REVIEW ARTICLE

Inborn errors of metabolism associated with hyperglycaemic ketoacidosis and diabetes mellitus: narrative review

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ABSTRACT

Inborn errors of metabolism (IEM) are heterogeneous group of disorders that might present in the clinics or emergency departments in different phenotypes, and one of these is a diabetes scenario. Diabetes is the most common endocrine disorder among children. The mechanism of how IEM could lead to diabetes is unclear; however, the postulated pathogenesis consists of three mechanisms: 1) accumulation of toxic substance in the gland, ruining structure and normal functionality, 2) disturbing energy availability required for hormone synthesis and 3) defect of complex molecules. The differential diagnosis of IEM associated with hyperglycaemic ketoacidosis and diabetes include: organic acidemias specifically propionic acidemia, methylmalonic acidemia, isovaleric acidemia, hereditary hemochromatosis, aceruloplasminemia, holocarboxylase synthetase deficiency, β-ketothiolase deficiency and finally, cystinosis, Rogers syndrome (thiamine-responsive megaloblastic anaemia) and congenital disorders of glycosylation type Ia. Clinical approach will help in ready diagnosis and treatment for IEM disorders in early detection of diabetes. In this review, we will discuss the differential diagnosis, clinical features and diagnostic approaches of IEM presenting as hyperglycaemic ketoacidosis and diabetes.

KEYWORDS:

Aceruloplasminemia; Congenital disorders of glycosylation; Cystinosis; Diabetes mellitus; Hemochromatosis; Inborn errors of metabolism; Mitochondrial disorders; Organic aciduria; Rogers syndrome.

INTRODUCTION

Inborn errors are genetic disorders affecting the biochemical processes of the cells. Most inborn errors of metabolism (IEM) are caused

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by enzymes defects, which result in insufficient or absent end products. In many cases, the accumulation of toxic substances generated along the processes causes serious consequences [1]. Garrod et al. in the year 1909 were the first to report on genetic and biochemical natures of albinism, cystinuria and alkaptonuria by developing a concept of chemical individuality. Different classes of IEM's have been expanding into huge diversity of biochemical disorders that fall into IEM category. The online resource of metabolic and molecular bases of inherited diseases describes more than 90 chapters discussing such disorders related to IEMs [2].

The classification of IEM is challenging. Several classifications currently exist. The favourable classification is to **small molecules diseases** such as carbohydrate, protein, lipid and nucleic acids and **large molecules diseases** such as lysosomes, mitochondria, peroxisomes and cytoplasm [3].

Another classification is based on the affected metabolic process or enzymes involved in generating toxic substances such as the individual disorders of amino acid, urea cycle, organic acid, carbohydrate, protein glycosylation as well as lysosomal and peroxisomal disorders and mitochondrial diseases.

Based on pathophysiology, perspective IEMs are divided into three sub groups, i.e., disorders that cause intoxication, disorders of energy metabolism and disorders of complex molecules [4].

A. Intoxication causing disorders: can lead to acute or progressive intoxication, which involves IEMs such as amino acid metabolism (phenylketonuria, homocystinuria, maple syrup urine disease etc.), urea cycle defects, sugar intolerances (hereditary fructose intolerance, galactosemia), organic acidurias, metal intoxication and phorphyrias. All of these diseases share similar clinical features such as vomiting, coma, liver failure and thromboembolic complications in acute phase, developmental delay and failure to thrive, in chronic stage.

B. Disorders involving energy metabolism: are usually related to deficiency of energy production or utilisation in liver, muscle, myocardium, brain or other tissues. These disorders can be sub divided into mitochondrial and cytoplasmic energy deficiencies. Mitochondrial defects lead to congenital lactic acidemia (Krebs cycle enzymes) and mitochondrial respirator chain disorders (respiratory chain, impaired synthesis of coenzyme Q10) are the most severe and untreatable. Cytoplasmic disorders are less severe and treatable such as defects in glycolysis, glycogen metabolism and gluconeogenesis and hyperinsulinism. Symptoms of disorders involving energy metabolism include hypoglycaemia, hyperlactatemia, severe generalised hypotonia, hepatomegaly, cardiomyopathy, failure to thrive, myopathy, sudden death in infancy and impaired brain development.

C. Disorders involving complex molecules: are related to synthesis or catabolism of cellular organelles like lysosome, peroxisome and mitochondria.

Diabetes mellitus (DM) is one of the metabolic endocrine disorders which has main characteristic of elevated levels of glucose in blood (hyperglycaemia) and deficiency of insulin secreted by the pancreas inside the human body [5].

The number of people with diabetes has increased from 108 million in 1980 to 422 million in 2014. The world prevalence of diabetes among adults over 18 years of age has risen from 4.7% in 1980 to 8.5% in 2014 [6]. There are three major types of diabetes: type 1 diabetes (T1DM), type 2 diabetes (T2DM) and gestational diabetes [6].

