Hypoglycemia

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Agenda

- *Definition*
- *Pathophysiology*
- *Prevalence*
- *Treatment*
- *Prevention*

خانمي 67 ساله بعلت اختلال هوشياري به اورژانس بيمارستان آورده شده ،همراه بيمارسابقه حملات مشابه را در يكسال قبل ذكر می كند كه در بعد از ظهر ها بوده وبا مصرف غذا بهتر مي شده .سابقه بيماري ديابت از 35 سال قبل كه تحت درمان با انسولين NPH 60 واحد صبح و 30 واحد عصر ,سابقهفشار خون بالاو مصرف ايندرال mg 60 روزانه داشته از 5 روز قبل به دليل قندهای بالا متفورمين به رژيم دارويی بيمار اضافه شده است .از 2 روز قبل بيمار تب و لرز و استفراغ و اسهال داشته است .بدنبال تزريق گلوكز هيپرتونيك هوشياري بهبود مييابد.قند هنگام مراجعه 30 گزارش شده است .

چه اقدام تشخيصي را پيشنهاد مي كنيد؟

Definition

- *All episodes of an abnormally low plasma glucose concentration that expose the individual to potential harm*

- *A single threshold value for plasma glucose concentration that defines hypoglycemia in diabetes cannot be assigned because there are varying threshold for symptoms*

Introduction

Hypoglycemia is the most common endocrine medical emergency.

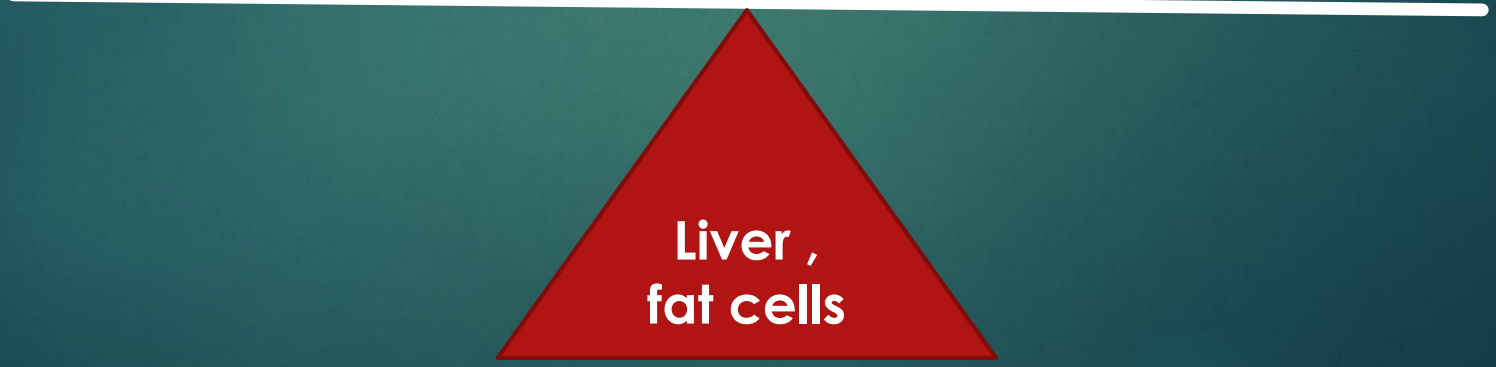
Hypoglycemia is a clinical syndrome due to *underproduction* and or over utilization of glucose .

