

Primary Etiological Profile Of Hospitalized Patients With Documented Episode Of Hypoglycemia

B.S.V.V.Ratnagiri^{1*}, Praveen Kasina², Lella Padmaja³, M.Jagan Mohan⁴, S.Meghana⁵, G.Teja Krishna⁶

¹Assistant Professor of Gastroenterology, Siddhartha Medical College, Vijayawada, A.P, India

²Intern, Siddhartha Medical College, Vijayawada, A.P, India

³Tutor in Obstetrics and Gynecology Siddhartha Medical College, Vijayawada, A.P, India

⁴Professor & HOD of Gastroenterology, Siddhartha Medical College, Vijayawada, A.P, India

⁵Post graduate in General Medicine, Siddhartha Medical College, Vijayawada, A.P, India

⁶Intern, Pinnamaneni Siddhartha Institute of Medical Sciences, Chinna Avutapalli, Vijayawada, A.P, India

Received: 26-11-2021 / Revised: 21-12-2021 / Accepted: 08-01-2022

Abstract

Background: Glucose is a major fuel source for body tissues. Plasma glucose concentrations are maintained between 70 to 110 mg/dl in the fasting state. Homeostasis is maintained by stimulating counter hormone response and suppressing insulin secretion during hypoglycemic episodes. Any derangement in homeostasis can cause hypoglycemia. **Objectives:** To investigate, identify, determine and analyze the incidence of primary etiological profile of hospitalized patients. **Material and methods:** Patients admitted in the General Medicine wards who had at least one episode of documented hypoglycemia i.e less than 70mg/dl and age ≥ 18 years were included and observed over a period of 24 months i.e November 2019 to November 2021. The data obtained was analyzed statistically by using chi square test. **Results:** In present study of 119 patients 90 were male and 29 were females. Diabetes with Chronic Kidney Disease was found to be the most common primary diagnosis. As we analyze the presence of risk factors in hospitalized hypoglycemic patients, it was found that as the number of risk factors in a patient increases, chance of succumbing to them also increases. In the category of patients having 3 or more risk factors, the death rate was 15 out of 42 which is 35.71%. **Conclusions:** Hypoglycemia needs to be investigated thoroughly to know the causative factor and should be treated appropriately. Hypoglycemia is an important predicting factor of mortality in cases of heart failure and sepsis.

Keywords: Hypoglycemia, Diabetes mellitus, Heart failure, Chronic kidney disease, Mortality rate.

This is an Open Access article that uses a funding model which does not charge readers or their institutions for access and distributed under the terms of the Creative Commons Attribution License (<http://creativecommons.org/licenses/by/4.0>) and the Budapest Open Access Initiative (<http://www.budapestopenaccessinitiative.org/read>), which permit unrestricted use, distribution, and reproduction in any medium, provided original work is properly credited.

Introduction

Hypoglycemia is reported as an independent factor for mortality and morbidity in hospitalized patients in several studies (references). A major metabolic substrate for the brain is Glucose. The brain needs glucose supply continuously from systemic circulation as it can neither store nor synthesize glucose. The common cause of hypoglycemia is Insulin or Insulin secretagogues treated diabetes but various other hazardous factors are responsible for hypoglycemia in an individual. Significant pathology may or may not be associated with hypoglycemia. Hypoglycemia can occur in pathological states like sepsis, hormone deficiencies, Insulinoma, prior gastric surgeries, critical organ failure. Glucose is a major fuel source for body tissues. Plasma glucose concentrations are maintained between 70 to 110 mg/dl in the fasting state.

Homeostasis is maintained by stimulating counter hormone response and suppressing insulin secretion during hypoglycemic episodes. During fasting and between meals, glucose levels are maintained by gluconeogenesis and glycogenolysis. Any derangement in homeostasis can cause hypoglycemia. Altered homeostasis of glucose is a disease process. It is important to recognize risk factors for hypoglycemia in patients and prevent its recurrence. In our hospital, we have many patients with episodes of hypoglycemia admitted with different diseases. The aim of this study is to analyze the risk factors and disease process of hypoglycemia and to predict in-hospital mortality due to hypoglycemia.