A single IEM could present as hyperglycaemic ketoacidosis and may display several endocrine disorders. Among the most frequent disorders associated with IEM are DM, followed by hypogonadism and thyroid dysfunction [7].

T1DM is an autoimmune disease. It is caused by autoimmune destruction of insulin-producing beta cells of the pancreas, which leads to lack of insulin resulting in an increase of glucose levels in blood and urine. Disorders requiring anabolism and prevention of protein degradation represent a threat by accumulating toxic metabolites that can affect the pancreas leading to or complicating non-autoimmune

T1DM. In addition, disorders requiring glucose stabilisation, glycogen degradation and gluconeogenesis can cause hypoglycaemia complicating the management of T1DM. In addition to insulinopenia, the dysfunction in liver and muscles in IEMs may lead to insulin resistance and T2DM.

In this review, we will discuss the differential diagnosis, clinical features and diagnostic approaches of IEM presenting as hyperglycaemic ketoacidosis and DM.

MECHANISM OF IEM LEADING TO DIABETES MELLITUS

Hormones are essential in coordinating various functions such as growth, metabolism, reproduction and energy equilibrium. Hormonal impairments could contribute to IEM complications. The endocrine coordination also has autocrine and paracrine systems and is closely connected with central nervous system and immunology networks through neuromodulators and cytokines. In case of diabetes, insulin hormone is the major player and insulinopenia is the main cause of IEM related diabetes, although insulin resistance could also be implicated (Table 1). Beta cells of the pancreas produce the peptide hormone, insulin, which is considered the main anabolic hormone in the body.

The three known mechanisms that have shown to interfere with insulin regulation in IEM are either by accumulation of a toxic substance in the pancreas gland ruining the structure and normal functionality, as in hemochromatosis (iron accumulation), cystinosis (cysteine accumulation), organic acidemia (organic acid accumulations); or by disturbing the energy source needed for the hormone synthesis as in respiratory chain disorders [Maternally inherited diabetes and deafness (MIDD), Mitochondrial myopathy, encephalopathy, lactic acidosis and stroke-like episodes (MELAS), Kearns-Sayre syndrome and diabetes insipidus, diabetes mellitus with optic atrophy and deafness (DIDMOAD) syndrome or the hormone release as in Rogers syndrome] causing DM due to under production of insulin [7].

SUMMARY OF INBORN ERRORS OF METABOLISM (IEM) DISEASES ASSOCIATED WITH DIABETES MELLITUS

Organic aciduria

Organic aciduria is a group of disorders caused by abnormal metabolism of proteins, fats or carbohydrates which leads to an unexpected accumulation of particular acids known as organic acids, and is characterised by noticeable metabolic acidosis with ketosis. Aciduria disorder may be life threatening as such build up causes severe damage to the tissues and organs. Various genes and huge number of mutations variants are involved in organic aciduria, depending on the impaired organic acid metabolism. Statistic studies have shown that 1 in 50,000 to 250,000 people was diagnosed with this genetic disorder [2,4,8]. However, the prevalence of these disorders is higher in certain parts of the world such as Saudi Arabia [9,10].

Few organic acidemia were reported to present with DM in the form of diabetes ketoacidosis. These include methylmalonic acidemia (MMA), propionic acidemia (PA), isovaleric acidemia (IVA), β-ketothiolase deficiency (BKT) and holocarboxylase synthetase deficiency (HCSD) [11,12]. The mechanism is generally unclear; however, it seems to be due to accumulation of toxic substances in the pancreas, which impairs the structure normal functionality leading to insulinopenia and diabetes.

Propionic acidemia (PA)

It is one of the organic acids disorders and odd-chain fatty acid metabolism, which was initially described by Childs and Nyhan et al. in 1961 [13,14]. It is inherited in an autosomal recessive pattern. Initially, was named ketotic hyperglycaemia because of its characteristic of high glycine level in plasma and urine [14]. Hsia et al., 1969 described deficient oxidation of propionate while Gompertz et al., 1970 demonstrated enzyme deficiency in hepatocytes, then, in leukocytes of affected individuals [15–17]. The PA term was used after illustration of

Table 1 - Summary of IEM diseases associated with DM.