Normal Glucose Metabolism

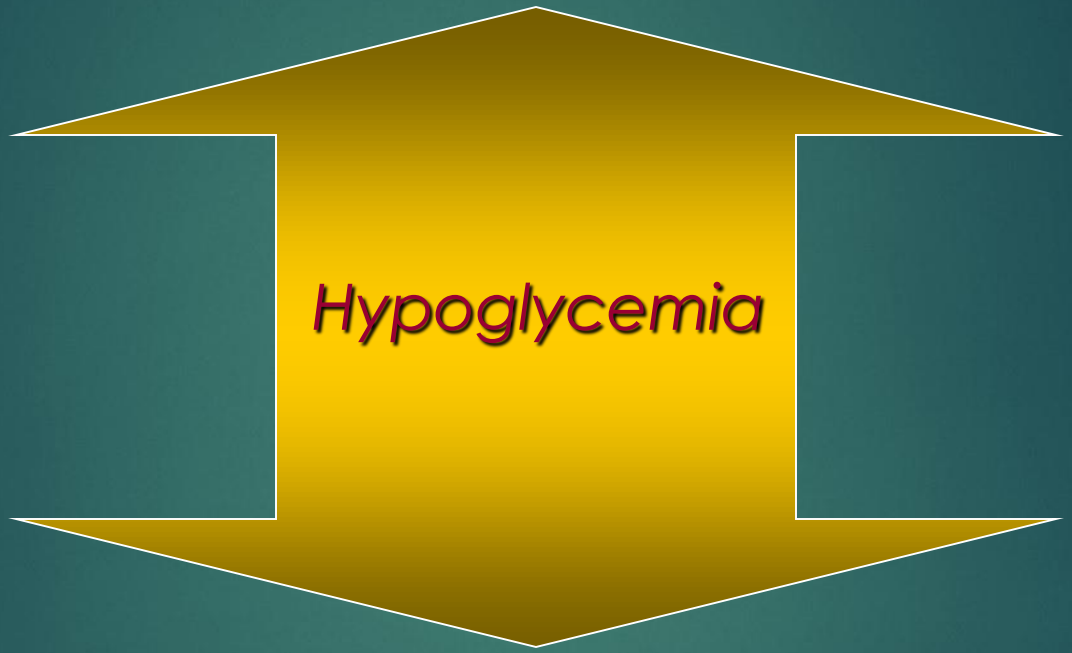
Metabolic state
50-140mg/dl

- insulin

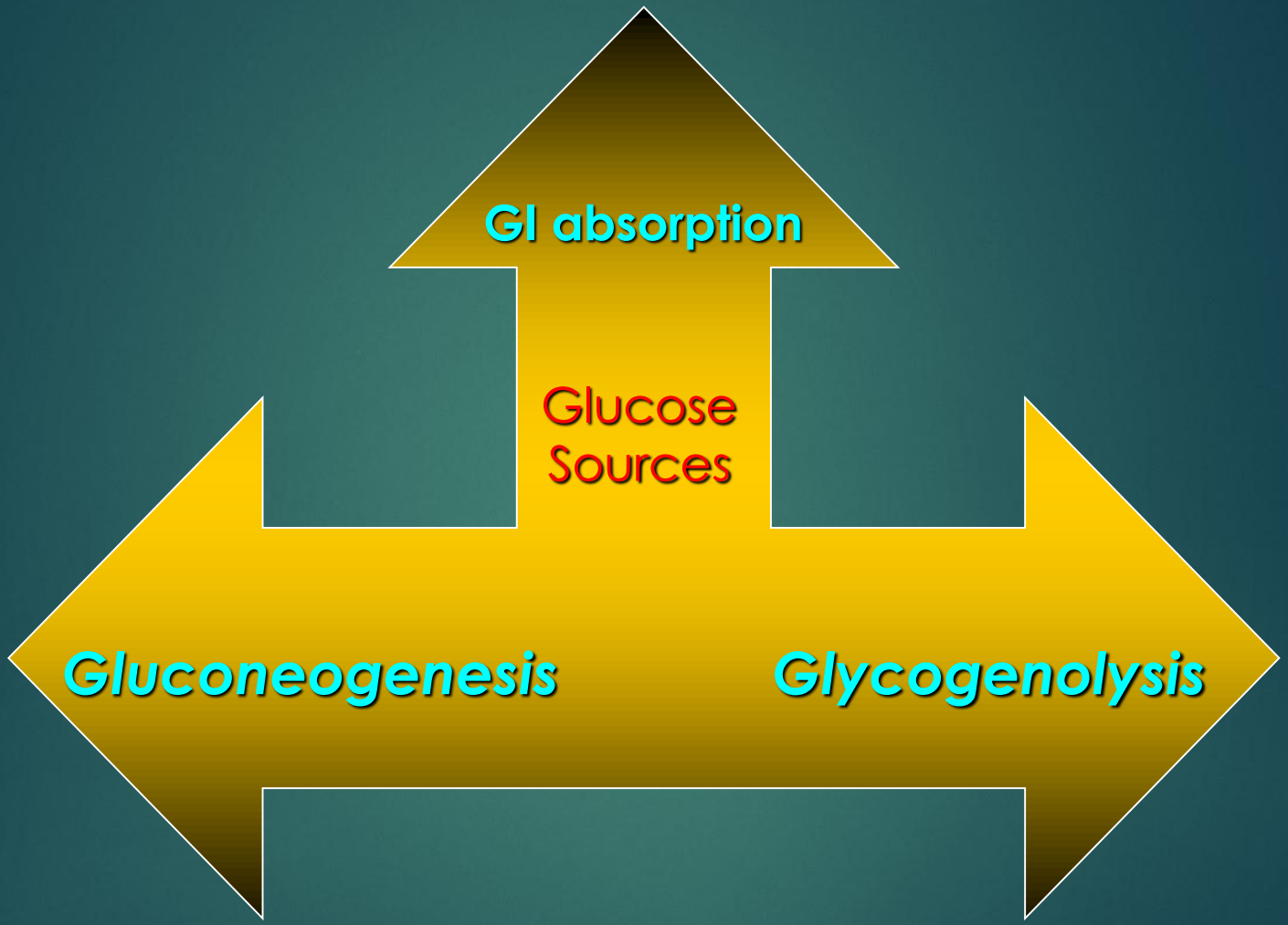
- Glucagon
- Cathecholamines
- GH
- Cortisol



