CASE REPORT

Adult-Onset Nesidioblastosis (Non-Insulinoma Pancreatogenous Hypoglycemia Syndrome): a Rare Case

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ABSTRACT

Finding the etiology of hypoglycemia in adult patients can be challenging because of the wide variety of etiologies. Ninety percent of endogenous hyperinsulinemic hypoglycemia is caused by insulinoma, the rest are caused by insulin antibodies and pancreatic β cell dysfunction (nesidioblastosis) which indicates neoformation of nesidioblasts (stem cells that form the islets of Langerhans). A 28-year-old female complained of neuroglycopenia and adrenergic symptoms that improved with drinking sugar, so she had weight gain. The 72 hours of prolonged fasting test results are C-peptide ≥0.2 mmol/L, insulin ≥21 pmol/L, insulin to C-peptide molar ratio ≤1, and negative insulin antibody. Imaging tests were normal and there is no evidence of malignancies. When blood glucose falls, the first defense mechanism to prevent hypoglycemia is decreased in insulin secretion. When this mechanism fails, insulin and C-peptide levels remain high in circulation. Confirmation of Whipple's triad is required, followed by insulin tests in hypoglycemic conditions. Imaging tests, biomarkers, and hormonal malignancies were done to rule out differential diagnoses. Nuclear diagnostics, SACST, biopsy, and histopathology are currently in capable of being carried out. The diagnosis of adult-onset Nesidioblastosis/NIPHS in this patient was made through the diagnosis of exclusion, namely by eliminating all diagnostic appeals because several examination modalities cannot be carried out. The gold standard for diagnosing Nesidioblastosis/NIPHS is SACST and histopathological examination of pancreatic tissue. The patient is well-controlled with Amlodipine 2.5 mg.

Keywords: Hypoglycemia, hyperinsulinemia, nesidioblastosis, non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS)

INTRODUCTION

Hypoglycemia is a life-threatening condition that can occur in various circumstances. Establishing an etiological of hypoglycemia in adult patients can be a challenge, because of the wide variety of causes such as the effects of diabetes treatment (insulin, insulin secretagogue), alcohol consumption, critical illness (sepsis, liver failure, kidney failure), endocrine diseases (adrenal insufficiency, pituitary), a tumor that produces insulin like-growth factor (IGF) or insulin, and endogenous hyperinsulinemia.[1-7]

Ninety percent of hyperinsulinemic endogenous hypoglycemia in adults is caused by insulinoma. In contrast, the rest is caused by the presence of antibodies to insulin (Hirata's disease) and pancreatic β cell dysfunction. Insulinoma is a tumor originating from the islets of Langerhans β cells of the pancreas. Hirata's disease is a disease caused by antibodies to insulin. Meanwhile, dysfunction of pancreatic β cells is the presence of inappropriate secretion of endogenous insulin, which is called nesidioblastosis, which shows the origin of the cells, namely neoformation of nesidioblasts, the stem cells that form the islets of Langerhans.[1-7]

Nesidioblastosis is characterized by focal or diffuse hypertrophy, hyperplasia, and hyperfunction of the β cells of the pancreatic islets of Langerhans without any abnormalities found in pancreatic cells. Nesidioblastosis began to be termed non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS) by Service et al. in 1999.[7-9]

The following is a rare case reported, namely adult-onset NIPHS in a 28-year-old woman with problems in diagnosis and management.

CASE ILLUSTRATION

A 28-year-old woman came to the Endocrine metabolic diabetes polyclinic with the main complaint felt suddenly weak and getting worse for 3 years ago. Additional complaints were dizziness, cold sweat, muscle aches, palpitations, and intense hunger even after eating. To get rid of the feeling of weakness, she drank a sugar solution or syrup. She checked herself at the community health center and found that his blood sugar value without fasting at that time was 90mg/dL. She ate larger portions than usual to prevent her body from becoming weak. She had weight gain from 57 kg to 78 kg in the past 3 years.

Previous medical history did not reveal a history of hypertension, diabetes, kidney disease, tumors, or a history of surgery or taking medication or herbal medicine. Family history revealed diabetes in her biological mother and older siblings. Eating habits revealed eating patterns as follows when she woke up, immediately drink 1 glass of water plus 3 tablespoons of granulated sugar, around 7 breakfasts: 2 cups white rice, side dishes, vegetables, around 10 o'clock have a snack: fried food or fruit, around 12 lunches: 2 cups white rice, side dish, vegetables, around 15 o'clock have a snack: fried food or fruit, around 18 o'clock dinner: 2 cups white rice, side dish, vegetables, around 20 o'clock have a snack: fried food or fruit, before going to bed, drink 1 glass of water plus 3 tablespoons of sugar

General physical examination revealed weight: 78 Kg, Height: 160 cm with BMI: 30.4 (obesity 1). The organ-specific examination did not reveal any abnormalities.

Figure 1. Clinical picture

From the history, physical examination, and blood sugar examination, it was concluded that the Whipple's Triad criteria for Hypoglycemia in this patient had been confirmed so that it could be included in the Hypoglycemia diagnosis algorithm as in Figure 2.