General classification	Impaired mechanism	IEM Associated gene mutation	IEM disease	Prevalence	Diabetes characteristic
Cellular intoxication	Metal intoxication *Iron storage*	*HAMP, HFE, HFE2, SLC40A1 and TFR2*	Hemochroma-tosis	1:200 to 1:400	T1DM (due to reduced B cell mass) and T2DM (due to insulin resistance and liver cirrhosis) with possible inaugural ketoacidosis
	Metal intoxication *Iron storage*	*CP*	Aceruloplas-minemia	1:2,000,000	DM (both T1D and T2D) due to similar mechanism (as above; in hemochromatosis)
	Organic acid intoxication *Abnormal metabolism of organic acids*	*MUT, MMAA, MMAB, MMADHC, MCEE, ACSF3, IVD ACAT1 and HLCS*	Methylmalonic aciduria Propionic aciduria Isovaleric aciduria β-ketothiolase deficiency HCSD	1: 50,000 to 1:250,000	Transient hyperglycaemic ketoacidosis
Energy defect	Mitochon-drial energy defect *Deficient energy production in respiratory chain*	*MT-TL1, MT-TK, MT-TE, WFS1 and CISD2*	MIDD & MELAS, Wolfram syndrome	1:4,000 to 1:500,000	Non-autoimmune diabetes with possible inaugural ketoacidosis and diabetes insipidus
Complex molecules defect	Lysosomal disorder *Cystine in lysosomes*	*CTNS*	Cystinosis	1:100,000 to 1:200,000	DM (Due to defective insulin expression because of abnormal tRNAs or DNA mutations)
	Congenital disorders of glycosylation	*PMM2*	Congenital disorders of glycosylation type Ia	1:20,000	DM or hyperinsulinemic hypoglycaemia (due to defect in B cell function and to some extend associated liver fibrosis)
	Transporter defect *Defective ATP production in β cells*	*SLC19A2*	Rogers syndrome (Thiamine-sensi-tive megaloblas-tic anaemia)	30 families world wide	Thiamine-sensitive DM with possible ketoacidosis

propionyl-CoA carboxylase (PCC) deficiency. PCC is responsible for the conversion of propionyl-CoA to methylmalonyl-CoA and its deficiency leads to accumulation of a toxic substance (propionyl–CoA) in plasma and urine [18,19]. Clinically, the patients usually present in the neonatal period between the 3rd and 7th day of life with poor feeding, vomiting, lethargy and decreased level of consciousness. If left untreated, it will lead to progressive encephalopathy and seizures, coma or even death. Patients may frequently develop metabolic acidosis with high anion gap, lactic acidosis, ketonuria, hypoglycaemia, hyperammonaemia and cytopenias [20]. Other rare forms include: late-onset, in which the patient suffers a metabolic crisis only under stress (e.g., illness, surgery, fasting) or may have a more slowly progressive onset with global developmental delay, hypotonia, failure to thrive, movement disorders, protein intolerance or cardiomyopathy. Isolated cardiomyopathy form can rarely be the presentation without a metabolic decompensation or neurocognitive complications [20]. Diagnosis can be achieved by the aforementioned clinical presentation and laboratory findings like increase propionyl carnitine in acylcarnitine profile measured by MS/MS (increase C3, C3/C2 ratio), and high plasma glycine. Additionally, urine organic acids measurement shows increased propionylcarnitine, 3-hydroxypropionate, methylcitrate and intermediates of the isoleucine pathway: tiglic acid, tiglylglycine, 2-methyl-3-hydroxybutyrate, 3-hydroxybutyrate and propionylglycine. Enzyme assay of PCC in lymphocytes or cultured skin fibroblasts and DNA molecular testing of *PCCA* or *PCCB* genes confirm the diagnosis. Treatment of PA consists of acute life-saving management during metabolic crises; summarised as basic life support, high caloric intake (Intravenous fluids of 10% Dextrose and Normal saline 1½ maintenance) and carnitine as chelating agent for propionyl–CoA, which forms propionylcarnitine and excreted in the urine. Moreover, Metronidazole that helps in reducing product of propionate by bacterial gut metabolism, hyperammonemia scavengers such as carglumic acid and sodium benzoate can be used. If not responding, dialysis by continuous veno-venous hemodiafiltration. Nutritional therapy consists of lipids (2 grams/kg) and amino acid free parenteral solution. The latter is suitable for the first 24–48 hours but synthetic protein must then be introduced after reduction of ammonia to <100 µmol/L using commercially available formulas like Propimex® or MMA/PA Anamix in addition to natural protein such as any regular milk formula for infants or food containing protein for children and adults. Initially, starting with 50% of natural protein that the individual usually takes at home, then, followed by the full amount and concentration, which are given at home. Calories source is also essential like prophree or polycose as tolerated. Chronic management consists of Carnitine, metronidazole and biotin, which is a co-enzyme for PCC enzyme, in addition, to nutritional therapy. Dweikat et al., 2011, reported a 9-month-old Palestinian male who presented with diabetic ketoacidosis (DKA) [21]. Similarly, Joshi and Phatarpekar, 2011, reported an 11-month-old girl diagnosed to have PA appearing as DKA [22].

