

## Diabetes: A Syndrome leads to Coma

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### Abstract:

The most common and most serious diabetic emergencies in type 2 diabetic mellitus (T2DM) individuals are diabetic ketoacidosis and hyperosmolar hyperglycaemic (HH) state or hyperosmolar non-ketotic hyperglycaemia. Hyperosmolar hyperglycemia state is a serious condition caused by extreme hyperglycemia in T2DM. HH is usually characterized by extreme elevations in serum glucose level and hyperosmolality in individuals with no significant ketosis. These metabolic disturbances are the result from synergistic factors mainly insulin deficiency as well as increased levels of counter regulatory hormones viz. glucagon, catecholamines, cortisol, and other growth hormone. Wolfram Syndrome (WS) or DIDMOAD syndrome (Diabetes Insipidus Diabetes Mellitus Optic Atrophy and Deafness) is a rare genetic disorder to be known. DM is typically the first symptom of WS and onset is usually at the age of 6 years. A diabetic coma is a life-threatening and fatal diabetes complication that causes unconsciousness in long term T2DM patients. The severe conditions of both hypo- or hyper- glycemia may cause diabetic coma. Here we are describing the brief about Diabetic emergencies lead to coma and unconsciousness.

**Keywords:** T2DM, diabetic ketoacidosis, diabetic coma, wolfram syndrome, hyperosmolar hyperglycemia

### Background:

Diabetic ketoacidosis (DKA) is specifically a symptom of T1DM and T2DM[1,2]. Around the globe the most common precipitating cause of DKA and HH is infection, any traumatic or stressful situation such as cardiovascular attacks, myocardial infarction, drugs, etc. The pathogenesis of DKA or HH comprises insulin deficiency as well as increased levels of counter regulatory hormones viz. glucagon, catecholamines, cortisol, and other growth hormone which lead to increase glucose production in liver and their decreased consumption in peripheral tissues[3]. In DKA, the severe shortage in insulin and elevated counter-regulatory hormones lead to upregulate the lipolysis and production of ketone bodies which lead to metabolic acidosis[4]. It is not known till date that individuals with HH don't develop ketoacidosis, but it is predicted to be owing decreased level of free fatty acids (FFA) or increased level of portal vein insulin [5]. There are many types of diabetic syndromes with associated complications that may cause the coma in an individuals.

### Hyperglycemia:

Hyperglycemia or high blood glucose level is the condition in which an excessive increase in amount of glucose level which circulates in the plasma of blood. For diabetic individuals, level of glucose may vary from one individual to other, mainly due to the individual's renal threshold of glucose and overall glucose tolerance in an individual. Several other factors can contribute to hyperglycemia in

diabetic individual, including life style and genetic makeup as well physical activity and kind of profession. Other factors include illness, nondiabetes medications, or skipping or not taking enough glucose-lowering anti-diabetic drugs. It is important to check and regulate hyperglycemia, because if left untreated it can become adverse and lead to very serious complications such as diabetic coma. In the long term persistent high glucose level, even if not severe, may lead to other associated complications affecting your eyes (retinopathy), kidneys (nephropathy), nerves (neuropathy) and heart problems. There are no physiological symptoms during hyperglycemia until glucose level values are significantly increased - usually above 180 to 200 mg/dL. There are progressive increments in symptoms over several days or weeks. If it is untreated, it may cause toxicity in the individual usually as ketone bodies formation (elevated ketones in blood and urine) results ketoacidosis.

### Hypoglycemia:

Hypoglycemia, a reciprocal of hyperglycemia or low blood sugar level, is when blood sugar level decreases to below normal glucose levels. It comprises a variety of symptoms like trouble while talking, confusion in mind, unconsciousness, etc. The most common cause of it is medications i.e. anti-diabetic drugs and their combinations used to treat T2DM. Risk is high in diabetic individuals who have eaten less than usual intake, exercised more than usual or have drunk alcohol[6]. Other major causes of it include kidney failure, certain kind of tumors such as insulinoma, liver associated diseases, hypothyroidism, prolonged starvation, inborn error metabolic disorders, severe pathogenic infections, reactive

hypoglycemia and a number of drugs and prolonged use of alcohol. Immediate treatment and attention is required for hypoglycemia when blood sugar levels are less than 70 mg/dL. The severe hypoglycemic condition may lead to coma.