Routine blood screening, liver function, and kidney function showed normal results. Adrenal function screening through morning Cortisole examination and Pituitary function through TSH examination showed normal results. Screening for diabetes with HbA1C examination resulted in 5.7%, comparable to an average blood sugar of 110 mg/dL, and screening for hyperinsulinemia through C-Peptide examination with high result 5.19 mmol/L (normal 0.26-1, 72 mmol/L).
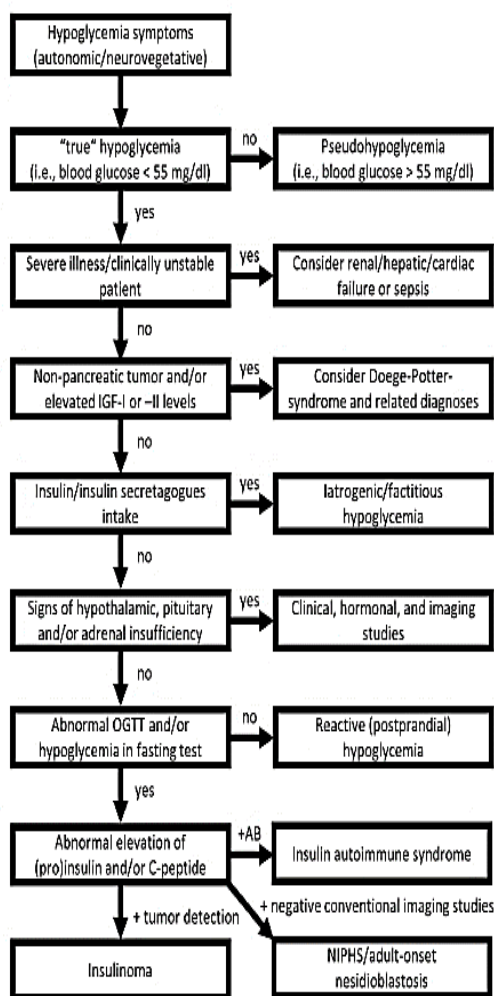
The 72 hours prolong fasting test, a hypoglycemia provocation test, was carried out (figure 3) and the results showed that C-peptide ≥0.2 mmol/L and insulin ≥21 pmol/L which means that still increased although the patient's blood sugar was 53 mg/dL at the 53rd hour of fasting (Figure 3).
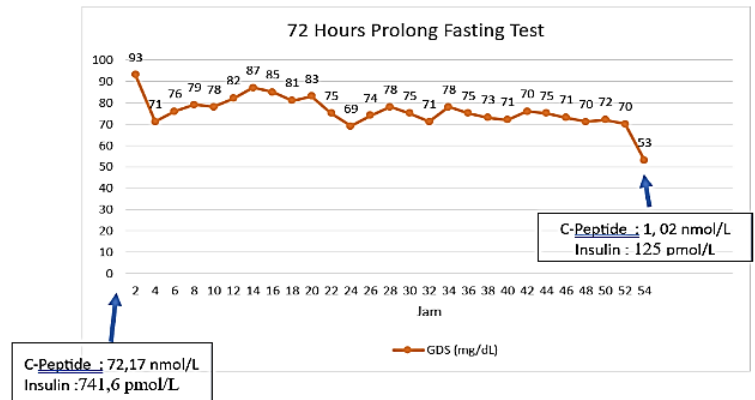

Figure 3. 72 Hours Prolong Fasting Test

We performed the calculation of the Insulin: C-peptide molar ratio that obtained a value of ≤1 which corresponds to endogenous hyperinsulinemic Hypo-glycemia (Table 1). Next, an insulin antibody test was carried out with negative results.

Table 1. Dynamic Test Result

Test	Pre-Test	Post Test	Normal Value
C-Peptide	72,17	1, 02	0,26 - 1,72 nmol/L
Insulin	741,6	125	34,7 - 69,4 pmol/L
Insulin: C-peptide molar ratio (pmol/L)	0,01	0,12	≤ 1 Hiperinsulinemic Hypoglicemi Endogen > 1 Hiperinsulinemic Hypoglicemi Eksogen/ Insulin autoantibody

CT scan of the abdomen with contrast and MRI of the abdomen with contrast did not reveal an intra-abdominal mass. Thoracic imaging examination, thyroid, and parathyroid ultrasound as well as biomarkers of malignancy, namely intact PTH, Calcium, CEA, Cyfra 21-1, and CA 19-9 to rule out insulin-secreting NET and MEN-1 syndrome, showed normal results.
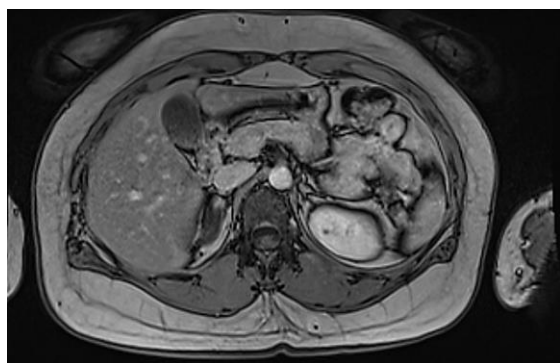

Figure 2. Diagnostic Algorithm of Hypoglicemia

Figure 4. Abdomen contrast MRI

The β-OHB examination cannot be carried out, so it is not carried out, but the β-OHB examination is needed only if insulin levels are low. Blood and urine sulfonylurea screening examinations were not carried out because the patient had no history of consuming drugs or herbs. The insulin receptor antibody examination was not carried out because the physical examination and supporting examinations did not reveal any manifestations of severe insulin resistance. Examination of mutations in the gene that forms the K-ATP channel protein is not yet possible because it cannot be done if there is only 1 patient sample. Meanwhile, the diagnosis of Congenital Hyperinsulinemi (CHI) and Familial Hyperinsulinemia (FHI) usually occurs at birth and in childhood.

To establish a definite diagnosis of adult-onset NIPHS, a Selective Arterial Calcium Stimulation Test (SACST) or histopathology of the pancreas gland is required. To date, the SACST examination has never been carried out in the vascular surgery department but theoretically, it can be carried out, while pancreatic gland biopsy can be carried out in the digestive surgery department, but these two invasive examinations are hampered because the patient is not yet willing to undergo surgery. After eliminating all differential diagnoses, the patient was diagnosed with Suspected Adult-Onset NIPHS.

Patients are given non-pharmacological therapy in the form of diet modification in consultation with a clinical nutritionist. Diet modification with complex carbohydrates, low glycemic index, high fiber, and diet frequency every 2-3 hours, wake up and eat complex carbohydrates, for example, boiled corn, boiled sweet potatoes, at 8 breakfasts: 1.5 cups white rice, side dishes, a larger portion of vegetable, at 10 o'clock have a snack: 1 large piece of fruit, 12 o'clock lunch: 1.5 cups white rice, side dishes, a larger portion of vegetables, at 15 o'clock have a snack: fruit, 18 o'clock dinner: 1.5 cups white rice, side dishes, a larger portion of vegetables, at 20 o'clock have a snack: fruit, before going to bed, don't eat or drink sugar water anymore, if symptoms of hypoglycemia appear (cold sweat, body weakness, dizziness, palpitations) you can drink sugar water, diet will be monitored every week

At 2 weeks of follow-up with diet modification, it was found that blood sugar was stable, and the frequency of hypoglycemia events began to decrease. Diet modification therapy was continued. In the 3rd month of follow-up, the incidence of hypoglycemia decreased but when woke up she still drank 1.5 tablespoons of sugar water, and her weight increased by 1 kg. Amlodipine therapy was given 5 mg at night before bed. After 2 weeks of amlodipine administration, the symptoms of hypoglycemia did not appear, but the systolic blood pressure dropped to 100 mmHg, and the dose was reduced to 1x 2.5 mg at night. The prognosis of this patient is poor due to the requirement for lifelong treatment and monitoring.