Methylmalonic acidemia (MMA)

Similar to propionicacidemia, MMA is one of organic acids disorders and an odd-chain fatty acid metabolism disorder. It is inherited in autosomal recessive pattern and was first described by Rosenberg et al., 1968, who also demonstrated in the same year the metabolic block localisation and vitamin B12 dependency [23,24]. This is a heterogeneous genetic disorder of methylmalonic acid and cobalamin metabolism. Different forms of isolated methylmalonic aciduria are identified. They are classified according to in vitro complementation groups of cells, which include the following:

- Methylmalonyl-CoA mutase complete or partial deficiency (mut0 enzymatic or mut$^-$ enzymatic subtype, respectively).
- Cobalamin and its cofactors synthesis and transport; adenosyl-cobalamin (cblA, cblB or cblD variant 2 type).
- Methylmalonyl-CoA epimerase deficiency.

Clinically, the patient presentation is similar to PA, usually in the neonatal period between the 3rd and 7th day of life with poor feeding, lethargy, vomiting and decreased level of consciousness,

if left untreated, it will lead to progressive encephalopathy, seizures, coma or even death. Patients may frequently develop metabolic acidosis with high anion gap, lactic acidosis, ketonuria, hypoglycaemia, hyperammonemia and cytopenias [25]. Other forms include the infantile non-B12-responsive form, intermediate B12-responsive phenotype and atypical and "benign" adult MMA. In infantile non-B12-responsive form, patients are usually normal at birth but present with poor feeding, lethargy, vomiting, dehydration, failure to thrive, hypotonia, hepatomegaly and encephalopathy in the first few weeks to months of life. The intermediate B12-responsive phenotype presents later; affected children experience poor appetite, hypotonia, developmental delay, failure to thrive and sometimes suffer from protein aversion and/or decompensation after taking protein. The Atypical and "benign" adult MMA form is usually asymptomatic and has a high excretion of methylmalonic acid [25–27]. Diagnosis can be achieved by the aforementioned clinical presentation and laboratory findings like increase propionyl carnitine in acylcarnitine profile measured by MS/MS (increase C3, C3/C2 ratio), high plasma glycine and elevated serum methylmalonic acid. Additionally, urine organic acids measurement shows increased methylmalonate, 3-hydroxypropionate and methylcitrate. Enzyme assay of methylmalonyl co-A mutase in lymphocytes or cultured skin fibroblasts and DNA molecular testing of MMA gene panel confirm the diagnosis. Treatment of MMA consists of acute lifesaving management during metabolic crises in exactly the same way we treat the patients with PA. Chronic management consists of Carnitine, metronidazole and vitamin B12, which is a cofactor for methylmalonyl Co-A mutase enzyme, in addition, to nutritional therapy. Importantly, vitamin B12 responsiveness should be determined for all patients by vitamin B12 loading test [25–27]. Guven et al., 2012, reported a 13-month-old Turkish girl with MMA, who presented with DKA [28]. Similarly, Dejkhamron et al., 2016, described a 2-year-old Thai girl who presented with hyperglycaemia, acidosis and ketosis [29]. She had developmental impairment, optic atrophy, seizures and poor growth, and was confirmed to have previously reported compound heterozygous mutations in *MUT* gene (p.R694W and p.Q476*) [29].

Isovaleric acidemia (IVA)

Similar to PA and MMA, IVA is one of the organic acids, and odd-chain fatty acid metabolism disorders, that is inherited in autosomal recessive pattern. Specifically, it is a disorder of leucine metabolism. Historically, it is the first organic acidemia described in literature by Tanaka et al., 1966, who subsequently described the clinical, biochemical and molecular defects of this disorder [30–35]. Biochemically, the defect is due to deficiency of the enzyme isovaleryl Co-A dehydrogenase, which is responsible of conversion of isovaleryl Co-A to 3-methylcrotonyl Co-A in leucine metabolism. Clinically, the patients present in a similar way to PA and MMA with a common neonatal and late onset forms. Diagnosis can be achieved by the aforementioned clinical presentation and laboratory findings like increased isovaleryl carnitine in acylcarnitine profile measured by MS/MS (increase C5 level), and high plasma glycine. Additionally, urine organic acids test shows increased isovaleric acid, isovalerylglycine and 3-hydroxy isovaleric acid. Enzyme assay of isovaleryl Co-A dehydrogenase in lymphocytes or cultured skin fibroblasts and DNA molecular testing of IVD gene confirm the diagnosis. Treatment of IVA consists of acute lifesaving management during metabolic crises in exactly the same way we treat PA and MMA. Chronic management consists of carnitine, metronidazole and glycine [36–38]. Hou et al., 1990, described a 3-year-old IVA male patient, who presented with DKA, mild psychomotor retardation, recurrent episodes of acute encephalopathy, and pancytopenia after upper respiratory tract infection. On admission, he had vomiting associated with dehydration, acidosis, ketonuria, coma and a pungent odour. Laboratory findings included hyperglycaemia, hyperammonemia, hyperamylasemia, hypocalcemia, neutropenia, thrombocytopenia and subsequent anaemia [39]. Later, Attia et al., 1996, reported a Saudi child with IVA and had DKA [40]. Subsequently, few reports confirmed the previous findings of IVA in several children with DKA [41,42].