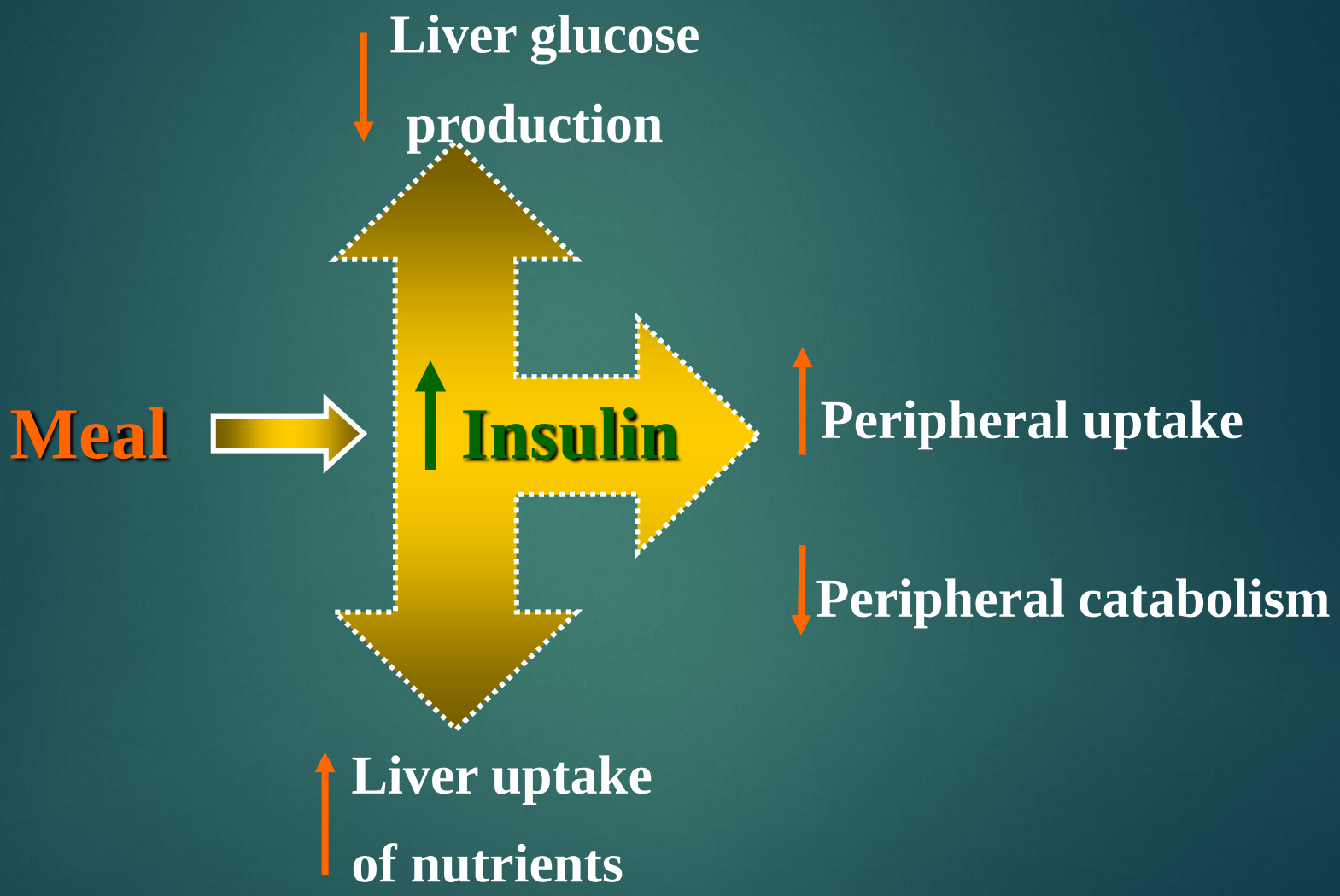
Glucose is unique fuel for brain neurons