*Correspondence

Dr. B.S.V.V.Ratnagiri

Assistant Professor of Gastroenterology, Siddhartha Medical College, Vijayawada, A.P, India

E-mail: drratnagiri@gmail.com

Definition of hypoglycemia

The diagnosis of hypoglycemia is based on Whipple's triad[20].

- Low blood glucose concentration
- Symptoms consistent with hypoglycemia
- Relief of symptoms when the blood glucose level is raised to normal by exogenous administration of glucose.

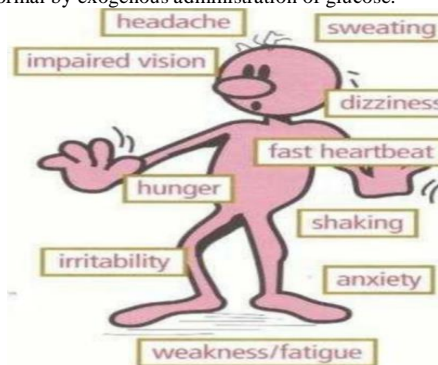


Fig1: Signs and symptoms of hypoglycemia

Plasma glucose level below 70 mg/dl is taken as hypoglycemia as per ADA guidelines.

Adult hypoglycemia

- A. Internal causes**
- 1. Insulin mediated**

Causes of Insulin mediated hypoglycemia are Insulinoma, Nesidioblastosis, Reactive hypoglycemia, and Insulin antibody-mediated.

- Frequent self monitoring of blood glucose(SMBG) or continuous glucose monitoring(CGM).
- Patient education and empowerment.

For glucose levels between 55-69mg/DL, 15-15 rule is applied, consume 15g of fast acting carbohydrates and blood glucose is rechecked after 15 minutes.

Fig2:Regulation of blood glucose levels. In the treatment of Diabetes, hypoglycemic episode is significant limiting factor[7,8]. In type 1 and type 2 diabetes mellitus, hypoglycemic episodes cause severe morbidity and an important risk factor for predicting mortality[9,10].

2. Insulin independent

Causes of Insulin independent hypoglycemia are neoplasia, sepsis, kidney failure, liver disorders, congestive cardiac failure, endocrine abnormalities, antibody to Insulin receptor.

- During fasting states, gluconeogenesis occurs in liver and kidney, as this is hampered in chronic renal failure hypoglycemia occurs[11,12].
- Hypoglycemia may also lead to hypokalaemia that may cause cardiac repolarisation abnormalities[13,14,15].
- Hypoglycaemic episodes are associated with the release of inflammatory cytokines which include IL-8, IL-6, CRP, TNF α and endothelin-1. Thus, endothelial dysfunction and

inflammation can potentiate cardiovascular risk in hypoglycaemia[15,16,17].

B. External causes

1. Medications

i) Direct effect

Sulfonylureas
Insulin
Pentamidine
Antimalarial
Disopyramide
Beta2 adrenoceptor agonist

ii) Drug interaction

- Biguanides
- PPR γ agonists
- Beta-blockers
- ACE inhibitors
- 2. Ethanol: consuming alcohol in young children may cause hypoglycemia[18]. In 18-56% of people admitted due to severe hypoglycemia alcohol is the underlying cause[19].
- 3. Toxins and factitious

Management of hypoglycaemia

Reducing the risk of hypoglycaemia while maintaining glycaemic controls involves:

- Individualised glycaemic controls.
- Flexible and rational insulin regimens.
- Ongoing professional guidance and support.



Fig 2: Defense against hypoglycemia.

Aim of the study

1. To recognize the primary etiological profile of hospitalized patients with at least one documented episode of hypoglycemia.
2. To investigate and identify the risk factors associated with hypoglycemia.
3. To determine the incidence of hypoglycemia in patients admitted to the medicine ward.
4. To identify if hypoglycemia with associated risk factors predicts increased mortality rate in hospitalized patients.

Materials and methods

Study Population

All patients were admitted to medical ward with hypoglycemia in Siddhartha Medical College and Government General Hospital, Vijayawada.

