacidosis. In 20-30% of the cases, no precipitating factors are noted. Emotional factors and stress, particularly in children, are thought to contribute to the development of diabetic acidosis.

Catecholamines, cortisol, glucagon, and growth hormone antagonize insulin by increasing glucose production. In addition, catecholamines, cortisol, and growth hormone decrease the use of glucose. Insulin deficiency results in decreased glucose usage, an increase in the release of fatty acids, accelerated gluconeogenesis, and accelerated ketogenesis. Relatively increased glucagon levels are simultaneously responsible for activation of gluconeogenic (glucose-forming), and ketogenic (ketone-forming) pathways in the liver. Because of the insulin deficiency, hepatic over-production of b-hydroxy-butyrate and acetoacetic acids causes increased ketone concentrations. Ordinarily, ketones, used by the brain or skeletal muscle as an energy source, regenerate bicarbonate. This balances the loss of bicarbonate, which occurs when the ketone is formed. Hyperketonaemia may be a result of impairment in the use of ketones by peripheral tissue, which permits strong organic acids to circulate freely. Bicarbonate buffering then does not occur, and the individual develops a metabolic acidosis

1.2.1. Clinical Manifestations

The signs and symptoms of diabetic ketoacidosis are fairly non-specific, and an individual rarely progresses to complete coma without intervention. Polyuria and dehydration result from the osmotic diuresis associated with hyperglycaemia. Here the plasma glucose level is higher than the individual's renal threshold, allowing much glucose to be lost in the urine. Although water deficits may reach 100 ml/kg body weight, they are generally not as severe as those experienced by the diabetic individual with a hyperosmolar non-acidotic condition. Sodium, phosphorous, and magnesium deficits are common. The most important electrolyte disturbance, however, is a marked deficiency in total body potassium. Although the serum potassium may appear normal or elevated because of volume contraction and a shift of potassium from the cell caused by metabolic acidosis, total deficiencies reach 3-5 mEq/kg. Symptoms of diabetic ketoacidosis include Kussmaul respirations (hyperventilation in an attempt to compensate for the acidosis), postural dizziness, central nervous system depression, ketonuria, anorexia, nausea, abdominal pain, thirst, and polyuria.

1.2.2. Evaluation and Treatment

The diagnosis of ketoacidosis is suggested when individuals have symptoms of vomiting, abdominal pain, dehydration, and an acetone odour on the breath. Laboratory findings include serum glucose greater than 300 mg/dl (17mmol/L), arterial pH less than 7.30, and positive urine and serum ketones.

The treatment of diabetic ketoacidosis involves continual administration of low-dose insulin to decrease glucose levels. Fluids are administered to replace lost fluid volume, and electrolytes – particularly sodium, potassium and phosphorous – are administered as needed. Fluid and electrolytes should be closely monitored. Electrolyte deficits become apparent as fluid volume is replaced. After the administration of insulin, the concentration of b-hydroxybutyrate promptly begins to decrease and, after a slight increase, acetoacetate also begins to decrease. A persistent ketonuria may be observed for several days after treatment. As with hypoglycaemia, prevention is the long-term goal. Health teaching emphasizes predisposing factors and strategies for avoiding diabetic ketoacidosis.

1.3.   Hyperosmolar Non-Acidotic Diabetes

Hyperosmolar nonacidotic diabetes (HNAD), also called hyperosmolar hyperglycaemia nonketotic coma, was first described in 1886, but even today no satisfactory evidence has explained how HNAD differs pathophysiologically from diabetic ketoacidosis. Levels of free fatty acids are consistently lower in HNAD than those found in diabetic ketoacidosis. HNAD is also characterized by a lack of ketosis. Because the amount of insulin required to inhibit fat breakdown is less than that needed for effective glucose transport, insulin levels are sufficient to prevent excessive lipolysis but not to use glucose properly. Glucose levels are considerably higher in HNAD than in diabetic ketoacidosis. One hypothesis is that the lack of ketonuria in HNAD permits greater synthesis of glucose and thus more severe hyperglycaemia.

