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Genetic Variations in Hyperinsulinemic Hypoglycemia: Active versus Inactive Mutations

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Abstract: Hyperinsulinemic Hypoglycemia (HH) is a rare condition that affects newborn children in the postnatal period, represented by dangerously low levels of blood glucose in a persistent manner, which puts the baby at high risk of multiple issues, especially regarding the brain cells if the baby does not take the appropriate medication or have the correct diagnosis. Hyperinsulinemic Hypoglycemia can happen due to an active or inactive mutation in 16 genes responsible for glucose metabolism and insulin secretion (*GLUD1*, *GCK*, *SLC16A1*, *HK1*, *CACNA1D*, *KCNJ11*, *ABCC8*, *FOXA2*, *HNF1A*, *HNF4A*, *HADH*, *PGM1*, *UCP2*, *KCNQ1*, *PMM2*, *EIF2S3*). These mutations can take place in many forms, either defused or local, affecting several or all pancreatic beta cells respectively. This review summarizes genetic variations diagnosis and treatment of Hyperinsulinemic Hypoglycemia.

Keywords: Hyperinsulinemic Hypoglycemia, nesidioblastosis, *GLUD1*, *hexokinase*, *FOXA2*

Introduction

Hyperinsulinemic, idiopathic hypoglycemia of infancy, leucine-sensitive hypoglycemia, or nesidioblastosis are terms that refer to a rare condition characterized by immediate severe persistent Hyperinsulinemic Hypoglycemia (HH) in infants and newborn babies in the postnatal period. HH is considered a complex of disorders related to dysregulated insulin secretion. It occurs when plasma glucose levels decrease, leading cells to inappropriate insulin secretion. This leads to HH in children.[1] HH affects the neurological system in patients because it causes a decrease in blood glucose concentration, leading to a high risk of brain damage. There are different factors that lead to HH, suxh as birth asphyxia, intrauterine growth retardation, maternal diabetes mellitus, and Beckwith-Wiedemann syndrome. From this, the important diagnosis must be done to prevent some diseases like epilepsy and neuro-developmental defects.[2]

The metabolism of insulin on glucose increases the neurological injury; when a human consumes a meal, it leads to glucose increases in the bloodstream, this leading to activating glucose secretion pathways that play an important role in regulating blood glucose during and after eating. While eating, the glucose level will increase above its normal range, activating the "triggering pathway" which is induced by glucose metabolism to produce Adenosine triphosphate (ATP) molecules that trigger the production of insulin by causing the (*KATP)* channel to close, depolarizing the beta cells membrane, and finally activating the calcium channels to enter the calcium to beta cells and bind to insulin granules to become exocytic it to bloodstream; this pathway is known to be rapid in its response.

Even some hours after eating the meal, the second "amplifying pathway" will take its place to keep managing the glucose level by secreting insulin at sustained lower rates than the "triggering pathway". Insulin stimulates lipogenesis by inhibiting free fatty acid release, β-oxidation, and ketone body formation which leads to brain injury. Although these phases aim toward the same goal, which is keeping blood glucose in a normal range all the time, they also differ in the insulin granules they trigger, the first phase "triggering phase" must be rapid so it uses the readily releasable insulin granules located on the beta cell membrane surface consuming only 1% of these granules, while on the other hand the

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"amplifying pathway" works hours after eating so it uses the recruited granules from the storage pool in addition to the membrane surface granules.[3]

This review discusses how insulin metabolism affects the neurological system and leads to different diseases depending on different literature searches on HH using the PubMed database. It also investigates molecular and genetic mutations leading to HH, whether activating or inactivating mutation, with an example for each type. In addition it suggests ways to diagnose and treatpatients with Hyperinsulinemic Hypoglycemia.

Mutations in Hyperinsulinemic Hypoglycemia

Islets of Langerhans and Their Functions

Many mutations in 16 different key genes, that are known to be responsible for regulating insulin secretion from beta-cells of the pancreas, would cause Hyperinsulinemic Hypoglycemia (HH). Multiple different syndromes are associated with Hyperinsulinemic Hypoglycemia.[4]

Islets of Langerhans are the functional units of the pancreas (ranging from 1 to 15 million), each containing 2,000 endocrine hormone-producing cells, that play important roles in the glucose regulating process, including alpha cells, beta cells, polypeptide cells, somatostatin cells, ghrelin cells, each with a specific function (Table 1).

Hyperinsulinism Hypoglycemia Forms

Hyperinsulinemic Hypoglycemia can manifest in three distinct forms: (1) The diffuse form, which is characterized by hypertrophic beta cells affecting all the islet cells and occurs mostly due to a mutation in the (*KATP*) channel's subunits genes and is known to be unresponsive for diazoxide treatment.[5]

(2) The focal form, where hyperactive beta cells undergo changes within localized adenomatoid hyperplastic regions due to a parentally inherited mutation on the (*KATP*) channel's subunits genes which can affect any region of the pancreas, especially at the tail and the body of the pancreas.[6]

(3) The atypical form, which is considered to happen due to an enlargement of the pancreatic beta cells nuclei leading to an up normality in glucose metabolism.[7]

Molecular Changes in Hyperinsulinemic Hypoglycemia

Mutations could be activating some genes and inactivating others, leading to over-secretion of insulin causing dangerous Hyperinsulinemic Hypoglycemia.[4] Activating mutations lead to increases in the activity or the function of a gene or its protein product, resulting in a gain-of-function alternation, and those mutations are relatively rare among autosomal gene mutations. Many of these mutations occur in the regulatory region of the gene rather than the coding region.[8]

In this case, mutation can arise in five genes (*GLUD1*, *GCK*, *SLC16A1*, *HK1*, *CACNA1D*) that play a role in the insulin secretion process, leading to Hyperinsulinemic Hypoglycemia.[9,10]