Holocarboxylase synthetase deficiency (HCSD)

HCSD is one of the biotin responsive disorders. Alternatively, it is called multiple carboxylase deficiency. It is inherited in autosomal recessive pattern and was first described by Roth et al., 1980 [43]. In HCSD, the affinity of biotin to apocarboxylases is impaired, which leads to reduction in the production of the four holocarboxylases from their corresponding inactive apocarboxylases at physiological biotin concentrations. These are PCC, 3-methylcrotonyl-CoA carboxylase (3-MCC), Pyruvate carboxylase and acetyl-CoA carboxylase (ACC). Such disturbance is responsible for the whole biochemical profile of this disease. Clinically, the most common form is the neonatal form with poor feeding, vomiting, lethargy and decreased level of consciousness, if left untreated, will lead to progressive encephalopathy, seizures, coma or even death. Additionally, it is associated with metabolic acidosis, neurological manifestations like seizure and skin features of a scaly skin rash that spreads all over the body or may look like seborrheic dermatitis or ichthyosis [4,44–46]. Biochemically, PCC deficiency leads to accumulation of propionylcarnitine (C3) detected by MS/MS in dry blood spot and elevation of propionyl co-A, methylcitrate, 3-hydroxypro pionate, propionylglycine, tiglylglycine and propionic acid in urine, while PC and ACC deficiency lead to high level of lactate and ketosis in blood and urine. 3-MCC deficiency leads to high level of Hydroxyisovalerylcarnitine (C5-OH) detected by MS/MS in dry blood spots and increased 3-hydroxyisovaleric acid and 3-methylcrotonylglycine in urine. Diagnosis is achieved by molecular confirmation of the biochemical profile through DNA molecular testing of *HLCS* gene. HCSD is one of treatable IEM and treatment is effective with oral biotin in pharmacologic doses [47]. Hou et al., 2004 reported a 30-month-old female patient who presented with the features of DKA, lactic acidemia and moderate hyperammonemia [12].

β-ketothiolase deficiency (BKT)

BKT is one of ketolysis defects. It is specifically a defect of isoleucine metabolism and is inherited in autosomal recessive manner. It is due to deficiency of mitochondrial β-ketothiolase enzyme, which converts acetoacetyl Co-A to Acetyl Co-A in isoleucine metabolic pathway. Clinically, bouts of decompensation initially start with tachypnea and vomiting, and followed by dehydration and altered level of consciousness. Biochemically, the patients suffer from severe metabolic acidosis, ketosis and ketonuria. Lactate and ammonia levels are normal in most patients. Diagnosis is achieved through elevation of 3-hydroxyisovaleryl carnitine (C5) by MS/MS and finding of a significant elevation of 2-methylacetoacetate, 2-methyl-3-hydroxybutyric acid and tiglylglycine with high excretion of ketone bodies and dicarboxylic acids and confirmed by molecular genetic testing of ACAT1 gene. Treatment of acute crises is typically with high caloric intake by sufficient glucose infusion and correction of acidosis. Chronic management includes avoidance of fasting and mild protein restriction. The outcome of this disorder is usually favourable. Clinical consequences can be prevented by applying the aforementioned measures [4,48,49]. Ketoacidosis is often associated with hypoglycaemia leading to endocrine and metabolic disorders of glucose and glucagon metabolism [50].

Hemochromatosis

Hereditary hemochromatosis, also known as iron overload disorder, is the most frequent IEM, observed with 1 in 200 to 400 prevalence [51]. It is a condition where the body absorbs excess amount of iron leading to accumulation of this metal, which usually occurs in skin, heart, pancreas liver and joints, and eventually damages these organs. The disease phenotype varies according to the mutations' penetrance, with possible inaugural ketoacidosis and 10% prevalence for diabetes. It is inherited in autosomal recessive manner and genetic studies have linked hemochromatosis to mutations in several genes, including the human hemochromatosis protein (HFE), hepcidin (HAMP), transferrin receptor 2 (TFR2), ferroportin (SLC40A1) and hemojuvelin (HFE2). Despite the phenotypic and genetic diversity of hereditary hemochromatosis, it is presumed that the main pathogenic mechanism underlying this

disease is the hepcidin–ferroportin axis abnormal regulation, leading to a failure in preventing excess iron from entering the circulation [52]. Eighty percent of cases have DM and the majority has liver iron loading and cirrhosis. Post mortem evaluation reveals severe hemosiderin deposition and eventually iron-induced fibrosis of the islets of Langerhans and pancreatic acini [53]. The diagnosis of hereditary hemochromatosis in patients with suggestive clinical findings is based on the following:

- Elevated transferrin-iron saturation at 45% or more.
- Serum ferritin concentration exceeding the upper limit of normal range (i.e., >300 ng/mL in men and >200 ng/mL in women).
- Two pathogenic variants in *HFE* genetic testing.