DISCUSSION

Hypoglycemia is a decrease in blood sugar levels low enough to cause symptoms and signs to appear. Blood sugar concentration is normally maintained within a narrow range of 72-144 mg/dL through a balance between glucose entry (exogenous glucose intake and endogenous glucose production) and glucose output (glucose utilization by insulin-sensitive tissues such as muscle and insulin-insensitive tissues such as the brain). Hypoglycemia occurs due to an imbalance between the entry and exit of glucose either due to an increase in the rate of glucose clearance from the circulation, a lack of glucose delivery into the circulation, or both.[8]

Under physiological conditions, insulin secretion from pancreatic β cells is precisely regulated in response to changes in glucose concentration in the blood. The increase in post-prandial blood glucose and the release of glucagon-like peptide 1 (GLP-1), an incretin hormone from the intestine, will stimulate the synthesis and secretion of insulin from pancreatic β cells. Insulin secretion will return to basal levels around 2-4 hours after eating. [5,8]

When blood glucose falls, the first defense mechanism to prevent hypoglycemia is decreased insulin secretion. When blood sugar falls below 3.8 mmol/L (68.4 mg/dL), there is a rapid increase in glucagon and epinephrine secretion to prevent hypoglycemia. If hypoglycemia continues, the secretion of cortisol and growth hormone increases as a further counter-regulatory response. All these effects aim to suppress insulin secretion, induce hunger, increase glucose levels, reduce peripheral glucose uptake and provide alternative fuel when blood glucose falls, the first defense mechanism to prevent hypoglycemia is a decrease in insulin secretion. When blood sugar falls below 3.8 mmol/L (68.4 mg/dL), there is a rapid increase in glucagon and epinephrine secretion to prevent hypoglycemia. If hypoglycemia continues, the secretion of cortisol and Growth Hormone increases as a further counterregulatory response. All these effects aim to suppress insulin secretion, induce hunger, increase glucose levels, reduce peripheral glucose uptake, and provide alternative fuel for the brainl for the brain. [5,8]

Insulin secretion is completely suppressed at blood sugar levels of 3 mmol/L (54 mg/dL). Post-prandial hypoglycemia occurs when insulin secretion fails to be suppressed due to falling glucose concentrations and there is a blunting of the response to glucagon and epinephrine. Excessive insulin will suppress the processes of glycogenolysis and gluconeogenesis so that hypoglycemia occurs because of a decrease in glucose production compared to an increase in utility. Meanwhile, suppression of the lipolysis process will reduce

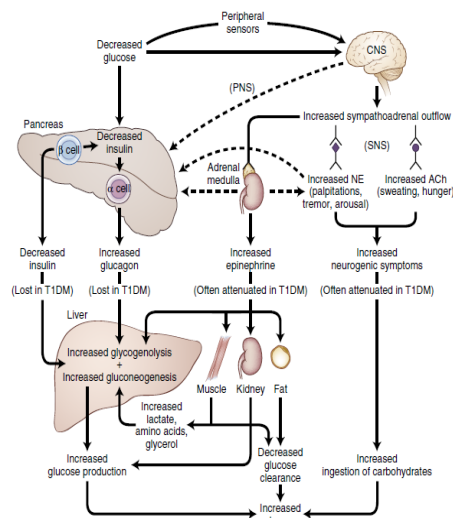ketogenesis so that there is no alternative fuel for brain metabolism which is dangerous for the brain. [5,8]

Figure 5. Physiological and behavioral defenses against hypoglycemia. [8]

Hypoglycemia in non-diabetic individuals is rare. It is important to explore the history of Whipple triad (neuroglycopenic symptoms, low blood sugar, improvement of symptoms after glucose administration) in non-diabetic individuals who are suspected of having hypoglycemia before starting further tests. The etiology of hypoglycemia can be seen in Tables 2 and 3. DM drugs are currently still the most common cause of hypoglycemia. [5,8]

Spontaneous hypoglycemia in apparently normal individuals may occur in a single episode or subacute neuroglycopenic symptoms. The clinical history should assess whether hypoglycemia occurred during fasting or postprandially, the nature of symptom onset (e.g., cold sweats, anxiety, tremors, palpitations, intense hunger, and tingling), and the resolutions of symptoms after ingesting sugar. Family history should be explored for transient symptom, such as hemiplegia, strabismus, hypothermia, hyperthermia, seizures, and involuntary movements. [5,8] Additionally, document, any history of medication, supplement, herbs, alcohol use, and prior gastric surgery.

In this patient, after anamnesis and initial examination, Whipple's Triad was confirmed, namely the presence of

neuroglycopenic symptoms, low blood sugar below 3.0 mmol/L (54 mg/dL), and improvement in symptoms after administration of glucose. Next, an assessment is carried out as to whether the patient is experiencing a critical illness condition through a thorough physical examination and supporting examinations. From the anamnesis, there were no complaints that indicated a sign of malignancy such as weight loss, lumps, persistent pain, or changes in urination and defecation patterns. On physical examination, the patient was found to be in stable condition, only the BMI was increased and there were no signs of other diseases.

Table 2. Etiology of Hypoglycemia

Ill or Medicated Individual

Drugs

Insulin or insulin secretagogue
Alcohol
Others (see Table 38.8)

Critical Illnesses

Hepatic, renal, or cardiac failure
Sepsis
Inanition

Hormonal Deficiency

Cortisol
Glucagon and epinephrine (in insulin-deficient diabetes mellitus)

Non–Islet Cell Tumor

Seemingly Well Individual

Endogenous Hyperinsulinism

Insulinoma
Functional beta-cell disorders (nesidioblastosis)
Noninsulinoma pancreatogenous hypoglycemia
Post–gastric bypass hypoglycemia
Autoimmune hypoglycemia
    Antibody to insulin
    Antibody to insulin receptor
Insulin secretagogue
Other

