ORAL ANTIDIABETIC DRUGS INDUCED RECURRENT HYPOGLYCEMIA -A CASE SERIES

Akhila Bollam[1], Harshini Kancherla[1], Gayathri Konduri[1]*, Ramya Bala Prabha. G[2], Ramarao Tadikinda.[3]

1.PharmD Intern, Department of PharmD, CMR College of Pharmacy, Kandlakoya, Hyderabad.

2.PharmD Intern Department of PharmD, CMR College of Pharmacy, Kandlakoya, Hyderabad.

3.PharmD Intern Department of PharmD, CMR College of Pharmacy, Kandlakoya, Hyderabad.

4.Assistant professor, Department of PharmD, CMR College of Pharmacy, Kandlakoya, Hyderabad.

5. Principal and professor, Department of PharmD, CMR College of Pharmacy, Kandlakoya, Hyderabad.

Corresponding Author:

Name: Gayathri Konduri

Address: CMR College of Pharmacy, Kandlakoya, Hyderabad.

ABSTRACT

Diabetes is a chronic disease and its symptoms range from high blood glucose levels and low blood glucose levels. In this study, we are mainly focused on hypoglycemia and its fluctuating factors which are caused by anti-diabetic drugs. Incidence of hypoglycemia in a population is mild-moderate- 45% and severe- 6% In this we are discussing two cases.

Case-1 A 70years old female had chief complaints of shortness of breath for 2 days it is insidious in onset and gradual progression from grade-I to grade III, with dry cough occasionally. The patient was asymptomatic, later, her GRBS levels became high which was treated with insulin, and IV fluids and GRBS was 260mg/dl. And diagnosed with dilated cardiomyopathy with moderate LV dysfunction with fluctuating sugar with hyperglycaemia and hypoglycaemia. Case-2 A 65 years old female was brought to the hospital in an unconscious state with chief complaints of repeated episodes of altered sensorium for 1 day relieved with food/ORS intake within a few minutes. and diagnosed with K/C/O breast carcinoma with recurrent hypoglycaemia secondary to oral anti-diabetic usage. We conclude Hypoglycemia symptoms can be treated by providing patient education and upon continuous monitoring, a physician can minimise the risk in an individual and can provide a better quality of life to a patient.

KEYWORDS: *Diabetes, Hypoglycemia, Antidiabetic drugs*.

INTRODUCTION:

Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Insulin is a hormone that regulates blood sugar.[1]

Diabetes symptoms depend on the elevation of blood sugar levels. Some of the signs and symptoms of diabetes are increased thirst, frequent urination, extreme hunger, unexplained weight loss, fatigue, irritability, blurred vision, slow healing of sores, presence of ketones in urine, and frequent infections like gums or skin infections and vaginal infections.[2]

DRUGS USED IN DIABETES:

A. Enhance insulin secretion:

1. Sulfonylureas: Glibenclamide, Glipizide, Glimepride.

2. Glucagon-like peptide-1(GLP-1) receptor agonist: Exenatide, Liraglutide.
3. Dipeptidyl peptidase-4(DPP-4) inhibitors: Sitagliptin, Vildagliptin, Linagliptin.

B. Overcome Insulin Resistance:

1. Biguanide: Metformin

2. Thiazolidinediones: Pioglitazone.

C. Miscellaneous antidiabetic drugs:

1. Alpha-Glucosidase inhibitors: Acarbose, Voglibose.

2. Sodium- glucose cotransport-2(SGLT-2) inhibitor: Dapaglifazone.[3]

Hypoglycaemia is a condition that occurs when blood glucose or blood sugar levels are lower than the standard range and this condition occurs in people with diabetes having issues with medicine, food or exercise. People having fasting blood sugar of 70 milligrams per deciliter (mg/dl) or 3.9 mill moles per litre (mmol/L) or below are considered hypoglycemia.[4]

CAUSES:

