Hypoglycemia: implications and its consequences

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Conflict of Interest

I have participated in clinical investigations of MSD and Sanofi; received speaker fees from MSD, Novartis, Astra Zeneca, Sanofi and Novo Nordisk and participated in Advisory Boards of Novo Nordisk and Sanofi.

I also have received research grants from Sanofi and Novo Nordisk in 2014, 2018 and 2019.

My presentations reflect my own view and are constructed based on current medical literature.
Diabetes control

Strict glycemic control prevents micro and macrovascular complications in diabetes.

Goals of glycemic control
HbA1c: < 7.0% or < 6.5%

Diabetes control

However, hypoglycemic events are 2-3 times more frequent with treatment intensification.

Treatment intensification may have different results during diabetes evolution.


Diabetes control

In the ACCORD study diabetics with higher HbA1c levels had higher rates of hypoglycemia (both study arms).

Poorly controlled diabetics had more hypoglycemic events.

Recently....

Emerging evidence suggest that other variables such as:

- Time in range
- Time in hypoglycaemia
- Glucose variability

Are complementary measures to HbA1c which need to be considered when setting glycemic goal in diabetics
Diabetes control

Guidelines have recommended a patient centered approach and individualization of treatment strategies to avoid HYPOGLYCEMIA.
Hypoglycemia

Definition

Normal and abnormal glucose control

How big is the problem?

Hypoglycemia: causes, risk factors and clinical consequences

Prevention and management of hypoglycemia
How often do you see hypoglycemia in your patients?

Have any of you ever experienced hypoglycemia?
Clinical definition

"all episodes of abnormally low plasma glucose concentration that expose the individual to potential harm"

That Includes asymptomatic hypoglycemia

Cryer, PE, Hypoglycemia in Diabetes. Pathophysiology, prevalence and prevention 3rd Edition. ADA. DOI:10.2337/9781580406400
Important consideration

"Because the glycemic threshold for symptoms, among other responses to hypoglycemia, shifts to lower plasma glucose concentrations in patients with recurrent hypoglycemia and to higher plasma glucose concentrations in those with poorly controlled diabetes, it is not possible to state a single plasma glucose concentration that defines hypoglycemia."

Cryer, PE, Hypoglycemia in Diabetes. Pathophysiology, prevalence and prevention 3rd Edition. ADA. DOI:10.2337/9781580406400
Definition

Hypoglycemia alert (Level 1)
Glycemia ≤ 70 mg/dL.

Clinically significant hypoglycemia (Level 2)
Glycemia 54 mg/dL.

Severe Hypoglycemia (Level 3)
There is no specific threshold

ADA 2018- IHSG 2017
# Systemic glucose balance

<table>
<thead>
<tr>
<th>Glucose flux into the circulation</th>
<th>Glucose flux out the circulation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intermittent exogenous glucose delivery</td>
<td>Ongoing glucose utilization (brain plus strictly glycolytic tissues)</td>
</tr>
<tr>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Regulated endogenous glucose production</td>
<td>Regulated glucose utilization</td>
</tr>
<tr>
<td>• Liver glycogenolysis and gluconeogenesis a,c, d</td>
<td>• Muscle, fat, liver, kidney b,e</td>
</tr>
<tr>
<td>• Kidneys gluconeogenesis a,d</td>
<td></td>
</tr>
</tbody>
</table>

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a Decreased by insulin; b increased by insulin; c increased by glucagon; d increased by epinephrine

Adapted from Cryer, PE, Hypoglycemia in Diabetes. Pathophysiology, prevalence and prevention 3rd Edition. ADA. DOI:10.2337/9781580406400
Symptoms and signs of progressive hypoglycemia in a non-diabetic individuals

- Glycemia (mg/dL)
- Neuronal Death
- Seizures, coma
- Behavioral changes
- Hunger, cognitive dysfunction
- Palpitations, perspiration
- Increase of glucagon, epinephrine, ACTH, cortisol and growth hormone
- Reduction of insulin secretion