Accidental, Surreptitious, or Malicious Hypoglycemia

The next diagnostic step is to look at insulin levels in a fasting condition with a 72-hour long fasting test. The principle of the 72-hour prolonged fasting test is that when blood sugar conditions drop, the body's first response is to reduce insulin/C-peptide secretion to prevent hypoglycemia (Fiigure 3). In conditions of hyperinsulinemic endogenous hypo-glycemia, this suppression mechanism fails, so that insulin to C-peptide ratio levels remain high in the circulation and cause hypoglycemia. The examination procedure is that the patient is installed with intravenous access and then fasted from food and drinks that contain

calories. Peripheral blood sugar is checked every 2-4 hours then every 1 hour if blood sugar is below 70 mg/dL. The test is stopped, and insulin and C-peptide samples are taken before adding glucose. These conditions include 72 hours have been reached, patients without symptoms of hypoglycemia but GDS < 2.5 mmol/L (45 mg/dL), and symptoms of hypoglycemia appear even though the capillary GDS is > 2.5 mmol/L (45 mg/dL).[7]

In this patient, after carrying out a 72-hour prolonged fasting test, the patient's glucose level was 53 mg/dL at the 53rd hour of examination and a high insulin level was found, namely 18 μU/mL (>3 μU/mL/ 18 pmol/L), C -peptide 1.02 nmol/L (>0.2 nmol/L) and Insulin to C-peptide molar ratio < 1. These results support a state of endogenous hypoglycemic hyperinsulinemia (Table 3).[6-8]

Insulinoma, although rare, is the most common Neuroendocrine Tumor (NET) in the gastrointestinal tract with an annual incidence of around 0.5 – 1 per 1 million population per year. Insulinoma occurs more often in women. It can occur at any age but especially in middle age (mean age 47 years in sporadic cases and 23 years in MEN1 syndrome cases). [7,8]

To rule out the differential diagnosis of insulinoma, MEN1 syndrome, and insulin-secreting NET, the patient underwent an imaging examination to localize the tumor using Computer Tomography (CT) with a sensitivity of 70% and Magnetic Resonance Imaging (MRI) with a sensitivity of 80% for the diagnosis of insulinoma. Biomarker examination of malignancy also yielded positive results normal so that MEN1 syndrome and insulin-secreting NETs can be ruled out.[1,5,7,8]

If there is no intra-mass image, the next examination is the SACST to confirm the diagnosis of NIPHS. In this patient, imaging examination did not reveal an insulinoma. Meanwhile, the SACS test was not yet able to be carried out, so it was not carried out. This patient has never had surgery on the stomach and intestines so the differential diagnosis of Post Gastric By-Pass Surgery (PGBH) can be ruled out. Meanwhile, Congenital

Hyperinsulinemia (CHI) and Familial Hyperinsulinemia (FHI) have onset from birth to childhood. The examination of insulin auto-antibodies in this patient was negative. After ruling out all differential diagnoses a diagnosis of adult-onset NIPHS can now be established.[5,6,11-13]

Table 3. Patterns of findings after fasting test

Symptoms, Signs, or Both	Glucose (mg/dL)	Insulin (μU/mL)	C-Peptide (nmol/L)	Proinsulin (pmol/L)	β-Hydroxybutyrate (mmol/L)	Glucose Increase After Glucagon (mg/dL)	Circulating Oral Hypoglycemic Agent	Antibody to Insulin	Diagnostic Interpretation
No	<55	<3	<0.2	<5	>2.7	<25	No	No	Normal
Yes	<55	≫3	<0.2	<5	≤2.7	>25	No	Neg (Pos)	Exogenous insulin
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	No	Neg	Insulinoma, NIPHS, PGBH
Yes	<55	≥3	≥0.2	≥5	≤2.7	>25	Yes	Neg	Oral hypoglycemic agent
Yes	<55	≫3	≫0.2[b]	≫5[b]	≤2.7	>25	No	Pos	Insulin autoimmune
Yes	<55	<3	<0.2	<5	≤2.7	>25	No	Neg	IGF[c]
Yes	<55	<3	<0.2	<5	>2.7	<25	No	Neg	Not insulin- or IGF mediated

Table title: Patterns of Findings During Fasting or After a Mixed Meal in Normal Individuals[a] and in Individuals With Hyperinsulinemic (or IGF-Mediated) Hypoglycemia or Hypoglycemia Caused by Other Mechanisms

Epidemiologically, the etiology of endogenous hyperinsulinemic hypo-glycemia in adults is the most common cause by insulinoma which is 90%, while adult-onset NIPHS only occurs in around 0.5-5% of cases of endogenous hyperinsulinemic hypo-glycemic.[1,2,4,7]

Epidemiological research in Japan by Yamada et al., which was launched in 2020, regarding the incidence of endogenous hyperinsulinemic hypoglycemia in 2017-2018, resulted in 447 CHI patients, 205 insulinoma patients, 111 NIPHS patients, and 22 insulin autoimmune syndrome patients. The incidence of adult-onset NIPHS is estimated to occur in 1: 10,000,000 people per year aged 28-63 years with an average age of 48 years.[14]

The physiological mechanism of insulin secretion begins with the entry of glucose into pancreatic β cells through glucose transport proteins (GLUT) 1 and 3. Glucose is phosphorylated by glucokinase (GCK) to form Glucose-6-phosphate, and then the glycolysis process occurs in the Krebs cycle and the oxidative phosphorylation chain which ultimately forms adenosine triphosphate (ATP). Increasing ATP concentration will increase the ATP to ADP ratio. ATP inhibits K-ATP channel activity resulting in a decrease in the efflux of potassium ions (K+) which causes an increase in cell membrane potential. If the membrane potential limit is reached, calcium ions (Ca2+) channels open, resulting in an influx of calcium which stimulates the fusion of vesicles containing insulin at the plasma membrane and stimulates insulin secretion.[1,8]

In patients who experience NIPHS, there is a change in mechanism. GCK gene mutations cause excessive GCK enzyme activity. This increases the oxidative metabolic pathway increased in an increase in the ATP to ADP ratio which will cause KATP channel inhibition so that K+ ions cannot exit which causes a higher resting membrane potential and causes greater Ca2+ channel opening. Apart from that, NIPHS patients also found increased insulin synthesis and storage. Likewise, the basal rate of insulin secretion is higher than in normal cells. So, it was concluded that in NIPHS patients there was increased insulin secretion from pancreatic B cells, resulting in hyperinsulinemic hypoglycemia which was associated with clinical symptoms.[1,8]
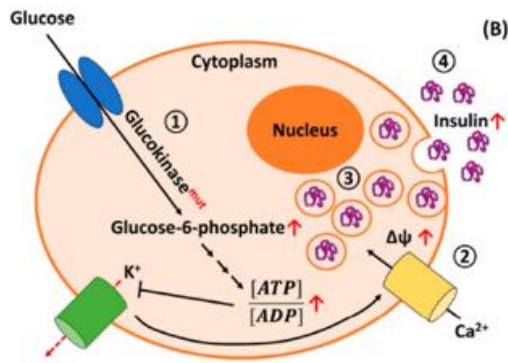
Figure 6. Insulin secration in Nesidioblastosis/ NIPHS[1]