Inclusion Criteria

1. Patients admitted in the medical ward who have at least one episode of documented hypoglycemia i.e less than 70mg/dl.
2. Age greater than or equal to 18 years

Exclusion Criteria

1. Pregnant woman.
2. Patient's less than 18 years of age.
3. Patients not willing to participate in the study

Study Centre

Department of General Medicine, Siddhartha Medical College and Government General Hospital, Vijayawada.

Study Design

Prospective, Observational study

Sample Size

One hundred and nineteen cases

Duration of the study

November 2019 to November 2021

At the time of admission or during the hospital stay patients with documented hypoglycemia are taken up for the study. Symptoms of hypoglycemia may vary from mild to severe. Patients presenting with sudden onset of a seizure, altered behavior, or altered sensorium either in the emergency department or in the medical wards are checked immediately for blood sugar with capillary blood glucose measurement. Any documented blood sugar value less than 70 mg/dl is taken as hypoglycemia and the patient is taken up for study after obtaining consent from the patient or the relatives, if the patient is in altered sensorium. Even those patients whose routine blood sugar shows hypoglycemia (<70 mg/dl) are included in the study, even if they are asymptomatic. Only pregnant patients and patients less than 18 years of age are excluded from the study. Detailed informed consent is obtained from the patient or from his close relatives, if the patient is in altered sensorium. All patients who qualify for the study and had given consent are evaluated by means of a questionnaire that contains details of-

1. Clinical history which includes relevant symptoms
2. Detailed past medical history that includes the presence or absence of diabetes, duration of diabetes, and other known clinical illnesses like RHD, CAD, CKD, DCLD, Pulmonary Tuberculosis, Bronchial Asthma, Seizure disorder, etc.
3. Personal habits which include diet, sleep pattern, Alcohol/tobacco/cannabis/ cocaine, and other drug abuse.

4. Previous drug and treatment including insulin injection, oral-hypoglycaemic drugs, and other medications
5. History of recent poisoning, native drug abuse, tattooing, blood transfusion.
6. Sexual behaviour and proximity
7. Detailed physical examination
 - General examination including vital signs
 - Anthropometry
 - Cardiovascular system
 - Respiratory system
 - Abdomen
 - Central nervous system
8. Laboratory investigations

- Complete blood count, ESR,CRP,Urine routine, Renal function tests, Liver function tests, Serum electrolytes, Thyroid function test, Urine culture and sensitivity, Blood culture and sensitivity, Electrocardiography
9. Relevant investigations
 - Chest X-ray
 - Ultra sonogram of the abdomen
 - CT Brain and MRI Brain

Observation and results

In the 24 months, period study around 119 patients were admitted in General Medicine wards of Siddhartha Medical College, Government General Hospital, Vijayawada were found to have at least one episode of documented hypoglycemia. Patients were further investigated and data obtained analyzed statistically. The primary etiological profile of the patient are as follows

Table 1: Primary etiological profile in study sample

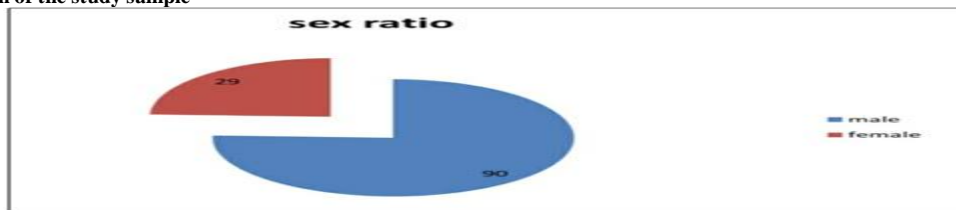
Diabetes with Chronic kidney disease	45 (37.81%)	
● Chronic kidney disease	17	(14.28%)
● Acute liver dysfunction	17	(14.28%)
● Chronic liver disease	4	(3.36%)
● Sepsis	10	(8.4%)
● Congestive cardiac failure	11	(9.24%)
● Alcohol intoxication	3	(2.52%)
● Malignancy	3	(2.52%)
● Chronic Pancreatitis	3	(2.52%)
● Diabetes Therapy related	5	(4.20%)
● Reactive	1	(0.84%)

