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# ACUTE COMPLICATIONS
# of
# DIABETES MELLITUS
# and it´s
# SEQUEL

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# *Acute Complications of Diabetes Mellitus and its Sequel*

## *Written Declaration*

I declare that I completed the submitted work individually and only used the mentioned resources and literature. Concurrently, I give my permission for this diploma-bachelor thesis to be used for study purposes.

In Prague on March 2010 Adrianna Natalie Frank

# *Acute Complications of Diabetes Mellitus and its Sequel*

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## *Table of Contents*


*1). Summary*

*2). Introduction*

*3). The most significant acute complications of diabetes mellitus*

- *a). Diabetic Ketoacidosis*
- *b). Hyperglycemic Hyperosmolar State*
- *c). Hypoglycemia*

*4). Other complications linked to DKA and HHS*

- *a). ARDS*
- *b). Hyperchloremic Metabolic Acidosis*
- *c). Vascular Thrombosis*

*5). Conclusion*

*6). References*

## *Summary*

The basis of this thesis is intended to inform the reader about the general complications of acute diabetes mellitus and its consequences. It focuses on the general definitions of the diseases, etiology, morbidity, mortality, pathogenesis of the disease, clinical presentation, treatment, and future developments in hopes of treating the disease. The major focus highlights the differences between diabetic ketoacidosis and hyperglycemic hyperosmolar state, as well as understanding the complications of diabetic hypoglycemia. The most critical effects of these disorders are also emphasized; cerebral edema, vascular thrombosis, and hyperchloremic metabolic acidosis.

## *Introduction*

Diabetes mellitus is one of the most common diseases affecting a significant percentage of the population in both industrialized and non-industrialized countries (15). It is currently one of the fastest growing debilitating diseases in the world (15). The overall

prevalence of diabetes in the United States is one of the highest. Approximately 1 in 17 in the United Stated is affected by diabetes mellitus (48). Approximately 1 in 800 is diagnosed with diabetes mellitus type I; a significantly larger amount of people, 1 in 17, are affected by diabetes mellitus type II (48). As of 1995, it was estimated that 135 million people were affected worldwide (48). According to recent estimates, the prevalence of diabetes in the United States is predicted to be 8.9 percent of the population by 2025(48). As these statistics rise, so do the risks of complications of the disease. Understanding diabetes, the differences between the acute complications and their symptoms will help in faster diagnosis, more efficient therapy, and improve the prognosis for the patient.

## *The Most Significant Acute Complications of Diabetes Mellitus: DKA, Hyperglycemic Hyperosmolar State, and Hypoglycemia*

### *Diabetic Ketoacidosis (DKA)*

*What is diabetic ketoacidosis*

Diabetic Ketoacidosis, commonly known by its abbreviation DKA, is a medical emergency defined by hyperglycemia, ketonemia and ketonuria , decreased arterial blood pH (1) and, or in addition to, decreased serum bicarbonate (2). DKA represents a state of either absolute or relative insulin deficiency aggravated by ensuing hyperglycemia, dehydration, and acidosis-producing derangements in intermediary metabolism (47).

Although definitions vary according to source, DKA can be subdivided according to severity, which will resultantly determine treatment and prognosis.

*Epidemiology and etiology of DKA:*

DKA is primarily associated with diabetes type I, therefore typically affecting patients younger than 19 years of age (27). Young children and adolescents are affected far more commonly than adults. The incidence of DKA is between 4.6 and 8.0 per 1000 person-years among patients with diabetes (9) with about 3% of patients with type 1 diabetes initially presenting with diabetic ketoacidosis (47).

It is important to note that DKA is not only restricted to type I diabetes. DKA also occurs in DM II patients as well, however the incidence is much less (probably due to loss of insulin production).

The incidence of diabetic ketoacidosis is higher in whites because it is relative to the higher incidence of type 1 diabetes in this racial group (19). DKA is slightly greater in females than in males for reasons that are unclear (19).