Symptomatic hypoglycemia threshold varies with age

Increasing age reduces reaction time of hypoglycemic symptoms\(^1,2,*\)

*Based on data in nondiabetic patients with no family history of diabetes

Clinical manifestations of hypoglycemia

Symptoms and signs of hypoglycemia are not specific

Symptoms:

- Neuroglycopenic
- Neurogenic
### Table 1
Symptoms of hypoglycemia

<table>
<thead>
<tr>
<th>Neurogenic (autonomic)</th>
<th>Neuroglycopenic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trembling</td>
<td>Difficulty concentrating</td>
</tr>
<tr>
<td>Palpitations</td>
<td>Confusion, weakness, drowsiness, vision changes</td>
</tr>
<tr>
<td>Sweating</td>
<td>Difficulty speaking, headache, dizziness</td>
</tr>
<tr>
<td>Anxiety</td>
<td></td>
</tr>
<tr>
<td>Hunger</td>
<td></td>
</tr>
<tr>
<td>Nausea</td>
<td></td>
</tr>
<tr>
<td>Tingling</td>
<td></td>
</tr>
</tbody>
</table>
Hypoglycemia

Is it a common condition?
Estimated Rates of Emergency Hospitalizations (99,628) for Adverse Drug Events in Older > 65y U.S. Adults, 2007–2009

Data from the National Electronic Injury Surveillance System–Cooperative Adverse Drug Event Surveillance project (2007 through 2009) to estimate the frequency and rates of hospitalization after emergency department visits for adverse drug events in older.

Medications implicated in 67.0% of hospitalizations:
- warfarin (33.3%)
- insulins (13.9%)
- oral antiplatelet agents (13.3%)
- oral hypoglycemic agents (10.7%)
Figure 2: Rates of Severe Hypoglycemia Intensive vs Standard Therapy

<table>
<thead>
<tr>
<th></th>
<th>UKPDS$^1$</th>
<th>ADVANCE$^2$</th>
<th>ACCORD$^3$</th>
<th>VADT$^4$</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$P&lt;0.001$</td>
<td>HR 1.86 (1.42-2.40)</td>
<td>$P&lt;0.001$</td>
<td>$P=0.01$</td>
</tr>
<tr>
<td>Annualized rate of severe hypoglycemia$^9$%</td>
<td>0.7</td>
<td>1.4</td>
<td>1.8</td>
<td>0.4</td>
</tr>
<tr>
<td>A1C=</td>
<td>7.9%</td>
<td>7.1%</td>
<td>7.2%</td>
<td>7.3%</td>
</tr>
</tbody>
</table>

$^a$Hypoglycemia requiring any assistance;  
$^b$Intensive glycemic control was defined differently in these trials.

CON, conventional therapy; GLY, glibenclamide; HR, hazard ratio; INS, insulin; INT, intensive therapy; STD, standard therapy.

Hypoglycemia is a common cause of hospitalizations in T2DM

Among 887,182 patients with T2DM, nearly 1 in 4 (23.5%) were hospitalized during the observation period (2007–2010). Hypoglycemia was a common cause for T2DM-related hospitalizations (22.9%), particularly in older patients.
Severe hypoglycemia in an Emergency Department of a General Hospital in Costa Rica

55620 patients were attended at the ED
4434 had chronic non-communicable conditions,
961 were diabetics.
61 presented Severe Hypoglycemic Events (1.37 % of diabetic patients)

There were: 37 females aged 70 ± 16.01 yo and 24 males aged 62.9 ± 13.4 yo

In females glucose level was 42 ± 15.44 mg/dl and in males 32.6 ± 8.8 mg/dL

Figure 1: Clustering of comorbidities in diabetic patients admitted with severe hypoglycemia into the Emergency Department.
Treatment in diabetic patients with severe hypoglycemia attended at the emergency department Hospital San Juan de Dios