The aim of the study is to analyze the clinical pattern of patients admitted with hypoglycemia. This is done by analyzing the

- Primary Diagnosis.
- Sex pattern.
- Age pattern

Diabetes with Chronic Kidney Disease was found to be the most common primary diagnosis

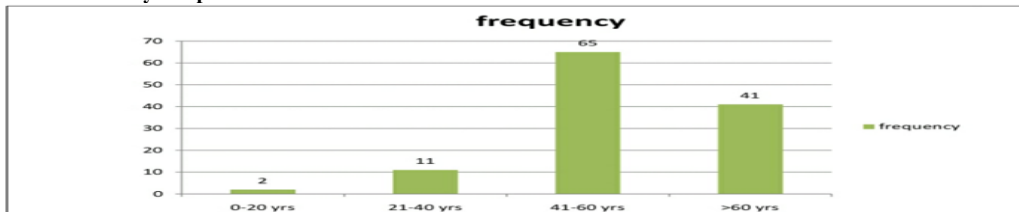
Sex distribution of the study sample



In the present study, the male population accounted for 75.63% and females accounted for 24.36%. Thus in the present study male gender constituted for significant 3/4th of the study sample.

There were total of 45 patients in this category which accounts for 37.81%. Non diabetic CKD and Acute liver dysfunction account for 14.28% each. Sepsis and congestive heart failure constituted 8.4% and 9.24% respectively. Contrary to the popular belief, Diabetes therapy related cases account for 4.2% only.

Age distribution of the study sample



Age distribution of the study sample

In the present study, patients in the age group of 41 to 60 years accounted for 54.6% followed by 61 to 80 years age group which constituted 34%.

Incidence of hypoglycaemia during the study period

One hundred and nineteen patients have documented episodes of hypoglycemia. Eleven thousand two hundred and seventy-six patients are admitted in the ward during the study period.

The incidence of hypoglycemia in the present study is about 1.05%. The incidence of hypoglycemia was calculated by taking into account the patients admitted in medical wards alone during the study period.

Table 4: Etiological profile in diabetic patients

Diabetes Association	Frequency	Percentage
CKD	45	67.1%
SEPSIS	5	7.46%
THERAPY RELATED	5	7.46%
HEART FAILURE	5	7.46%
ALD	3	4.47%
CHRONIC PANCREATITIS	3	4.47%
CLD	1	1.49%

In diabetic patients, kidney disease accounts for the major cause of hypoglycemia accounting for 67.1%. Therapy related hypoglycemia accounts for only 7.46% in the present study. Sepsis and Heart failure accounts for 7.46% each.

