Clinical significance of hypoglycemia, with presentation of cases

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UNIVERSITY OF ZAGREB
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Clinical significance of hypoglycemia, with presentation of cases

GRADUATION THESIS

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ABBREVIATIONS

ACTH:	Adrenocorticotropic hormone
ASVS:	Arterial Stimulation with Venous Sampling
CGMS:	Continuous Glucose Monitoring System
CRP:	C-reactive protein
CT:	Computed tomography
DPP-4:	Dipeptidyl peptidase-4
DSA:	Digital subtraction angiography
EUS:	Endoscopic ultrasound
F18 DOPA:	^{18}Fluoro-dihydroxyphenylalanine
IGF-1:	Insulin-like growth factor 1
IGF-BP3:	Insulin-like growth factor binding protein 3
KBC:	Klinički bolniči centar
MRI:	Magnetic resonance imaging
MSCT:	Multi-slice computed tomography
NIPHS:	Noninsulinoma pancreatogenous hypoglycemia syndrome
PanNETs:	Pancreatic neuroendocrine tumors
PET-CT:	Positron emission tomography-computed tomography
RBCs:	Red blood cells
SGLT-2:	Sodium-glucose co-transporter 2
T1DM:	Diabetes mellitus type 1
T2DM:	Diabetes mellitus type 2
TIA:	Transient ischemic attack
WBCs:	White blood cells

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Abstract

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The clinical significance of hypoglycemia is important to understand as there are many etiologies and, if not treated, can have devastating consequences, such as coma or even death. Etiologies range from tumors to iatrogenic hypoglycemia, from postprandial hypoglycemia to renal failure. The majority of those who are at risk of getting hypoglycemia are patients treated with insulin or insulin secretion stimulating drugs. However, there are many other causes of hypoglycemia, but the most of them are rare. To diagnose hypoglycemia, Whipple's triad must be met: symptoms of hypoglycemia, low blood glucose measured at the time of symptoms and relief of symptoms after the blood glucose level is corrected. The cases discussed in this thesis will explore a more common cause of hypoglycemia, sulfonylurea-induced (iatrogenic), and a rare cause, insulinoma. In the first case, an elderly patient with renal insufficiency developed hypoglycemia due to the use of glimepiride, a second-generation sulfonylurea. By simply taking the medicine out of her regimen the patient did not experience any further hypoglycemic attacks. In the second case, a middle aged woman presented with episodes of lightheadedness and tremors for years with occasional loss of consciousness and weight. These attacks happened at any time, even during fasting, and were relieved by a sweet drink. These signs and symptoms lead to the suspicion of an insulinoma, which was later confirmed with laboratory testing and diagnostic imaging. The tumor was resected, and since, the patient has not had any further hypoglycemic attacks.

Keywords: hypoglycemia, insulinoma, sulfonylurea, fasting test, calcium stimulation

Sažetak

Klinički značaj hipoglikemije, s prikazom slučajeva

Staffan Johnsson

Kako neki oblici hipoglikemije mogu imati ozbiljne posljedice i neliječene mogu biti smrtonosne važno je razlučiti etiologiju hipoglikemije. Ona je vrlo različita: od tumora do jatrogene hipoglikemije, od postrandijalne hipoglikemije do zatajenja bubrega. Većinu pacijenata koji su u riziku hipoglikemija su osobe sa šećernom bolešću liječenje inzulinom ili lijekovima koji stmuliraju sekreciju inzulina. Međutim, brojni su drugi uzroci, pojedinačno rijetki. Glavni kriterij za dijagnozu hipoglikemije je Whippleova triada: simptomi, izmjerena niska glikemija u vrijeme simptoma i nestanak simptoma kada se glikemija korigira. U ovom radu će se prikazati jedan primjer uobičajenog slučaja hipoglikemije: jatrogene, uzrokovane sulfonilurejom i jedan rijedak uzrok - inzulinom. U prvom prikazu, starija žena s renalnom insuficijencijom razvija hipoglikemiju uz glimepirid, sulfonilureju druge generacije. Nakon izostavljanja lijeka iz terapije pacijentica nije imala više napada hipoglikemije. U drugom prikazu, sredovječna žena je imala epizode omaglica i tremora s povremenim nesvjesticama i porastom težine godinama. Napadi su se događali u bilo koje vrijeme, i natašte i ublažavani su slatkim napitcima. Ovi znakovi i simptomi su pobudili sumnji na inzulinom što je dokazano laboratorijskim i slikovnim tehnikama. Tumor je nađen u repu pankreasa i nakon resekcije istog više nije bilo hipoglikemijskih napada.

Ključne riječi: hipoglikemija, inzulinom, sulfonilureja, test gladi, stimulacija kalcijem

Introduction

Glucose is, under physiological conditions, an indispensable energy source not only for the brain, but also for red blood cells and the renal medulla. Since the brain is essential for other organs in the body to function, the energy supply to this organ is of utmost importance. In contrast to the rest of the body, the brain cannot synthesize glucose and barely has any glycogen stores. Therefore, the brain requires a constant supply of glucose, via the bloodstream, to survive. Glucose can be taken up exogenously, through diet, and/or be made endogenously by gluconeogenesis and glycogenolysis. During prolonged fasting, the brain can use ketone bodies as an alternative fuel that reduces the need for gluconeogenesis from amino acid carbon skeletons, thus preserving essential proteins (1). The brain of an adult makes up only 2.5% of the total body weight but accounts for 25% of the basal metabolic rate and more than 50% of the whole body glucose usage (2).