Most hypoglycemia instances occur in diabetes who are undergoing therapeutic intervention with meglitinides, sulfonylureas, or insulin. Drugs are the common cause of hypoglycaemia. Metformin, glucagon-like peptide-1 (GLP-1) receptor agonists, sodium-glucose co-transporter 2 inhibitors (SGLT-2), and dipeptidyl peptidase-4 (DPP-four) inhibitors will often result in hypoglycaemia. Other capacity causes of hypoglycemia are essential illness, alcohol, cortisol deficiency, or malnourishment.[5]

CAUSE	SYMPTOMS [6]
Incorrect insulin administration	Insulin is taken in excess or at the wrong time relative to food intake and/or physical activity; incorrect type of insulin taken
Insufficient exogenous carbohydrate	Delayed or missed meals or overnight fast
Decreased endogenous glucose production	Excess alcohol consumption
Increased utilization of carbohydrate/depletion of hepatic glycogen stores.	Exercise or weight loss.
Increased insulin sensitivity	During the night, exercise, weight loss
Delayed gastric emptying	A condition such as a gastroparesis
Decreased insulin clearance	A condition such as progressive renal failure

SYMPTOMS:

If blood sugar levels are too low, hypoglycemia signs and symptoms can include:

1) Looking Pale
2) Shakiness
3) Sweating
4) An irregular or fast heartbeat
5) Fatigue
6) Difficulty concentrating
7) Dizziness or light-headedness
8) Tingling or numbness of the lips, tongue or check.[7]

EPIDEMIOLOGY:

A meta-analysis observes mentioned that the superiority of hypoglycaemia was 45% for mild/moderate and 6% for intense. Incidence of hypoglycaemic episodes in person per year with mild/moderate and excessive turned into 19 and 0.80, respectively. Hypoglycemia was prevalent among patients on insulin; the prevalence of mild-moderate and severe hypoglycemia episodes was 50 and 21%, respectively. Similarly, amongst the treatment of

sulfonylurea, the prevalence of mild-mild and severe hypoglycemia changed to 30 and 5%. The observed findings concluded that type 1 diabetes mellitus sufferers who are on extensive treatment may experience up to 10 episodes of hypoglycemia and extreme temporarily disabling hypoglycemia for a minimum once 12 months. It is estimated that 2–4% of deaths occur in humans with type 1 diabetes because of hypoglycemia. Hypoglycemia is also similarly commonplace in type 2 diabetes, with a prevalence of 70–80%.[8]

Even though diabetes is managed carefully drugs used to treat diabetes result in drug-induced low blood sugar and rarely non-diabetes-related drugs also cause low blood sugar. Drugs responsible for hypoglycemia i.e. low blood sugar are insulin, metformin, beta blockers like atenolol or propranolol overdose, quinidine, and thiazolidinedione when used with sulfonylureas.[9]

Causes of fluctuating blood sugar levels in diabetic patients are sleep disturbances, emotional disturbances, dehydration, hormonal fluctuations during periods of menopause, oral contraceptives, excessive physical activity, medications like steroids, diuretics and anti-depressants, emotional stress, inadequate intake of medication mainly causes hypoglycemia.[10]

DIAGNOSIS:

If you have signs or signs and symptoms of low blood sugar, take a look at your blood sugar degree with a blood glucose meter a small device that measures and displays your blood sugar level. You have hypoglycemia when your blood sugar level drops below 70 mg/dL. Some people have frequent and excessive hypoglycemia in those cases your health care provider will suggest you use a continuous glucose monitor a device that measures your blood sugar every couple of minutes the usage of a sensor inserted below the skin. Your health care provider will also suggest you have glucagon with you always and he will teach you how to use it.[11]

MANAGEMENT OF HYPOGLYCEMIA:

Mild to moderate hypoglycemia must be dealt with with the aid of the oral ingestion of 15g carbohydrate, ideally as glucose or sucrose tablets or solution. These are the finest orange juice and glucose gels [Grade B, Level 2 (35)]. Patients ought to retest BG in 15 mins and re-treat with some other 15 g carbohydrate if the BG stage stays <4. Zero mmol/L [Grade D, Consensus].