*Morbidity and mortality:*

Thanks to the evolution of modern pharmaceutical management, increasing patient awareness, and physicians' knowledge of the subject, the mortality rate of DKA has decreased significantly over the past years. Before the discovery of insulin in 1922, the mortality rate was 100% (47). Between 1980 and 2005, the age-adjusted death rate for hyperglycemic crises in the general population declined (12). In 2005, the age-adjusted death rate for hyperglycemic crises was 0.8 per 100,000 general population, almost half the rate in 1980 (1.5 per 100,000) (12). Currently, the overall mortality rate from DKA ranges between 1-10% of all DKA admissions (19). This varies widely according to hospital facilities and the inevitably the experiences of medical staff who have dealt with this acute metabolic condition (19). When diabetic ketoacidosis is diagnosed quickly, and treated promptly and appropriately, it rarely causes any residual effects (19). The incidence and mortality linked to DKA in developing countries is not precisely known, however, due to decreased medical and pharmaceutical availability and it is higher than in industrialized nations (19).

DKA still accounts for 50% of diabetes-related admissions in young persons and 1-2% of all primary diabetes-related admissions (19). Better understanding of the pathophysiology of DKA and proper monitoring and correction of electrolytes has resulted in significant reduction in the overall mortality rate from this life-threatening condition in most developed countries. Mortality rates from DKA have markedly decreased from 7.96% 20 years ago to 0.67% (19).

Best results are always observed in patients treated in ICUs during the first 1-2 days of hospitalization (19). In contrast, the mortality rate still is high in developing countries and among non-hospitalized patients. This high mortality rate illustrates the necessity of early diagnosis and the implementation of effective prevention programs. Cerebral edema remains the most common cause of mortality, particularly in young children and adolescents. Cerebral edema frequently results from rapid intracellular fluid shifts. Other causes of mortality include severe hypokalemia, adult respiratory distress syndrome, and comorbid states (eg, pneumonia, acute myocardial infarction) (19).

*Pathogenesis of DKA:*

The effects of DKA are a result of insulin deficiency or absence with concomitant elevation of counterregulatory hormones (glucagon, catecholamines, cortisol, and growth hormone) and its consequences on the organism (46).

Insulin is a critical hormone necessary for glucose uptake and metabolism in hepatocytes, myocytes and adiposities (37). When insulin is deficient or absent, the body is forced to metabolize triglycerides and muscular tissue instead of glucose for energy, therefore mimicking a starvation state. Resultantly, lipolysis and myolysis occur, leading to increasing levels of glycerol and free fatty acids and alanine respectively. Both glycerol and alanine provide substrates for hepatic gluconeogenesis, which is stimulated by the excess of glucagon that accompanies insulin deficiency (37). Glucagon also stimulates mitochondrial conversion of FFAs into ketones. Insulin normally blocks ketogenesis by inhibiting the transport of FFA derivatives into the mitochondrial matrix, but ketogenesis proceeds in the absence of insulin. The major ketoacids produced, acetoacetic acid and β-hydroxybutyric acid, are strong organic acids that create metabolic acidosis (37). Acetone derived from the metabolism of acetoacetic acid accumulates in serum and is slowly disposed of by respiration (37).

Decreased insulin levels leads to hyperglycemia and hyperosmolarity resulting in osmotic diuresis and an osmotic shift of fluid into the intravascular space. This mechanism creates a viscous circle of further intracellular dehydration (24). Osmotic diuresis leads to renal loss of water and electrolytes such as sodium and potassium. Urinary excretion of ketones attributes to additional losses of Na and K. Serum Na may fall from natriuresis or rise due to excretion of large volumes of free water. K is also lost in large quantities, sometimes > 300 mEq/24 h (37). Despite a significant total body deficit of K, initial serum K is typically normal or elevated because of the extracellular migration of K in response to

acidosis. K levels generally fall further during treatment as insulin therapy drives K into cells. If serum K is not monitored and replaced as needed, life-threatening hypokalemia may develop (37).

*What causes the onset of DKA*

Generally DKA is caused by three major complications:

1) Infection in 40% of cases and physiological stresses leading to a higher requirement of insulin (37)
2) Inadequate insulin administration
3) Undiagnosed Diabetes (15%) (37)

Common physiologic stresses that can trigger DKA include acute infection (particularly pneumonia and UTI), MI , stroke, pancreatitis, and trauma. Drugs implicated in causing DKA include corticosteroids, thiazide diuretics, and sympathomimetics. As before mentioned, DKA is less common in type 2 DM, but it may occur in situations of unusual physiologic stress atypical ketosis-prone diabetes mellitus (27).

Inadequate insulin administration may be seen in various cases. Most commonly it is seen in physically active youth who fail to adapt the dosage of insulin in accordance to the amount of physical exertion produced. In other cases it is a result of poor patient education,

patient inadequacy (in patients suffering from dementia or physical disabilities), or patient ignorance (27).