The definition of hypoglycemia, according to Melmed et al. (2), is a ”plasma glucose concentration that is low enough to cause symptoms or signs, including impairment of brain function.” The level at which signs and symptoms of hypoglycemia begin to develop varies in different patient populations (e.g. healthy persons, those with impaired blood glucose regulation, etc.) (2). Additionally, the plasma glucose concentration at which patients become symptomatic or become at risk for hypoglycemia differs in patient populations. For example, symptomatic or clinical hypoglycemia, in healthy persons, often manifests when plasma glucose levels fall below 3.0 mmol/L (3). In contrast, in the diabetic patient, special considerations and precautions should be taken. Hypoglycemia, in a symptomatic diabetic patient, can be considered at a blood glucose level less than or equal to 3.9 mmol/L. However the same blood glucose value in an asymptomatic diabetic patient should warrant clinical concern and precaution (4).

Most commonly, hypoglycemia can be a side effect in diabetic patients taking insulin or sulphonylurea drugs. In those who do not have diabetes, clinically significant hypoglycemia is rare. On the other hand, it is not uncommon to detect a blood glucose level of less than 3.0 mmol/L in an asymptomatic individual. For this reason and because the signs and symptoms of hypoglycemia are nonspecific, a hypoglycemic disorder should only be diagnosed if all three conditions of Whipple´s triad are met. The Whipple´s triad consists of symptoms of hypoglycemia, low blood glucose measured at the time of symptoms and relief of symptoms after the blood glucose level is corrected (5).

As previously mentioned, hypoglycemia is rare in non-diabetic people. This is because the body has three hormones, insulin, glucagon and epinephrine, that together act as a defense mechanism to prevent hypoglycemia and maintain normoglycemia. Insulin secretion from the beta cells in the pancreas is decreased when plasma glucose falls within the physiological range. When the glucose level drops below the physiological range, the counterregulatory hormone to insulin, glucagon, is excreted from the alpha cells in the pancreas in order to activate glucose production in the liver, mainly by glycogenolysis, but also by gluconeogenesis. If glucagon is insufficient and the glucose level is below the physiological range, the third defense, epinephrine, becomes critically important. The secretion of epinephrine from the adrenal medulla increases to help correct the hypoglycemia through the activation of glycogenolysis, gluconeogenesis and lipolysis. Together, the aforementioned defense mechanisms usually manage to halt the hypoglycemia before it becomes critically low. Additionally, if the hypoglycemia is prolonged beyond four hours, the stress hormones cortisol and growth hormone contribute to the defense (2).

Although the symptoms of hypoglycemia are nonspecific, they can be classified as neurogenic (autonomic/adrenergic) and neuroglycopenic. The neurogenic symptoms and signs are due to the adrenergic and cholinergic release of catecholamines and acetylcholine, respectively. Release of catecholamines leads to sympathetic symptoms: tremor, palpitations, tachycardia, anxiety and/or arousal. Acetylcholine release results in diaphoresis, hunger and paresthesiae. The neuroglycopenic signs and symptoms are a due to a shortage of glucose delivery to the brain, causing cerebral dysfunction. They include dizziness, visual disturbance, decreased cognition, headache, confusion, seizures, coma, and ultimately death, if untreated. In an aware individual, both neurogenic and neuroglycopenic signs and symptoms drive the individual to eat, most specifically, carbohydrates to correct hypoglycemia (2).

Although less common, in the non-diabetic patient, there are many causes of hypoglycemia including postprandial (reactive) hypoglycemia, excessive alcohol intake, tumors (e.g. insulinoma), hepatic failure, renal failure, heart failure, sepsis and adrenal insufficiency (6).

Before the case presentations, some information about endogenous and exogenous hyperinsulinism with subsequent hypoglycemia will be presented, as well as a frequent cause of hypoglycemia: postprandial (reactive) hypoglycemia.

Insulinoma

Insulinomas are a type of Pancreatic neuroendocrine tumors (PanNETs) that secrete insulin. The PanNETs, or islet cell tumors, are rare in comparison with tumors of the exocrine pancreas, constituting only 2% of all pancreatic tumors. Insulinomas are the most common PanNETs and are the most common cause of hypoglycemia due to endogenous hyperinsulinism. Nonetheless, they are still very rare, with an incidence of only 1-4 people per million population (7,8). They are usually sporadic and the median age of presentation is usually around 50 years. Less commonly, it can also be part of multiple endocrine neoplasia type 1 (MEN1), where the median age of presentation is 30 years (9).

These insulin-secreting tumors are usually benign (90%) and can be located anywhere in the pancreas, but are most often found at intrapancreatic sites. They are usually solitary and small - less than 2 cm in diameter. The tumor secretes insulin in an intermittent fashion and, therefore, the hypoglycemic symptoms and signs can appear intermittently and sporadically, but most often present during fasting. The signs and symptoms commonly seen include diaphoresis, tremor, palpitations, confusion, behavioral and personality changes, visual disturbances, seizures and coma (8,10). Often these patients are misdiagnosed with psychiatric or neurological disorders (e.g. epilepsy) before the correct diagnosis has been made due to the nonspecific symptoms and erratic behavior often observed in this patient population. Additionally, these patients attempt to prevent hypoglycemic episodes and ”treat” their hypoglycemic symptoms with foods high in sugar content. Thus, these patients also tend to present with a history of weight gain (11).