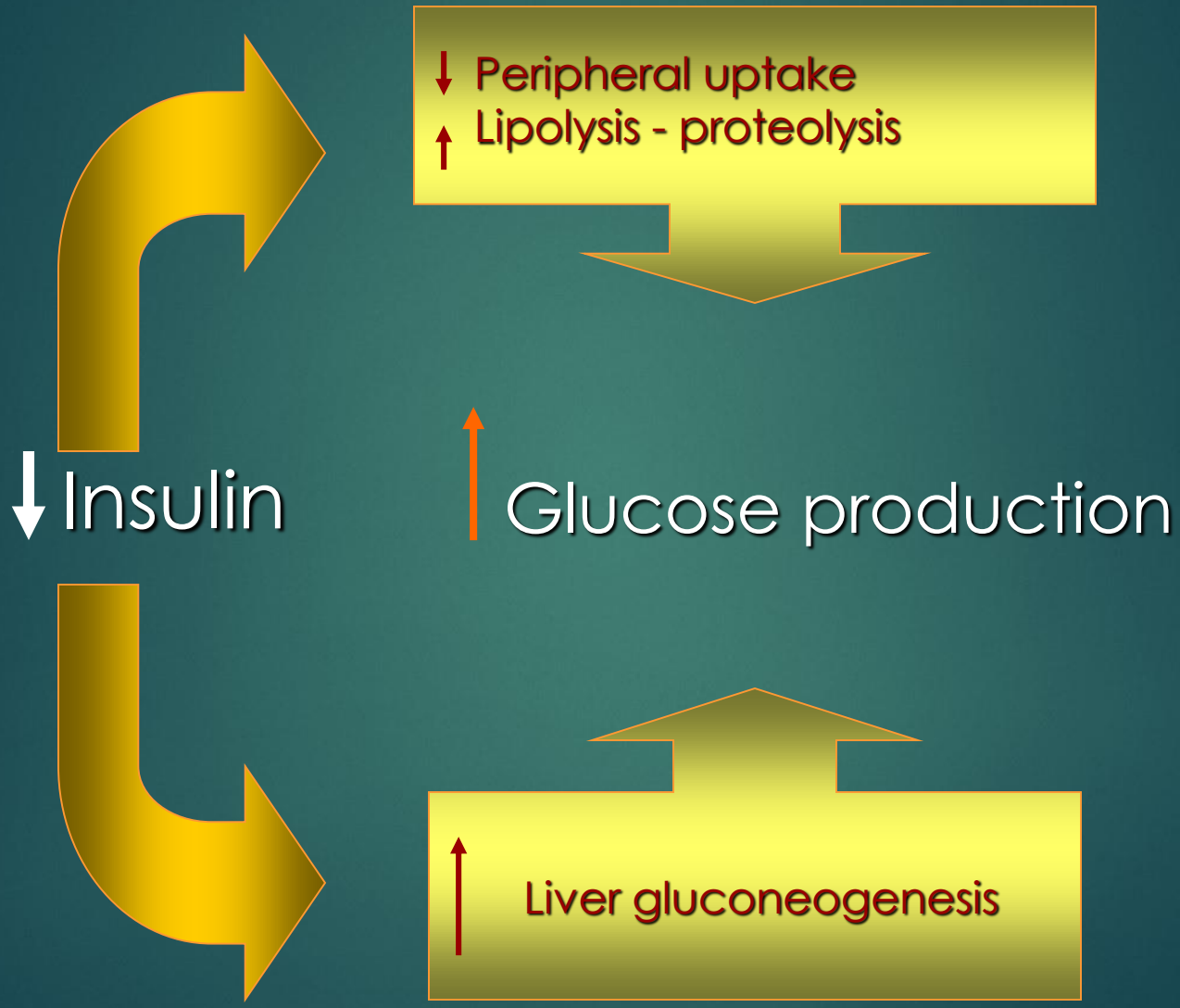
Irreversible brain damage


GI absorption
Glucose
Sources
Gluconeogenesis
Glycogenolysis

Fed state


Liver glucose production
Meal
Insulin
Peripheral uptake
Peripheral catabolism
Liver uptake of nutrients

Fasting state



Defense against hypoglycemia in normal situation

BG

< 80	Insulin
< 65	Glucagon
	Epinephrine
	G.H - Cortisol

Neuradrenergic

< 48	Glu.auto regulation
< 40	Lethargy
< 30	Coma, Convulsion
< 20	Permanent damage
< 10	Death

Neuroglycopenic

RESPONSE TO HYPOGLYCEMIA IN NORMAL SUBJECT

Normal subject :

- ***Ability to suppress insulin release***
- ***Increase counter-regulatory hormones***

Response to hypoglycemia in Diabetic patient

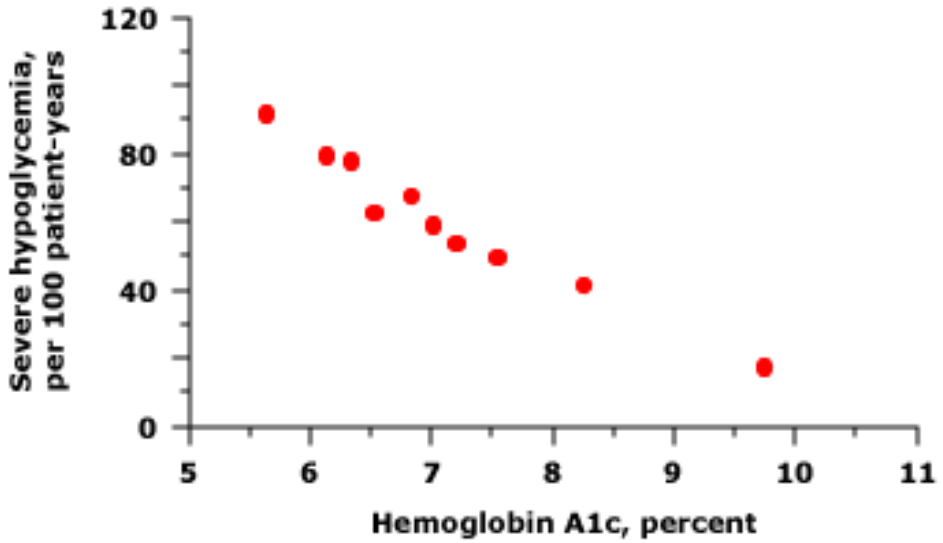
- ***Protective response to hypoglycemia impaired in many diabetic patient:***
- ***Insulin release cannot turn off***
- ***Effectiveness of counter-regulatory reduce***

Impairment of Conterregulatory Responses in Diabetic Patient

- *Glucagon response to hypoglycemia markedly impaired first few years → Normal at onset of Diabetes*

- *Patient with glucagon secretion defect dependent to epinephrine protection which may impaired due to autonomous neuropathy.*

Increased risk of hypoglycemia with strict glycemic control



In the Diabetes Control and Complications Trial, there was a progressive increase in the incidence of severe hypoglycemic episodes (per 100 patient-years) at lower attained hemoglobin A1c values during intensive insulin therapy in patients with type 1 diabetes.

Data from The Diabetes Control and Complications Trial Research Group, N Engl J Med 1993; 329:977.