<table>
<thead>
<tr>
<th>Agent</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>NPH + regular insulin</td>
<td>28</td>
<td>45.9</td>
</tr>
<tr>
<td>NPH alone</td>
<td>24</td>
<td>40</td>
</tr>
<tr>
<td>Metformin + insulin</td>
<td>22</td>
<td>36</td>
</tr>
<tr>
<td>Unknown</td>
<td>3</td>
<td>4.9</td>
</tr>
<tr>
<td>Glibenclamide</td>
<td>2</td>
<td>3.3</td>
</tr>
<tr>
<td>Insuline (unknown)</td>
<td>2</td>
<td>3.2</td>
</tr>
<tr>
<td>Regular insulin</td>
<td>1</td>
<td>1.6</td>
</tr>
</tbody>
</table>


Grace K. Mahoney, MS; Henry J. Henk, PhD; and Rozalina G. McCoy, MD, MS
HAT study: Level of global hypoglycemia defined as events/patient/year.

<table>
<thead>
<tr>
<th></th>
<th>T1DM</th>
<th>T2DM</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Any hypoglycemia:</strong></td>
<td>73.3 [95% (IC) 72.6–74.0]</td>
<td>19.3 (95% CI 19.1–19.6)</td>
</tr>
<tr>
<td><strong>Nocturnal hypoglycemia:</strong></td>
<td>11.3 (95% CI 11.0–11.6)</td>
<td>3.7 (95% CI 3.6–3.8)</td>
</tr>
<tr>
<td><strong>Severe hypoglycemia:</strong></td>
<td>4.9 (95% CI 4.7–5.1)</td>
<td>2.5 (95% CI 2.4–2.5)</td>
</tr>
</tbody>
</table>

Khunti et al Diabetes Obesity Metab 2016;18: 907-915
Higher rates of hypoglycemia were observed in Latin America in T1DM and in T2DM in Russia.

HbA1c was not a significant predictor of hypoglycemia.
Why hypoglycemia is underreported?
Why hypoglycemia is underreported?

We do not ask patients about hypoglycemia

Patients do not report hypoglycemic episodes

We do not routinely perform glucose monitoring

Cryer, PE, Hypoglycemia in Diabetes. Pathophysiology, prevalence and prevention 3rd Edition. ADA. DOI:10.2337/9781580406400
Why hypoglycemia is underreported?

Patients may have amnesia after a severe hypoglycemia

Symptoms are not recognized as hypoglycemia

Clinical manifestations are attributed to other medical condition (hypotension)

Cryer, PE, Hypoglycemia in Diabetes. Pathophysiology, prevalence and prevention 3rd Edition. ADA. DOI:10.2337/9781580406400
Masked hypoglycemia: not recognized by the doctor neither by the patient

Anxiety or panic attacks

Nocturnal hypoglycemia

Impaired awareness of hypoglycemia
Recurrent Hypoglycemia: It is not recognized and can occur in apparently well controlled T2DM patients

A 24-hour CGMS glucose profile from one patient with T2DM well controlled (A1C=6.2%) on OADs showing recurrent unrecognized hypoglycemia; data were collected over 5 consecutive days.

Nocturnal hypoglycemia
Nocturnal hypoglycemia

- Nightmares
- Morning headache
- Morning humor changes
- Insomnia
- Fatigue, lethargy
- Depressive symptoms
- Abnormal sleeping pattern
- Nocturnal perspiration
- Wet pills
- Nocturnal jumps and seizures
- Enuresis (Children)

Cryer, PE, Hypoglycemia in Diabetes. Pathophysiology, prevalence and prevention 3rd Edition. ADA. DOI:10.2337/9781580406400
Nocturnal hypoglycemia

Coma
Seizures
Lesions (fractures, dislocations)
Cardiovascular events (arrhythmias)
Bed death syndrome
Impaired awareness of hypoglycemia

Cryer, PE, Hypoglycemia in Diabetes. Pathophysiology, prevalence and prevention 3rd Edition. ADA. DOI:10.2337/9781580406400
Impaired awareness of hypoglycemia
Impaired awareness of hypoglycemia

Asymptomatic hypoglycemic episodes

Affects 20-25% of adults with T1DM and < 10% of persons with T2DM.