Whipple’s triad, now used to define hypoglycemia, was originally used for the diagnosis of insulinomas. If all of the parameters were met, the patient was thus diagnosed with an insulinoma and prepared for surgery. Nowadays, a consensus for a biochemical diagnosis of insulinoma has made been made. During a maximal duration of a 72 hours fast, supervised in a hospital, the patient must present clinically with Whipple’s triad and biochemically, on blood tests, present with the following: a plasma insulin level $\geq$ 3 mU/mL when the plasma glucose concentration is below 3.0 mmol/L, plasma C-peptide $\geq$ 0.2 nmol/L, and proinsulin $\geq$ 5 pmol/L. This extended fasting test can detect up to 99% of insulinomas (8,12). Plasma levels of beta-hydroxybutyrate are lower in patients with insulinoma than in healthy individuals, and a level of $\leq$ 2.7 mmol/L can confirm the diagnosis if the values of insulin and C-peptide are borderline. Another alternative for confirmation of insulinoma for borderline

patients is to check for the glycemic response to glucagon at the end of a 72-hour fast. There should be a higher rise in plasma glucose in people with insulinomas than in those without (12).

If the biochemical blood tests meet the aforementioned criteria, the next step is to localize the tumor in order to confirm the diagnosis. Multislice computed tomography (MSCT), Magnetic resonance imaging (MRI) and transabdominal ultrasonography usually detect the insulinoma (13). If the tumor cannot be found with these non-invasive imaging tools, invasive methods such as endoscopic ultrasound (EUS) or selective arterial calcium stimulation and hepatic venous sampling (ASVS) can be used. The selective ASVS test is based on the fact that calcium stimulates secretion of insulin from hyperfunctional beta cells constituting an insulinoma, but not from normal beta cells. Calcium gluconate is first injected to the blood vessels supplying the pancreas; the gastroduodenal, the splenic and the superior mesenteric arteries. Then, the insulin level is measured in the right hepatic vein. If the insulin level is more than twofold over the baseline, the sensitivity is high to localize the tumor. The insulin level is increased only in the feeding arteries of the insulinoma, which therefore helps to localize the tumor for the operation (8,10,11,13).

The treatment of choice is surgical resection by enucleation, partial pancreatectomy or by laparoscopic resection. Medical therapy with diazoxide or octreotide may control symptoms in some patients, but only surgery is curative (13).

Iatrogenic hypoglycemia

After insulin, sulfonylureas are the most common cause of iatrogenic hypoglycemia. Sulfonylureas, a common oral hypoglycemic, are used by patients with diabetes mellitus type 2 (T2DM) and were first introduced in 1954, making them the oldest class of oral hypoglycemic drugs. These agents promote insulin release from the pancreatic beta cells and are therefore called insulin secretagogues. The mechanism of action is the blocking of a sulfonylurea on an ATP-potassium sensitive channel in beta cells, causing trapping of potassium inside the cell, leading to depolarization. This in turn causes calcium influx that activates insulin release. Since these drugs cause the release of endogenous insulin, sulfonylureas do not have any function in those with diabetes mellitus type 1 and in late phase T2DM, since the dysfunctional and/or destructed beta cells in these patients cannot produce

any more insulin. Sulfonylureas are most effective in people with T2DM who have been relatively recently diagnosed (<5 years) since, in the early stages of the disease, there is still some preserved beta cells function and, thus, these cells can still produce insulin.

The hypoglycemic signs and symptoms are similar to the those previously described in patients with insulinomas. Most commonly it manifests with diaphoresis, tremors, confusion and personality changes (9,14,15).

There are two generations of sulfonylureas; first and second. The second generation is prescribed more often than the first, due to fewer side effects and drug interactions. Examples of these preferred drugs include glibenclamide, glipizide, gliclazide and glimepiride (16). These drugs also have a more rapid onset of action, shorter half-life and better control of the postprandial glucose rise than the those from the first generation. They decrease both the fasting and the postprandial glucose and should be given in low doses and increased at one- to two-week intervals based on the patient's self-monitoring of blood glucose. Sulfonylureas cause a quick release of insulin and should therefore be taken shortly before meals. The sulfonylureas are usually well tolerated, but the longer acting ones, especially from the first generation, can cause serious and long-term hypoglycemia, especially in the elderly (17). Risk factors for iatrogenic hypoglycemia are renal or hepatic insufficiency, patients over 65 years of age, frequent hospitalization and poor management of diabetes (15). Many of the sulfonylureas are converted in the liver to an active metabolite and are later excreted in the kidney. Therefore it is not recommended to use these drugs in patients with liver and/or kidney dysfunction. In general, elderly patients have less well functioning livers and kidneys than younger people and should therefore be aware of the risks with these drugs (17). Additionally, the possibility of an intentional or accidental overdose of sulfonylurea drugs must be considered in all patients and thus, investigated appropriately. Due to the often long term hypoglycemia caused by sulfonylureas, the patients need to be treated and monitored at the hospital for 24 hours or, sometimes, even longer (6).

The diagnosis is made clinically with a presentation of hypoglycemia and, usually, with a history of sulfonylurea use. If there is any suspicion, a possible history of overdose must be considered/explored. If a medication list can be found, for example, it could reveal the possibility of an intentional or accident overdose of a sulfonylurea. Laboratory tests can help to confirm hypoglycemia, but should not delay treatment. Sulfonylureas cause the release of

endogenous insulin, and if these drugs are the cause of hypoglycemia, then there should be elevated levels of proinsulin, c-peptide and, insulin in laboratory tests.