Apart from conventional diagnostic modalities, there are other diagnostic modalities:

1. 68Ga-DOTATE PET/CT and 68Ga-DOTA-Extendine-4 PET/CT

Pancreatic neuroendocrine cells express the high-affinity somatostatin receptor (SSTR). 68Ga-DOTATE specifically binds SSTR type 2 which is in high concentration in pancreatic islet B cells, so imaging based on SSTR is an option to confirm the diagnosis of NIPHS. The latest guidelines recommend that SSTR PET/CT examination should be used as the main modality to diagnose NIPHS with a sensitivity of 80-90% and a specificity of 82-90%. The newest is 68Ga-DOTA-Extendine-4 PET/CT where the target is cells that express GLP-1 with an accuracy of 93.9%. In NIPHS, tracer capture is diffuse, whereas in insulinoma the tracer capture is localized.

Figure 7. [6,8]Ga-DOTA-Extendine-4 PET/C[1]

NIPHS Clinically and biochemically, cannot be differentiated from insulinoma, especially insulinomas < 1 cm in size that cannot be detected using imaging techniques. In this case, the SACST can be used to differentiate them.

With SACST is since calcium will stimulate insulin secretion from hyperfunctioning pancreatic B cells, but not from normal pancreatic B cells. A positive result occurs if there is a twofold increase in hepatic vein insulin concentration after calcium injection in the pancreatic artery. Thompson et al., research found in NIPHS increased insulin concentration is diffuse whereas in insulinoma patients it is more localized.[1-3,10,15,19]
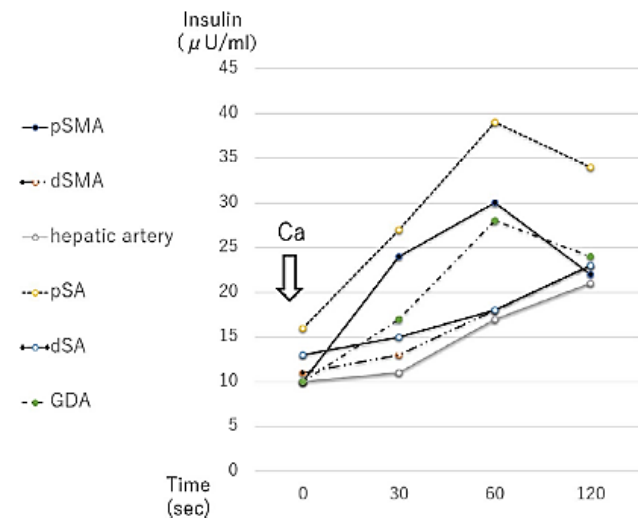

Figure 8. Sample of SACST

2. Histopathology of the Pancreatic Gland

The gold standard for the diagnosis of NIPHS is a histopathological picture with pancreatic B cells in the form of enlarged nuclei and cytoplasm throughout the pancreas. There were no abnormalities in somatostatin cells, glucagon cells, and pancreatic polypeptide cells, and an increase in the number of ductuloinsular complexes. Table 4 shows the histopathological criteria of nesidioblastosis.[20-22]

The terminology nesidioblastosis was first described by George F Laidlaw (1938) from the Greek "nesidion" which means island and
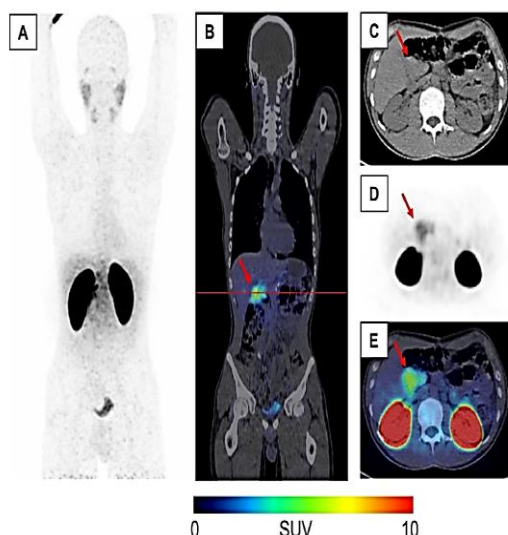
"blastos" which means stem cell (germ). It is characterized by hypertrophy and hyperplasia of B cells of the islets of Langerhans, enlarged and hyperchromatic cell nuclei, and neoformation of pancreatic islets from the ductal epithelium.[3,16,20]

Figure 9. Comparison of Islets of Langerhans cells using insulin immunohistochemical staining.

Images of a normal person (A) and a NIPHS patient (B). NIPHS patients show hypertrophic nuclei and brighter cytoplasm, clusters of islets with varying sizes and shapes, and contain more insulin. [20]
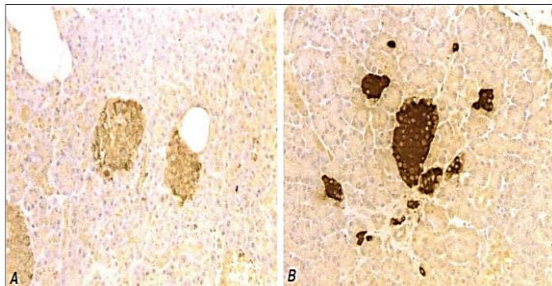
Table 4. Histopathological Criteria for NIPHS[1,2]

| MAJOR CRITERIA	MINOR CRITERIA
-Exclusion of an insulinoma by macroscopic, microscopic, and immunohistochemical examination	-Irregular shape and occasional enlargement of islets
-Multiple b-cells with an enlarged and hyperchromatic nucleus and abundant clear cytoplasm	-Increased number of islets
-Islets with normal spatial distribution of the various cell types	-Lobulated islet structure
-No proliferative activity of endocrine cells	-Macronucleoli in b-cells