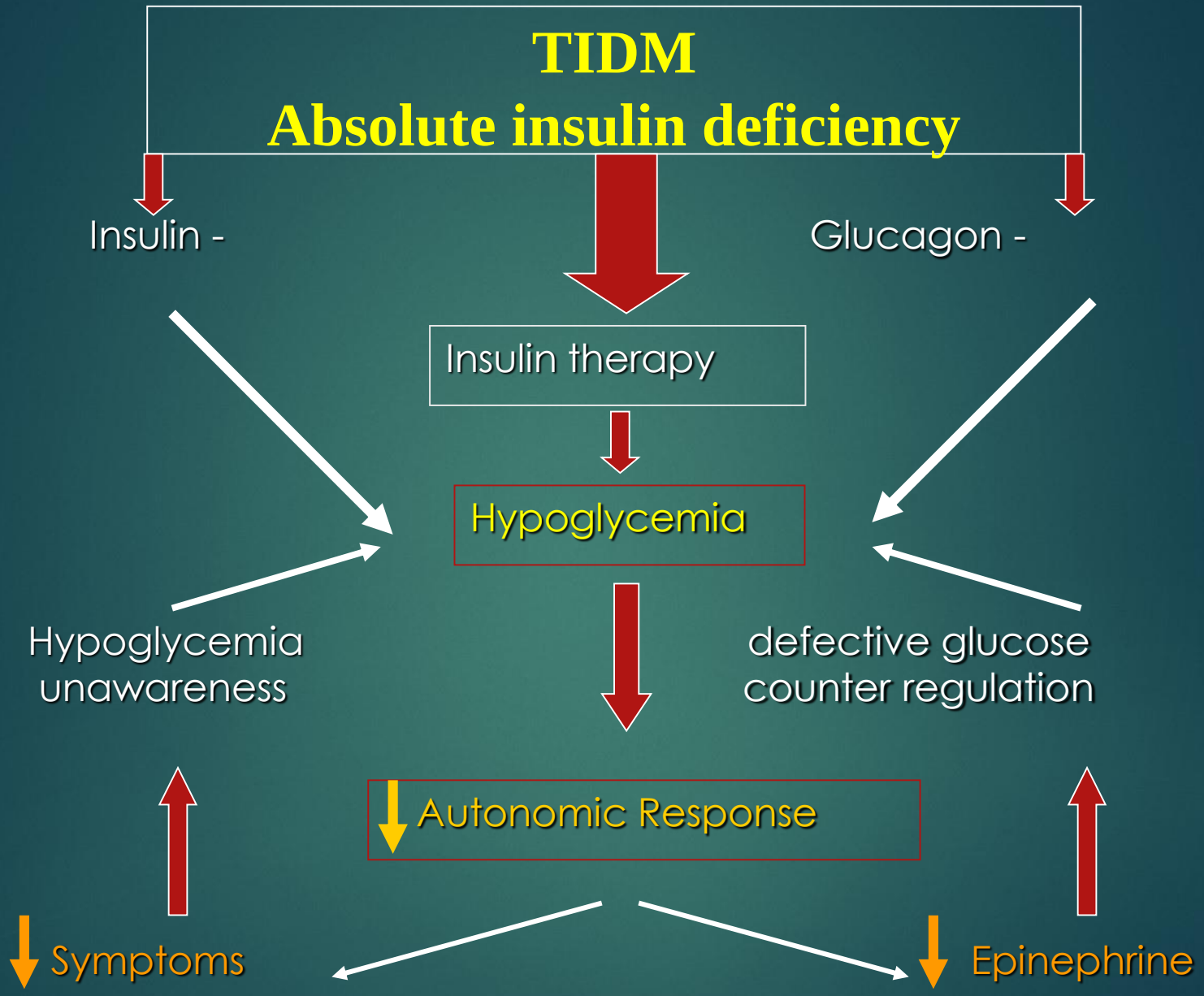
Table 2. Rates of Hypoglycemia in the ACCORD, VADT, and ADVANCE Clinical Trials

	Standard Glucose Control Arm, %	Intensive Glucose Control Arm, %	*P* Value
ACCORD	5.1	16.2	<0.001
ADVANCE	1.5	2.7	<0.001
VADT	9.9	21.2	<0.001

Hypoglycemia-Associated Autonomic Failure (HAAF)

- ***Reduced counterregulatory hormone responses***, which result in ***impaired glucose generation***

- ***Hypoglycemia unawareness, which precludes appropriate behavioral responses, such as eating***


TIDM
Absolute insulin deficiency
Insulin -
Glucagon -
Insulin therapy
Hypoglycemia
Hypoglycemia unawareness
defective glucose counter regulation
Autonomic Response
Symptoms
Epinephrine

Pathophysiology of glucose counter-regulation

Plasma glucose	Individuals	Plasma		
		Insulin	Glucagon	Epinephrine
↓	Non-diabetic	↓	↑	↑
↓	T1DM*	No ↓	No ↑	Attenuated ↑
↓	Early T2DM	↓	↑	↑
↓	Late T2DM*	No ↓	No ↑	Attenuated ↑

Hypoglycemia unawareness

is reversible and require more than 2 weeks avoidance of hypoglycemia.

Etiology

Etiology in adults

1. Fasting (more than 5 hours P.P)

2. Postprandial (Less than 5 hours P.P)

Fasting hypoglycemia

a. Underproduction:

- **Alcoholism**
- **Organ failure**
  - *Diffuse hepatic failure*
  - *Uremia*
- **Endocrine deficiency**
  - *G.H*
  - *Glucocorticoid*
  - *Catecholamines*
  - *Glucagon*
  - *Hypothyroidism*
- **Drugs**
- **Inanition**

b. Over utilization:

- **Prolong exercise**
- **Sever sepsis**
- **Mesenchymal tumors**
  - *Hepatoma - Sarcoma*
  - *Lymphoma - Carcinoma…*
- **Hyperinsulinism**
  - *Drugs*
  - *Autoimmune insulin syn.*
  - *Insulinoma*
  - *Insulin receptor Ab.*

Postprandial (Less than 5 hours P.P)

G.I surgery (alimentary)

Inborn error of metabolism

- ***Galactosemia***
- ***Fructose intolerance***
- ***Glycogen storage dis.***
- ***Fructose 1,6 diphosphatase def.***

Autoimmun insulin syn.

Functional (idiopathic)

Insulinoma (rarely)

Prediabetes

Drugs are the most common cause of hypoglycemia

- *Insulin*
- *S.U*
- *Alcohol*

- *Sulfonamides*
- *Salicylates*
- *Quinine*
- *Pentamidine*
- *Beta blockers*

HYPOGLYCEMIA IN DIABETES

HYPOGLYCEMIA IN DIABETES

Never occurs : ***in patients on diet and exercise .***

Rare occurs : α-glucosidase inhibitors, biguanides and thiazolidinediones.

Exceptions*: *Elderly

Chronically ill patients

Prolonged fasting.