The treatment of hypoglycemia is glucose supplementation. While waiting for IV access to be gained, oral glucose can be given or 5 mg of glucagon can be given subcutaneously or intramuscularly. Once IV access has been obtained, 25g (50mL) of 50% intravenous dextrose solution is given and blood glucose levels are carefully monitored (15).

Postprandial hypoglycemia

Postprandial hypoglycemia, previously called reactive hypoglycemia, is hypoglycemia within four hours after a meal. It is not a diagnosis per se but a description of the timing of hypoglycemia and there can be different underlying causes.

Often the term is used in the wrong way as a disease by itself, like the idiopathic postprandial syndrome; a collection of signs and symptoms similar to true hypoglycemia but without any biochemical evidence. The danger of this, instead of using it as a time descriptor, is to not search for the actual cause of the hypoglycemia with its potentially more serious adverse effects.

In the evaluation for postprandial hypoglycemia, the purpose is to see if the patient can meet the criteria for Whipple's triad or not. First, blood glucose measurements have to be done when the patient experiences hypoglycemic symptoms. Almost always the blood glucose concentration is normal in these patients and the majority have actually been shown to have some type of psychoneurosis.

For those few patients who actually have low blood glucose, further evaluation should proceed in terms of a mixed meal test. The patient is instructed to consume a solid and liquid meal that usually leads to symptoms and is then observed for up to five hours. Before the ingestion of the mixed meal, samples should be taken for blood glucose, insulin, C-peptide and proinsulin. These samples should be repeated every 30 minutes for five hours. If the patient gets severe signs and symptoms before five hours, samples should be taken before the patient is given carbohydrates to check for the correction of symptoms and signs. If Whipple's triad is met, sulfonylureas, meglitinides and antibodies to insulin should also be measured, to rule out these potential causes.

Differential diagnoses include primarily post-bariatric surgery syndrome, insulin autoimmune hypoglycemia and noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS). These cause hypoglycemia usually in the postprandial state. Factitious hypoglycemia can be at any time, including postprandial, depending when the person uses too much insulin or an insulin secretagogue. Although insulinomas usually cause hypoglycemia in the fasting state it also can happen postprandially, making it a less obvious differential.

Apart from trying to find the underlying cause of postprandial hypoglycemia and treat it, advice should be given to decrease or prevent the symptoms. Those include food rich in fiber, low sugar content, frequent small meals or snacks (every three hours) and regular exercise (18).

CASE REPORTS

Iatrogenic hypoglycemia

A 70-year-old female presented to the emergency department with an episode of confusion and dysphasia. A stroke or transient ischemic attack (TIA) were the initial main differential diagnoses.

She had a past medical history of hypertension (20 year history) and type 2 diabetes mellitus (10 year history). Additionally, an ischemic stroke three years prior left the patient with residual weakness of the right arm and a discrete right facial paresis. Surgical history included a cholecystectomy at age 40. Her current drug history included: metformin 2x850 mg, glimepiride 2 mg, ramipril 5 mg, indapamide 2.5 mg, rosuvastatin 10 mg, acetylsalicylate 100 mg.

On examination, the patient was confused and sweaty and looked anxious. Body systems examination was otherwise unremarkable save for a known discrete right facial paresis. Vital signs were also unremarkable, save for a slight tachypnea and tachycardia. Her ECG showed sinus tachycardia with a right bundle branch block.

Blood tests revealed a low glucose concentration of 2.2 mmol/L, worsening renal function (serum creatinine 119 umol/L, estimated glomerular filtration rate 41 ml/min/1,73m^2, potassium 4.9 mmol/L, sodium 139 mmol/L), glycated hemoglobin (HbA1c) 8%. Complete blood count, inflammatory markers and liver function tests were normal.

The patient was given IV glucose and recovered quickly. However, three hours later, her presenting signs and symptoms returned and she was found to have had another hypoglycemic episode.

Insulinoma

A 48-year-old woman, mother of one, was referred to the tertiary centre at University Hospital Centre Zagreb with a history of attacks of lightheadedness and tremors for years. There was no preceding aura. These attacks could happen at any time, including at night and when fasting. On several occasions, she had brief losses of consciousness and these episodes would usually resolve with a sweet drink. Over the past five years, she also reported gaining approximately 10 kg.

The patient had a surgical history of tonsillectomy in early childhood, cholecystectomy in 1988 and corrective surgery for nasal septum in 1998. In 1996, she was seen and treated by a psychiatrist for panic attacks. Her father had a history of hypertension and died at the age of 80. Her mother was alive with no remarkable medical history. Her daughter had type 1 diabetes mellitus (T1DM) and was diagnosed at the age of 13.

The patient was referred to neurologists for evaluation of migraine-type headaches in 2006 and it was then that an insulinoma was first suspected. She was then referred for endocrinological evaluation. A prolonged fasting test was discontinued after 12 hours due to hypoglycemia. A high-normal insulin level with blood glucose of 1.9 mmol/L was found. Diagnostic imaging (EUS, repeated MSCT, ^{18}Fluoro-dihydroxyphenylalanine positron emission-computed tomography (18F-DOPA PET-CT) did not localize any tumors. Additional blood tests were performed: Insulin-like growth factor-binding protein 3 (IGF-BP3), cortisol and adrenocorticotropic hormone (ACTH) were normal and insulin-like growth factor 1 (IGF1) was slightly elevated. At some point was diazoxide prescribed. The hypoglycemic episodes became more rare but the patient discontinued treatment due to hirsutism, a side effect of diazoxide, and in fear of further side effects.