Inactive mutations are the most common type of autosomal mutations and, are known to reduce or even eliminate the protein function resulting in loss-of-function alternation in the gene affected with it. These mutations are frequently recessive because when a heterozygous individual carries two copies of the gene one of them is mutant while the other is not, which will enable the production of a fully functional protein which in turn compensates for the effect of the mutant one.[8]

Table 1 Islets of Langerhans and Their Functions

Cells	Function
Alpha cells	Produce glucagon, which is a catabolic hormone, it suppresses elevation in glucose and insulin, and is stimulated by the amino acid, ranging from 30–50% of the islet cells.[4]
Beta cells	Produce insulin, which is an anabolic hormone, in response to the post-prandial increase in glucose concentration, they make up 50–60% of islet cells, these cells also known as amylin.[4]
Somatostatin cells	Work as a suppressor in the pancreas for both insulin and glucagon, found in about 5% of all cells in islets.
Pancreatic polypeptide cells	Work as a suppressant and stimulate the pancreas to secrete digestive enzymes.[4]
Ghrelin cells	Stimulate appetite, they are the fewest among other types making up less than 1% of islet cells.[4]

In Hyperinsulinemic Hypoglycemia, 11 genes could be affected with this type of mutation leading to an uncontrolled dangerous insulin secretion process, and they are: (*KCNJ11*, *ABCC8*, *FOXA2*, *HNF1A*, *HNF4A*, *HADH*, *PGM1*, *UCP2*, *KCNQ1*, *PMM2*, *EIF2S3*).[10–15]

Activating Mutations Cause Hyperinsulinemic (Table 2)

Glutamate Dehydrogenase 1 (GLUD1) Gain-of-Function Mutation Leads to (HI)

Glutamate dehydrogenase 1 (*GLUD1*) is important because it encodes the mitochondrial glutamate dehydrogenase (GDH) enzyme, which is responsible for catalyzing a biochemical reaction that converts nicotinamide adenine (NADP) or its phosphate form into (NADPH), glutamate into alpha-ketoglutarate, and NH4+(ammonium ions) into NH3 (ammonia).[16]

This enzyme becomes functional after six identical monomers assemble to form a hexametric configuration, but if these hexametric structures are high in concentration, they can even bind together, forming a larger structure. The (*GDH*) enzyme has four activators (leucine, adenosine diphosphate (ADP), succinyl-CoA, and 2-aminobicyclo hebtan-2-carboxylic acid (BCH)), and two inhibitors (guanosine triphosphate (GTP), and palmitoyl-CoA) (Fahien, Teller et al, 1992).

All these ligands do not need to undergo chemical alternation to bind to their sites on this enzyme. In addition, the binding sites of these ligands are overlapping, leading one activator or one inhibitor in some cases to displace the other, causing over-activation or over-inhibition of the (*GDH*) enzyme. Eighty perrcent OF *GDH-HI* cases are due to de novo mutations in *GLUD1* and 20% of the cases are due to autosomal dominant mutations which lead to missense amino acid substitutions in *GLUD1*, affecting the GTP-binding site. The overlapping of the Lucien activator makes the *GDH* extremely sensitive to it leading to the over-activating of this enzyme and more insulin will be released causing Lucien-sensitive Hypoglycemia. Another mutation affects the *GDH* when it increases in activity, leading to an oxidation reaction of glutamate to alpha-ketoglutarate. Alpha-ketoglutarate enters the Krebs cycle which increases NADH, $FADH_2$, and ATP levels. Increased ATP levels lead to insulin secretion, as mentioned before.[16]

Glucokinase (GCK) Gain-of-Function Mutations Lead to (HI)

Glucokinase (*GCK*) is an important protein that plays a crucial role in catalyzing the phosphorylation process of glucose into glucose-6-phosphate (G6P), initiating the pivotal entry point for glucose into various metabolic processes, in pancreatic beta cells it assumes a distinctive role as a "glucose sensor". This protein exerts regulating control over the glucose-stimulated-insulin-secretion-threshold (GSIS-T) and various mutations on this protein gene, either active or inactive, known to be a reason for different types of diabets due to its effect on (GSIS-T) by increasing or decreasing it.[17]

Also, researchers have discovered eight different mutations (*p.S64P*, *p.E67V*, *p.S69_E70insVPL*, *p.S69P*, *p.V91L*, *p.W99C*, *p.Y215C*, *p.R447L*) that can affect the (*GCK*) protein near to the allosteric site, but four of them (*p.S64P*, *p.S69P*, *p.S69_E70insVPL*, *p.W99C*) are found in a specific part called the "loop structure" which extends from the 41 residues to 71, helping different parts of the protein to work together, by facilitating the cooperativity between the large and the small domain of (*GCK*). Shortening or lengthening of this loop leads to a dysregulated function of the enzyme, the lengthening of the loop at 69 and 70 positions can boost the enzyme activity as in mutation *p.S69-E70insVPL*, while the shortening can impair the enzyme function.[18]

Table 2 Summary of Activating Mutations and Their Mode of Action

Mutation Type	Location	Mode of Action
Glutamate dehydrogenase 1	10q23.3	Oxidative deamination of glutamate to α-ketoglutarate to increase the production of citrate
Glucokinase	7p15.3–15.1	Catalyzes the phosphorylation of glucose to glucose-6-phosphate and increases ATP production
Hexokinase	10q22	Catalyzes the first step of glycolysis phosphorylation of glucose
Monocarboxylate transporter	1p13	Transport and release of lactate and ketone bodies
Calcium voltage-gated channel subunit alpha 1D	19p13	Provide instructions for making calcium channels