*Clinical Presentation of DKA (including signs and symptoms)*

Hyperglycemia is the cause of early DKA symptoms and signs. Later signs are results of progression of hyperglycemia and the organism's compensation mechanisms as explained under pathophysiology.

Early signs of polyphagia, polydypsia, and polyuria as a consequence of osmotic dieresis (4) lead to weight loss, fatigue, and mental obtundation. These signs are classic warnings of a for-coming DKA episode; however, they may not be the only ones (46). Since DKA is usually preceded by a bodily stress reaction, concomitant signs and symptoms of infection may be present such as fever. The early DKA episode often last several days to weeks before the onset of late signs of DKA, however, according to the patients immune and stress status, the time of progression can vary.

Late signs represent the clinical onset of ketoacidosis, which progresses rapidly, often less than 24 hours (46). In 40-75% of affected patients, and most commonly in children, the presenting late sign is abdominal pain often mimicking acute abdomen (46). Typical clinical presenting signs include rebound tenderness (also known as positive Blumberg sign), guarding, and rigidity (39). Abdominal pain is linked to hypovolemia leading to decreased blood circulation to the bowel as a result of dehydration. However, the major cause of

abdominal pain is acidosis. According to Diabetes Journals, the institution observed that the presence of abdominal pain is associated with a more severe metabolic acidosis and with a history of alcohol or cocaine abuse (39). Although the potential of an acute abdominal problem requiring surgical intervention should not be overlooked, in the majority of patients, the abdominal pain spontaneously resolves after correction of the metabolic disturbance (46). However, if not treated promptly, severe bowel ischemia can progress to bowel infarct giving a high risk of bowel rupture and sepsis, and death (46). It is important to note that Gastrointestinal manifestations (abdominal pain, vomiting) commonly attributed to DKA but are not typically present in HHS. Thus, the presence of abdominal pain in patients without significant metabolic acidosis needs to be investigated if not already done (46).

Other presenting signs include anorexia, nausea (37), and in 25% of DKA patients, vomiting(8). The vomitus may present as guaiac positive, with a classic coffee-ground appearance, often mimicking peptic ulcer and other gastric related disorders (8).

*Physical Examination:*

Upon patient admission, in mild to moderate DKA, physical examination reveals signs of volume depletion such as decreased skin turgor and dry mucous membranes. Dehydration is typically mild ( <3% of total body weight loss; presenting with slightly dry buccal mucous membranes, polydypsia, and a minor decrease in urine output), however, in some cases, especially elderly, dehydration can be severe (7-9% of total body weight loss;

tachycardia with weak pulse, cyanosis, tachypnoea, delayed capillary refill, hypotension, coma) (39).

Fever due to underlying infection is common, and signs of acidosis (Kussmaul respiration, and fruity acetone breath) can initially be absent, however, appear as severity of decompensation increases (46).

Once severe DKA is reached, tachycardia and hypotension as a result of dehydration and acidosis can lead to hypovolemic shock and cardiac arrest in susceptible patients if left untreated.

If present, headache is a warning sign of increased intracranial pressure and a warning of progression to acute cerebral edema. Acute cerebral edema is complication found in approximately 1% of DKA patients (37). It occurs primarily in children and less often in adolescents and young adults. It is a consequence of too-rapid reductions in serum osmolality or to brain ischemia (37) as a consequence of too rapid rehydration therapy (32). In some patients, focal neurological signs (hemiparesis, hemianopsia) and seizures (partial motor seizures more common than generalized) may be the dominant clinical features, resulting in a common misdiagnosis of stroke, especially in elderly. Despite the focal nature of neurological findings, these manifestations often reverse completely after correction of the metabolic disorder (32). When DKA is mild, the patient is mentally alert and hyperreactive to painful stimuli. Typically, less than 20% of patients are admitted with loss of

consciousness (46). As the condition progresses, rapid mental deterioration can be noted. Once the patient reaches the category of severe decompensation, signs of stupor or coma are present.