17 times more frequent in persons treated with insulin

Impaired awareness of hypoglycemia

The sympathoadrenal response to hypoglycemia is reduced during sleep, and following exercise or alcohol consumption. Inability to respond and to recover from subsequent hypoglycemic episodes.


Impaired awareness of hypoglycemia is associated with higher rates of severe hypoglycemia

Severe hypoglycemia was defined as an episode requiring external assistance for recovery. Subjective changes in hypoglycemia symptom intensity were recorded by the participants based on a hypoglycemia awareness scale of 1 to 7, where 1 equals always aware and 7 equals never aware and a score of 4 or more correlates with impaired awareness.

* Based on data from a retrospective survey of 215 patients with T2DM treated with ≥2 injections of insulin daily for ≥1 year.

Hypoglycemia unawareness or impaired awareness of hypoglycemia

Component of hypoglycemia-associated autonomic failure
Episodes of hypoglycemia, (non-symptomatic) which alter the contra regulatory mechanisms resulting in an inability to respond and recover to subsequent hypoglycemic events.
Hypoglycemia-associated with autonomic failure (HAAF)

Hypoglycemia-associated with autonomic failure

$\uparrow x 2.5$ risk of severe hypoglycemia

Hypoglycemia in children can cause cognitive and structure deficits cognitivo mainly in those <5 years old

Pediatr Diabetes 2008; 9: 87-95
Identification of HAAF

Clarke et al:
◦ 8 questions about t patient’s hypoglycemic experience

Pedersen Bjergaard et al:
◦ Do you recognized symptoms when you have hypo? (always, occasionally, never)

Cryer, PE, Hypoglycemia in Diabetes. Pathophysiology, prevalence and prevention 3rd Edition. ADA. DOI:10.2337/9781580406400
## Hypoglycemia: Clinical consequences

<table>
<thead>
<tr>
<th>Acute</th>
<th>Long term</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perspiration, irritability, confusion</td>
<td>Recurrent unawareness hypoglycemia</td>
</tr>
<tr>
<td>Accidents</td>
<td>Refractory diabetes</td>
</tr>
<tr>
<td>Vehicles</td>
<td>Dementia</td>
</tr>
<tr>
<td>Falls</td>
<td>Cardiovascular events</td>
</tr>
<tr>
<td>Fractures</td>
<td>Neuropathic autonomic cardiac/ Ischemic cardiovascular disease/ Fatal arrhythmia / Angina</td>
</tr>
</tbody>
</table>

Hypoglycemia is more than...

Perspiration, palpitations, trembling, anxiety, hunger...
Severe hypoglycemia is associated with major clinical outcomes

In the ADVANCE study, severe hypoglycaemia was associated with increased risk of adverse clinical outcomes: major macrovascular events, major microvascular events, all-cause mortality and CV death (all P<0.001)

<table>
<thead>
<tr>
<th>Clinical outcome</th>
<th>Adjusted HR (95% CI) for outcomes among patients who had severe hypoglycemia vs those who did not</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major macrovascular events</td>
<td>2.88 (2.01–4.12)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major microvascular events</td>
<td>1.81 (1.19–2.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from CV cause</td>
<td>2.68 (1.72–4.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>2.69 (1.97–3.67)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

• ADVANCE analysis
• T2DM
• N=11,140
• 5 year follow-up

ZOUNGAS S ET AL ADVANCE, ACTION IN DIABETES AND VASCULAR DISEASE: PRETERAX AND DIAMICRON MODIFIED RELEASE CONTROLLED EVALUATION STUDY; HR, HAZARD RATIO N ENGL J MED. 2010;363:1410-1418
In ORIGIN*, severe hypoglycemia was associated with a greater risk for the major CV events, mortality, CV death and arrhythmic death.