Glucokinase (*GCK*) has two main properties, which make it a reason for (HI) if it was affected by an active mutation, the first one displays a low affinity for glucose, with an active mutation this affinity will be heightened, which in turn enable the (*GCK*) to dynamically modulate its enzymic activity in response to the concentration of glucose across the physiological range (4–15 mmol/L). The second property of (*GCK*) is that it can remain impervious to inhibition by its product the glucose-6-phosphate (G6P), and with an active mutation this property will alter the threshold of the inhibition process and (*GCK*) will become less susceptible to the inhibition by glucose-6-phosphate (G6P), leading to a continuous catalyzing of the phosphorylation process indeed increasing insulin secretion even when blood glucose is low and, at this stage, the patient will be in a dangerous condition of Hyperinsulinemic Hypoglycemia.[19]

Drawing upon the insight of a new novel, ten patients from eight families with glucokinase Hyperinsulinemic Hypoglycemia (*GCK-HI*), revealed that in addition to the effect of the activation mutation on the (*GSIS-T*) by lowering it, it can affect the counter-regulatory glucagon secretory response in the liver by decreasing it. They could detect that, when glucose concentration was 3 and 6 millimoles per liter (mM), with the presence of glucokinase regulatory protein (GKRP) in a 1:1 ratio with (*GCK*) there was a clear notable inhibition in the wild type (*GCK*) activity with a percentage of 20%, and this percentage mitigated by half settling at approximately 10% when glucose elevated to 12 (mM). However, this ratio had no inhibitory effect on the activating of two specific activating *GCK* mutants (*p.V91L*, *p.S69-E70insVPL*) across multiple glucose concentrations.

Even when this ratio increases there was no inhibitor effect in the (*p.V91L*) variant, while only a partial reduction in activity was discernible in the (*p.S69-E70insVPL*) variant. This diminished responsive to *GKRP*-mediated inhibition within select (*GCK*) mutants implicit a border mechanistic framework underlying (*GCK-HH*) this framework extends beyond islet dysfunction, suggesting a potential role for the liver where the (*GKRP*) exerts its regulatory control over (*GCK*) activity in pathophysiology of Hyperinsulinemic Hypoglycemia.[20]

After a comprehensive analysis was carried out to compare normal islets (*GCK-HH*) and mutant islets (*p.S69_E70insVPL*, *p.W99C*, *p.R447L*) to distinguish the insulin secretion dynamics in the (*GCK-HI*) islets, the results showed that:

- The (*GCK-HI*) islets exhibit a conspicuous augmentation in (GSIS-T) under heightened glucose concentration (25 mm) coupled with a noteworthy reduction of the (GSIS-T) with (*p.S69_E70insVPL*, *p.W99C*, *p.R447L*) mutants' thresholds (1.9 mm, 3.1 mm, 1.2 mm, respectively). In contrast, the normal islets threshold was 6.9 mM.[20]
- (*GCK-HH*) islets did not exhibit a substantial elevation in the basal insulin release, unlike the HI caused by a mutation in the voltage-gated potassium channel (*KATP*).[21]
- (*GCK-HH*) islets displayed conspicuously subdued basal glucagon secretion. Stimulation with a 4 mm amino acid mixture failed to elicit glucagon secretion from these islets' alpha-cells. In contrast, in normal control islets when they were exposed to a 4 mm amino acid mixture they resulted in a nearly 4-fold surge in glucagon secretion, with a minimal impact of insulin release, and when 3 mm amino acid mixture glucagon secretion was repressed, the introduction of 16.7 mm glucose further dampened glucagon secretion while concurrently provoking biphasic insulin secretion.[22]

(GCK-HI) has three phenotypes, which are

- **Asymptotic (*GCK-HH*)**: individuals with (GCK) mutation may have a genetic predisposition that leads to low blood sugar levels with an absence of noticeable symptoms like shakiness, sweating, or confusion.[19]
- **Medically unresponsive (*GCK-HH*)**: known as Hyperinsulinemic of infancy. where the diazoxide therapy or other treatment cannot effectively control the insulin secretion on this level, which can pose significant challenges in managing this condition and prevent dangerously low blood sugar surge episodes.[19]

- **Mild responsive Hyperinsulinemic Hypoglycemia:**

where a significant proportion of cases involve patients with active (*GCK*) mutations who experience a mild HH and are positively responsive to the diazoxide treatment.[19] In 2022, a case study was done by Anojina Koneshamoorthy et al on an adult patient and his mother who were suffering from Hyperinsulinemic Hypoglycemia. A genetic test resulted in

a genetic variation of the *GCK* gene. Computer tools were used in the analysis and suggested that a genetic cause could be a reason of the Hyperinsulinemic Hypoglycemia, but it was not known if it was significant or not. To get more clarity, this test was carried out on the patient's sister and her son, and the results showed they had the same genetic changes in the (*GCK*) gene.

Finally, it was significant that the Hyperinsulinemic Hypoglycemia was due to a crucial genetic change after it was uncertain. This means that testing and considering genetic factors when adults experience Hyperinsulinemic Hypoglycemia is no less important than doing these tests only for children.[23]

Hexokinase (HK1) Gain-of-Function Mutation Leads to HH

Hexokinase is an enzyme that catalyses the first step of glucose metabolism, the phosphorylation process, which converts the glucose molecule into glucose-6-phosphate (G6P); this enzyme is encoded by the (*HK1*) gene on chromosome number 10.[10]

Hexokinase is normally "silenced" or "forbidden" from expression in the pancreatic beta cells, which helps prevent the stimulation of the insulin secretion process when the glucose level is low in the bloodstream.[14,24]