Serum ferritin concentration is not specific for hemochromatosis, despite its progressive increase over time in untreated individuals, and therefore, it cannot be used as a standalone test for identifying the disease [54]. Treatment of diabetes in hemochromatosis requires insulin, phlebotomies with or without insulin sensitisers. Phlebotomy alone would not be sufficient to treat diabetes due to hemochromatosis. This is because of the underlying pathogenesis that includes reduction of B cell mass and increased hepatic and extra hepatic insulin resistance. Established tissue damage resulting in cirrhosis, insulin dependent diabetes (T1DM) is only partially reversible by iron depletion (phlebotomy). Similar to other liver diseases glucose intolerance due to insulin resistance precedes DM also in hemochromatosis. Insulin resistance is probably caused by alterations of insulin or glucose metabolism in the liver and potentially also in extra-hepatic peripheral tissue. In advanced iron overload, iron accumulation in pancreatic B-cells deteriorates pancreatic insulin secretion and leads to insulin-dependent DM, which cannot be reversed by iron removal. In contrast, early alteration of glucose intolerance and insulin resistance may partially be improved by phlebotomies. Thus, the best strategy should aim at early diagnosis of hemochromatosis in early stages to prevent both mechanisms that lead to DM due to insulin insufficiency or liver cirrhosis. This strategy led to marked reduction of the prevalence of diabetes related to hemochromatosis from 80% to less than 20% with early detection (1935–2014) [53,54]. Liver transplantation is only indicated in case of end-stage liver disease due to iron overload and cirrhosis [54].

Aceruloplasminemia

Aceruloplasminemia is an autosomal recessive disorder. In this disease, iron also gradually accumulates but in other uncommon sites or organs especially the brain. The accumulation of iron in the brain results in neurological sequel that generally appears in adulthood and worsens over time. Statistical studies have shown that only 1 in 2,000,000 people were diagnosed with this rare genetic disorder [55]. Clinically, aceruloplasminemia patients present in triad of retinal degeneration, DM and neurologic disease [56]. They may develop a variety of cognitive problems, in addition to the high prevalence of DM (68.5%) due to iron accumulation in beta pancreas cells [57]. The clinical features of aceruloplasminemia and phenotypic severity may vary, as various mutations in ceruloplasmin (*CP*) gene have been identified to correlate with this disease [58–61].

CP catalyses iron transport and processing, by assisting iron attachment to transferrin, which transports it to the red blood cells to support oxygen transportation and supplementation throughout the human body. Alternative form of *CP*, known as the glycosylphosphatidylinositol-anchored, which is produced specifically by the nerve cells, and is responsible of the iron regulation in the brain tissue. The involvement of the central nervous system differentiates aceruloplasminemia from other acquired and inherited iron storage disorders [62–64].

The biochemical profile of patients with aceruloplasminemia includes: deficient serum *CP*, low serum iron concentration, low serum copper concentration, elevated serum ferritin level, and increased hepatic iron load. The enzyme activity of plasma *CP* ferroxidase is not detectable using the technique illustrated by Erel, 1998 [58,65,66]. MRI features are characterised by low intensities indicating iron accumulation in

the brain (namely in thalamus, striatum, dentate nucleus) and liver on both T1 and T2 weighted images [66]. Iron deposition in visceral organs, especially the pancreas, liver and heart can be found in histopathology studies. The liver usually does not show cirrhotic changes. The iron load in the liver is more than that in the brain. Iron deposition in beta cells of the pancreas leads to DM [58,60,66]. The diagnosis is achieved by identification of biallelic pathogenic variants in *CP* gene on molecular genetic testing [58,60,66]. The treatment consists of iron chelating medications like desferrioxamine or deferasirox to lower serum ferritin level, and to decrease the brain and liver iron loads, and accordingly to prevent progression of neurological features in affected patients with blood haemoglobin level > 9 g/dL. The combination of IV desferrioxamine and fresh-frozen human plasma (FFP) is an effective approach in lowering iron load in the liver. Repetitive FFP treatment might improve the neurologic manifestations. Antioxidant agents like vitamin E may be given with chelation in addition to zinc to prevent liver and pancreas damages [58,60,66].