In 2011, the patient was admitted to University Hospital Centre Zagreb for further testing. Blood tests, on arrival, showed a low fasting blood glucose of 1.8 mmol/L and a high fasting insulin of 10.9 mU/mL or 70 pmol/L. Plasma ACTH had a normal value of 3.5 pmol/L and serum cortisol had a normal level of 270 nmol/L. The amended insulin/blood glucose ratio: [insulin (mU/mL) x 100] / [glucose (mg/dL) – 30] = 545.

She then had a monitored 72-hour fasting test with Continuous glucose Monitoring System (CGMS) (Image 1) that was discontinued after 15 hours because the patient lost consciousness. Blood tests were taken at that point and showed a low blood glucose of 1.7

mmol/L, a high serum insulin concentration of 6.2 mU/mL or 42 pmol/L, and a normal value of serum cortisol of 106 nmol/L. The insulin (mU/L) - blood glucose (ng/mL) ratio was 0.2. The amended ratio was found to be 620. C-peptide was measured at 0.37 nmol/L.

With a biochemical diagnosis of insulinoma, the patient went on to further diagnostic imaging to see if a tumor could be localized. A MSCT was performed and showed an unremarkable pancreas with homogenous structure, no focal lesions either native or post contrast. Close to the splenic vein, a 2-2.5 cm structure was seen with vascularization, but most probably thought to be an accessory spleen. The patient underwent an MRI that revealed round shape with irregular borders axially 2.7 x 1.8cm, with a different intensity than the pancreas and the close-by spleen, undivided from the pancreas at one segment and close to the splenic hilus. EUS was also made and was unremarkable.

Digital subtraction angiography and arterial stimulation and/with venous sampling was performed using a concomitant right transfemoral arterial and venous route (Image 2). Selective catheterization of the right hepatic vein was performed first and a diagnostic catheter for sampling was placed. Selective catheterization followed in the following order: 1. Superior mesenteric artery, 2. Gastroduodenal artery and 3. Splenic artery.

After selective angiographic series, 5 ml of calcium gluconate solution was injected in each artery. Venous samples for each stimulation were taken from the right hepatic vein at 0, 30, 60, 90, 120 and 180 seconds. The samples showed an insulin level of 20-30 mU/L at basal level and up to 100 mU/L with stimulation of calcium gluconate, which therefore was clearly positive.

The patient was referred for surgical removal of the tumor and from post-operative notes the surgeon stated that they found ”…one tumor in the caudal part of the pancreas approximately 2 cm. One tumor approximately 1 cm in the upper pancreatic border, close to the splenic artery. Possibly a lymph node. The body and the tail of the pancreas were removed. The spleen was removed.”

Histological and immunohistochemical testing of the tissue removed was performed. 1.3 cm from the resection border a grayish tumor of 1.9 cm could be grossly visualized. Solid and trabecular with relatively uniform cells with basophilic cytoplasm and round nuclei. Infiltration/angioinvasion of the surrounding tissue was found. There was 1 mitotic figure noted per 10 high power fields. The spleen was macroscopically and histologically normal.

Immunohistochemistry staining showed: chromogranin A+ , synaptophysin+ , insulin+ , Ki-67 index 4%.

From 2011-2016, the patient was regularly followed-up and had no further hypoglycemic episodes. She was consistently found to be in good health and had voluntarily lost some weight. Repeated MRI abdomen and pelvis showed no evidence of residual tumor or tumor recurrence. Blood glucose levels were measured at 4.7-6.5 mmol/L repeatedly. In 2016 a 18F-DOPA PET/CT showed no pathological metabolism.

