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Biochemicophysiological Mechanisms Underlying Signs
and Symptoms Associated with Diabetes mellitus

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Abstract: Diabetes mellitus is a disorder, which has become a major health burden all over the world. This metabolic disorder currently has no cure. A search of database sites such as Medline, Elsevier, Springer, Science Direct, PubMed, Google Scholar, Web of science, as well as other sources of literature available across public libraries was conducted to obtain information related to the topic. This review has presented a discussion on the biochemical and physiological mechanisms underlying the associated signs and symptoms of diabetes mellitus by relating it to the role of insulin in glucose uptake in cells and fuel metabolism. This exposé is anticipated to enlighten researchers on specific management targets, which may warrant future research into developing pharmacological and non-pharmacological therapies as a means of managing diabetes mellitus, its associated signs and symptoms and ultimately chronic complications. An understanding of how these signs and symptoms develop, early recognition of it by patients and diagnosis of condition by healthcare professionals coupled with early management can prevent or delay the onset of chronic complications and ultimately reduce mortality and morbidity rate in the general population.

Key words: Diabetes Mellitus • Signs and Symptoms • Impaired Glucose Metabolism

INTRODUCTION

Diabetes mellitus (DM) is an endocrine and metabolic disorder, which is on the ascendency all over the world. It is a disorder involving lipid and carbohydrate metabolism and it is characterized by persistent hyperglycaemia resulting from defective insulin secretion, resistance to insulin hormone by receptors or both [1]. The disorder is a progressive one affecting all ages of the population. The alarming incidence of the disorder [2], which is rapidly reaching epidemic proportions, is a growing concern all over the world. Due to the unavailability of a cure for this medical condition research is needed in this direction. Inadequate management or uncontrolled hyperglycaemia manifest into signs and symptoms which can also be referred to as acute complications. When these signs and symptoms are overlooked or not detected early, it could lead to chronic complications. Early diagnosis and management has been reported to prevent or delay the development of chronic complications and even death. Delay in controlling hyperglycaemia in diabetes mellitus individuals has been reported to hasten and/or increase the risk of developing chronic complications such as cardiovascular diseases [3, 4]. Despite the availability of pharmacological and non-pharmacological therapies, globally diabetes mellitus has remained one of the leading causes of death. Understanding the pathophysiology of signs and symptoms is essential in diagnosis, management and prevention of the disorder. This review has put together information on the biochemicophysiological effects of glucose uptake, its consequence on metabolism and onset of signs and symptoms in diabetes mellitus.

Classification of Diabetes Mellitus: Diabetes mellitus has long been classified on the basis of specific clinical features namely (age of onset and insulin dependence) into maturity onset diabetes or non-insulin-dependent diabetes mellitus (NIDDM) and juvenile onset diabetes or insulin-dependent diabetes mellitus (IDDM). As a result of inaccuracies and confusion resulting from diagnosis based solely on age and descriptive terms, the National Diabetes Data Group in 1979 standardized the
nomenclature and definitions for diabetes mellitus, which was endorsed by WHO in 1980 [5, 6]. The two major types of diabetes mellitus were given names descriptive of their clinical presentation, thus type-1-diabetes mellitus (T-1-DM) replaced insulin-dependent diabetes mellitus (IDDM) or juvenile onset diabetes and type-2-diabetes mellitus (T-2-DM) used in place of non-insulin-dependent diabetes mellitus (NIDDM) or maturity onset diabetes. This did not solve the problems encountered during classification. These problems, alongside new insights into the pathophysiology of diabetes mellitus, provided a major momentum for the advancement of a new classification system in 1985.

In response to the major growth in knowledge about the aetiology and pathogenesis of the different types of diabetes mellitus and about the predictive value of different blood glucose levels for development of complications, classification of the different types of diabetes mellitus was redefined [7]. The various types of diabetes mellitus extend across a clinical continuum of hyperglycaemia and insulin requirements. The new classification system identifies four major types of diabetes mellitus; (i) Type -1- diabetes mellitus which is immune mediated and could be in children with a more rapid onset or adults with a slower onset-‘late autoimmune diabetes of adults’ (LADA) (ii) Type-2-diabetes mellitus which is insulin resistant (iii) Gestational diabetes mellitus (GDM) and (iv) “Other specific types”, of diabetes mellitus of various aetiologies [8, 9].