Two major electrolyte disturbances- hypokalemia and hyponatremia- present severe clinical effects complicating both DKA and HHS. Hypokalemia if mild (levels greater than 3 mEq/L) is usually asymptomatic, however, it can result in minor elevations of blood pressure (7). Moderate serum potassium levels (2.5-3 mEq/L) presents itself clinically as muscular fatigue, myalgia, and constipation (7). Once severe, (< 2.5 mEq/L) neurological symptoms become significant; flaccid paralysis, hyporeflexia, tetany are the presenting symptoms (7). Respiratory depression from impairment of accessory respiratory muscles can further aggravate acidosis by inhibiting the respiratory rate and therefore release of CO2 (7). The clinical presentation of Hyponatremia (levels of plasma sodium < 130 mmol/L) can range from asymptomatic to producing nausea, vomiting, headache, malaise, and change in consciousness. Levels <125 mmol/L can induce seizures and coma (31).

*Diagnosis:*

The criteria for the diagnosis of DKA are relatively clear-cut. It includes hyperglycemia with presenting blood glucose equal or greater than 11.1 mmol/L;

acidosis with findings of venous pH <7.3 and/or bicarbonate <15 mmol/L; ketosis- the presence of ketones in the blood, urine, or both. (4); and anion gap >12 (Merck, 1290).

In 2006, American Diabetes Association stated that DKA cases can be roughly divided further into mild (pH 7.20–7.29, bicarbonate 10–14) alert patient, moderate (pH 7.10–7.29, bicarbonate 5–9) drowsiness, and severe (pH <7.10, bicarbonate <5) stupor or coma (4).

In some cases, as is typical with medicine, diabetic ketoacidosis may present itself with other ironic complications due to regulatory mechanisms, meaning that the ketoacidosis may not be only strictly ketoacidosis. In some cases we can see euglycemic DKA, where glycemia is just slightly increased. Then there is alkalemic DKA where the expected acidosis is combined with metabolic alkalosis. Lastly, there is nonketotic DKA where low levels of acetoacetate can "trick" lab results.

*Euglycemic DKA*

In cases where a patient maintains a state of adequate hydration, or has an increased glomerular filtration rate (as seen in a pregnant patient), ketoacidosis may occur in the presence of minimal hyperglycemia (13). It may also be seen in patients who are taking insulin, but the amount of insulin is not adequate for a ketogenic process, such as acute

illness. A careful history is mandatory in diagnosis since it can usually explain the minimal elevation of glucose and lead to appropriate treatment.

### *Alkalemic DKA*

This is a condition of the expected primary metabolic acidosis, being mixed with a primary metabolic alkalosis (13). A markedly elevated anion gap is typically present. This condition most commonly occurs in a patient with DKA who develops severe, protracted vomiting. It may also be seen in those on diuretics, or those with Cushing's syndrome (13). The laboratory results come from DKA, which lowers the bicarbonate, and vomiting which lowers the chloride. Taken together there is a marked elevation of the anion gap, but the pH is not as low as predicted by the PCO2 (13).

### *Nonketotic DKA*

In normal conditions there is approximately a 1:5 ratio of acetoacetate to beta-hydroxybutyrate (13). In conditions that cause tissue hypoxemia (such as sepsis, shock, severe hypotension) this reaction gets driven toward beta-hydroxybutyrate and the ratio may reach 1:20 (acetoacetate to beta-hydroxybutyrate) (13). This situation leaves little acetoacetate to be measured by the nitroprusside reaction and can make the diagnosis of DKA less clear. These patients still have an elevated anion gap and, usually, and elevated glucose (13).

*Therapy*

Treatment and management of DKA requires three critical steps; volume repletion, correction of hypoglycemia and acidosis, and prevention of hypoglycemia.

Volume repletion is achieved by rapid IV infusion of 1-3 L of 0.9% saline solution followed by saline infusion at the rate of 1 L per hour or faster according to the vital signs (Merk, 1291). Generally adults with DKA need a minimum of 3L of saline over the first 5 hours. Hyperglycemia is corrected by administration of regular insulin (Humulin) 0.15 U/kg IV bolus followed by IV infusion of 0.1 U/kg/hr in 0.9% saline solution. Insulin should be withheld until serum potassium is equal to or greater than 3.3 mEq/L (Merk, 1292). When plasma glucose becomes 250-300 mg/dl (13.88-16.65 mmol/L) 5% dextrose solution should be added to IV fluids in order to prevent hypoglycemia (4). Hypokalemia prevention requires replacement of 20-30 mEq of potassium in each liter of IV fluid to maintain serum potassium between 4-5mEq/L (Merk, 1292). In case of cerebral edema mannitol (Osmitrol, Resectisol), an osmotic diuretic, is traditionally used. It is presented as a 10% or 20% solution for infusion, the latter being preferable for pediatric use and administered as 0.2-0.5 g/kg over 15-20 min (1-2.5 mL/kg of 20% solution); can be repeated after 1 h (4). Additional treatment of cerebral edema includes hyperventilation and corticosteroids, however, once the onset of respiratory arrest, this therapy is often ineffective (Merck, 1292).