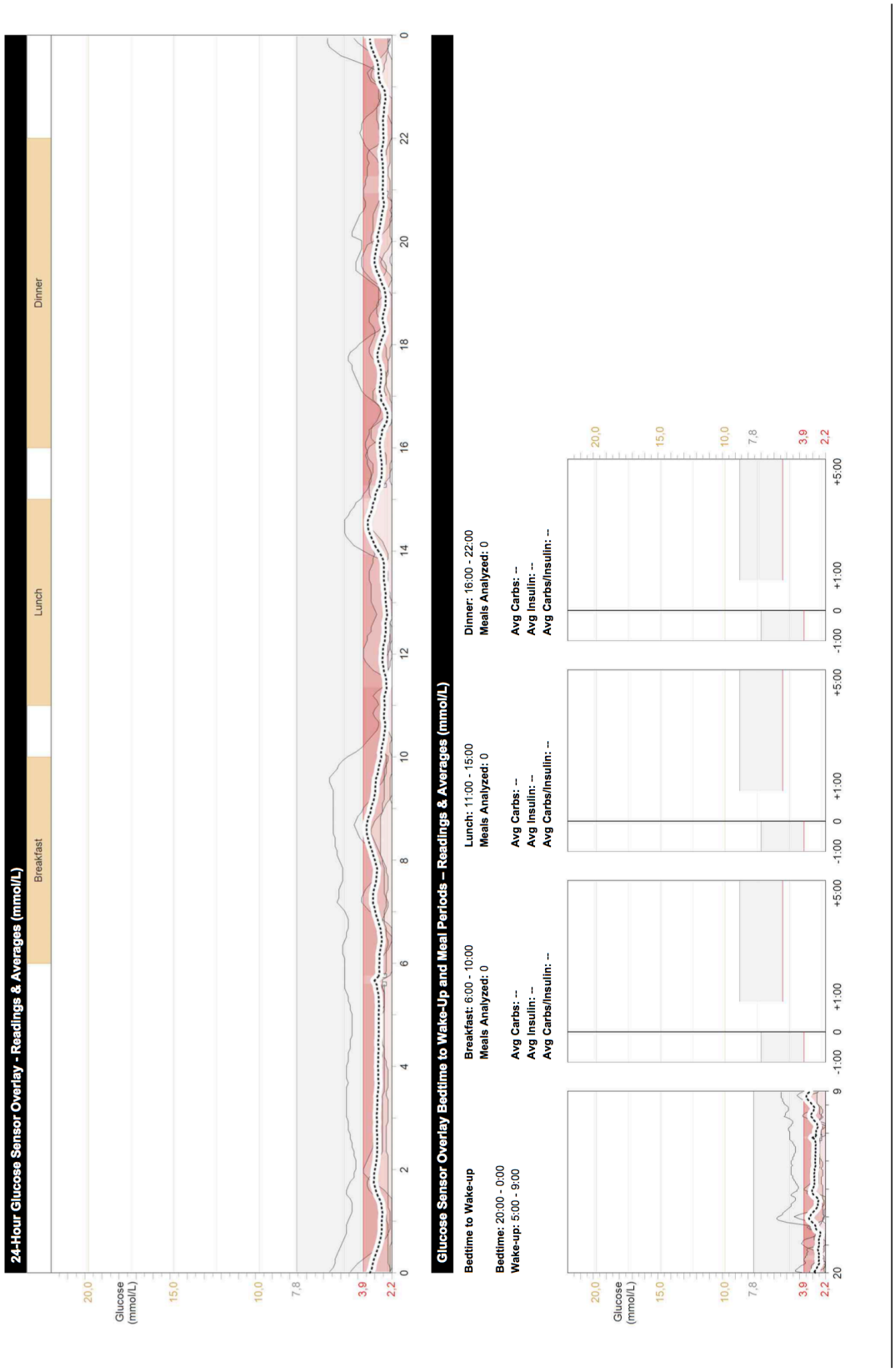


Figure 1. The patient's continuous glucose monitoring during fasting as an inpatient. Courtesy of Clinical Hospital Centre Zagreb.