Severe hypoglycemia is associated with major CV outcomes

<table>
<thead>
<tr>
<th>Severe hypoglycemia</th>
<th>Adjusted HR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death or nonfatal MI or stroke</td>
<td>1.58 (1.24–2.02)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total mortality</td>
<td>1.74 (1.39–2.19)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>CV death</td>
<td>1.71 (1.27–2.30)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Arrhythmic death</td>
<td>1.77 (1.17–2.67)</td>
<td>0.007</td>
</tr>
</tbody>
</table>

ORIGIN

- IGT, IFG or early T2DM at high CV risk; N=12,537
- Randomized to Lantus® (target FPG ≤95 mg/dL [5.3 mmol/L]) vs standard care for 6.2 years
- Lantus® was associated with a neutral effect on CV outcomes vs standard care

ORIGIN Investigators. Eur Heart J. 2013;34:3137-44
Hypoglycemia May Be Associated With Increased Rates of Chest Pain and ECG Abnormalities

<table>
<thead>
<tr>
<th>CGMS and Holter Monitoring Abnormalities</th>
<th>Total Episodes</th>
<th>Episodes With Chest Pain/Angina</th>
<th>Episodes With ECG Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia</td>
<td>54</td>
<td>10(^a)</td>
<td>6(^a)</td>
</tr>
<tr>
<td>Symptomatic</td>
<td>26</td>
<td>10(^a)</td>
<td>4(^a)</td>
</tr>
<tr>
<td>Asymptomatic</td>
<td>28</td>
<td>—</td>
<td>2</td>
</tr>
<tr>
<td>Normoglycemia without rapid changes</td>
<td>N/A</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>59</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Rapid changes in glucose (&gt;100 mg/dL/h)</td>
<td>50</td>
<td>9(^a)</td>
<td>2</td>
</tr>
</tbody>
</table>

\(^a\)P<0.01 vs episodes during hyperglycemia and normoglycemia.

Study included patients (n=19; mean age, 58±16 years) with type 2 diabetes, history of frequent hypoglycemia, mean A1C of 7.1%, and coronary artery disease (defined as history of myocardial infarction, coronary artery bypass surgery, or angioplasty). ECG=electrocardiographic; CGMS=continuous glucose monitoring system. Desouza C et al. *Diabetes Care*. 2003;26(5):1485–1489. Permission requested.
Hypoglycemia May Cause an Acquired Long QT Syndrome

The relative contribution of these factors and others, including cardiac autonomic neuropathy, is unclear.

Sudden Death in Diabetes

Iatrogenic Hypo → HAAF

Defective Glucose CR
Hypo Unawareness
→ Recurrent Hypo
With SAS Activation

↑ QTc Interval
↑ Intracellular Ca²⁺
↓ Potassium
↑ O₂ Consumption
↑ Platelet Function
↑ Coagulation
↑ Cytokines
↓ Vasodilation

Decreased Baroreflex
Sensitivity

→ Ventricular Arrhythmia
→ Sudden Death
Percent in-hospital mortality by glycemia status among patients with and without diabetes

Insulin-associated and spontaneous hypoglycemia are associated with increased mortality among hospitalized patients.
Hypoglycemia has a negative impact on patient care

Negative impact on QoL and physical, mental and social functioning\(^1,2\)

Deterioration of glucose control

Decreased work productivity\(^1,3\)

Loss of self confidence\(^3\)

Fear of future episodes\(^3\)

Limits efforts for treatment optimization and target achievement\(^3,4\)

Hypoglycemia has a negative impact on patient care

Higher risk of glucose-lowering treatment discontinuation\textsuperscript{5}

Increased costs to patient, healthcare system and society\textsuperscript{3,6–7}

Adverse long-term complications\textsuperscript{2,3,8,9}

- Weight gain
- Increased risk for major macro- and microvascular events
- Development of cognitive dysfunction and dementia
- Death from cardiac and/or any cause