*Prognosis:*

Mortality rates for DKA are between 1 and 10%, which is far less than in HHS (40). If present, consistent hypothermia (defined as core body temperature equal or less than 35 C) (14) indicates either poor peripheral circulation or hypothalamic dysfunction and is a poor prognostic indicator (8). Shock or coma upon admission worsens the prognosis. Main causes of death are circulatory collapse, hypokalemia, and infection. Among children with cerebral edema, 57% recover completely, 21% survive with neurologic sequel, and 21% die (1).

## *Hyperglycemic Hyperosmolar State aka Hyperosmolar Hyperglycemic Nonketotic Coma (HHNC)*

*What is HHS*

HHS is a medical emergency defined by hyperglycemia, hyperosmolarity, and dehydration differing from DKA with the absence of significant ketoacidosis (21).

*Epidemiology and Etiology of HHS*

Since HHS is usually, but not always, restricted to diabetes type II, the patients represent the classic categorization of a DMII patient. The typical patient is obese, Native American or Hispanic, ranging between 30-70 years of age (4). However, the mean age of HHS onset is typically later in age (around 70 years) due to increased incidence of dementia and inability to sustain adequate care the diabetes. It is important to note that, as the incidence of obesity in children is markedly rising, so is the incidence of DM II, and therefore HHS age of onset is significantly decreasing (21).

The overall incidence of hyperosmolar hyperglycemic state (HHS) is less than 1 case per 1000 person-years, making it significantly less common than DKA. As the prevalence of type 2 diabetes mellitus increases in all ages, the incidence of HHS is increasing as well (21).

*Morbidity and mortality*

The mortality rate of HHS is high (10-20%); ten to twenty times greater than that of DKA (21). It is often contributed to a comorbid illness. The mortality rate of HHS is found to increase with age, due to decreased immunity and insulin tolerance, and with higher levels of serum osmolality (i.e. it is directly proportionate to increased serum glucose levels), HHS should be considered in children presenting with hyperglycemia and hyperosmolarity without significant ketoacidosis (21). It is particularly important to distinguish HHS from

DKA in children and young adults, as they are at higher risk for the development of cerebral edema as a complication of aggressive fluid repletion. The mortality due to HHS in children also appears to be higher as compared to DKA, but there have been too few reported cases to calculate mortality accurately (21).

*Pathophysiology of HHS*

Understanding the differences between DKA and HHS requires understanding the underlying mechanism of the two disorders.

Hyperosmolar hyperglycemic state (HHS) most commonly occurs in patients with type 2 diabetes mellitus that have a concomitant illness which leads to an end result of dehydration (24). As with DKA and in DM I, infection is the most common cause of its onset.

The significant difference is that patients with HHS do not develop severe ketoacidosis as in DKA. Patients who suffer from a lack of or resistance to insulin (as in DM II) are highly susceptible to HHS, since even a minor stress reaction can result in an overall reduction of circulating insulin. The key underlying mechanism of HHS is a net reduction of effective circulating insulin in accordance with rising levels of stress hormones; catcholamines, crotisol, 5glucagon and growth hormone (24). Since the function of insulin is

defective- or relative- in HHS, myolysis occurs releasing amino acids to the liver for gluconeogenesis. After the liver produces glucose via gluconeogenesis and glycogenolysis blood glucose levels rapidly increase leading to osmotic diuresis and dehydration. However, unlike HHS, the minute presence of even defective insulin prevents the formation of large amounts of ketone bodies (24).

In DKA insulin availability is absent –or absolute- meaning that adipose tissue is broken down to form free fatty acids for the production of ketone bodies in the liver (19). The overall result is ketonemia- ketone bodies found in the blood and urine resulting in metabolic acidosis.

Overall, it can be stated that three contributing factors inhibit the development of ketoacidosis in HHNS. They include the limitation of ketogenesis by hyperosmolarity, decreased levels of free fatty acids available for ketogenesis and the avialibility of insulin in amounts sufficient enough to inhibit ketogenesis (21).