Aetiology of Diabetes Mellitus: The aetiology of diabetes mellitus is unknown; however, genetic and environmental factors have been linked to its development. The destruction of β-cells of the islets of Langerhans in the pancreas is known to be triggered by multiple factors, which include environmental factors like rubella infection and genetic factors like inheritance of Human Leukocyte Antigen – Death Receptor 3 and 4 (HLA-DR3 and DR4) genes [10]. These factors are suggested to interact synergistically. However, environmental factors like sedentary lifestyles and unhealthy eating habits are known to influence the progression of the disease. In type-1, 75% of β-cells are destroyed leading to an almost absolute insulin deficiency [11]. The type 2 form of the disease is due to insulin insufficiency as a result of secretory defects of the β-cells of pancreas or insulin resistance in peripheral tissues or receptors leading to poor uptake of glucose into tissues. Pregnancy state of an individual is known to be responsible for gestational diabetes mellitus which goes away after pregnancy. During normal pregnancy, resistance to insulin action increases. In most pregnancies, pancreatic β-cells are able to compensate for increased insulin demands and normoglycaemia is maintained. Women who develop GDM have deficits in β-cells response leading to insufficient insulin secretion to compensate for the increased insulin demands [12].

Physiology of Glucose Uptake into Tissues: It is imperative to understand the physiology of glucose uptake into cells and tissues, which subsequently affects most metabolic processes. All cells and tissues in the body utilize glucose for generation of energy in the form of Adenosine triphosphate (ATP). The brain does not store glucose meanwhile it prefers it to other fuel sources and predominately depends on it for ATP generation which is needed to maintain membrane potential. The maintenance of membrane potential is required for nerve impulse transmission. This implies that, there is the need for a constant and consistent availability of glucose to brain cells. To maintain this constant source of glucose, blood glucose level must be kept between 3.6-7.2 mmol/L. Blood glucose level is considered too high if it is above 7.8 mmol/L before a meal or higher than 10.8 mmol/L two hours after a first meal [13]. There are several physiological processes that occur in the body to ensure normal glucose level. Several hormones namely glucagon, cortisol, epinephrine, somatostatin and insulin are required to ensure a constant blood glucose level. These hormones are secreted and released based on changes in blood glucose, amino acid and fatty acid levels [14]. Though insulin is regarded as a key player for assurance of a normal blood glucose level, glucagon, cortisol, epinephrine and somatostatin collectively contribute to maintaining glucose homeostasis. The absence of these hormones [glucagon, cortisol, epinephrine and somatostatin] or their deficiency in cells hastens the development of diabetes mellitus [14].

Insulin is the hormone mostly associated with impaired glucose metabolism and diabetes mellitus [15]. A normal pancreas releases between 35 and 50 enzyme units of insulin daily, with several hundred units still available to be released if blood glucose concentration rises above normal levels [15]. When insulin is released, it binds to insulin receptors on the membrane of tissues such as liver, muscle and adipose tissues and thus facilitates glucose uptake into these tissues. When a person without diabetes mellitus ingests carbohydrate rich food, it is absorbed through the gastrointestinal tract and then into blood circulation. The presence of glucose
In a person without diabetes mellitus, insulin that is released from the pancreas acts as a key to open the cell “door” for glucose from the blood to enter. Implicitly glucose level is low (I represents Insulin) and (G represents Glucose) represents Insulin and (G represents Glucose) (adopted from Akeenobumatsu, 2008).

In type 1 diabetes mellitus, insulin, which serves as a key to open cell “doors”, is not present, so glucose cannot enter into the cells thus glucose level is low (adopted from Akeenobumatsu, 2008).

In type-2-diabetes mellitus, insulin which serves as a key to open cell “doors”, is present, but the receptors are unresponsive or less sensitive to it, so the glucose still has difficulty getting into the cell thus glucose level is also low (adopted from Akeenobumatsu, 2008).

in the blood is detected by the pancreas, which quickly starts producing insulin. Glucose then flows through the pancreatic cells via a special protein called GLUT-2 (glucose-transporter-2) [16]. Insulin can be considered as the key to open the door for glucose to enter tissues. When insulin is released into circulation, it comes in contact with cells in the peripheral tissues of muscles and adipose [16]. Special pores (the doors) are opened, allowing glucose to move into cells for metabolism and subsequent generation of ATP or energy. These ‘special doors’ in the peripheral tissues are made up of a special protein similar to those on the pancreas known as GLUT-4. This series of events is the mechanism that keeps blood glucose at normal levels (Fig. 1-3).