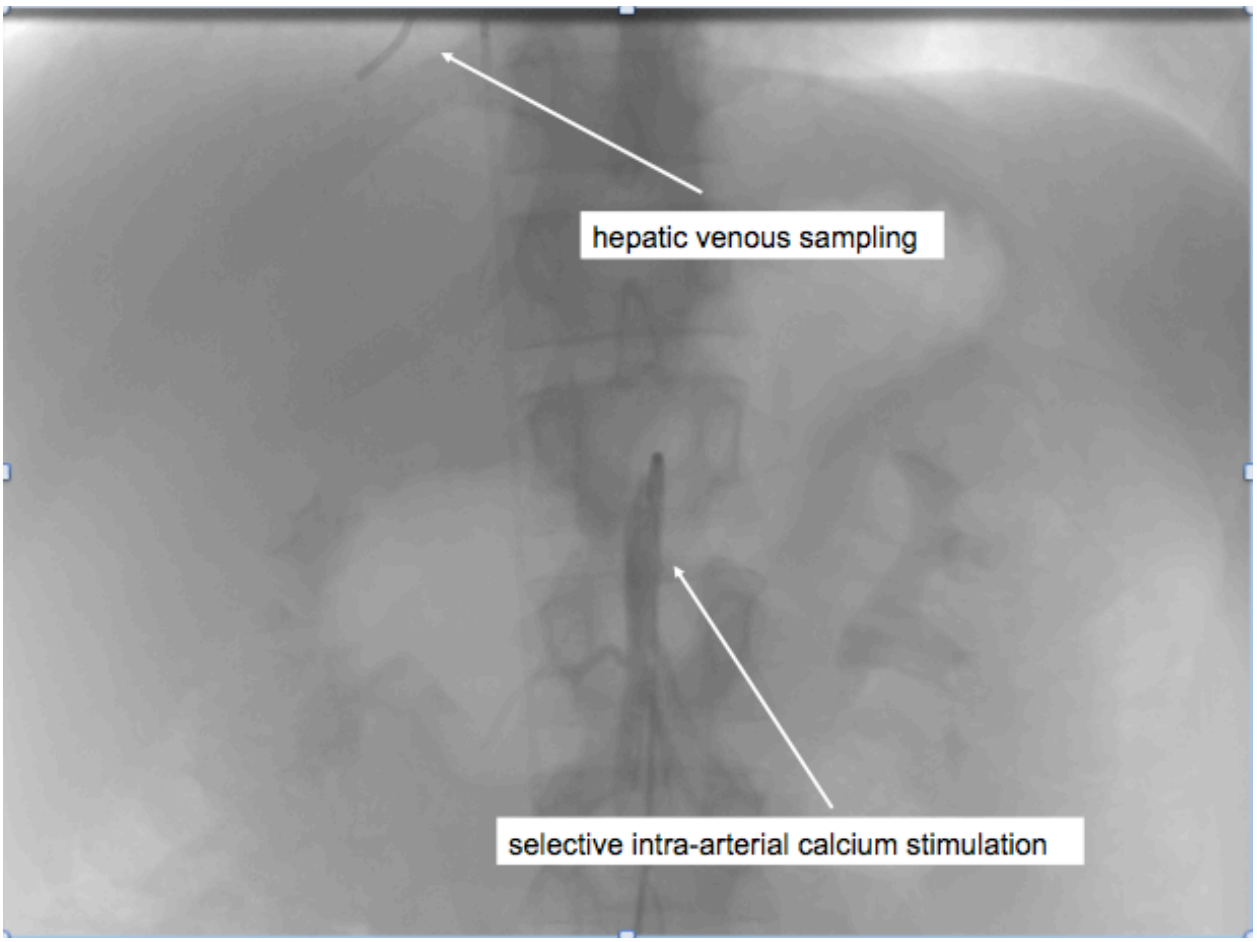


Figure 2. Digital subtraction angiography and arterial stimulation with venous sampling. Courtesy of Clinical Hospital Centre Zagreb.

Discussion

The 70-year-old woman with T2DM discussed in the first case presented to the emergency room with vague and nonspecific symptoms. As quickly discovered, her blood glucose levels were very low. Her symptoms resolved quickly with IV glucose, however, they returned after some time with a correlating drop in blood glucose. On blood tests it was found that she had a moderate reduction in kidney function with a eGFR of 41ml/min/1.73m^2 , corresponding to the 3B stage of chronic kidney disease (CKD). The two most common causes of chronic kidney disease are (in fact) diabetes and hypertension, which accounts for up to two-thirds of cases (19). Since glimepiride, like most of the sulfonylureas, is primarily excreted by the kidneys, the woman's decreased function of glomerular filtration caused build up of the sulfonylurea drug in her circulation. This in turn caused hypoglycemia (20).

Elderly people usually have less clear symptoms of hypoglycemia and it can be difficult to recognize them quickly. The reason for this is that the threshold for neurogenic symptoms of hypoglycemia is lower in older people. On the other hand, the threshold for neuroglycopenic symptoms is higher than in younger people. Consequently, the neurogenic and neuroglycopenic symptoms occur almost at the same time. This leads to less warning of impending hypoglycemia and is called impaired awareness of hypoglycemia (20).

The 70-year-old patient from the case presentation had a repeated hypoglycemic attack three hours after her recovery with IV glucose. This most likely happened due to the sulfonylurea medication, glimepiride, still being active in the patient's circulation as a result of impaired renal excretion. An important aspect to mention is that after each hypoglycemic episode, major cognitive changes occur which can lead to post-hypoglycemic encephalopathy. Due to this, recurrent hypoglycemia may be associated with future impaired cognitive function and development of dementia (21).

To prevent further hypoglycemic attacks for this patient the best solution would be to discontinue the sulfonylurea glimepiride. An alternative to use together with metformin could be pioglitazone, a thiazolidinedione. Pioglitazone lowers insulin resistance and does not cause hypoglycemia. Additionally, two other benefits from using this drug in this type of patient with reduced renal function and with a past medical history of a cerebrovascular event, are that it reduces recurrent stroke and major vascular events in ischemic stroke patients with diabetes and that no dosage adjustment is required in renal impairment (14, 22). The risk factors with pioglitazone include congestive heart failure and demineralization with increased

risk of bone fractures in women (22). Other alternatives like dipeptidyl peptidase 4 inhibitors (DPP-4 inhibitor) and sodium-glucose co-transporter 2 inhibitors (SGLT2 inhibitor) neither cause hypoglycemia but they each have their own drawbacks. DPP-4 inhibitors are less effective in lowering glucose concentrations, and have, apart from side effects of nasopharyngitis, upper respiratory tract infections and headaches, also been associated with an increased risk of acute pancreatitis (24,25) and pancreatic cancer (26). SGLT2 inhibitors are less effective in lowering blood glucose in patients with impaired renal function, which therefore would not be a good choice in this patient (27).

The second case explores another cause of hypoglycemia. The 48-year-old woman was referred from another hospital with a strong suspicion of insulinoma. The symptoms of tremor and lightheadedness occurring during fasting and night, the relief of a sweet drink and weight gain were strong indicators of insulinoma. At University Hospital Centre Zagreb, the patient underwent a 72-hour fasting test under supervision. This is the most reliable test to diagnose insulinoma. If the patient becomes symptomatic the test should be cancelled and samples taken before glucose administration, as occurred with the patient after 15 hours. Around 70-80% of patients with insulinomas will get hypoglycemic signs and symptoms within the first 24 hours and 98% within 48 hours (9).

The 72-hour fasting test was carried out with the help of a Continuous Glucose Monitor System (CGMS) developed by Medtronic. This is a diagnostic tool that is inserted in the subcutaneous tissue in the abdomen and functions similar to an EKG Holter monitor, with storing of continuous glucose data measured every five minutes. The advantages with the CGMS comparing to do only the traditionally finger stick tests is that it can measure the erratic fluctuations of blood glucose and catch abnormal measurements at night when the patient might be asymptomatic (28, 29).