More frequent occurs:

on s.urea and especially insulin

Hypoglycemia In Diaberes

1)Insulin (or oral agent) doses are: excessive, ill timed, or of the wrong type

2) Influx of exogenous glucose is reduced (during an overnight fast or following missed meals or snacks)

3) Insulin-independent glucose utilization is increased (during exercise)

4) Insulin sensitivity is increased (with effective intensive therapy, in the middle of the night, late after exercise, or with increased fitness or weight loss)

5) Endogenous glucose production is reduced (following alcohol ingestion)

6) Insulin clearance is reduced (in renal failure).

Clinical Manifestation

Clinical manifestation

1. Neuroadrenergic: (B.S < 55 - 60)

- *Sweating*
- *Hunger*
- *Tremor*
- *Tingling*
- *Palpitation*
- *Anxiety*
- *Hypertension*

2. Neuroglycopenia: (B.S < 45 - 50)

- ***Nonspecific:***

  Headach - restlessness - aggressiveness - bizarre behavior - weakness

- ***Focal sign:***

  Monoplegia - babinski - paresthesia - diplopia - trismus - vision loss

- ***Global sign:***

  Stupor - convulsion - flaccidity - hypothermia - decerebrate rigidity - coma

Symptoms thresholds

The level of glucose that produces symptoms of hypoglycemia ***varies from person to person****.*

Diagnosis

Classification

Table 6.3–Classification of hypoglycemia (61)

Level	Glycemic criteria	Description
Glucose alert value (level 1)	≤70 mg/dL (3.9 mmol/L)	Sufficiently low for treatment with fast-acting carbohydrate and dose adjustment of glucose-lowering therapy
Clinically significant hypoglycemia (level 2)	<54 mg/dL (3.0 mmol/L)	Sufficiently low to indicate serious, clinically important hypoglycemia
Severe hypoglycemia (level 3)	No specific glucose threshold	Hypoglycemia associated with severe cognitive impairment requiring external assistance for recovery

Harm of Clinically significant hypoglycemia

- *Falling*
- *Motor vehicle accidents and other injueries*
- *Increased risk of dementia (older adults)*

Diagnosis

1. Pseudohypoglycemia:

a. Lab.error

b.Over utilization:

Leukemoid reaction - Leukemia

Hemolytic crisis - Polycytemia Vera

c. Incorrect method for analysis:

Lipemic serum

Definition

Hypoglycemia is threshold dependent

B.S less than 45 - 50 mg/dl with symptoms

recovery with treatment.

(Whipple triad)

Differential Diagnosis

- **T.I.A**
- **Epilepsy**
- **Orthostatic hypotension**
- **Arrhythmia**

Treatment

Treatment

- Urgent Treatment necessary.
- When possible → sample for documentation of plasma glucose should be obtained prior to treatment
- glucose administration → need not delay until the result for initial sample report.

Treatment(emergency)

- *For treatment of BG <70 mg/dl in a patient who is alert and able to eat and drink, administer 15–20 g of rapid-acting carbohydrate such as:a one–15–30 g tube glucose gel or (4 g) glucose tabs(preferred for patients with end stage renal disease).*
- *4–6 ounces orange or apple juice.*
- *6 ounces regular sugar sweetened soda.*

Treatment(emergency)

- *For treatment of BG <70 mg/dl in an alert and awake patient who is NPO or unable to swallow, administer 20 ml dextrose 50% solution iv and start iv dextrose 5% in water at 100 ml/h.*

Treatment (emergency)

- *For treatment of BG <70mg/dl in a patient with an altered level of consciousness, administer 25 ml dextrose 50% (1/2 amp) and start iv dextrose 5% in water at 100 ml/h.*

- *In a patient with an altered level of consciousness and no available iv access, give glucagon 1 mg im. Limit, two times.*
- *Recheck BG and repeat treatment every 15 min until glucose level is at least 80 mg/dl*

Treatment (emergency)

- *Hypoglycemic patient cause by:*
  - *Regular insulin excess-nutritional deficit or*
  - *Alcohol*

  can be stabilized and discharged.

- *hypoglycemia caused by :*
  - *intermediate or long acting insulin,*
  - *First generation or second generation sulfonylurea*

  at risk for prolong hypoglycemia

ADA Recommendation

- *Individuals at risk for hypoglycemia should be asked about symptomatic and asymptomatic hypoglycemia at each encounter*

ADA 2025:

6.8a Deintensify hypoglycemia-causing medications (insulin, sulfonylureas, or meglitinides), or switch to a medication class with lower hypoglycemia risk, for individuals who are at high risk for hypoglycemia, within individualized glycemic goals. **B**

6.8b Deintensify diabetes medications for individuals for whom the harms and/or burdens of treatment may be greater than the benefits, within individualized glycemic goals. **B**

ADA 2025:

HYPOGLYCEMIA ASSESSMENT, PREVENTION, AND TREATMENT

Recommendations

6.11a History of hypoglycemia should be reviewed at every clinical encounter for all individuals at risk for hypoglycemia and evaluated as indicated. **C**

6.11b Clinicians should screen all individuals at risk for hypoglycemia for impaired hypoglycemia awareness. **E**

6.11c Clinicians should consider an individual's risk for hypoglycemia (see **Table 6.5**) when selecting diabetes medications and glycemic goals. **E**

6.11d Use of CGM is beneficial and recommended for individuals at high risk for hypoglycemia. **A**

ADA 2025:

Table 6.5—Assessment of hypoglycemia risk among individuals treated with insulin, sulfonylureas, or meglitinides