According to this, if an active mutation affects this gene, this will lead to an inappropriate and dangerous insulin secretion leading to Hyperinsulinemic Hypoglycemia. The mutation of this gene is mainly located in a non-coding regulatory region of *HK1* (in intron 2) which reflects the enzyme action leading to insulin secretion during Hyperinsulinemic Hypoglycemia. A family was identified to be affected with idiopathic-hypoglycemia-of-infancy due to an active gain-of-function mutation on the (*HK1*) gene (Pinney et al, 2013). Another in vitro study showed inappropriate (*HK1*) expression which was a reason for (HH) and uncontrolled insulin secretion with the normal functioning of ATP-sensitive-potassium-channel (KATP).[25]

Monocarboxylate Transporter (MCT1) Gene (SLC16A1) Gain-of-Function Mutation Leads to (HH)

This gene encodes a normal unexpressed enzyme in pancreatic beta cells which is the monocarboxylate transporter (*MCT1*), that transports the insulin secretomotor (pyruvate and lactate) helping beta cells by preventing insulin secretion in response to them.[26]

Autosomal dominant gain-of-function mutation within the promoter region of (*SLC16A1*) results in heightened expression of (*MCT1*) within the pancreatic beta cells. Consequently, this prompts a persistent influx of glycolysis-produced pyruvate into the Krebs cycle, thereby provoking insulin secretion in instances of low blood glucose, notably during anaerobic exercise and particularly strenuous physical exertion.[24,27]

Calcium Voltage-Gated Channel Subunit Alpha 1D (CACNA1D) Gain-of-Function-Mutation Can Be Caused (HH)

This gene encodes the L-type calcium voltage-gated channel subunit alpha 1D. It has a crucial role in the insulin secretion process, it allows the calcium ions to enter the beta cells after the depolarization of membrane (specifically the depolymerization of potassium channel) due to increased ATP production as a result of fuel metabolism, in which these molecules attach to the insulin vesicles and move them to the membrane surface for exocytosis of insulin. This gene is prominently expressed in pancreatic beta cells.[10,28]

A second case was reported by Flanagan et al, a patient harboring a pathogenic *CACNA1D* variant necessitated prolonged diazoxide therapy for condition control. They exhibited a satisfactory clinical response during the initial 18 months of life.[29]

Inactivating Mutations Cause Hyperinsulinism (Table 3)

The Coding Genes of the ATP-Sensitive-Potassium-Channel (KATP) Subunits (Kir6.2 and SUR1) the (KCNJ11, ABCC8) Loss-of-Function Mutation Leads to (HH)

These two genes (*KCNJ11*, *ABCC8*) are the coding genes of the ATP-sensitive-potassium-channel (*KATP*) subunits (*Kir6.2* and *SUR1*, respectively) and are located on the short arm of chromosome 11 (11p15.1). If these genes alternate

Table 3 Summary of Inactivating Mutations and Their Mode of Action

Mutation Type	Location	Mode of Action
ATP-sensitive-potassium channel (*KATP*)	11p15.1	*KATP* senses metabolic changes in the pancreatic beta-cell, thereby coupling metabolism to electrical activity and ultimately to insulin secretion.
Fork-head box protein A2 (*FOXA2*)	20p11	*FOXA2* regulates the expression of genes important for glucose sensing in pancreatic beta-cells.
Hepatocyte nuclear factor genes (HNF)	12q24.31	*HNF* is impaired insulin secretion by pancreatic beta-cells.
Hydroxy Acyl-CoA Dehydrogenase (*HADH*)	4q22-26	*HADH* genes make an enzyme called 3-hydroxyacyl-CoA dehydrogenase by process called fatty acid oxidation (to break down fats and convert them to energy).
Phosphoglucomutase1 (*PGM1*)	1p31	Affects a phosphoryl group shift by exchanging glucose-1-phosphate and glucose-6-phosphate. PGM1 mutations lead to decreased glucose mediated insulin secretion from the pancreas.
Mitochondrial carrier protein (*UCP2*)	11q13	*UCP2* exerts a negative regulatory influence on glucose-insulin-mediated secretion by impeding ATP generation through mitochondrial oxidative metabolism.
Eukaryotic translation initiation factor 2 subunit 3 (*eIF2S3*)	Xp22.11	Impaired (*eIf2S3*) function associated with glucose dysregulation by affecting translation initiation near the start codon leads to different diseases like HH.
Phosphomannomutase 2 (*PMM2*)	16p13.2	*PMM2* mutation leads to abnormal glycosylation and alteration in insulin secretion by affecting the formation of a chromatin loop.

their activity due to an inactive mutation this will lead to the most common type of Hyperinsulinemic Hypoglycemia (*KATP-HH*) accounting for 40–50% of cases.[10]

The adenosine triphosphate-sensitive-potassium channel (*KATP*) plays a very important role in the glucose-stimulated insulin secretion pathway. After the glucose level increases in the blood, it will pass through the glucose transporter (*GLUT*) and then the glycolysis process will occur in the cytosol of the beta cells, producing pyruvate, ATP, and NADH, which in turn will go through the citric acid cycle to produce ATP, NADH, and FADH2 in the mitochondria of the pancreatic beta cells. Finally, the phosphorylation process takes its place for generating the largest amount of adenosine triphosphate (ATP).[30]

After these adenosine triphosphates (ATP) molecules accumulate inside the pancreatic beta cells leading to changes in the adenosine triphosphate:adenosine diphosphate ratio (ATP:ADP ratio), they activate the adenosine triphosphate-sensitive-potassium channel (*KATP*) by binding to it, inducing the closure of (*KATP*) channel subunits, which in turn leads to the depolarization of the membrane by the entry of sodium ions (Na+). After that the voltage-dependent-calcium channels will open, letting the calcium (Ca2+) enter the cell and, finally, these ions induce the insulin secretion from the pancreatic beta cells by binding to the insulin vesicles found in beta cells taking them to the membrane surface, then insulin will exocytosis into the bloodstream to control the high blood glucose.[28]