Mitochondrial disorders

Mitochondrial disorders also known as respiratory chain disorders, are group of diseases that mainly affect the mitochondria (energy-making organelle) activity, and are characterised by apparent developmental delay, muscle weakness, neurological problem, autistic spectrum, gastrointestinal disorders, impaired vision/hearing, thyroid/adrenal abnormalities, heart/liver/kidney disease, DM, high risk of infection, autonomic dysfunction and dementia. Mitochondrial disorders could be life threatening as such defects may cause severe damage to the organs. Various genes and huge number of mutation variants are involved, and statistical studies have shown that 1 in 4,000–500,000 people was diagnosed with these genetic disorders, which accounts for 0.06%–2.8% of diabetes cases with possible inaugural ketoacidosis and adrenal failure [67].

They can be caused by nuclear or mitochondrial DNA mutations. It is not easy to classify the mitochondrial diseases, as a single syndrome may display wide variants of mutations [68]. The most frequently reported mitochondrial disorder associated with diabetes is the single mitochondrial transfer RNA (tRNA) genes (*MT-TL1*, *MT-TK* and *MT-TE*). The DNA mutation A3243G (located in *MT-TL1* gene), found especially in the MIDD and MELAS syndrome, which accounts for 80%–99% of the cases. Another genotype abnormality identified within the tRNA gene associated with diabetes is the C12258A mutation. These tRNAs help to assemble proteins involved in oxidative phosphorylation, which is the main energy source for the cells. Furthermore, defectiveness in the mitochondria might also implicate the beta cells of the pancreas, which is responsible of controlling blood glucose by regulating the expression of insulin [69,70].

Additionally, DNA mutations (deletions and duplications) found within complex rearrangement of gene (WFS1 and CISD2) of mtDNA was shown to be the causative reasons for Wolfram syndrome, which is also known as DIDMOAD. Another mitochondrial disorder associated with diabetes, is the Kearns-Sayre syndrome, which presents as progressive external ophthalmoplegia, retinal pigmentary degeneration and heart block. It is caused by a single yet large DNA deletion (commonly 4,997 base pair) resulting in loss of 12 mitochondrial genes that are important for complex protein rearrangement and oxidative phosphorylation. Such deletions of mtDNA indirectly impairs oxidative phosphorylation, hence, diminishes cellular energy production [71,72].

Cystinosis

Cystinosis is a rare genetic disorder with 1 in 100,000–200,000 of yearly prevalence. Emil Abderhalden (1877–1950) first described it in 1903 [73]. The pathophysiology of cystinosis is deficiency of a cystine carrier in the lysosomal membrane, which will lead to the accumulation cystine in many organs. It is due to a mutation in *CTNS* gene (located on the short arm of chromosome 17p13.2), which encodes the cystinosin protein (lysosomal cystine transporter) [74,75]. Cystine buildup often forms a crystal-like structure, which typically troubles the eye and kidney. More than 80 *CTNS* mutations were reported to cause cystinosis. Clinically, it has three

phenotypes: first, nephropathic cystinosis, which presents with renal fanconi syndrome (polyuria, polydipsia, dehydration and acidosis), poor growth, hypophosphatemic rickets, renal failure and accumulation of cystine in almost all organs leading to tissues damage. Additionally, patients suffer from corneal opacity, hypothyroidism, DM and hypogonadism. Central nervous system manifestations including tremor, gross and fine motor impairment, hypotonia, speech delay, idiopathic intracranial hypertension, behavioural problems neurocognitive dysfunction and encephalopathy [73]. The onset of this phenotype typically occurs by 6 month of age. The second phenotype is intermediate cystinosis, which has the same clinical findings of nephropathic cystinosis, but onset is at a later age. The third phenotype is the non-nephropathic (ocular) cystinosis, which is clinically presents with photophobia resulting from corneal cystine crystal build up [76]. The diagnosis is achieved either by the demonstration of corneal cystine crystals on slit lamp examination, finding a high cystine concentration in white blood cells (WBC) or by the identification of elevated cystine content in cultured fibroblasts or in the placenta at the time of birth and is confirmed by DNA molecular testing of *CTNS* gene. Few therapeutic options are available for cystinosis including supportive treatment, aiming to maintain fluid and electrolyte exchange at adequate level and protection of the acid–base balance, prevent rickets, ensure appropriate replacement of required hormones and provide nutritional support. Other options include: the use of cysteamine to deplete cystine, renal replacement therapy and renal transplantation; however, no curative treatment is available yet [76]. DM in cystinosis usually occurs in the second or third decade of life. The risk of DM in cystionosis is approximately 24% [77]. Interestingly, the frequency of DM decreases along with the duration of cysteamine therapy [77].