Clinical/biological risk factors	Social, cultural, and economic risk factors
Major risk factors • Recent (within the past 3–6 months) level 2 or 3 hypoglycemia • Intensive insulin therapy* • Impaired hypoglycemia awareness • End-stage kidney disease • Cognitive impairment or dementia	Major risk factors • Food insecurity • Low-income status§ • Homelessness • Fasting for religious or cultural reasons
Other risk factors • Multiple recent episodes of level 1 hypoglycemia • Basal insulin therapy* • Age ≥75 years† • Female sex • High glycemic variability‡ • Polypharmacy • Cardiovascular disease • Chronic kidney disease (eGFR <60 mL/min/1.73 m^2 or albuminuria) • Neuropathy • Retinopathy • Major depressive disorder	Other risk factors • Low health literacy • Alcohol or substance use disorder

ADA Recommendation

- *Glucose (15–20 g) is the preferred treatment for the conscious individual with hypoglycemia (glucose alert value of <70 mg/dL), although any form of carbohydrate that contains glucose may be used.*
- *Fifteen minutes after treatment, if SMBG shows continued hypoglycemia, the treatment should be repeated.*

ADA Recommendation

- *Once SMBG returns to normal, the individual should consume a meal or snack to prevent recurrence of hypoglycemia*

ADA 2025

6.13 Glucagon should be prescribed for all individuals taking insulin or at high risk for hypoglycemia. Family, caregivers, school personnel, and others providing support to these individuals should know its location and be educated on how to administer it.

Glucagon preparations that do not have to be reconstituted are preferred. **E**

ADA 2025

Table 6.7—Components of hypoglycemia prevention for individuals at risk for hypoglycemia at initial, follow-up, and annual visits

Hypoglycemia prevention action	Initial visit	Every follow-up visit	Annual visit
Hypoglycemia history assessment	✓	✓	✓
Hypoglycemia awareness assessment	✓		✓
Cognitive function and other hypoglycemia risk factor assessment	✓		✓
Structured patient education for hypoglycemia prevention and treatment	✓	✓*	✓*
Consideration of continuous glucose monitoring needs	✓	✓	✓
Reevaluation of diabetes treatment plan with deintensification, simplification, or agent modification as appropriate	✓	✓†	✓†
Glucagon prescription and training for close contacts for insulin-treated individuals or those at high hypoglycemic risk	✓		✓
Training to reestablish awareness of hypoglycemia	✓‡		✓‡

The listed frequencies are the recommended minimum; actions for hypoglycemia prevention should be done more often as needed based on clinical judgment. *Indicated with recurrent hypoglycemic events or at initiation of medication with a high risk for hypoglycemia. †Indicated with any level 2 or 3 hypoglycemia, intercurrent illness, or initiating interacting medications. ‡Indicated when impaired hypoglycemia awareness is detected.

ADA Recommendation

- *Insulin-treated patients with hypoglycemia unawareness or an episode of clinically significant hypoglycemia should be **advised to raise their glycemic targets to strictly avoid hypoglycemia for at least several weeks** in order to partially reverse hypoglycemia unawareness and reduce risk of future episodes. A*

Prevention

- *Patient education*
- *Close observation and control*
- *SMBG*
- *Sick day monitoring*


Thanks for your attention

Diagnosis

1. Overnight F.B.S

2. 72 hours fasting test:

- **Admit and discontinue all nonessential medication.**
- **Patient may consume calorie and caffeine free liquids and should ambulate.**
- **Baseline glucose - Insulin - G.H - (Glucagon - Cortisol).**
- **Check B.S every 6 hours (B.S >60) then every 1 hour.**
- **The fast is ended at 72 hrs. or earlier if the patient has a B.S <45 with neuroglicopenic symptoms and check B.S - Insulin - G.H - Proinsulin - C.Peptid - Glucagon - Cortisol - S.U.**

2. Reactive or alimentary:

- **Omit simple sugar and alcohol.**
- **Frequent small high protein - low C.H.O. meal**
- **Fiber**
- **Drug:**
- **Anticholinergic drugs: *Atropin***
  Propantheline
- **A- glucosidase inh. :**
  Acarbose - Miglitol

Etiologic management

1. Fasting:

Tumors : ***Surgery***

Autoimmune: ***Glucocorticoid - Plasmapheresis***

Insulinoma:

Surgery

Drug

: Diazoxide

Dilantin

Calcium blockers

Octerotide

Chemotherapy

B.S < 45 mg/dl
with symptoms

Insulin<6 uU/m :

Autoimmune

Tumors

Endocrine def.

Organ failure..