In people with impaired glucose metabolism due to diabetes mellitus, this mechanism functions abnormally. It is important to note that the brain and other cells have special protein transporters called GLUT-1 and GLUT-3 that are independent of insulin in terms of transport of glucose.

**Effect of Insulin on Metabolism:** Insulin is a very important hormone that plays a major role in fuel metabolism, thus this section elaborates on its effect on metabolism. Insulin hormone stimulates glucose uptake by cells as such its absence, insufficiency or unresponsiveness by receptors consequently affects many metabolic processes. Insulin metabolically supports glycolysis by increasing its rate, stimulates protein synthesis and inhibits glycogenolysis and lipolysis [17-19]. It also stimulates rate of glycolysis, which provides the precursors for the formation of fatty acids and also decreases the rate of production of ketone bodies. Insulin deficiency decreases the expression of a number of genes necessary for target tissues to respond normally to insulin such as glucokinase in liver and the GLUT-4 class of glucose transporters in adipose tissue. The major metabolic derangements that result from insulin deficiency in diabetes mellitus are impaired glucose, lipid and protein metabolism.

**Glucose Metabolism:** In individuals without any metabolic or endocrine disorder, after carbohydrate breakdown, glucose ends up in blood circulation and later transported into cells for ATP to be generated through metabolic processes such as glycolysis, Tricarboxylic acid (TCA) cycle, glycogenesis etc. Other enzymes involved in anabolic metabolism of glucose are affected by insulin basically through covalent modification.

In uncontrolled diabetes mellitus, TCA cycle is in a state of suppression due to diminished availability of oxaloacetate, which is routed towards the pathway of gluconeogenesis. In such uncontrolled condition, hyperglycemia occurs due to decreased utilization of glucose from blood as a result of failure to transport it into cells for metabolism. Diabetes mellitus also impairs non-hepatic tissue utilization of glucose particularly in adipose
Fig. 4: Tricarboxylic acid cycle suppression and ketogenesis in diabetes mellitus (Adopted from Diabetes Mellitus | Biochemistry for Medics–Lecture Notes. http://www.namrata.co/category/diabetes-mellitus.)

tissue and skeletal muscle, where insulin stimulates glucose uptake. Implicitly there is a reduced state of glucose uptake by peripheral tissues that ends up in a reduction in the rate of glucose metabolism [17-19].

The processes of glucose utilization such as glycolysis, TCA cycle, Hexose monophosphate (HMP) and glycogenesis occur at a diminished rate, whereas rates of gluconeogenesis and glycolysis are increased due to upset in insulin to glucagon ratio in diabetes mellitus. Oxaloacetate is a common intermediate of TCA cycle and gluconeogenesis. The utilization of oxaloacetate in the pathway of gluconeogenesis depletes the amount that is required for TCA cycle. It is worth noting that oxaloacetate acts as a “catalyst” in that an optimum amount of oxaloacetate is required for the functioning of TCA cycle. As glucose utilization is decreased in diabetes mellitus, alternatively fatty acids are oxidized to compensate for the energy requirements. The fall out from the increase in the rate of fatty acid oxidation is (i) Accumulation of NADH that further suppresses TCA cycle. Excess NADH generated decreases the catalytic activities of 3NAD’ requiring enzymes of TCA cycle namely isocitrate dehydrogenase, α-ketoglutarate dehydrogenase and malate dehydrogenase in addition to the activity of PDH complex. (ii) There is also accumulation of acetyl CoA, the end product of fatty acid oxidation, which cannot be oxidized in TCA cycle at the same rate as that of it’s production. As a result, acetyl co A is directed either towards pathways of ketogenesis, or of cholesterol synthesis (Fig. 4). It is imperative to mention that though other intermediates in TCA cycle; succinate, malate and α-ketoglutarate are involved in glucose metabolism, there are not depleted in diabetes mellitus.

Though pyruvate is depleted, it does not directly affect the functioning of TCA cycle, since there are other sources available.