### Hyperosmolar Hyperglycemia State:

Hyperosmolar hyperglycemia state (HHS) is a serious condition which is caused by extremely high blood glucose levels (hyperglycemia) in T2DM individuals. The first cases of HHS was reported in the 1880s in an individual with an “unusual diabetic coma” characterized by severe hyperglycemia. This is mainly characterized by severe hyperglycemia, hyperosmolality and dehydration in the absence of ketoacidosis[7], and it is mostly found in elder T2DM patients however, it has also been reported in children as well as in young adults[8]. The overall mortality rate is upto 20%, which is almost 10 times greater than the mortality in individuals with diabetic ketoacidosis (DKA)[9].

### Pathophysiology:

HHS is mainly characterized by extreme elevations in serum glucose level and hyperosmolality in an individual without significant ketosis. Such metabolic derangements result from many synergistic factors mainly insulin deficiency and high levels of counterregulatory hormones.<sup>10</sup> The main reason for the development of Hyperglycemia are because of an increased gluconeogenesis and rapid conversion of glycogen to glucose during glycogenolysis and by inadequate use of this glucose by peripheral tissues especially by muscle. The increased hepatic glucose level and its production represents the major pathogenic imbalance as well as disturbance responsible for hyperglycemia in DKA individuals [11]. As the concentration of glucose and osmolality of extracellular fluid increase, an osmolar gradient is created that will draw water out from the cells. Initially it prevents the development of severe hyperglycemia as long as the glomerular filtration rate is normal and the acellular fluid increase, an osmolar gradient is created that draws water out from the cells[12]. The Higher concentration of insulin in hepatic and circulating fluid as well as decreased glucagon are present in HHS compared with individuals with ketoacidosis. The higher circulating ratio of insulin/glucagon in HHS individuals prevents ketogenesis and the manifestation of ketoacidosis. This concept is supported by animals and humans clinical studies, which have shown that the half-maximal insulin concentration and antilipolysis is lower than for glucose use by the peripheral tissues[13]. Severe hyperglycemia is associated with a severe inflammatory state which is characterized by an elevation of pro-inflammatory cytokines (tumor necrosis factor- $\alpha$ , interleukin-1 $\beta$ , Interleukin-6 and Interleukin -8) as well as reactive oxygen species with insulin secretion and its action. Hyperglycemia causes an increase in oxidative stress markers such as peroxidation of membrane lipids[14]. The degree of lipid peroxidation is directly proportional to the concentrations of glucose in T2DM individuals. The increase in the level of circulating proinflammatory cytokines are reduced to normal levels promptly in response to insulin therapy and causes normalization of blood glucose level[15].

### Diagnostic Criteria of HHS:

According to definition and diagnostic criteria of HHS, it provided an insights into the pathophysiology of the syndrome they called “hyperglycemic hyperosmolar nonketotic coma” (HHNK). It included a blood glucose level >600 mg/dL, a total serum osmolality level >350 mOsm/L and a serum acetone reaction from 0 to 2 pluses when the serum was diluted 1:1 with distilled water[13,17]. The term HHNK has now replaced with “hyperglycemic hyperosmolar state (HHS)” to reflect the current fact that many HHNK individuals present without significant decrease in the consciousness level (less than 1/3 of coma patients) and because many individuals may present with mild to moderate degrees of ketosis[18]. In some previous reports, up to 20% of individuals with

severe hyperglycemia and hyperosmolality were reported to have combined features of both HHS and DKA[19].

### Wolfram Syndrome:

Wolfram Syndrome, a rare genetic disorder or DIDMOAD syndrome (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness). Patients demonstrate T2DM followed by optic atrophy in the first ten years, diabetes insipidus and sensorineural deafness in the next ten years, dilated renal outflow tracts early in the next ten years and multiple neurological abnormalities early in the prolonged forties. The hallmark features of this DIDMOAD syndrome are high blood glucose levels resulting from a shortage of the insulin hormone (T2DM) and progressive vision loss due to degeneration of the optic nerves that carry information from the eyes to brain usually optic atrophy and people with Wolfram syndrome often also have dysfunction of pituitary gland that results in the excretion of excessive amounts of diluted urine (diabetes insipidus), hearing loss caused by changes in the inner ear (sensorineural deafness), urinary tract problems, reduced amounts of the sex hormone testosterone in males (hypogonadism) or neurological or psychiatric disorders as well. T2DM is typically the primary symptom of Wolfram syndrome, usually diagnosed around age 6. For the first time in 1938, wolfram described four siblings with T2DM and optic atrophy[20]. Wolfram individuals usually die from central respiratory failure as a result of brain stem atrophy[21]. Wolfram syndrome is considered a rare disease and estimated to afflict about 1 in 1.6–7.7 lakh individuals[22].