2. Severe hypoglycemia in a conscious person ought to be treated by way of oral inges tion of 20 g carbohydrate, ideally as glucose capsules or equal. BG have to be retested in 15 mins and then re-treated with any other 15 glucose if the BG degree stays <4.0 mmol/L [Grade D, Consensus].

3. Severe hypoglycemia in an unconscious individual

a. With no IV access: 1 mg glucagon should be given subcutaneously intramuscularly. Caregivers or support persons should call for emergency services and the episode should be discussed with the diabetes healthcare team as soon as possible [Grade D, Consensus].

B. With IV access: 10-25 g (20-50 cc of D50W) of glucose should be given intravenously over 1-3 minutes [Grade D, Consensus].

4. For individuals at risk of severe hypoglycemia, support persons should be taught how to administer glucagon by injection [Grade D, Consensus].

5. Once the hypoglycaemia has been reversed, the person should have the usual meal or snack that is due at that time of the day to prevent repeated hypoglycemia. If a meal is >1 hour away, a snack (which includes 15 g carbohydrate and a protein source) needs to be eaten up [Grade D, Consensus].

6. Patients receiving antihyperglycemic sellers which can purpose hypoglycemia need to be counselled approximately techniques for prevention, recognition and remedy of hypoglycemia related to riding and be made aware of provincial driving rules [Grade D, Consensus].[12]

Preventive measures for hypoglycaemia are a few changes that help to maintain steady blood sugar levels like eating at least three evenly spaced meals each day with between-meal snacks as prescribed and exercising for 30 minutes to 1 hour after meals. Check sugar levels before and after exercise, double check insulin and dose of diabetes medicine before taking it, if you drink alcohol, be moderate and monitor blood sugar levels.[4]

CONSEQUENCES OF HU IN THE ELDERLY:

Patients in the older age groups are specifically prone to hypoglycaemic unawareness. Ageing modifies the cognitive, symptomatic, and counter-regulatory hormonal responses to hypoglycaemia. Older adults with diabetes are at much better risk for the geriatric syndrome, which incorporates falls, incontinence, frailty, cognitive impairment and depressive symptoms. In the elderly subjects, episodes of intense hypoglycaemia are more likely to be followed by changes in the blood-brain move which may add further boom the danger of neurological harm to this population. In older patients with T2DM, Whitmer et al discovered a considerable affiliation between the quantity of severe hypoglycaemic episodes and dementia; with ≥ 3 episodes nearly doubling the threat greater episodes of severe hypoglycemia secondary to HU had an increased likelihood of being subsequently recognized with dementia. These reports advocate that intense hypoglycemia and HU in older humans with diabetes may be related to cognitive decline.[13]

CASE:1

A 70years old female had chief complaints of shortness of breath for 2 days it is insidious in onset and gradual progression from grade-I to Grade-III, and dry cough occasionally. The patient was asymptomatic, later, her GRBS levels became high which was treated with insulin, and IV fluids and GRBS was 260mg/dl. Later, when the USG abdomen revealed B/L pleural effusion and mild ascites for which she was admitted. The patient had a history of pedal oedema for 2 days in the ankle and constipation in the last 2 days.

On Physical examinations, vital signs were Blood pressure -140/90 mmHg, Pulse rate is 98b/min, SPO_2-84%@RA and 95%@5LT O_2, CVS-S_1 S_2+, P/A- Soft, RS- BAE+ B/L coarse crept +. GRBS was 85mg/dl for which 1 pint of 25% dextrose was given.

The patient has a history of cardiovascular disease in 2017, and Diabetes mellitus her anti-diabetic drugs are T. Glimp M_1 T. Glimp M_2 and Teneglipton/Metformin (50/500).