*What causes the onset of HHS*

As with DKA, a physiological stress reaction is the major initiator of a HHS episode. Some factors in addition increase the risk of HHS. Total parenteral nutrition and drugs that impair glucose tolerance (Merck, 1290), such as beta-blockers, H2 blockers, diuretics, increase the incidence of HHS (24). Medical non-adherence and medical disorders can

increase the risk (Merck, 1292). Dialysis patients are found to have a higher rate of HHS compared to non-dialysis patients (24).

*Clinical Presentation (signs and symptoms)*

Generally the clinical presentation of HHS is quite similar to that of DKA. In as many as one third of cases, the clinical features of HHS and DKA overlap and are observed simultaneously (overlap cases) (21).

As in DKA, HHS also presents itself with and early stage and late stage. Early stage mimics that of DKA, lasting days to weeks before the onset of the later stage (30), however, in comparison to DKA, HHS onset is generally more gradual (7). Late stage differs in the absence or decreased severity of abdominal pain, nausea, and vomiting. The significant difference between the two diseases is based on the presence or absence of ketones. In HHS, the classic fruity odor and Kussmaul breathing is absent.

Coma may complicate HHS, however, thankfully, the occurrence is rare since it is found in less than 10% of admitted patients.

*Diagnosis of HHS*

Diagnosis is based on patient history, clinical presentation, and confirmed by laboratory results. Elevated blood glucose levels (hyperglycemia > 600 mg/dL), serum

osmolality (> 310 mosm/kg), absence of acidosis ( blood pH above 7.3; serum bicarbonate > 15 mEq/L) and a normal anion gap (< 14 mEq/L) are typical findings (29).

*Therapy of HHS*

Treatment is similar to that of DKA. Management of vitals is the first essential step in patient recovery. Maintain airways, establish a functional intravenous access, initiate vigorous fluid resuscitation, and obtain appropriate laboratory and radiographic studies.

Generally, fluid deficits in hyperosmolar hyperglycemic state (HHS) are large; much larger than those of DKA. The fluid deficit of an adult may be 10 L or more (21), and prompt rehydration is required to prevent hypovolemia and its consequences. Especially in HHS, however, rehydration therapy is a double-edged sword. It is critical to prevent too quick a reduction in serum osmolality because the resulting consequence can be cerebral edema (36). Therefore, careful monitoring of vitals and calculation of fluid administration (amount and rate) is critical in determining the prognosis of the patient's state.

Detection and treatment of an underlying illness is essential and broad spectrum antibiotics need to be administered immediately (21). Frequent re-evaluation of the patient's clinical and laboratory parameters are necessary. Serum glucose concentrations should be re-

chacked every hour in the beginning of therapy. Electrolytes and blood gasses should be monitored every 2-4 hours or as clinically indicated (21).

## *Hypoglycemia; A result of inefficient diabetes control*

### *What is hypoglycemia*

Hypoglycemia is the decrease in blood glucose less than (70 mg/dl or 4 mmol/L). It occurs when insulin levels exceed that of the glucose levels in blood (20). Normal glucose fasting levels range between 60-100 mg/dL [3.3-5.6 mmol/L]) (5).

### *Etiology and epidemiology*

In 7.7% of hospital admissions of diabetic patients, hypoglycemia is the major admitting diagnosis (42).

### *Morbidity and mortality:*

Generally the mortality of hypoglycemic attacks is quite low since the presenting symptoms force the patient to the hospital in time before the condition can progress to a critical state. The odds of inpatient death also rose threefold for every 10 mg/dl decrease in the lowest blood glucose during hospitalization (42).

*Causes*

Hypoglycemia may take several forms. In a diabetic patient, it may result from administration of too much insulin or, less commonly, too much oral antidiabetic medication. In a mildly diabetic patient (or one in the early stages of diabetes mellitus), reactive hypoglycemia may result from delayed and excessive insulin production after carbohydrate ingestion (49).

In diabetics, however, hypoglycemia is most commonly found in insulin dependant patients (DM I) where an excess amount of insulin had been administered (18). Less commonly, it is seen in non insulin dependant patients taking other forms of diabetic medications (eg. Sulfonylureas) (18). Other causes include inadequate calorie intake, large time gaps between meals, increasing physical activity without and consuming high levels of alcohol adjusting medication/insulin levels (32). Concomitant use of medications such as beta blockers, pentamidine, and sulfamethoxazole and trimethoprim (Bactrim, Septra) can provoke hypoglycemic attacks (45).