3. Genomics

Various genetic mutations are responsible for pancreatic B cell hyperplasia. Two genes encoding the proteins ABCC8 (formerly known as SUR1) and KCNJ11 (formerly known as Kir6.2) which form K-ATP channels in the membrane of pancreatic B cells, are the main genetic defects causing diffuse NIPHS. This gene mutation is located on chromosome 11p14-15.1, causing changes or inactivation of the K-ATP channel. Inactivation of K-ATP channels cause the closure of potassium channels so that calcium ions enter the cell, resulting in depolarization of the cell membrane which causes continuous insulin secretion.[1,2,4,23,24]

Normal production of K-ATP channel proteins includes transcription of the ABCC8 and KCNJ11 to produce pre-mRNA which then becomes mRNA (mature RNA). The mRNA exits the nucleus and is translated into protein in the ribosomes embedded in the endoplasmic reticulum. Next, the polypeptide is folded into a tertiary structure and enters the Golgi Apparatus for post-translational modification. Vesicles containing the assembled K-ATP channel protein are then expressed on the plasma membrane. In CHI there is a defect in the regulation, biogenesis and movement of K-ATP channel proteins which results in ineffective K-ATP channel degradation in lysosomes (Figure 10) [23,24]

Apart from that, defects were also found in the Glucokinase (GCK), Hexokinase (HK), Glutamate Dehydrogenase type-1 (GLUD-1) genes causing changes in insulin secretion as explained in Figure 6.[1, 2, 4, 23, 24]
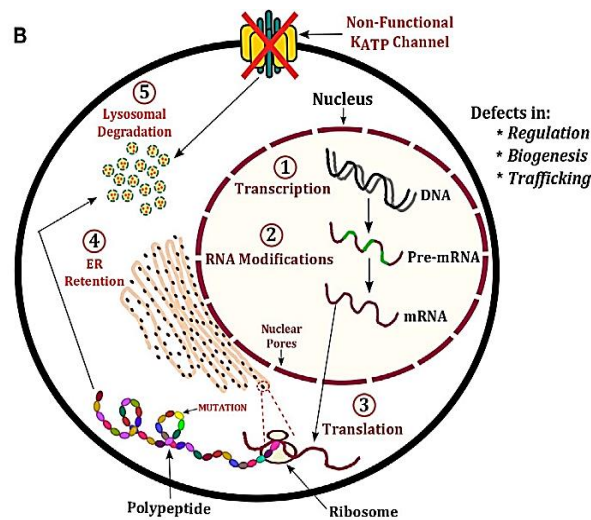
Figure 10. KATP channel protein gene mutations in the pathophysiology of hyperinsulinemia.[23]

Table 5. Gene Mutations in Familial Hyperinsulinemia[24]

Gene	ABCC8	KCNJ11	GCK	GLUD1	HADH1	SLC16A1	HNF4A, HNF1A	UCP2
Protein	SUR1 ATP-binding cassette, subfamily C; sulfonylurea receptor	Kir6.2 inwardly rectifying potassium channel	GCK glucokinase	GLUD1 glutamate dehydrogenase	SCHAD 3-hydroxyacyl-CoA dehydrogenase	SLC16A1/ MCT1 Solute carrier family 16 member 1/ monocarboxylate transporter 1	HNF4A, HNF1A hepatocyte nuclear factors 4α and 1α	UCP2 mitochondrial uncoupling protein 2
Function	Subunits of the β-cell ATP-dependent potassium channel		β-cell glucose metabolism	Amino acid-stimulated insulin secretion	Enzyme involved in fatty acid oxidation	Plasma membrane pyruvate transporter	Nuclear transcription factor	Mitochondrial uncoupling protein
Autosomal mutations	—— recessive: • severe form of neonatal hypoglycaemia [48, 49] • diffuse FHI** [6] —— dominant: • milder form [48, 49] • focal FHI —— caused by a paternal mutation of one of the genes and a specific loss of maternal alleles [8]		Dominant, activating [10, 14—16]	Dominant, activating [4, 19] Relatively mild FHI, may escape recognition in infancy [20]	Recessive, loss of function [4, 25—28]	Dominant, increased expression [29]	Dominant, loss of function [35] Also associated with MODY1 (HNF4a) and MODY3 (HNF1a) [35]	Dominant, loss of function
Characteristic	Large birth weight [4] Increased risk of diabetes in adulthood [4]		Normal birth weight [15]	Hyperammonaemia [21] Leucine-dependent protein- stimulated hypoglycaemia [4]	Elevated urinary 3-hydroxyglutaric acid excretion [4] Leucine-dependent protein-stimulated hypoglycaemia [25]	hypoglycaemia after intensive exercise [29]	Large birth weight [34] Evolution of neonatal hyperinsulinism to diabetes later in life [34, 35]	
Diazoxide treatment effective-ness	—* [4]		— or + Depending on the mutation [10, 14—16]	+ [4, 20]	+ [4, 28]	Partial response [50, 51]	+ [32, 34, 35]	+ [42]

*Cases with dominant KATP mutations may be responsive to diazoxide [48, 49]. **Most cases. Dominant diffuse FHI is also being observed [6]

Therapeutic options for adult-onset NIPHS currently remain limited. Because the pathophysiology of this disease is not yet fully understood, interventions aimed at treating the causes of impaired pancreatic β-cell function do not yet exist. The first step is a low-carbohydrate diet with a low glycemic index to reduce the strong stimulation of insulin secretion. Furthermore, existing pharmacological therapies are α-glucosidase inhibitors (Acarbose), K-ATP channel agonists (Diazoxide), calcium channel antagonists (Amlodipine), and somatostatin analogs (Octreotide, Lanreotide, Pasireotide)[1,25-30] and some cases, glucocorticoids, β-blockers, antipsychotics/antiepileptics such as phenytoin are also used as therapy for NIPHS through effects that cause hyperglycemia. Everolimus, a nuclear cell signaling inhibitor, was also tried in the treatment of NIPHS but failed to maintain euglycemic conditions.[1]

Refer to Table 6 for comprehensive details on therapy options and their respective mechanisms for adult-onset NIPHS.[1] In some patients, total/subtotal pancreatectomy is still an option to control symptoms. Current resection limits are still a matter of debate, some limit it to 50-60%, and some suggest 80-95%. Surgical intervention is associated with increased postoperative morbidity, and type 3C diabetes mellitus (exocrine pancreatic insufficiency) can occur.[1]

Because current management options are unsatisfactory, a less innovative strategy is needed invasive. Boss et al conducted experimental studies on the GLP-1 receptor. Exendin-4 paired with a photosensitizer will carry out internal irradiation to selectively kill the GLP1 receptor. Therefore, this therapy may be promising in reducing pancreatic β-cell mass without surgery.