Her cholesterol levels were 124.8mg/dl, Urea-47.95mg/dl, Creatinine- 0.90mg/dl, ALT- 85.9U/L, AST-64.8U/L, ALP-119.4U/L, Globulin-3.79g/dl, Blood urea nitrogen- 22.4, and her electrolytes were normal. Her chest x-ray revealed cardiomegaly and B/L pleural effusion which is higher on the left side. The provisional diagnosis was a congestive cardiac failure with polysclerois with B/L pleural effusion with ascites with recurrent hypoglycaemia. Echocardiogram revealed dilation of all chambers, global hypokinesia of LV, grade 1 diastolic dysfunction, severe mitral regurgitation, severe tricuspid regurgitation, and moderate pulmonary hypertension. CT brain showed old infarct.

On Day 2 GRBS was 314mg/dl and was diagnosed with fluctuating GRBS with altered sensorium, heart failure and anasarca. On day 3, GRBS was 104 mg/dl in the morning and 469mg/dl at 7 pm. on day 4, GRBS was 51mg/dl, 25% Dextrose was added and GRBS was 220mg/dl. On day 5, before breakfast, the GRBS was 79mg/dl, After breakfast 311mg/dl

Based on the patient's signs and symptoms, the patient was diagnosed with dilated cardiomyopathy with moderate LV dysfunction with fluctuating sugar hyperglycaemia and hypoglycaemia.

The patient was started on oxygen inhalation@ 5liters/min, Inj Augmentin-1.2gm IV BD, Inj Pantoprazole 40mg IV OD, Inj Lasix 40mg IV BD, T. Enam 2.5mg BD, T. Cardivas 3.125mg BD, T. Asprin 75mg OD, T. Atrovas 40mg OD, Inj HAI, Inj Actrapid according to GRBs.

On discharge her medications were T. Asprin 75mg OD, T. Atrovas 40mg OD, T. MetXL 25md OD, T. Enam 2.5mg BD, T. Lasilactone 20/50 BD, and Injection Actrapid insulin according to GRBs.

CASE: 2

A 65 years old female was brought to the hospital in an unconscious state with chief complaints of repeated episodes of altered sensorium for 1 day relieved with food/ORS intake within a few minutes.

On physical examination, vital signs were Patient was moderately built, nourished, irritable, and conscious, her blood pressure-220/100 mmHg, Pulse rate= 80b/min, SPO_2 = 96%, CVS-S_1 S_2, CNS-Irritable, tone power could not be elicited, P/A- Soft, not distended, Pupils- Right/Left-3mm. GRBS was 37mg/dl which was later increased to 171mg/dl after administration of 25% Dextrose.

The patient has a history of breast carcinoma she has received chemotherapy with doxorubicin, and cyclophosphamide and two cycles were completed, before the third cycle, she was attacked with covid-19 2 weeks back and treated with steroids. At discharge, the patient developed high glucose levels and was diagnosed with steroid-induced hyperglycaemia and was started on Metformin + Glimepiride BID for 1week. The patient has developed repeated episodes of altered sensorium for 1 day relieved with food/ORS intake within a few minutes.

Her urea levels 14.82mg/dl, Creatinine-0.63mg/dl, ALT-20.3U/L, AST-20.4U/L, ALP-69.5U/L, ALB-2.48g/dl, TP-5.27g/dl, TBILC-0.59mg/dl, DBILC-0.12mg/dl, Globulin-2.79g/dl, BUN-6.9, Her electrolytes levels were normal.

Based on the subjective and objective data, the patient was diagnosed with K/C/O breast carcinoma with recurrent hypoglycaemia secondary to oral anti-diabetic usage.

The patients were started on Injection Pantop-40mg IV OD, IVF 25%Dextrose TID, IVF 2Pint Normal saline@ 50cc/hr, T. MVT OD, Stop oral anti-diabetic drugs. The GRBS levels became normal on day 3.

On discharge, her medications were T. Pan 40mg OD, T. Pofenidone 200mg TID for 2 weeks, and T. BC OD.