The lab results that were taken after she fainted showed a low blood glucose of 1.7 mmol/L with an elevated insulin level of 6.2 mU/mL and an elevated C-peptide level of 0.37 nmol/L. The differential diagnosis with these values of endogenous insulin-mediated hypoglycemia includes sulfonylurea medications, noninsulinoma pancreatogenous hypoglycemia syndrome (NIPHS) and insulinoma. Since this patient did not have T2DM she would most probably not have ingested any sulfonylurea medications, so therefore no iatrogenic cause would be the likely. Hypoglycemia with NIPHS occurs most often postprandially, in comparison with insulinomas, where hypoglycemia most often occurs in the fasting state (12).

From clinical notes, the staff members as University Hospital Centre Zagreb believed the 48-year-old woman possibly exhibited some odd behaviors when she presented to the hospital. This could have been be either due to the hypoglycemia or due to some psychiatric illness. Since her daughter had T1DM, the staff members wanted to assure and rule out that the patient had not taken her daughter's insulin surreptitiously, causing what is called factitious hypoglycemia. To do this, they measured the plasma C-peptide level. C-peptide is a polypeptide that connects the A-chain to its B-chain in the proinsulin molecule, and is cleaved from insulin before it is released in equal amounts from the beta cells (30). Therefore, C-peptide levels can help distinguish if the insulin in the blood stream of the patient came from an endogenous or exogenous source. If insulin is secreted from the pancreas (endogenous source), then C-peptide level will also be increased. If insulin is injected (exogenous source), then C-peptide level will be suppressed (31). In this case, the patient had a C-peptide level of 0.37 nmol/L. A level of 0.2 nmol/L or higher means the source of insulin is endogenous (32). Therefore they could in this case rule out that the hypoglycemia was factitious. Cortisol, which showed normal levels, was measured to rule out adrenal insufficiency, which can cause hypoglycemia. The laboratory values, her history of hypoglycemic attacks that could happen anytime, that she fainted after only 15 hours during the fasting state and the measurement from the CGMS of a low mean value of glucose concentration during the test pointed towards insulinoma.

As mentioned previously in the introduction, when the biochemical diagnosis is positive, then localization of the tumor is the next step. First, non-imaging methods should be used. CT, MRI and transabdominal ultrasonography detect around 75% of insulinomas (2). At University Hospital Centre Zagreb, the patient was first investigated with a MSCT of her abdomen where nothing could be found after which an MRI was performed. The MRI revealed a round mass close to the spleen hilus with irregular borders axially 2.7 x 1.8 cm and with different intensity than the pancreas and the close-by spleen. To further determine if this mass was an insulinoma, an invasive procedure was undertaken in the form of DSA and ASVS. The ASVS had a two- to threefold increase in hepatic venous insulin levels over the baseline and up to a ten-fold increase with stimulation, which made it possible to localize the tumor.

The surgeons removed the body and tail of the pancreas and the spleen. On histological evaluation, a solid 1.9 cm gray tumor with infiltration of surrounding tissue through angioinvasion was appreciated. The mitotic index was 1 per 10 HPF and the Ki-index 4%.

The well-differentiated endocrine tumors are sub-classified as those with benign or uncertain behavior. The well-differentiated endocrine tumors with benign behavior are small (< 2 cm diameter) and low-grade (≤2 mitoses per 10 high power fields, ≤2% Ki-67 staining, and absent vascular or perineural invasion). Therefore, this tumor displayed characteristics of both benign and uncertain behavior endocrine tumors as it had low-grade mitoses and was small, but had a slightly higher Ki-index of 4% and had surrounding angioinvasion. According to the WHO classification of PanNets, this insulinoma is therefore a well-differentiated endocrine carcinoma, due to the local angioinvasion (33). The immunohistochemistry showed positive results of chromogranin (CgA), synaptophysin and insulin. The two former are common markers for neuroendocrine tumors (11).

After the operation in the fall 2011 and up until 2016, the patient did not experience any further hypoglycemic attacks. She was, during this period, in good health and had voluntarily lost some weight. Imaging with F-18DOPA PET/CT did not show any pathological metabolism in 2016. As is showed with this patient, patients usually live a normal life after the operation (34). Thus, quick identification of insulinomas and speedy intervention can provide very favorable outcomes.

Conclusion

Hypoglycemia can present in many different ways and can have many different causes. As explored in this thesis, one cause could be iatrogenic due to hypoglycemic medications, like sulfonylureas, and another cause could be due to endogenous insulin secretion from an insulinoma. Although the incidence of the aforementioned causes of hypoglycemia differs greatly, with iatrogenic hypoglycemia being far more common than insulinomas, the significance of diagnosing the cause of hypoglycemia as soon as possible is nevertheless of equal importance. It is imperative to recognize signs and symptoms hypoglycemia and diagnose the underlying cause because if it is not treated quickly, there can be serious, if not fatal, consequences.

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Biography

Staffan Johnsson was born and raised in Markaryd in the South of Sweden where he graduated from Rikspappersskolan (nowadays Kunskapscentrum Markaryd; KCM). After studying classical piano at the Sankt Sigfrids folkhögskola i Växjö and Vadstena folkhögskola, he entered the Royal Academy of Music (Det Jyske Musikkonservatorium) in Aarhus, Denmark in 2007 and graduated with a Bachelor of Music in classical piano in 2010. In 2011, he decided to change paths and pursue a career in medicine and started his studies at the University of Zagreb School of Medicine. In his free time he enjoys listening to music, playing the piano and playing sports, especially football. He plans to continue his training in Sweden and is interested in infectious diseases, general practice, or neurology as possible specialties.