Fear of hypoglycemia reduces patient adherence

Proportion of patients modifying insulin dose to avoid future hypoglycemia

Cost impact of hypoglycemia is high

Cost-driving factors induced by hypoglycemia include hospital admissions, emergency visits, out-of-pocket expenses required to manage hypoglycemic events\(^1,2\)

There are also indirect costs associated with the reduced well-being, reduced work capacity and increased long-term complications

<table>
<thead>
<tr>
<th>Complication</th>
<th>Estimated direct medical costs per patient per episode in the US, USD(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypoglycemia requiring hospitalization</td>
<td>16,478</td>
</tr>
<tr>
<td>Hypoglycemia requiring ED visit</td>
<td>1,331</td>
</tr>
<tr>
<td>Hypoglycemia requiring glucagon injection</td>
<td>176</td>
</tr>
</tbody>
</table>

Cost impact of hypoglycemia is high

Patients who experienced hypoglycemia vs those who did not incurred higher total healthcare cost (P<0.01) and total number of inpatient days (P<0.01)

A hypoglycemia-related hospitalization cost was $20,838
An estimated average medical cost of $733 can be saved for every event avoided
10% risk reduction in hypoglycemia was associated with an annual saving of $496

<table>
<thead>
<tr>
<th></th>
<th>Cost, with hypoglycemia</th>
<th>Cost, without hypoglycemia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted total healthcare cost</td>
<td>$36,680</td>
<td>$16,850</td>
</tr>
<tr>
<td>Mean total number of inpatient days</td>
<td>19.8</td>
<td>3.4</td>
</tr>
</tbody>
</table>

Chou E, et al. Presented at ADA 2014; Abstract 254-OR
Hypoglycemia has an emotional and economic burden

About one-third of insulin-treated patients were very worried about hypoglycemia and a similar proportion reported maintaining hyperglycemia to avoid hypoglycemia

13% reported 1 to 2 major hypoglycemic events in previous year

17–50% reported 1 to 10 minor hypoglycemic events in previous year

Reported events associated with hypoglycemia in prior 12 months, %

- European online survey (T1DM and T2DM)
- N=1,848

ED, emergency department; HCP, healthcare professional
Causes and Risk factors
Causes of Hypoglycemia in Diabetics

Absolut or relative insulin excess
- Doses and drug administration
- Eating pattern and exercise level.
- Interactions with alcohol/other drugs.
- ↑ insulin sensitivity ↓ reduced insulin clearance.

Altered contra regulatory mechanisms
- Endogenous insulin deficiency
- Prior severe hypoglycemia
- Impaired awareness of hypoglycemia
- Aggressive anti-hyperglycemic therapy

## Risk factors for hypoglycemia

<table>
<thead>
<tr>
<th>Patient related</th>
<th>Life style related</th>
<th>Pharmacologic related</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Advance age</td>
<td>• Deficit nutrition or prolonged fasting</td>
<td>• Sulfonylureas or insulin</td>
</tr>
<tr>
<td>• Long lasting diabetes</td>
<td>• Prolonged physical activity</td>
<td>• Drug Interactions</td>
</tr>
<tr>
<td>• Recent hospitalization/ Intercurrent conditions</td>
<td>• Ethanol intake</td>
<td></td>
</tr>
<tr>
<td>• Hepatic, renal or cardiovascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Endocrine deficiency</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Loss of contra-regulation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>• Lack of knowledge of hypoglycemia</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Hypoglycemia associated autonomic failure

1. Absolute endogenous insulin deficiency.

2. A history of severe hypoglycemia, hypoglycemia unawareness, recent antecedent of hypoglycemia, prior exercise and sleep.