DISCUSSION:

Recurrent hypoglycaemia can be a life-threatening situation. Here, case 1 describes the patient with signs and symptoms of drug-induced hypoglycaemia in diabetes patient and case 2 describes the patient with signs and symptoms of drug-induced hypoglycaemia which is caused due to anti-diabetic drugs which are given to treat steroid-induced hyperglycaemia. In the first case, the patient's urea, globulin, BUN, ALT, and AST levels were high and the patient also had a previous history of cardiovascular disease, and diabetes the fluctuation in the glucose levels might have increased the workload on the heart worsening the current condition. A possible link between hypoglycemia and acute vascular events like angina, myocardial infarction, and acute cerebrovascular disease has been proposed by several studies[14,15]. Hypoglycemia is a significant restricting element in the management of diabetes and may increase vascular occasions[16]. hypoglycemia is more likely to be associated with cardiac ischemia than hyperglycaemia and normoglycemia[17]. Using metformin in this patient regularly led to hypoglycaemia which is generally not frequent. Occasional hypoglycaemia with Metformin, the most commonly used anti-diabetic drug, is reported when an imbalance between food intake and dose of Metformin is reported. combinations of metformin and thiazolidinediones with sulphonylureas or meglitinides may considerably increase the risk of hypoglycaemia[18]. Generally, hypoglycaemia is frequently observed with insulin therapy which is administered to the patient because of recurrent hyperglycaemia. In type 2 diabetes progressive insulin deficiency and duration of insulin therapy increase the risk of hypoglycemia as in type 1 diabetes, and the risk of hypoglycemia is highest in those with type 2 diabetes who have received insulin for more than 10 years[19]. Catecholamine release and increased myocardial work and oxygen consumption have been shown to occur with hypoglycemia and rapid falls in blood glucose which explains the cardiac failure in the patient[20]. CAD may be a marker for dyslipidemia, which is associated with insulin resistance and metabolic abnormalities[21].

Case 2 describes the case of a 65year old female who has undergone steroid treatment for COVID 19. The patient is not a diabetic, however, she developed hyperglycaemia which is steroid-induced. T. Metformin+Glimiperide were given which caused hypoglycemia in the patient. Here, given doses of GC therapy potentially lead to hyperglycaemia in both hospitalized patients and patients in outpatient care exposing them to a higher risk of acute and chronic complications[22]. In studies where glucose levels were tested systematically amongst patients treated with high dose prednisone or prednisolone in hospital, 53–70% of non-diabetic individuals developed hyperglycaemia[23,24]. Steroids increase insulin resistance in muscle and adipose tissue, reducing peripheral glucose Uptake. Hepatic insulin resistance is also increased, increasing hepatic glucose production through gluconeogenesis and glycogenolysis. Insulin production and release from pancreatic beta-cells are decreased by steroids. These mechanisms contribute to hyperglycaemia and predispose the individual to diabetes[25]. It is understood that hyperglycaemia induced by steroids is through a rise In post-prandial blood glucose levels rather than fasting blood glucose levels[26]. The higher the dose and the greater the potency of the steroid, the greater the risk of Steroid-induced diabetes[27,28]. In the longer-term, steroid-induced diabetes, as with other types of diabetes, places the individual at risk of microvascular such as nephropathy, retinopathy and neuropathy and macrovascular such as cardiovascular complications[29].

Altered sensorium is found in both cases which is due to hypoglycemia. In both cases, hypoglycemia is associated with hypoalbuminemia where albumin levels were 2.64g/dl in case 1 and 2.48g/dl in case 2. Hypoalbuminemia in the recurrent hypoglycemia group may be a marker for undiagnosed inflammation or

infection and increased morbidity and mortality[30,31]. In both cases, the oral antidiabetic drug used is metformin and glimepiride which might have caused the hypoglycemia. Potential mechanisms of metformin-induced hypoglycemia include decreased hepatic glucose production, decreased glucose absorption, and poor oral intake[32]. Growing experimental and clinical evidence shows that metformin can induce lactic acidosis by inhibiting the mitochondrial respiratory chain. As a consequence, cellular glucose metabolism shifts from aerobic to anaerobic and lactate production increases. If energy production has to remain constant, glucose consumption will have to rise, as anaerobic is far less efficient than aerobic metabolism in terms of energy produced per mole of glucose consumed[33,34,35,36]. The risk of drug-induced hypoglycemia should be particularly considered when drugs containing blood glucose-lowering components are combined. Metformin does not usually cause hypoglycemia when administered as monotherapy[37].