### Common Clinical Presentation

The common manifestations of Wolfram syndrome include T2DM, optic nerve atrophy, diabetes insipidus, sensorineural deafness, urinary tract problems and progressive neurologic difficulties. T2DM is typically the first manifestation, usually diagnosed around age 6[23]. Optic nerve atrophy, marked by loss of color vision and peripheral vision, follows around age of 11 years[23]. Central diabetes insipidus is another common problem, affecting approximately 70 % of Wolfram patients[23]. Urinary tract problems are another major clinical challenge for Wolfram syndrome patients affecting 60 to 90 % of the population. These include obstruction of the ducts between the kidneys and bladder, high-capacity atonal bladder, disrupted urination, bladder sphincter dyssynergia and difficulty controlling urine flow[23]. Moreover to this mood disorder and autonomic dysfunction are commonly seen in Wolfram syndrome [24].

### Diagnosis

Suspicion of the diagnosis of Wolfram syndrome is generally based on history and clinical symptoms and their manifestations. Most commonly, the observation of optic nerve atrophy after the diagnosis of T2DM under the age of 16 years triggers the suspicion of this syndrome and the increasing avalanche indicates that Wolfram syndrome is a spectrum disorder. Diabetes insipidus, sensorineural deafness, neurological signs including ataxia, autonomic neuropathy, and epilepsy and neurogenic bladder in combination with T2DM or optic nerve atrophy could be a sign of Wolfram syndrome. The medical record and family histories and the clinical findings/physical examination are vital for the diagnosis of Wolfram syndrome, genetic testing has been proven to be useful to confirm the diagnosis of it.

The development of genetic tests for this syndrome has identified *WFS1* as the main locus mutated in the majority of patient[25]. Sanger sequencing-based genetic testing of the *WFS1* gene usually confirms the diagnosis of it. Majority of patient individual have recessive mutations in the *WFS1* gene[26]. Dominant mutations in the *WFS1* are a common cause of low-frequency sensorineural hearing loss [27]. A small number of individuals carry recessive mutations in the *CISD2* (*WFS2*) gene[28].

## Etiology

Initially this syndrome was categorized as mitochondrial disease due to its symptoms and several previous reports of mitochondrial mutations. However, it has now been established that Wolfram syndrome is a prototype of endoplasmic reticulum (ER) disease[29]. The ER is a membrane network of cells involved in protein synthesis, calcium storage, redox regulation, steroid synthesis, cell signaling and cell death. In Wolfram syndrome, mutations in the *WFS1* gene lead the destruction of pancreatic  $\beta$ -cells and neuronal cells. This gene encodes a transmembrane protein of ER and reflect that the ER dysfunction is a major pathogenic part of Wolfram syndrome. In Wolfram syndrome, *WFS1* mutations lead to increased level of ER stress, pancreatic  $\beta$  cell dysfunction, and the initiation of ER stress-associated cell death[27]. *WFS2* also encodes a ER localized transmembrane protein[30]. In individuals with *WFS2* mutation; T2DM and hearing impairment were reported. Their clinical presentation in individual carrying *WFS1* mutations for the absence of diabetes insipidus and for the presence of upper intestinal ulcers and defective platelet aggregation[30], suggesting that there are different and overlapping functions of *WFS1* and *WFS2*.

## Diabetic Coma

The reversible form of coma found in people with T2DM. A diabetic coma is a life-threatening diabetes associated complication that causes unconsciousness. The severe conditions of both Hypo- or Hyperglycemia can cause diabetic coma.

## Diabetic Ketoacidosis:

T1DM are found in approximately 1 in 300 individuals[31]. The prevalence of DKA is about 30% in children having T1DM[32]. DKA is defined by the American Diabetes Association (ADA), the European Society for Paediatric Endocrinology (ESPE) and the Pediatric Endocrine Society (PES) as hyperglycemia and venous pH < 7.3 and/or bicarbonate < 15 mmol/L. DKA increases the mortality rate in children with T1DM and the most common and primary complication of DKA is cerebral edema[33]. Many of DKA children are found in some degree of altered mental status. The altered status is due to acidosis or hyperosmolarity, although some reports showed that subclinical cerebral edema commonly occurs in DKA individuals[34]. Clinical studies of both adult and pediatric patients with T1DM and DKA have described a variety of transient changes in coagulation factors *viz.* increased platelet activation, fibrinolytic activity and endothelial activation[35]. The procoagulant state of DKA places individuals at increased risk of ischemic brain injury as well as subsequent hemorrhagic conversion mainly arising from hypoxia and vascular injury[36]. Early clinical signs and symptoms of CNS injury include nonspecific findings such as headache, confusion, lethargy and unexpected fluctuations in heart/respiratory rate or blood pressure, which lead to coma[37].

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## Conflict of interest

The authors declare no conflict of interest.

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