Table 6. Treatment Modalities for Nesidioblastosis/NIPHS[1]

Therapeutic Principle	Mechanism of Action [1]	Therapeutic Effect Based on the Current Literature [1]
Low carbohydrate diet/diet with low glycemic index	Limits insulin secretion postprandially due to low slope of glucose increase after food intake	Low but non-invasive
α-glucosidase inhibitors (Acarbose, Voglibose)	Slows down glucose resorption through inhibition of carbohydrate-digesting enzymes in the intestines	Low but non-invasive; few adverse effects
Diazoxide	Activates ATP-dependent potassium channels in β-cells → stabilizes resting membrane potential → inhibits insulin secretion	Sometimes effective; may have severe adverse effects (fluid retention, angina pectoris)
Calcium-channel antagonists (Verapamil, Amlodipine, Nifedipine)	Inhibit voltage-dependent calcium channels → inhibit depolarization of β-cells → inhibit insulin secretion	Sometimes effective; may have severe adverse effects (hypotension)
Somatostatin analogs (octreotide, lanreotide, pasireotide)	Stimulate somatostatin receptors (G-protein coupled receptors) on β-cells → inhibit insulin secretion	Sometimes effective; may lead to increased frequency/intensity of hypoglycemia (due to inhibition of glucagon; depends on receptor specificity)
Glucocorticoids	Induce gluconeogenesis and glycogenolysis in the liver; augment effects of glucagon; induce peripheral insulin resistance	Sometimes effective; long-term treatment associated with severe adverse effects
β-blockers (e.g., propranolol)	Mechanism not entirely clear (β1-adrenoceptor-mediated inhibition of insulin secretion?)	Rarely effective; β-blockers also tend to precipitate hypoglycemia (especially through inhibition of β2-adrenoceptor-dependent glycogenolysis)
Antipsychotics/Antiepileptics (e.g., phenytoin)	Probably through insulin insensitivity	Rarely effective; may have severe adverse effects
Everolimus	Inhibition of mammalian target of rapamycin (mTOR) signaling, which is involved in the regulation of insulin secretion	Rarely effective (more likely to be effective in the pediatric population [409])
(Sub)total pancreatectomy	Surgical removal of the islets of Langerhans	Effective, if enough endocrine tissue is removed; considerable morbidity and mortality
Receptor-targeted photodynamic therapy	Selective destruction of GLP-1 receptor-expressing cells	Experimental treatment (animal model)
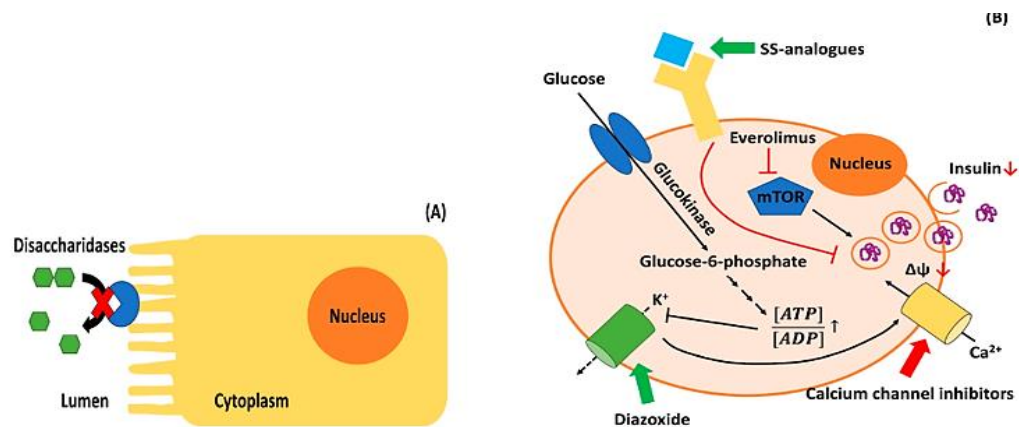
Figure 11. Mechanism of action of anti-hypoglycemia drugs[1]

This patient was given amlodipine therapy 1x 2.5 mg at night with consideration effectiveness and low side effects.[27,31]

CONCLUSION

A rare case of adult-onset NIPHS in a 28-year-old woman with recurrent clinical hypoglycemia has been reported. The diagnosis of adult-onset NIPHS in this patient was made through a diagnosis of exclusion, namely by eliminating all differential diagnoses because several examination modalities were not yet capable. The gold standard for diagnosis of adult-onset NIPHS is a histopathological examination of pancreatic tissue. The patient is currently still well controlled with conservative management and will continue to be monitored to see if alternative therapy or more progressive measures are needed.

REFERENCES

1. Dieterle MP, Husari A, Prozmann SN, Wiethoff H, Stenzinger A, Röhrich M, Pfeiffer U, Kießling WR, Engel H, Sourij H, Steinberg T, Tomakidi P, Kopf S, Szendroedi J. Diffuse, Adult-Onset Nesidioblastosis/Non- Insulinoma Pancreatogenous Hypoglycemia Syndrome (NIPHS): Review of the Literature of a Rare Cause of Hyperinsulinemic Hypoglycemia. Biomedicines. 2023;11(6):1732.

2. Lopes AA, Miranda AC, Maior MS, de Mello RV, Bandeira FA. Nesidioblastosis Associated with Pancreatic Heterotopia as a Differential Diagnosis of Hypoglycemia: A Literature Review and Case Report. Am J Case Rep. 2020;21:e922778.

3. Kowalewski AM, Szylberg Ł, Kasperska A, Marszałek A. The diagnosis and management of congenital and adult-onset hyperinsulinism (nesidioblastosis) - literature review. Pol J Pathol. 2017;68(2):97-101.5.

4. Elghobashy M, Gama R, Sulaiman RA. Investigation and Causes of Spontaneous (Non-Diabetic) Hypoglycaemia in Adults: Pitfalls to Avoid. Diagnostics (Basel). 2023;13(20):3275. 6.

5. Sulaiman RA. Postprandial hypoglycaemia in adults: Pathogenesis, diagnosis and management. Vol. 6, Journal of Laboratory and Precision Medicine. AME Publishing Company; 2021.