Different types of mutations on (*KATP*) channel subunits genes can cause multiple types of diabetes, one of them is Hyperinsulinemic Hypoglycemia (HH) which could happen due to an inactive mutation on the (*KATP*) channel subunits genes, and these mutations can be divided into four forms:

- **Recessive (*KATP*) mutations**:

These mutations disrupt (*KATP*) channel biogenesis by impeding various intracellular processes, leading to a complete absence of functional (*KATP*) channels in the plasma membrane, which results from interference with the correct trafficking of channel subunits.[14]

As a result of the absence of the channel, the beta cell membrane will stay in the depolarizing status, such as when it is present and enclosed in response to the (ATP), so this will lead to an uncontrolled continuous insulin secretion of insulin. However, in all cases mothers should be screened and tested for the presence of recessive mutations to avoid diffuse or focal disease in future pregnancies.[28]

- **Dominant (*KATP*) mutations**:

Dominant *KATP* mutations manifest as missense defects, allowing normal subunit trafficking to the plasma membrane, but they will act as dominant-negative factors within the hetero-octameric (*KATP*) complex.[14] This type of mutation severely compromises channel activity and remains unresponsive to the diazoxide, and somatostatin would help in this

case.[31] Dominant heterozygous mutations have 50%, while recessive homozygous mutations have 25% disease recurrency.[32]

- **Diazoxide-responsive dominant (*KATP*) channel mutations**:

Certain dominant (*KATP*) mutations exhibit partial preservation of (*KATP*) channel activity, rendering them amenable to modulation by diazoxide intervention. These three forms of (*KATP-HH*) are known to be diffuse and affect all pancreatic beta cells. Generally, genetics, pedigree of patients, and in vitro functional studies must be done to discover the cases.[14]

- **Focal form of (*KATP-HH*)**:

This form includes the inheritance of recessive (*KATP*) mutations transmitted from the parental side, coupled with secondary postzygotic events, that lead to loss of the maternal heterozygosity for the 11p15.1 genomic rejoin intricate interplay of genetic factors and culminates in the localized manifestation of (HH) within the pancreas while in diffuse form the entire pancreas is affected.[33,34]

There is difficulty in detecting a patient's infection by focal or diffuse disease. But there are some methods like PET imaging using F-fluoro-L-DOPA and genetic information from the parents to detect the type of disease. 95% of focal diseases have a recessive mutation in *ABCC8* or *KCNJ11*. In most cases, diffuse forms need pancreatectomy to avoid other complications of Hyperinsulinemic Hypoglycemia if the patients does not respond to treatment.[35]

Fork-Head Box Protein A2 (FOXA2) Loss-of-Function Mutation on Its Gene Can Cause (HH)

FOXA2 is located on chromosome 20 (20p11). Mutations in the Fork-head box protein A2 (*FOXA2*) have been identified as responsible for a set of medical conditions including hypopituitarism, Congenital Hyperinsulinemic Hypoglycemia (CHH), and various structural anomalies within endoderm-derived organs.[10] *FOXA2*, considered as DNA-binding proteins, plays a role in multiple tissue development. Mutation in this gene – loss of function – leads to embryonic lethal. There is a connection between *FOXA2*, *ABCC8*, and *KCNJ11* in the regulation of insulin secretion. Any mutation in any of these genes leads to HH.[36]

Children affected by these mutations exhibit a unique clinical profile characterized by manifestations of hypopituitarism, (CHH), dysmorphic facial characteristics, as well as aberrations affecting vital organs such as the liver, pancreas, heart, and gastrointestinal system. Also, *FOXA2* plays a major role in morphogenesis of the central nervous system by controlling the expression of *Gli2*, *SHH*, and *Nkx2*.[11]

Hepatocyte Nuclear Factor Genes (HNF1A, HNF4A) Loss-of-Function Mutation Causes (HH)

Hepatocyte nuclear factor genes (namely *HNF14* and *HNF4A*) encode the *HNF-1* alpha and *HNF-4* alpha, respectively, and they are transcription factors that play a pivotal role in glucose-insulin-secretion in pancreatic beta cells. They are normally expressed in these cells, and it is considered as autosomal dominant disease that manifest in youth.[24]

Loss-of-function mutations in these genes have been identified in individuals with maturity-onset diabetes of young (MODY) and autosomal dominant diabetes type typically diagnosed before age 25. Inactivating mutations in *HNF1A* and *HNF4A* cause the maturity-onset diabetes of youth (MODY)-3 and (MODY)-1 forms of monogenic diabetes, respectively.[13]

Mutations on (*HNF1*) were described to be the second most common reason for having HH after the (*KATP-HH*).[6] (*HNF4A*) mutations have a unique impact, causing a two-phase phenotype, with some individuals initially experiencing macrosomia and transient neonatal Hyperinsulinemic Hypoglycemia followed by diabetes later in life.[37]

In 2017 a case study was performed by Jonna Yuet et al who reported that, even when *HNF1A*, and *HNF4A* were not statistically significantly different between individuals with mutations on these genes, notably those with inactive

mutations on the *HNF4A* gene were highly probable to be born with large weight for gestational age than those with an inactive mutation on the (*HNF1A*) gene. The inheritance of (*HNF1A*) mutation was mostly from the father's side, while the percentage of inheriting (*HNF4A*) mutations from both parents was close in this study and only one case was described to be "de novo" mutation. The third common cause of diazoxide-responsive congenital Hyperinsulinemic Hypoglycemia is mutation in *HNF4A*.[29]