However, in both cases after stopping the oral antidiabetic drugs, the glucose levels were normal with insulin. But a proper alternative must be chosen as recurrent hypoglycemia is another concern.

CONCLUSION:

Drug-induced hypoglycaemia is a life-threatening complication of antidiabetic drugs whereas oral antidiabetics-induced hypoglycaemia is not commonly reported but equally important. Fluctuation in glucose levels can be due to many causes, hence it is important to find the underlying causes before the treatment is considered. The physician should carefully evaluate the symptoms of hypoglycemia and educate the patients regarding the symptoms which are caused by the drugs. Close monitoring of the patient is very important. So, their reoccurrence can be minimised in future, and achieve a better quality of life.

REFERENCE:

1)https://www.who.int/news-room/fact-sheets/detail/diabetes.

2)https://www.mayoclinic.org/diseases-conditions/diabetes/symptoms-causes/syc-20371444

3)Philip Mathew, Deepu Thopil. Hypoglycemia. National Library of Medicine.2022 Jan 4; PMID:30521262

4) https://www.webmd.com/diabetes/hypoglycemia-overview

5) KD Tripathi Text Book of Essential of Medical Pharmacology.258-281.

6)Kalra et al. Hypoglycemia- The neglected complication. Indian Journal of Endocrinology and Metabolism. Sep-Oct 2013; Vol 17 (Issue 5).

7) https://www.mayoclinic.org/diseases-conditions/hypoglycemia/symptoms-causes/syc-20373685

8)Thenmozhi Paluchamy. Hypoglycemia DOI: http://dx.doi.org/10.5772/intechopen.86994.

9) https://medlineplus.gov/ency/article/000310.htm

10) https://www.pacehospital.com/roller-coaster-effect-in-diabetes

11) https://www.mayoclinic.org/diseases-conditions/hypoglycemia/symptoms-causes/syc-20373685

12) D. Clayton et al. Hypoglycemia. Can J Diabetes. 2013;37: 69-71.

13)Martín-Timón I, Del Cañizo-Gómez FJ. Mechanisms of hypoglycemia unawareness and implications in diabetic patients. World J Diabetes. 2015 Jul 10;6(7):912-26. DOI: 10.4239/wjd. v 6. i7.912. PMID: 26185599; PMCID: PMC4499525.

14) Desouza C, Salazar H, Cheong B, et al.: Association of hypoglycemia and cardiac ischemia: a study based on continuous monitoring. Diabetes Care 2003, 26: 1485–1489. 10.2337/diacare.26.5.1485

15)Wei M, Gibbons LW, Mitchell TL, Kampert JB, Stern MP, Blair SN. Low fasting plasma glucose level as a predictor of cardiovascular disease and all-cause mortality. Circulation. 2000 May 2;101(17):2047-52. DOI: 10.1161/01.cir.101.17.2047. PMID: 10790345

16) Shafiee, G., Mohajeri-Tehrani, M., Pajouhi, M. et al. The importance of hypoglycemia in diabetic patients. J Diabetes Metab Disord 11, 17 (2012).

17) Desouza C, Salazar H, Cheong B, Murgo J, Fonseca V. Association of hypoglycemia and cardiac ischemia: a study based on continuous monitoring. Diabetes Care. 2003 May;26(5):1485-9. DOI: 10.2337/diacare.26.5.1485. PMID: 12716809.