In frequent attacks of hypoglycemia, and/or where the diabetes has been poorly compensated, suspicion of renal failure due to diabetic nephropathy is high. Renal failure causes hypoglycemia in three separate ways. The kidneys help to generate new glucose from amino acids (called gluconeogenesis) (18). Gluconeogenesis is impaired in kidney failure. Also, insulin circulates for a longer period of time and is cleared slowly when kidney

function is poor. The third important reason is that kidney failure reduces the appetite and consequently, oral intake of food (18).

*Signs and symptoms of hypoglycemias*:

Typically, the onset of clinical signs and symptoms occurs once blood glucose levels fall below 60mg/dl, but this is not a strict rule (26). Some patients, however, may experience clinical manifestations of hypoglycemia with blood glucose levels of 65mg/dl, and others may be only mildly affected with blood glucose levels of 40 mg/dl (26). Very often, the more the incidence of attacks increases over time, the less visible the clinical manifestations of hypoglycemia are to the patient. This can be seen especially in DM I patients, where the frequency of attacks are much more common than in DM II or insulin independent patients (26).

Generally signs and symptoms are either of autonomic or neuroglycopenic origin. In the early stage of hypoglycemia, where glucose levels are only slightly below normal, Autonomic symptoms include diaphoresis (sweating), trembling, feelings of warmth, anxiety, and nausea (34). Neuroglycopenic symptoms include feelings of dizziness, confusion, fatigue, headache, and inability to concentrate (34). Severe hypoglycemia is a medical emergency that may result in seizures and permanent damage to the nervous system if not treated. Severe hypoglycemia that results in unconsciousness is also called insulin

shock (22). If hypoglycemia is not reversed in adequate time, it can progress to coma, cardiac dysrrhythmia, and death (34).

*Physical findings of Hypoglycemia*

Physical findings are nonspecific in hypoglycemia and generally are related to the central and autonomic nervous systems. Assessing vital often show signs of hypothermia, tachypnea, tachycardia, hypertension, and bradycardia (34). These findings tend to be specifically exaggerated in younger adults and children (22). In older patients, cardiovascular disturbances, on the contrary, may include tachycardia, hypertension or hypotension, and dysrhythmias. Respiratory disturbances may include dyspnea, tachypnea, and acute pulmonary edema. GI disturbances often mimic typical signs of gastroenteritis, including nausea, vomiting, dyspepsia, and abdominal cramping (34). Skin may be diaphoretic and warm or show signs of dehydration with decrease in turgor (22). In severe cases of hypoglycemia, neurologic conditions include coma, confusion, fatigue, loss of coordination, combative or agitated disposition, stroke syndrome, tremors, convulsions, and diplopia (22).

*Prevention of hypoglycemic attacks in diabetic patients*

Adequate patient education is critical in prevention of hypoglycemic attacks. Advising patients to monitor blood glucose levels minimally 3-5 times per day can reduce hypoglycemic episodes as high as 92% (3). In patients with recurrent episodes of

hypoglycemia who do not respond well to other forms of treatment, a glucagon kit is often advisable to patients compatible with the administration process. In all patients who tend to have frequent fluctuation glucose levels, especially in young athletes and in elderly or handicapped patients, continuous subcutaneous infusion (insulin pump) is the best current option (17).

*Diagnosis of hypoglycemia*

Diagnosis of hypoglycemia is quite simple. It is based on patient history, clinical presentation, and confirmed by blood glucose levels less than 70 mg/dl (Merck, 1294). A 72 hour fast, when performed under a controlled setting, is critical for diagnosis (22). If glucose levels are abnormally low, serum insulin, C-peptide, and pro-insulin should be measured in order to rule out the possibility of factitious hypoglycemia (Merck, 1294).

*Therapy*

Immediate treatment requires quick administration of glucose. Infants or younger children are given 10% dextrose solution 2-5ml/kg IV bolus (Merck, 1294). Older children and adults who are unable to eat are given glucagon 0.5 – 1 mg s.c./ i.m. or 50% dextrose 50-100 ml IV bolus with or without continuous infusion of 5-10% dextrose solution (Merck, 1294). Drugs that aggravate hypoglycemia must be stopped immediately. If dehydration is present, adequate measures of therapy must be taken (Merks, 1294).