The HADH Gene, Which Encodes the Short Chain L-3 hydroxy Acyl-CoA Dehydrogenase (SCHAD), Inactive Mutation Leads to HH

HADH is the recessive mutation in gene encoding the hydroxy Acyl-CoA Dehydrogenase that encodes SCHAD enzyme 3-hydroxy acyl-CoA dehydrogenase, which is the inhibitor for the Glutamate dehydrogenase (GDH) enzyme which catalyzes the oxidative deamination of glutamate into alpha-ketoglutarate and ammonia processes. *HADH* is located on chromosome 4 (4 q 22–26) with eight exons, and is known to be highly expressed in the pancreatic beta cells under the transcription factors controlled. If a deficiency of this short-chain inhibitor occurs this will lead to a loss of the inhibition process to the (GDH) enzyme. This will happen due to inactive mutation on the (SCHAD) binding site encoded gene by the (*HADH*) on (GDH) enzyme. At the same time, it is binding to the (BCH) activator.[7,16]

In summary to what happened in this case, the (GDH) enzyme is binding to the activator (BCH) leading to catalyzing the oxidative deamination of the glutamate, which in turn leads to an increase in alpha-ketoglutarate amount, NADH, and NADPH in the mitochondria. These elevated levels of these products will inhibit the isocitrate dehydrogenase enzyme, which will cause to an accumulation of citrate without being converted into isocitrate after this citrate will be transported from the mitochondria to the cytosol where the citrate utilize to synthesize the short and long chain of Acyl-CoA, that is known to be an insulin secretion signaling molecules. Finally, when the glucose level rises and stimulates the insulin secretion, while there is also a high amount of citrate, this will be a reason to start an uncontrolled insulin secretion process causing HH.[16]

Most patients who are affected by this type of HH are diazoxide-responsive. In rare cases, patients with *HADH* deficiency suffer from elevated plasma 3-hydroxy butyryl-carnitine levels. Genetic testing of the (*HADH*) gene is also recommended in this case which is negative for (*KATP*) mutations.[29]

Phosphoglucomutase1 (PGM1) Loss-of-Function Mutation Leads to HH

Phosphoglucomutase1 (*PGM1*) is a crucial enzyme that is responsible for the reversible conversion between glucose-6-phosphate (G6P) and glucose-1-phosphate (G1P). Also, it plays a vital role in different biological processes such as glucagon formation, glycogenesis, and protein glycosylation.[7] PGM1 is located on chromosome 1 (1p31). Loss-of-function mutations on this enzyme when inherited in a recessive manner can lead to rare disorders characterized by various clinical features including Hyperinsulinemic Hypoglycemia; because *PGM1* mutations lead to decreased glucose mediated insulin secretion from the pancreas.[38]

Patients who have mutations in *PGM1* show symptoms like glycogenesis (type XIV) and glycosylation (CDG type 1t). Children affected by this enzyme mutation suffer from both fasting ketonic hypoglycemia (which is low blood glucose with elevated ketone levels), symptomatic postprandial hypoketotic (which is characterized by low blood glucose levels without elevated ketone levels), short stature, dilated cardiomyopathy, and cardiac arrest.[39]

Mitochondrial Carrier Protein (UCP2) Inactive Mutation and HH

UCP2, an inner mitochondrial carrier protein encoded by the (*UCP2*) gene, exhibits widespread tissue expressions including pancreatic cells. It functions as a mediator of proton leak across the inner mitochondrial membrane, thus impeding ATP generation through mitochondrial oxidative metabolism. This in turn exerts a negative regulatory influence on glucose-insulin-mediated secretion.[40–42]

When the (*UCP2*) gene has inactivating mutations that make it less effective, which in turn can lead to increased glucose metabolism due to the increase in ATP production causing HH. This type of HH caused by loss-of-function on the (*UCP2*) gene can range from short-term to long-lasting episodes.[21,41,43]

A previous study that was done in 2017 by Laver et al showed that 206 diazoxide-responsive patients did not have any significant (*UCP2*) mutations, only a common genetic variation.[44] Only one case showed a positive result for a mutation of the (*UCP2*) gene among 211 patients who were diazoxide-responsive in a study that was done by Ferrara et al.[21]

Eukaryotic Translation Initiation Factor 2 Subunit 3 (eIF2S3) Loss-of-Function Mutation and HH

Eukaryotic translation factor 2 subunit 3 is a heterotrimeric GTP-binding protein with 40S ribosomal subunit and methionyl-tRNA with a start codon to initiate the protein synthesis. It's located on chromosome X (Xp22.11) and it has three subunits. Mutations in this translation factor affect translation initiation near the starting codon like AUU and UUG leads to different diseases. Individuals with variants in (*eIF2S3*) display an unusual pattern of glucose regulation. They experience fluctuations between being responsive to diazoxide for HH and experiencing postprandial hyperglycemia. Additionally, these individuals exhibit learning difficulties and hypopituitarism.[45]

Phosphomannomutase 2 (PMM2) Mutation and HH

The phosphomannomutase 2 encoding gene (*PMM2*) plays a pivotal role in the N-glycosylation process and led to glycoprotein synthesis, significantly influencing insulin secretion in pancreatic cells. 7 N-glycosylation means: glycans carbohydrates are covalently attached to protein from the N-terminal side which improves protein stability. *PMM2* gene is located on chromosome 16 (16p13.2). The *PMM2* enzyme is encoded by *PMM2* gene transfer mannose 6-phosphate to mannose 1 phosphate in the glycosylation process. Homozygous recessive mutation in *PMM2* leads to diseases related to CDG type 1a. As mentioned earlier, HH is a part of CDG type 1a, mutations in PMM2 gene promoter significantly influencing insulin secretion in pancreatic cells which lead to Hyperinsulinemic Hypoglycemia and polycystic kidney diseases because this mutation specifically affects the formation of the chromatin loop which changes the gene expression of organ. Patients are usually born larger than normal in gestational age, and experience Hyperinsulinemic Hypoglycemia in early life but usually respond to diazoxide treatment.[10,46,47]