Mortality pattern in diabetes mellitus

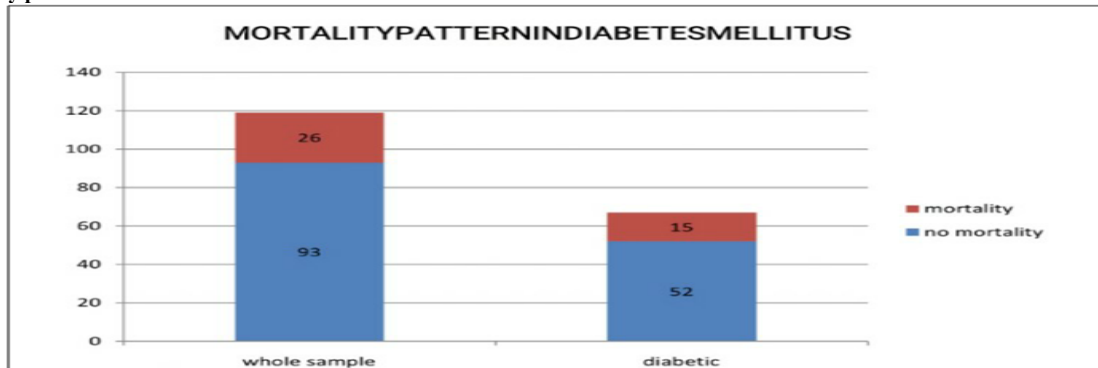


Fig 5: Bar diagram showing mortality pattern in diabetes mellitus

In the present study, there were 67 patients (56.3%) had diabetes mellitus. The number of deaths among the diabetic patients was fifteen (15) while it was twenty-six (26) for the whole study sample. Thus, diabetes mellitus accounted for 56.3% of cases and 57.9% of the mortality cases. In order to find out if diabetes mellitus is a predictor of mortality in hospitalized patients having hypoglycemia, statistical analysis by using the chi-square test was done with a significant p-value at 0.05.

The significance level of the p-value is 0.05.

The Chi-square value and p-value for the above data are 0.0261, 0.8716 respectively. The obtained p-value for the above data is

greater than 0.05, so the considered variable is not significant. Though Diabetes mellitus is commonly associated with hypoglycemia, it is not associated with increased mortality.

Mortality pattern of chronic kidney disease

Out of total of 119 patients, 69 patients had kidney disease. This accounts for around 57.98% of the study sample. 15 patients with kidney disease died out of total 69 patients with kidney disease which accounts for mortality in 21.73% of patients with kidney disease. Data is subjected to statistical analysis by using Chi square test to analyze if kidney disease is a predictor of mortality in hypoglycemia.

Table 6: Mortality pattern of CKD

Risk factor	Mortality	Deaths	Total
Kidney disease	15	54	69
Other diseases	11	39	50
Total	26	93	119

The significance value of the p-value is taken at 0.05

Chi -square value : 0.0012

Obtained p - value : 0.9728

The obtained p-value for the above data is 0.9728 which is greater than 0.05, so the variable considered is not significant. Kidney disease is commonly associated with hypoglycemia but is not a predictor of mortality.

Mortality pattern of heart failure

11 patients out of 119 patients with hypoglycemia are heart failure patients. They account for about 9.24% of the study sample. Out of 11 heart failure patients with hypoglycemia, 6 patients died. Mortality in heart failure patients with hypoglycemia is 23% of all deaths due to hypoglycemia. Mortality within this subcategory is 54.54%.

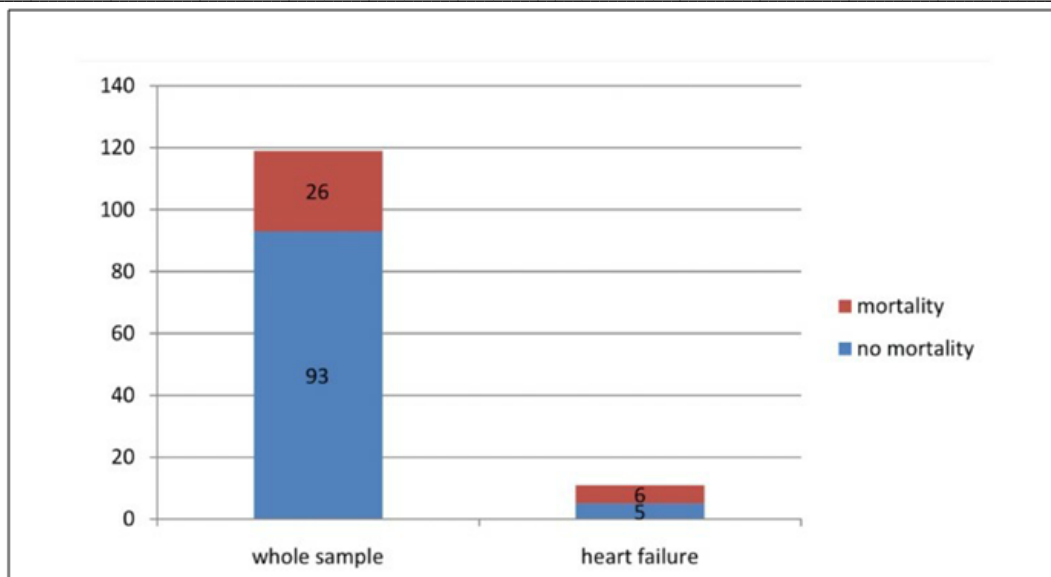


Fig 7: Bar diagram showing mortality of heart failure

The significance level of the p-value is 0.05 Chi-square value is 7.5886

Obtained p-value is 0.0058.