3. Aggressive glycemic therapy (strict glucose targets)

Adapted from Cryer, PE, Hypoglycemia in Diabetes. Pathophysiology, prevalence and prevention 3rd Edition. ADA. DOI:10.2337/9781580406400
## Treatment of hypoglycemia

### Table 4
Examples of 15 g of carbohydrate for the treatment of mild-to-moderate hypoglycemia

- 15 g of glucose in the form of glucose tablets
- 15 mL (3 teaspoons) or 3 packets of table sugar dissolved in water
- 5 cubes of sugar
- 150 mL of juice or regular soft drink
- 6 Life Savers™ (1 = 2.5 g of carbohydrate)
- 15 mL (1 tablespoon) of honey
Treatment of hypoglycemia

Glucagon 1 mg given subcutaneously or intramuscularly produces a significant increase in BG (from 3.0 to 12.0 mmol/L) within 60 minutes.

The effectiveness of glucagon is reduced in individuals who have consumed more than 2 standard alcoholic drinks in the previous few hours, after prolonged fasting, or in those who have advanced hepatic disease.
Hypoglycemia risk factor reduction

1. Acknowledge the problem
2. Consider risk factors
3. Apply the relevant principles of aggressive glycemic therapy
   ◦ a. Drug selection
   ◦ b. Diabetes treatment technologies
   ◦ c. Individualized glycemic goals
   ◦ d. Structured patient education
   ◦ e. Short-term scrupulous avoidance of hypoglycemia

Reducing the risk

**Education:**
Patients and relatives about the risk and the symptoms  
Diabetes education for the health care team

**Patient’s evaluation**
Functional state  
Presence of complications

**Pharmacologic treatment:**
Avoid SU’s particularly in the elderly, DPP-4 are preferred medication is such patients  
Avoid complex therapeutic schemes specially intensive insulin regimens in elderly population

Now days...

We have newer drugs for diabetes management which includes:

- DPP-4 inhibitors
- SGLT-2 inhibitors
- GLP-1 receptor analogs
- Insulin analogs

Particularly useful in patients at risk of hypoglycemia

Yale J-FPaty, Breay Paty, Senio PA. Hypoglycemia Diabetes Canada Clinical Practice Guidelines Expert Committee
Risk of hypoglycemia with agents added to metformin

Initial treatment

Less hypoglycemia

Metformin

More hypoglycemia

Additional treatment

- DPP-4 inhibitors
- GLP-1 receptor agonists
- TZDs
- Sulfonylureas
- Insulin (basal, basal-plus, mixtures)

Different determinants of absorption and duration of action of human and analogue insulins.
Different determinants of absorption and duration of action of human and analogue insulins.
Similar reductions of HbA$_{1c}$ in both groups (non-inferiority for Gla-300 vs IDeg-100)

<table>
<thead>
<tr>
<th></th>
<th>Gla-300</th>
<th>IDeg-100</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>462</td>
<td>462</td>
</tr>
<tr>
<td>BL</td>
<td>8,7</td>
<td>8,6</td>
</tr>
<tr>
<td>Sem 8</td>
<td>8,6</td>
<td>8,6</td>
</tr>
<tr>
<td>Sem 12</td>
<td>8,6</td>
<td>8,6</td>
</tr>
<tr>
<td>Sem 24</td>
<td>8,6</td>
<td>8,6</td>
</tr>
</tbody>
</table>

Change from basal week 24, mean values

BL, basal; ITT, intention to treat; LS, mínimos cuadrados; SD, error estándar;

Cheng et al, American Diabetes Association 2018, # OR 301
Similar reduction of HbA1c for both treatment arms

**General study population**

**> 75 years old**

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W: Semana de tratamiento; BL: semana 0; FPG: Glicemia plasmática en ayunas; SE: Desviación Estándar; LS: Cuadrados mínimos

1. Ritzel, R. et al. Diabetes Care 2018;41:1672–1680
Hypoglycemia

It is immerse in the forest of non-communicable chronic diseases

It is not recognized, neither reported

It is associated with elevated morbidity and mortality

BUT it is an avoidable condition
Thank you for your attention