1.4.   Clinical Manifestations:

Glycosuria and polyuria in HNAD result from the extreme serum glucose elevation. As much as 19 gr. of glucose per hour may be lost in diuresis, which also causes severe volume depletion and intracellular dehydration. Water losses are generally between 4.8 and 12.6 liter, and although some electrolytes are lost with the fluid, the urine is hypotonic. This, along with increased glucose levels, contributes to the increased serum osmolality. Neurological changes, such as stupor, correlate with the degree of hyperosmolality. Glomerular filtration also decreases with the hyperosmolality, resulting in further increases in plasma glucose concentration.

1.4.1.   Evaluation and Treatment

The serum ketone concentration is normal or only mildly elevated in HNAD. In addition to the depressed mental state, laboratory findings include serum glucose levels greater than 600 mg/dl (33mmol/L), serum osmolality greater than 310 mOsm/L, and BUN of 70-90 mg/dl. Diabetic ketoacidosis and HNAD show considerable overlap in symptoms and treatment. An important distinction, however, is that the dehydration experienced in HNAD is far more severe than that in diabetic ketoacidosis. Thus fluid replacement, with both crystalloids and colloids, is more rapid. As much as 2000 ml may be given in the first hour, together with monitoring of the response to therapy. Potassium deficits may be so extreme in HNAD that more than a week may be needed to correct the total body deficits. Phosphorous and sodium may also be needed. The mortality rate is also high in HNAD, currently 14-17%. Thus, though the exact mechanisms are unknown at this time, real differences exist be-

tween diabetic ketoacidosis and HNAD.

1.5. Somogyi Effect

The Somogyi effect is a unique combination of hypoglycaemia during the night with rebound hyperglycaemia in the morning. The problem is more common in individuals with Type I diabetes mellitus, particularly in children, and should be investigated whenever fluctuations in blood sugar levels are serious. The Somogyi effect occurs when hypoglycaemia stimulates glucose counter-regulation, including epinephrine, growth hormone, cortisol, and glucagon release. These hormones serve to increase blood glucose by gluconeogenesis and glycogenolysis. They mobilize fatty acids and proteins while inhibiting peripheral glucose use.

1.5.1. Clinical Manifestations

In addition to fluctuating glucose levels, subtle symptoms of hypoglycaemia occur. The individual often complains of nightmares and early morning headaches. Both symptoms probably reflect a hypoglycaemic state. Ketonuria may occur if the mobilization of energy sources overshoots the body's need for glucose and exogenous insulin is depleted.

1.5.2. Evaluation and Treatment

Diagnosis involves the documentation of night-time hypoglycaemia by several plasma glucose analyses at 2:00 AM, 4:00 AM, and 7:00 AM. Treatment consists of decreasing insulin dosage or changing the time of administration.

1.6. Dawn Phenomenon

The dawn phenomenon is an early morning rise in blood glucose concentration with no hypoglycaemic episodes during the night. It appears to be related to nocturnal elevations of growth hormone, which decreases metabolism of glucose by muscle and fat. Increased clearance of plasma insulin also may be involved. Periodic monitoring of plasma glucose values in the morning ascertains the need for additional morning insulin. Altering the time and dose of insulin manages the problem. Treating dawn phenomenon may result in the Somogyi effect and vice versa.

1.7. Infection

A variety of factors may predispose the diabetic patient to an increased incidence, or increased severity, of infections. These factors include adverse effects of dehydration, malnutrition, vascular insufficiency, and neuropathy. In addition, in hyperglycaemic individuals, polymorphonuclear leukocyte function is impaired and delayed hypersensitivity is reduced. With the exception of mucormycosis and malignant external otitis, most infections in the diabetic patients are similar to those observed in non-diabetics.

Rhinocerebral mucormycosis occurs almost exclusively in acidotic diabetic patients. The pathophysiology of mucormycosis infection is not completely understood, but it has been hypothesized that during acidosis iron metabolism is impaired leading to compromised cell-

mediated immunity.

Recommended literature:

1. Pathophysiology - The Biologic Basis for Disease in Adults and Children. McCance and Heuther, editors, 2nd Edition Mosby Press 1994;674-92.
2. Textbook of Internal Medicine. Editor-in-Chief William Kelley, Lippincott Press 1989; Chapter 428-430:2216-29.
3. Cryer P. Glucose Homeostasis and Hypoglycaemia. In Williams Textbook of Endocrinology. Wilson and Foster, editors, 8th Edition, Saunders Press