In Type 1 diabetes mellitus, the onset of the disease is sudden, which is why the body switches abruptly from glucose utilization to fatty acid oxidation for energy needs. Acetyl CoA resulting from excess fatty acid oxidation saturates TCA cycle and the other alternative pathways resulting in ketogenesis. Acetone, acetoacetate and β-hydroxybutyrate are the three ketone bodies formed. This is the reason ketoacidosis is far more commonly found in type-1-diabetes mellitus than type 2 diabetes. Diabetes mellitus and starvation depict a similar metabolic state, where cells are deprived of glucose and switch to alternative fuels for their energy needs thus the basis of ketoacidosis is thus the same in both conditions.

**Lipid Metabolism:** The metabolic pathways for utilization of lipids and carbohydrates are entwined. Considering insulin’s metabolic effects on carbohydrates, it is not by chance that it also has an effect on lipid metabolism. Insulin promotes synthesis of fatty acids in the liver. It also stimulates synthesis of glycogen in the liver. However, as glycogen accumulates to high levels, further synthesis is strongly suppressed. When the liver is saturated with glycogen, any additional glucose taken up by hepatocytes is shunted into pathways leading to synthesis of fatty acids, which are exported from the liver as lipoproteins. The lipoproteins are ripped apart in the circulation, providing free fatty acids for use in other tissues, including adipocytes, which use them to synthesize triglyceride. Insulin inhibits breakdown of fat in adipose tissue by inhibiting the intracellular lipoprotein
lipase (LPL) an enzyme on the surface of the endothelial cells lining the vessels that hydrolyzes triglycerides to release fatty acids [17-19].

Aside the fact that insulin stimulates glycogen energy stores in hepatocytes and skeletal muscle, it also stimulates hepatocytes to synthesize triglycerides and store in adipose tissue whilst inhibiting the process of lipolysis. Insulin facilitates entry of glucose into adipocytes and within those cells, glucose can be used to synthesize glyceral. These glycercals, along with fatty acids delivered from the liver, are used to synthesize triglyceride within the adipocyte. This means that insulin is involved in further accumulation of triglyceride in fat cells and thus has a fat-sparing effect. Not only does it drive most cells to preferentially oxidize carbohydrates instead of fatty acids for energy, it indirectly stimulates accumulation of fat in adipose tissue [17-19].

In uncontrolled type-1-diabetes mellitus, there is a rapid mobilization of triglycerides leading to increased levels of plasma free fatty acids. The free fatty acids are taken up by numerous tissues except the brain and metabolized to produce ATP. The liver also takes up free fatty acids. Normally, the levels of malonyl-CoA are high in the presence of insulin. The presence of high levels of malonyl-CoA inhibits carnitine palmitoyltransferase I, the enzyme required for transport of fatty acyl-CoA's into the mitochondria where they are subjected to oxidation for energy production. Thus, in the absence of insulin, malonyl-CoA levels reduce and the rate of transport of fatty acyl-CoA's into the mitochondria increases. Mitochondrial oxidation of fatty acids generates acetyl-CoA, which can further be oxidized in the TCA cycle. However, in hepatocytes majority of the acetyl-CoA is not oxidized by the TCA cycle but is metabolized into ketone bodies; acetone, acetoacetate and β-hydroxybutyrate. These ketone bodies leave the liver and are used for energy production by the brain, heart and skeletal muscles. In type-1-diabetes mellitus, the increased availability of free fatty acids and ketone bodies exacerbates the reduced utilization of glucose thus promoting hyperglycaemia. Ketone bodies are thus produced in excess of the body's ability to utilize leading to ketoacidosis [17-19].

**Protein Metabolism:** Insulin regulates the synthesis of many genes, either positively or negatively that then affect the overall metabolic processes. In addition to insulin’s effect on entry of glucose into cells, it also stimulates the uptake of amino acids, thus contributing to its overall anabolic effect. When insulin levels are low, as in fasting state, the balance is pushed toward intracellular protein degradation (catabolism). This implies insulin has a universal effect on protein metabolism, increasing the rate of protein synthesis and decreasing the rate of protein degradation. Implicitly the presence of type-1-diabetes mellitus due to absolute lack of insulin would lead to increased rate of protein catabolism. The increased rate of proteolysis leads to elevated concentrations in plasma amino acids. These amino acids serve as precursors for hepatic and renal gluconeogenesis. In liver, the increased gluconeogenesis further contributes to the hyperglycaemia seen in type-1-diabetes mellitus. Additionally, insulin deficiency decreases the expression of a number of genes necessary for target tissues to respond normally to insulin such as glucokinase in liver and GLUT-4 a class of glucose transporter in adipose tissue [17-19].