Rogers syndrome (Thiamine-responsive megaloblastic anaemia)

Rogers syndrome also known as Thiamine-responsive megaloblastic anaemia is an extremely rare genetic disorder with only 30 families worldwide notable to acquire this disease. The case series have only been reported in kinships of Israeli, Arab, Lebanese, Alaskan, Brazil, Japan, Oman, Tunisia, Italy, Iran, Pakistan, Kashmir, Kurds ethnic, Caucasians and African Americans. The clinical condition is caused by mutation of *SLC19A2* gene (located on the long arm of chromosome 1q24.2), encoding thiamine transporter protein (member of the solute carrier family) responsible for the effective utilisation of thiamine molecules in various tissues including the pancreatic beta cells [78,79].

Clinically, the patients present with a triad of megaloblastic anaemia, progressive sensorineural hearing loss and DM. Megaloblastic anaemia occurs in the first decade of life. The anaemia resolves with thiamine administration, but the red cells continue to be macrocytic, and anaemia can recur when treatment is withdrawn. Progressive sensorineural hearing loss manifests early and can be detected in toddlers. Thiamine treatment may not prevent the irreversible hearing loss. The DM is usually non-type I, with age of onset ranging from infancy to adolescence. Thiamine treatment may delay the onset of DM in several patients. Treatment constitutes of 50–100 mg/day of oral thiamine for life [78].

Congenital disorder of glycosylation (CDG) Ia

Congenital disorder of glycosylation (CDG) Ia is a disorder caused by defect in the synthesis, assembly or processing of glycans. Glycosylation is process of adding glycans or sugars to proteins (both secreted and membrane-bound) and lipids, which is the most frequent modification in proteins. CDG Ia is caused by deficiency in Phosphomannomutase 2 (*PMM2*) gene. There are three phenotypes of CDG Ia and are classified based on the age of onset. The first phenotype is the infantile onset and patients usually present with multisystem involvement. Historically, the affected infants suffer from cerebellar hypoplasia, global developmental delay, facial dysmorphism and impaired subcutaneous fat distribution [80]. However, the clinical phenotype continues to be highly variable to include patients with normal cognitive function [81]. Some infants present with liver fibrosis and high liver enzymes. Additionally, other features include coagulopathy, renal hyperechogenicity, pericardial effusion,

hypertrophic cardiomyopathy, nephrotic syndrome, renal cysts and multiorgan failure. The second phenotype is the late infantile or childhood phenotypes, which are characterised by ataxia and intellectual disability. Finally, there is the adult phenotype with intellectual disability [82]. The endocrine dysfunction is not unusual and patients could have hyperglycaemia, hyperprolactinemia, hypothyroidism, insulin resistance and hyperinsulinemic hypoglycaemia [83,84]. The diagnosis is achieved by finding abnormal transferrin isoelectric focusing (TIF) (type I pattern) or a high level of carbohydrate deficient transferrin and confirmed by the DNA molecular testing of *PMM2* gene. One patient was reported with heterozygous mutation in the *PMM2* gene (c.470T>C (p. F157S), exon 6) diagnosed with CGD Ia had DM with hepatic dysfunction and hyperinsulinemic hypoglycaemia [82].

CLINICAL APPROACH

The early detection of IEM associated with diabetes leads to an early initiation of therapy; thus, prevent death in newborn infants as well as disruption of mental or physical health and inadequate growth. Detailed history, including three-generation family history and physical examination are the clue to diagnosis. Presence of multisystem involvement beside diabetes is a red flag for IEM. Screening methods for patients presented with diabetes include serum ammonia and lactate, creatine kinase (CK) level, acylcarnitine profile measured by MS/MS, plasma aminoacids, urine for organic acids and TIF. The aforementioned tests screen for organic acidemias and CDG type Ia. hereditary hemochromatosis and aceruloplasminemia could be detected by measurements of serum ferritin, transferrin-iron saturation, serum iron, copper and *CP*. Demonstration of cystine crystals in the cornea on slit lamp examination or findings of high cystine concentration in WBC are the clue for cystinosis. These biochemical investigations will tailor the appropriate DNA molecular testing for specific genes. Specific clinical pictures, high lactic acid, CK levels and measurement of respiratory chain enzymology in the muscle and fibroblasts as well as mitochondrial genome sequencing will confirm the diagnosis of mitochondrial disorders. If the above tests came unremarkable or inconclusive, then a whole exome and/or genome sequencing would be the methods of choice.

CONCLUSION

The current review of covers IEM based on genes and variants identified with potential targets of IEM and DM. It also gives insights into the mechanisms leading to diabetes of various IEM disorders, which elucidates several key pathways and essential enzymes to be targeted for therapeutic interventions. Clinical approach will help in ready diagnosis and treatment for IEM disorders at early detection of diabetes.

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