Other Genes Associated with Congenital Autosomal Form of Hyperinsulinemic Hypoglycemia

Insulin Receptor (INSR)

The *INSR* gene encoding insulin receptor protein located on chromosome 19 (19p13.2) is composed of 22 exons codes for alpha and beta subunits of 1,382 amino acid in the outer membrane of many types of cells that binds to insulin which are found in the bloodstream by trans-membrane receptor protein, it's a member of the Src family of tyrosine-specific protein kinases. From this function it plays a role in regulating blood glucose level by detecting how much sugar is entering the cells from the bloodstream to produce energy.[48]

INSR protein includes multiple functional domains, which can be summarized as:

1. Leucine-rich repeat domains (l1 and l2): these domains involved in ligand binding promoting the receptor capability to interact with insulin hormones and aid in receptor confirmation, respectively.
2. Cysteine-rich region: these are responsible for the conservation of a structure and stability of the receptor and can play a role in insulin binding too.
3. Three Fibronectin type III (FnIII) domains: these domains are crucial for receptor dimerization and stability, that are important for effectual signaling.
4. Tyrosine kinase domain: this domain has a substantial tyrosine kinase activity, and it becomes activated when insulin binds, it worked by phosphorylating various substrates which initiate a downstream signaling pathway.[49]

INSR mutations are classified into Homozygous, compound Heterozygous, and Heterozygous.

Homozygous and compound heterozygous are the most common type of mutations that lead to severe insulin resistance (IR) which may occurs due to many syndromes like Donahue syndrome and Rabson-Mendenhall syndrome, while heterozygous mutation in this gene can lead to a milder form of insulin resistance and episodes of Hyperinsulinemic Hypoglycemia, this mutation mainly affects skeletal muscles making them less responsive to insulin leading to a reduction in glycogen formation, which in other hand leads to an increase in the insulin resistance.

As skeletal muscles exhibit insulin resistance, the liver retains insulin sensitivity, therefore leading to reduced glucose production in the liver and causing an Hyperinsulinemic Hypoglycemia episode. The explanation of how this happens is that insulin works through proteins called insulin receptor substrates (IRS), which are found in skeletal muscle tissue and in hepatocytes in the liver. What happens simply is that IRS in skeletal muscle is constitutionally phosphorylated due to the mutated *INSR* gene preventing it from responding to insulin further, causing a poor glycogen production which leads to insulin resistance. Conversely the IRS in the liver maintains phosphorylation levels promoting insulin sensitivity in the liver which leads to low glucose production and increases the percentage of Hyperinsulinemic Hypoglycemia episodes. Symptoms of this type of mutation are having low blood sugar during fasting and high blood sugar after meals, but this case of having heterozygous *INSR* mutation with hypoglycemia episodes is rarely reported; one case was reported by Enkhtuvshin et al.[50]

Solute Carrier Family 25 Member 36 (SLC25A36)

SLC25A36 is a gene encoding pyrimidine nucleotide carrier 2 (*PNC2*). This gene is responsible for transporting guanine and pyrimidine across the mitochondrial membrane. Mutation in this gene (homozygous- splice site mutation) leads to errors in the mitochondrial GTP amount, leading to hyperactivation of the glutamate dehydrogenase enzyme (*GLUD-1*), mutation in *GLUD-1* leads to Hyperinsulinemic Hypoglycemia in childhood by increasing the enzymatic activity and reduces its sensitivity to allosteric inhibition by GTP. An individual with this mutation has low birth weight and tonic-clonic seizures which started from 6 months of age.[51]

Hydroxyacyl-Coenzyme A Dehydrogenase (HADHSC)

The level of *HADHSC* mRNA and protein is expressed by beta cells in all tissue specifically in those that have high rates of mitochondrial β-oxidation. A loss-of-function mutation in *HADHSC* leads to an increase in insulin level at low and high glucose concentration, resulting in Hyperinsulinemic Hypoglycemia. The reason for this is in losing the function of fatty acid β-oxidation enzyme in the liver and muscle, and due to the restriction in fatty acid utilization during fasting. On the other hand, deficiency in the mitochondrial β-oxidation enzyme *HADHSC* can affect the function of beta cells which elevate insulin release.[52]

In beta cells, high mitochondrial NADH decreased the β-oxidation at the level of *HADHSC*, thus leading to accumulation of the hydroxy-acyl-CoA. This alters a glucose metabolic rate which leads to Hyperinsulinemic Hypoglycemia.[53]

Diagnosis of Hyperinsulinemic Hypoglycemia

Diagnosing of Hyperinsulinemic Hypoglycemia is the most important thing because it determines the appropriate treatment. The diagnosis of Hyperinsulinemic Hypoglycemia can be detected by increasing insulin value demonstrated by an increased glucose requirement. The amount of Beta-hydroxybutyrate (BOHB <1.8 mmol/L), free fatty acids (FFA <1.7 mmol/L), and hormones (insulin >1.25 μU/mL, growth hormone and cortisol) in plasma are recommended in diagnosis of Hyperinsulinemic Hypoglycemia. Additionally, errors in response to glycogen are also used as a marker in diagnosis (≥30 mg/dL). But to confirm the diagnosis, the test must be repeated after 72 hours if Hyperinsulinemic Hypoglycemia is still present.[54]