**Signs and Symptoms of Diabetes Mellitus:** Signs and symptoms of diabetes mellitus can be divided into three main categories namely (i) those related to expression of physical symptoms e.g. polydipsia (increased thirst and consequent increased fluid intake), polyuria (Frequent urination) glycosuria (glucose in urine), polyphagia (extreme hunger or increased appetite), unexplained weight loss despite normal or increased eating, decreased in level of consciousness or dizziness, acetonuria, tachycardia (fast heart rate), dehydration and dry mouth. It is worth noting that most people experience what is generally referred to as the classical triad of diabetes mellitus symptoms i.e. polyuria, polydipsia and polyphagia or the 3P’s of diabetes mellitus symptoms. (ii) those arising from specific long term lesions of diabetes mellitus e.g. microangiopathy in the eye known as retinopathy (sudden vision changes), in the kidney referred to as nephropathy and in the nerves which shows as a tingling sensation or numbness in the hands or feet a condition called neuropathy (iii) those resulting from acceleration of predisposition to disease processes, e.g. atherosclerosis, frequent or recurrent skin and urinary tract infection [20].

**Biochemical and Pathophysiological Basis of Signs and Symptoms Associated with Diabetes Mellitus:** Diabetes mellitus is a disorder which when hyperglycaemia is controlled, does not pose any threat to individuals with the condition. It becomes a death trap when individuals
with the condition do not know their status. The onset of signs and symptoms in diabetes mellitus individuals is variable. Most of these signs and symptoms are seen in uncontrolled diabetes mellitus or persistent hyperglycaemia. It is important to note that some people may only experience a few symptoms listed earlier. An estimated 50% of people with type-2 diabetes mellitus do not experience any signs and symptoms [21, 22] and therefore do not know their status. In this piece the focus has been on those related to the expression of physical signs and symptoms. "Glucostat Theory of Feeding Regulation", glucose is excreted in glycosuria state, there is a concomitant loss of water and electrolytes needed to maintain normal osmolarity of the urine. This polyuria-glycosuria condition leads to decrease in blood volume, which is replaced or compensated for, osmolality by water held in body cells, causing dehydration in diabetes mellitus individuals and consequently weight loss. The loss in water also leads to increased thirst a condition termed polydipsia (Fig. 5).

Utilization of muscle protein (through gluconeogenesis) due to the inability of the body to transport glucose for energy production accounts for the loss in weight in individuals with diabetes mellitus. Additionally insulin inhibits breakdown of fat (lipolysis) in adipose tissue by inducing intracellular lipase that hydrolyzes triglycerides to release fatty acids, thus its absence leads to increased rate in lipolysis thus accounting for sudden weight loss in obese individuals who develop diabetes mellitus and unaware of their condition.

The negative caloric balance resulting from glycosuria and tissue catabolism leads to an increase in appetite and food intake, a condition referred to as polyphagia [19]. In uncontrolled diabetes mellitus, glucose from the blood cannot enter cells (Fig. 2 & 3) leading to intracellular glucose starvation; implicitly the body would be unable to convert the food eaten into ATP. This makes diabetes mellitus individuals feel weak and fatigue even after a heavy meal. Also, according to the "Glucostat Theory of Feeding Regulation", arteriovenous difference of glucose in the hypothalamus,
satiety and feeding centres regulates the feeding response [19]. If the difference is high due to the reason that glucose is more utilized by satiety centre, the satiety centre is activated and if the difference is low then feeding centre is activated. In diabetes mellitus, glucose cannot move into the cells of the satiety centre, thus the arteriovenous difference remains low and the feeding centre is chronically active thus creating a feeling of wanting to eat termed as polyphagia.