6. Mak IYF, Grossman AB. Insulinoma and HYpoglycemia. In : Wass JAH, Arlt W, Semple RK. Oxford Rext Book of Endocri-nology and Diabetes. 1007-15.

7. Melmed S, Auchus RJ, Goldfine AB, Koenig R, Rosen CJ, Preceded by:

Williams R Hardin. Williams textbook of endocrinology. 1525-51.

8. Yurekli BS, Kutbay NO, Altun I, Cetinkalp S, Nart D, Coker A, dkk. Adult nesidioblastosis with hypoglycemia mimicking an insulinoma: A challenging case. Int Surg. 2017;102(7-8):324-7.

9. Hatoko T, Murakami T, Sone M, Yabe D, Masui T, Nakamoto Y, Furuta A, Uza N, Kodama Y, Harada N, Ogura M, Yasoda A, Inagaki N. Low-dose Selective Arterial Calcium Stimulation Test for Localizing Insulinoma: A Single-center Experience of Five Consecutive Cases. Intern Med. 2020 ;59(19):2397-2403.

10. Lin M, Chen Y, Ning J. Insulin Autoimmune Syndrome: A Systematic Review. Int J Endocrinol. 2023;2023:1-12.

11. 12. Cappellani D, Macchia E, Falorni A, Marchetti P. Insulin autoimmune syndrome (Hirata disease): A comprehensive review fifty years after its first description. Vol. 13, Diabetes, Metabolic Syndrome and Obesity. Dove Med Press Ltd; 2020. hlm. 963-78.

12. Giannis D, Moris D, Karachaliou GS, Tsilimigras DI, Karaolanis G, Papalampros A, Felekouras E. Insulinomas: from diagnosis to treatment. A review of the literature. J BUON. 2020;25(3):1302-1314.

13. Yamada Y, Kitayama K, Oyachi M, Higuchi S, Kawakita R, Kanamori Y, dkk. Nationwide survey of endogenous hyperinsulinemic hypoglycemia in Japan (2017-2018): Congenital hyperinsulinism, insulinoma, non-insulinoma pancreatogenous hypoglycemia syndrome and insulin autoimmune syndrome (Hirata's disease). J Diab Investig. 2020;11(3):554-63.

14. Hercus JC, Pasha P, Al Lawati S, Kim P, Mattman A, Webber D, dkk. Functional Localization of Adult-Onset Idiopathic Nesidioblastosis. Case Rep Endocrinol. 2022;2022.

15. R. M, N. MC, S. P. Islets of hypoglycaemia: a rare case of adult-onset nesidioblastosis. Intern J of Advan in Med. 23. 2019;7(1):185.

16. Zhu G, Xie L, Hu X. Diagnosis of pancreatic focal nesidioblastosis assisted by dual-nuclide tracer positron emission tomography/computed tomography: A case report. 2023;27(1):42.

17. Demartin S, Goffette P, Christ E, Freitag MT, Maiter D, Furnica RM. Adult-onset nesidioblastosis: a challenging diagnosis revealed by glucagon-like-peptide-1 receptor imaging. Endocrinol Diabetes Metab Case Rep. 2022;2022(1).

18. Thompson SM, Vella A, Service FJ, Andrews JC. Selective arterial calcium stimulation with hepatic venous sampling in immune-mediated hypoglycemia. J Endocr Soc. 2017;1(6):671-5.

19. Sempoux C, Klöppel G. Pathological features in non-neoplastic congenital and adult hyperinsulinism: from nesidioblastosis to current terminology and understanding. Vol. 30, Endocrine-Related Cancer. BioScientifica Ltd.; 2023.

20. Thapa S, Kaur K, Yadav GK, Kumari D, Phulware RH. Non-insulinoma pancreatogenous hypoglycemia syndrome (NIPHS)/Nesidioblastosis as the underlying cause of recurrent hypoglycemia in a diabetic adult. Autops Case Rep. 2023;13.

21. Doi S, Yamada T, Kito Y, Obara S, Fujii Y, Nishimura T, dkk. Adult-Onset Focal Nesidioblastosis with Nodular Formation Mimicking Insulinoma. J Endocr Soc. 2022;6(1).

22. Nessa A, Rahman SA, Hussain K. Hyperinsulinemic Hypoglycemia - The Molecular Mechanisms. Front Endocrinol (Lausanne). 2016;7:29.

23. Gilis-Januszewska A, Piątkowski J, Skalniak A, Piwońska-Solska B, Nazim J, Pach D, dkk. Nieinsulinowa hipoglikemia trzustkowa u dorosłych - Przegląd genetyki. Endokrynol Pol. 2015;66(4):344-54.

24. Gomes V, Ferreira F. Successful medical treatment of hyperinsulinemic hypoglycemia in the adult: A case report and brief literature review. J Endocrinol Metab. 2019;9(6):199–202.

25. Haris B, Saraswathi S, Hussain K. Somatostatin analogues for the treatment of hyperinsulinaemic hypoglycaemia. Ther Adv Endocrinol Metab. 2020 Dec 2;11:2042018820965068.

26. Nam YH, Brensinger CM, Bilker WB, Flory JH, Leonard CE, Hennessy S. Association Between Serious Hypoglycemia and Calcium-Channel Blockers Used Concomitantly With Insulin Secretagogues. JAMA Netw Open. 2021;4(9):e2124443.

27. Davi MV, Pia A, Guarnotta V, Pizza G, Colao A, Faggiano A; NIKE Group. The treatment of hyperinsulinemic hypoglycaemia in adults: an update. J Endocrinol Invest. 2017;40(1):9–20.

28. DeGeeter M, Taylor SR, Cress J. Amlodipine-induced hyperglyc. Prac Diab. 2018;35(5):181–3.

29. Kato R, Nishimura A, Matsumura K, Kikuno S, Nagasawa K, Mori Y. Successful treatment of adult-onset nesidioblastosis by continuous subcutaneous octreotide infusion in a patient on hemodialysis. Clin Case Rep. 2021;9(1):278–81.

30. Rumi A, Fitriana A. The Evaluation of Fasting Plasma Glucose (FPG) Levels in Hypertensive Patients Using Calcium Channel Blocker (CCB) Drugs Class in Undata Regional Hospital. Galenika J of Pharm. 2021;7(2):166–80.