Genetic diagnosis must be tested for all genes mentioned earlier (*ABCC8*, *KCNJ11*, *GLUD1*, *GCK*, *HNF4A*, *HNF1A*, *HADH*, *SLC16A1*, *INSR*, *HK1*) to determine the Histology form; diffuse, focal, or mosaic. Diagnosis of Hyperinsulinemic Hypoglycemia must be in the newborn period because many cases need pancreatic isolation, and this is needed for long-term follow-up. If the disease is not diagnosed early, it can develop into insulinoma specifically in children above 2 years, whether benign or malignant.[55]

Treatment of Hyperinsulinemic Hypoglycemia

The main goal in treatment is to preserve the level of glucose in plasma within the normal range (70–100 mg/dL) and sufficient ketone production, this is depending on the type of Hyperinsulinemic Hypoglycemia.[56] The first step in treatment (after knowing exactly the glucose level by glucometer before meals and bedtime) is Dextrose (intravenous glucose) with a dose of 200 mg/kg. The alternative therapy is glycogen (intramuscularly glucose or subcutaneously) with a dose of 20–30 μg/kg, this is increasing the blood sugar by stimulating gluconeogenesis, ketogenesis, and lipolysis in the liver. The level of glucose should be increased within 10 minutes after treatment. And let us not forget that every medicine has its own side-effects. Vomiting (13%), rash (2%), and respiratory distress (19%) are all side-effects of Dextrose.[57]

The second line in treatment is Diazoxide, which is a benzothiadiazide responsible for beta-cell K_{ATP} channels opening to suppress the insulin secretion with a dose 5–15 mg/kg/day in children and 3–8 mg/kg/day in adults. Defects in the K_{ATP} channel lead to unresponsive Diazoxide treatment. Edema, hyponatremia, tachypnea, and respiratory failure are all side-effects of Diazoxide. In case of Diazoxide unresponsive and prevent pancreatomy, there is an alternative line for treatment which is the use of Somatostatin (SSA: Short acting Somatostatin Analogs, LAR: Long-Acting octreotide) including necrotizing enterocolitis and hemodynamic instability as a side-effect. This is subcutaneous with a dose of 5–10 μg/kg/day, or intramuscular injection singly per month of long-acting SSA. It is used in chronic treatment and has been proved to be more effective than conventional treatments.[58]

What do we do with children who suffer from Hyperinsulinemic Hypoglycemia despite taking treatment? Glucose or carbohydrates solution must be given with a concentration up to 20% by gastrostomy using portable pumps.[59]

Nifedipine and Sirolimus are calcium-channel blockers. They lack Adequate Proof of Efficacy and the success in treatment is low, despite it working to release insulin by the role of a voltage-dependent calcium channel. So, these medications are used as a final option in Hyperinsulinemic Hypoglycemia treatment.[60]

All these treatments are approved by the Food and Drug Administration (FDA by USA) except somatostatin. Finally, periodic examinations should be done every 6 months when taking these treatments such as Complete Blood Counting (CBC), ultrasound for gallbladder, check the liver enzyme, and thyroid function.[24]

If normoglycemia cannot be achieved and to avoid diabetes mellitus and ongoing hypoglycemia, surgery must be done. During the surgery, doctors should take two biopsy samples, one from the head of the pancreas and one from the tail to determine if it's a diffuse hypoglycemia (characterized by large nuclei with a high number of islets cells) or to establish the focal lesion (> 1 cm in diameter and large masses in endocrine cells). Immunohistochemical staining should be done after surgery using chromogranin and synaptophysin (neuroendocrine markers) to assess margin involvement as the loss of nuclear p57 staining in lesion cells indicates the loss of maternal heterozygosity at 11p15. After the operation, regardless of the primary diagnosis, the patient must be reviewed and the blood sugar level measured to determine whether they have recovered or need further treatment. But a high percentage of research shows that 95% of people who undergo pancreatic removal recover completely.[61]

Conclusion

In conclusion, the classification of the genes causing Hyperinsulinemic Hypoglycemia is according to the mutation types they could go through. Firstly, the active mutations which can affect five genes (*GLUD1*, *GCK*, *SLC16A1*, *HK1*, *CACNA1D*), with minimal research on the (*CACNA1D*) gene. Secondly, the inactive mutations that can affect 11 genes: (*KCNJ11*, *ABCC8*, *FOXA2*, *HNF1A*, *HNF4A*, *HADH*, *PGM1*, *UCP2*, *KCNQ1*, *PMM2*, *EIF2S3*) including the most common cause of Hyperinsulinemic Hypoglycemia which is the mutation on (*KCNJ11, ABCC8*) genes and limited research on the (*KCNQ1*) gene with only one case on the (*UCP2*) gene.

Respectively all these genes play an important role in glucose metabolism and insulin secretion individually and collectively to maintain blood glucose in the normal range.

Rapid maintenance of normoglycemia is important because Hyperinsulinemic Hypoglycemia affects neurons, leading to brain damage and epilepsy in the long-term. Therefore, diagnosis and treatment must be done without wasting time.

Recommendations

Considering all genetic causes of Hyperinsulinemic Hypoglycemia (HH) in its different types, there are still many genes that need to be studied more, such as (*UCP2*), (*KCNQ1*), and (*CACN1D*) to encode its enhancing role in continuous low blood glucose in the early years of life.

Since there are multiple studies focusing on the genetic variations connected with Hyperinsulinemic Hypoglycemia (HH), there are many other questions about the epigenetic variations related to it, which have always been done to be related only to the general types of diabetes mellitus. In addition to that we need to know more about how to avoid the effect of (HH) in the later life of patients, and what other technology could be practiced limiting these mutations from happening in an early stage to those people with a history of diabetes mellitus, and how to check it in early stages.

Disclosure

The authors report no conflicts of interest in this work.

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