Another sign and symptom exhibited by people with diabetes mellitus is the production of acetonic breath a condition termed diabetic ketoadiabosis (DKA) (Fig. 5). Often, a “ketosis” odour is present, which is often described as “fruity”. DKA is a state of inadequate insulin levels resulting in high blood glucose levels and accumulation of organic acids and ketones in the blood. It is a potentially life-threatening condition in individuals with diabetes mellitus. It happens predominantly in type-1 diabetes mellitus, but can also occur in type-2 diabetes mellitus. DKA results from relative or absolute insulin deficiency combined with counter regulatory excess hormone (glucagon, catecholamines, cortisol and growth hormone). The decreased ratio of insulin to glucagon promotes or increases the rate of gluconeogenesis, glycogenolysis and Ketone body formation in the liver [18, 19, 26]. The combination of insulin deficiency and hyperglycemia reduces the hepatic level of fructose-2, 6-phosphate, which alters the activity of phosphofructokinase and fructose-1, 6-bisphosphatase. Excess glucagon decreases the activity of pyruvate kinase, whereas insulin deficiency increases the activity of phosphoenolpyruvate carboxykinase. These changes shift the control of pyruvate toward glucose synthesis and away from glycolysis. The increased levels of glucagon, cortisol, growth hormone and catecholamines due to lack or low insulin levels promote glycogenolysis, gluconeogenesis and lipolysis (Fig. 5). Insulin deficiency also reduces levels of the GLUT-4, which impairs glucose uptake into skeletal muscle and reduces intracellular glucose metabolism. Usually, the free fatty acids released by adipolysis are converted to triglycerides or VLDL in the liver. However, in DKA, hyperglycogonemia alters hepatic metabolism to favour Ketone body formation, through activation of the enzyme carnitinepalmitoyl Transferase I. This enzyme is crucial for regulating fatty acid transport into the mitochondria, where β-oxidation and conversion to ketone bodies occur [19]. The accumulated ketone bodies are acidic in nature and as they deplete the bicarbonate alkali reserves, they cause metabolic acidosis. The body initially buffers this bicarbonate, but this is later overwhelmed by other mechanism to compensate for the acidosis, such as hyperventilation is turned on (Fig. 5). This hyperventilation, in its extreme form, may be observed as Kussmaul respiration.

Ketones bodies, too, participate in osmotic diuresis and lead to further electrolyte losses. As a result of the above mechanisms, the average adult DKA individual has a total body water shortage of about 6.0 L, in addition to substantial shortages in sodium, potassium, chloride, phosphate, magnesium and calcium. Glucose levels usually exceed 13.8 mmol/l or 250 mg/dl in DKA state. Increased lactic acid production also contributes to the acidosis [19]. The increased free fatty acids increase triglyceride and VLDL production. VLDL clearance is also reduced because the activity of insulin-sensitive lipoprotein lipase in muscle and fat is decreased. Most commonly, DKA is precipitated by increased insulin requirements, as might occur during a concurrent illness. DKA manifests with evidence of dehydration, such as a dry mouth or hyposalivation and decreased skin turgor. If the dehydration is profound enough to cause a decrease in the circulating blood volume, tachycardia (a fast heart rate) and hypotension may be occur (Fig. 5). In severe DKA, there is increased in respiratory rate and of a deep gasping character a condition referred to as Kussmaul respiration. The movement of ketone bodies along with positive charged ions out of the body fluids during polyuria condition creates an electrolyte imbalance resulting in abdominal pains, vomiting and stress reaction [27, 28]. Vomiting expels even more important electrolytes stimulating hypothalamic thirst centres causing polydipsia.

Hyposalivation is a common symptom that is related to polyuria. It is suggested that the substitution of the functioning tissue by adipose tissue modifies qualitatively and quantitatively saliva production and this is what facilitates hyposalivation symptom [29]. When saliva production is decreased, fungi such as Candida albicans and or even the associated development of other species can increase. Other factors which have also been mentioned as contributing to increase infections in diabetes mellitus individuals is insulin hyposcretion, underutilization of glucose and increased production of glucose [30-33].

CONCLUSIONS

Diabetes mellitus is still a public health burden. There is more to be unraveled about the disease. An understanding of how signs and symptoms develop in diabetes mellitus, early recognition of it and diagnosis coupled with early management can prevent or delay the
onset of chronic complications and ultimately reduce morbidity and mortality rate.

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