## *Other Complications Linked to DKA and HHS:*

### *ARDS*

Adult respiratory distress syndrome, also known as respiratory distress syndrome (RDS), or noncardiogenic pulmonary edema is a serious reaction to various forms of injuries to the lung (36). ARDS is a potentially fatal complication of DKA that fortunately occurs rarely, however, once it occurs, the mortality rate is on average 30% (36). Excessive crystalloid infusion favors the development of pulmonary edema, even in the presence of normal cardiac function. If cardiac function is limited, the risk of developing ARDS is much higher. Patients with an increased alveolar to arterial oxygen gradient ($AaO_2$) and patients with pulmonary rales on physical examination are at increased risk for ARDS. Frequent monitoring of oxygen saturation with pulse oximetry, and measurements of venous blood gasses assist greatly in the management of such patients (36).

### *Hyperchloremic metabolic acidosis (HMA)*

This phenomenon is quite common during the treatment of DKA. The key mechanism is the loss of substrates (ketoanions) in the urine that are necessary for bicarbonate

regeneration (10). As these metabolic by-products are lost, the availability of substrates for bicarbonate formation is lost making it difficult for the organism to compensate for the acidic environment. Three other major mechanisms leading to hyperchloremic metabolic acidosis are of iatrogenic etiology: administration of intravenous fluids containing chloride concentrations exceeding that of plasma, volume expansion with bicarbonate-free fluids, and intracellular shift of sodium bicarbonate during correction of DKA (10). Typically, HMA usually has no adverse effects on the organism as a whole and is corrected spontaneously in the subsequent 24–48 hours through enhanced renal acid excretion (10).

*Vascular thrombosis*

Many clinical features of DKA and HHS predispose the patient to vascular (particularly arterial) thrombosis. In the late 1800's a German physician, Rudolf Virchow, described three critical factors that lead to thrombosis (known as Virchow's triad): hypercoagulability, hemodynamic changes (stasis and turbulence), and endothelial injury (41). The effects of DKA and HHS manage to pertain to the entire triad. Factors which predispose the patient to a hypercoagulable state are seen in cases of dehydration, contracted vascular volume, increased blood viscosity, including increased blood osmolality. The risk of a hypercoagulable state is increased significantly if a concomitant nephritic syndrome exists. Hemodynamic changes are found in cases of decreased cardiac output, which is classic in both DKA and HHS. Endothelial injury is classic in cases of long-term diabetes, especially if it is poorly compensated; it typically presents itself as atherosclerosis and microangiopathy.

Although generally quite rare, arterial thrombosis complicating acute diabetic episodes can lead to a devastating prognosis. Acute abdominal aortic occlusion and femoral artery occlusion is associated with high rates of morbidity and mortality even with surgical intervention in adults (41). Recent evidence has also proven that there is a higher incidence of deep venous thrombosis with femoral central venous lines among children with DKA (43).Vascular thrombosis is not commonly known but nevertheless a serious complication of DKA that should be considered in every patient treated for DKA and should be added to the differential diagnoses if clinical signs are present (41). Since the risk of developing thrombosis is increased in susceptible patients, low-dose or low-molecular-weight heparin therapy should be considered for prophylaxis.

## *Conclusion*

Since diabetes is such a common disease and its incidence is on a steep rise, adequate education of medical staff and the patient about the disease and its consequences is critical in prevention of DKA, Hyperglcemic Hyperosmolar State, and hypoglycemic attacks and their dreaded seaquel. As anti-diabetic medications evolve and the usage of insulin pumps is increasing in popularity, the risk of developing acute (and chronic) complications of the disease is in fact decreasing, mainly in industrialized countries. In non-industrialized countries where society's education on diabetes and its consequences is poor, in addition to the fact that access to medical supplies are scanty, the opposite is true. The future hope in

gene therapy for those at high genetic risk for diabetes of both type I and II brings a positive outlook on the future. Pancreatic cell transplants and stem cell research brings same hope but from a different angle. In conclusion, as the incidence of diabetes increases, knowledge of the disease, its symptoms and consequences becomes more and more critical. Hopefully with the advent of future medical therapy, the disease itself, or at least the consequences of it will be eliminated or severely decreased. However, the general outcome can be said to depend on two critical individuals; the patient and his/her motivation and responsibility to manage with the disease, and the doctor, with his/her ability to quickly diagnose and effectively treat it.

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