Insulin >6uU/ml

Hyperinsulinism

C.peptide

< 200 pmol/L

Autoimmune

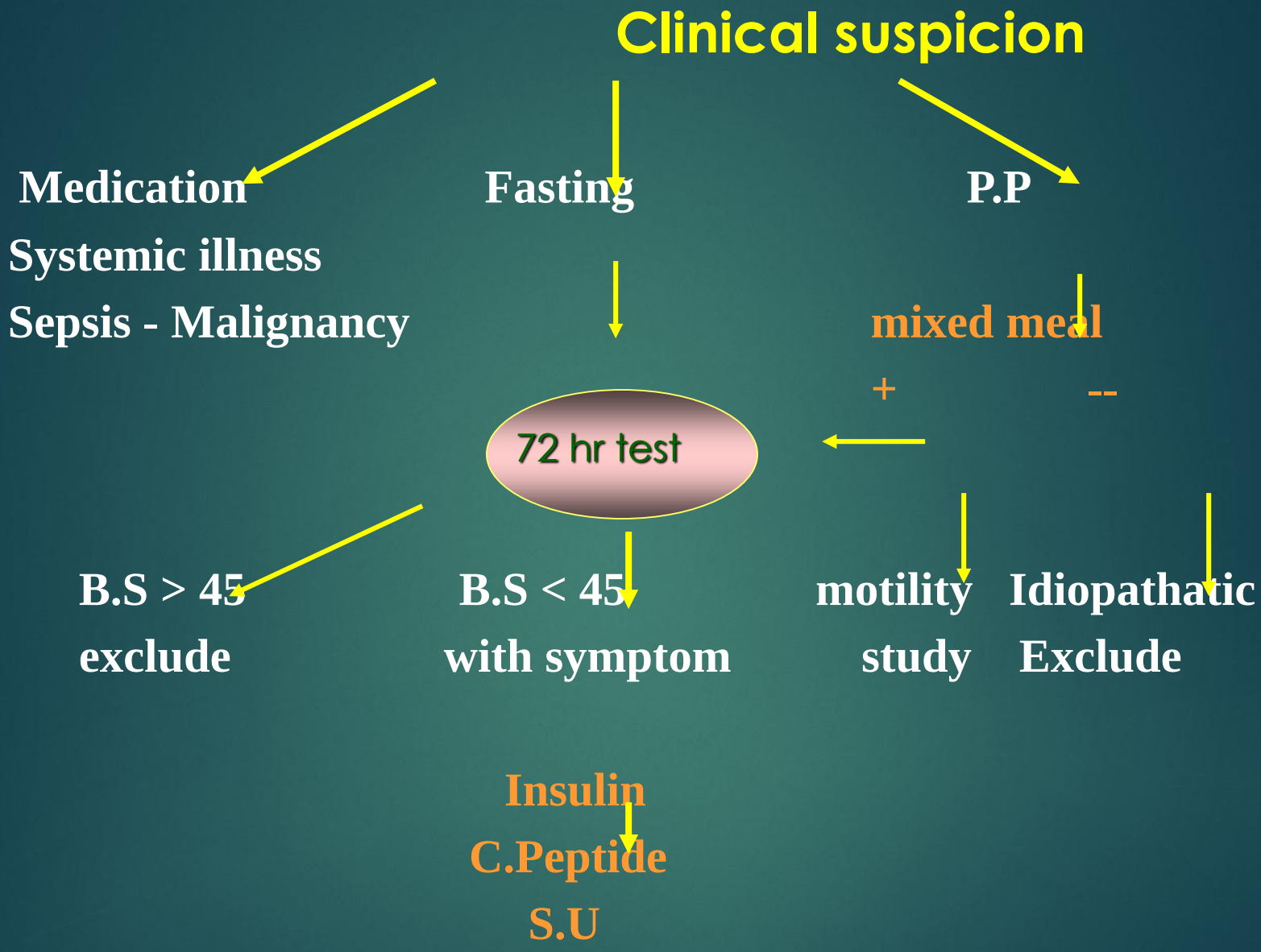
Insulin inj.

> 200pmol/L

\+ S.U –

Iatrogenic

Insulinoma


Clinical suspicion
Medication
Systemic illness
Sepsis - Malignancy
Fasting
P.P
mixed meal
+
--
72 hr test
B.S > 45
exclude
B.S < 45
with symptom
motility
study
Idiopathatic
Exclude
Insulin
C.Peptide
S.U

2. Clinical data:

- Fasting or p.p
- With or without activity
- First attack or recurrent
- D.H
- F.H of diabetes
- Signs and symptoms
- Reversible or irreversible
- Neurologic deficit
- Weight loss or weight gain
- PH.Exam

خانمی 54 ساله بعلت اختلال هوشیاری به اورژانس بیمارستان اورده شده و با تزریق گلوکوز هیپرتونیک بهبود یافته است سابقه حملات مشابه عصرگاهی که با مصرف غذا بهتر می شده رااز یکسال قبل می دهد . سابقه بیماری مصرف دارو ویا دیابت در خانواده نمی دهد ، معاینه بالینی نیز نکته خاصی ندارد. قند هنگام مراجعه 30 گذارش شده است .

چه اقدام تشخیصی را پیشنهاد می کنید؟

تست 72ساعته:

پس از 12ساعت از شروع تست بیمار علامتدار شد .

ازمایشات همزمان :

B.S = 32 mg / dl

Insulin = 21 uU / ml

C. Peptide = 860 pmol / L

Proinsulin = 19 Pmol / L

S.U = Negative

با تشخیص انسولینوما اقدامات تصویربرداري درخواست گردید.

Fasting hypoglycemia

a. Underproduction:

- **Alcoholism**
- **Organ failure**
  - ***Diffuse hepatic failure***
  - ***Uremia***
- **Endocrine deficiency**
  - ***G.H***
  - ***Glucocorticoid***
  - ***Catecholamines***
  - ***Glucagon***
- **Drugs**

b. Over utilization:

- **Prolong exercise**
- **Malnutrition**
- **Sever sepsis**
- **Mesenchymal tumors**
  - ***Hepatoma - Sarcoma***
  - ***Lymphoma - Carcinoma…***
- **Hyperinsulinism**
  - ***Drugs***
  - ***Autoimmune insulin syn.***
  - ***Insulinoma***
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2. Postprandial (Less than 5 hours P.P)

G.I surgery (alimentary)

Inborn error of metabolism

- ***Galactosemia***
- ***Fructose intolerance***
- ***Glycogen storage dis.***
- ***Fructose 1,6 diphosphatase def.***

Autoimmun insulin syn.

Functional (idiopathic)

Insulinoma (rarely)

Prediabetes

Classification

1- Ill appearance:

Mesenchymal tumors

Organ failure

Sepsis

T.P.N

Dialysis…

2 - Healthy appearance:

Drugs

Hyperinsulinism

Functional

Endocrinopathies...