18) Holstein A, Egberts EH: Risk of hypoglycaemia with oral antidiabetic agents in patients with Type 2 diabetes. Exp Clin Endocrinol Diabetes 2003, 111: 405–414.

19) Zammitt NN, Frier BM: Hypoglycemia in type 2 diabetes: pathophysiology, frequency, and effects of different treatment modalities. Diabetes Care 2005, 28: 2948–2961. 10.2337/diacare.28.12.2948

20) Libby P, Maroko PR, Braunwald E: The effect of hypoglycemia on a myocardial ischemic injury during acute experimental coronary artery occlusion. Circulation 51:621–626, 1975

21)Kreisberg RA. Diabetic dyslipidemia. Am J Cardiol. 1998. 82:67U–73U

22) Aberer F, Hochfellner DA, Sourij H, Mader JK. A Practical Guide for the Management of Steroid Induced Hyperglycaemia in the Hospital. Journal of Clinical Medicine. 2021; 10(10):2154

23)Fong AC, Cheung NW (2013) The high incidence of steroid-induced hyperglycaemia in hospital. Diabetes Res Clin Pract 99:277–280

24)Burt MG, Roberts GW, Aguilar-Loza NR, Frith P, Stranks SN (2011) Continuous monitoring of circadian glycemic patterns in patients receiving prednisolone for COPD. J Clin Endocrinol Metab 96:1789–1796

25) Geer EB, Islam J, Buettner C (2014) Mechanisms of glucocorticoid induced resistance: focus on adipose tissue function and lipid metabolism. Endocrinol Metab Clin North Am 43: 75–102

26) Mills E, Devendrea S (2015) Steroid-induced hyperglycaemia in primary care. London J Prim Care (Abingdon) 7: 103–6

27) Gurvitz JH, Bohn RL, Glynn RJ et al (1994) Glucocorticoids and the risk for initiation of hypoglycaemic therapy. Arch Int Med 154: 97–101

28)Clore JN, Thurby-Hay L (2009) Glucocorticoid-induced hyperglycaemia. Endocr Pract 15: 469–74

29) Morris D (2018) Steroid-induced diabetes and hyperglycaemia. Part 1: mechanisms and risks.Diabetes & Primary Care 20: 151–3

30) Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. Arch Intern Med. 1997. 157:1681–1686.

31)Fuhrman MP, Charney P, Mueller CM. Hepatic proteins and nutrition assessment. J Am Diet Assoc. 2004. 104:1258–1264.

32) Al-Abri SA, Hayashi S, Thoren KL, Olson KR. Metformin overdose-induced hypoglycemia in the absence of other antidiabetic drugs. Clin Toxicol (Phila). 2013 Jun;51(5):444-7. DOI: 10.3109/15563650.2013.784774. Epub 2013 Apr 1. PMID: 23544622.

33)Owen MR, Doran E, Halestrap AP. Evidence that metformin exerts its anti-diabetic effects through inhibition of complex 1 of the mitochondrial respiratory chain. Biochem J 2000; 348:607–614

34)Protti A, Fortunato F, Monti M, Vecchio S, Gatti S, Comi GP, et al. Metformin overdose, but not lactic acidosis per se, inhibits oxygen consumption in pigs. Crit Care 2012; 16: R75.

35)Protti A, Lecchi A, Fortunato F, Artoni A, Greppi N, Vecchio S, et al. Metformin overdose causes platelet mitochondrial dysfunction in humans. Crit Care 2012; 16: R180

36)Protti A. One other explanation for hypoglycemia during metformin overdose. Clin Toxicol (Phila). 2013 Jul;51(6):515. DOI: 10.3109/15563650.2013.808749. Epub 2013 Jun 14. PMID: 23768030.

37) Zitzmann S, Reimann IR, Schmechel H. Severe hypoglycemia in an elderly patient treated with metformin. International Journal of Clinical Pharmacology and Therapeutics. 2002 Mar;40(3):108-110. DOI: 10.5414/cpp40108. PMID: 11911598.