The obtained p-value is 0.0058 which is less than 0.05. So heart failure is a significant predictor of mortality.

Mortality pattern based on age group

The maximum number of people in the study were in the category of 41-60 years. This category accounted for 54.62% of the sample. Next

in order of frequency was 61-80years category. There were 41 patients (34.45%) in this age group. However, the maximum number of deaths belongs to this category of patients.

Chi-square statistical analysis was done on the age group data of the sample to know if increasing age was an important predictor of mortality in hypoglycaemic patient.

Table 9: Age group as a predictor of mortality

AGE(years)	Live cases	Death cases	Total
0 - 20	2(2.2%)	0(0%)	2(1.7%)
21 - 40	8(8.6%)	3(11.5%)	11(9.2%)
41 - 60	58(62.4%)	7(26.9%)	65(54.6%)
61 - 80	25(26.9%)	16(61.5%)	41(34.5%)
TOTAL	93(100%)	26(100%)	119(100%)

The significance level of the p-value is 0.05

Chi-square value :9.3063

Obtained p - value : 0.0022

The elderly age group is an important predictor of mortality of hypoglycemia as obtained p-value is lesser than 0.05.

Discussion

Incidence of hypoglycemia

In our study conducted in the medicine wards of Siddhartha Medical College, Government General hospital, around 119 patients were found to have at least one episode of hypoglycemia in a 6 month study period. The incidence is found to be 1.05%. This includes both diabetic and non-diabetic patients.

Alexander Turchin et al[4] have shown an incidence of 7.7% in patients with diabetes. The lower incidence in our study is probably due to considering hypoglycemia incidence in both diabetic and nondiabetic populations. Moreover incidence was calculated for the entire admissions to the medical wards in the entire study period that includes 11276 admissions

Age distribution

In our study the maximum number of patients was in the age group of 41-60 yrs accounting for 54.6% followed by >60 yrs age group constituting 34.5% of study population. But 61.5% of total deaths in the study population are documented in age group > 60 years. The

elderly age group is an important predictor of mortality in hypoglycaemic patients.

According to Ahmed H Abdelhafiz et al study[1], in elderly patients > 75 years of age autonomic symptoms are noticed at lower blood sugar levels but cognitive dysfunction occurs at relatively higher blood sugars than in the younger population. In the elderly age group, less specific symptoms of hypoglycemia are seen, so hypoglycemia is under-recognized. Hypoglycemia in the elderly is associated with increased mortality due to multiple factors like multiple coexisting risk factors and frailty.

In Shilo.S.et al[2] study, increasing age is a risk factor for hypoglycemia which is consistent with our present study. In the present study, the most common age group observed is 41-60 years. In the study done by Santra G et al[10], the mean age group observed is 42.84±10.09 and the most common age group observed is 32 – 52 years . This is similar to the present study.

In the study done by Jeon . J . Kim Se et al[3], mean age group identified was 66.3 +/- 10 years. Most common age group is 56.3 – 76.3 years .

Sex

In the present study, out of 119 patients , 90 are male and 29 are female . This is similar to a hospitalbased study done by Santra G et al, hypoglycemia is commonly seen in male patients when compared to female patients. In the study 55 patients were observed and of them 29 patients were male and 26 were female. In Jeon . J . Kim Se et al

study[3] , 129 patients were observed among them 3 were females remaining 76 patients were males.

Associated risk factors

In the present study, the majority of the patients 37.81% had primary diagnosis of CKD with diabetes mellitus. 14.28% of the patients had diagnosis of CKD. Indicating that hypoglycaemia is most commonly encountered in patients suffering from chronic kidney disease.

In the study done by Jared A Dendy et al,CKD is identified as common risk factor for hypoglycemia. 69.1% of the patients participated in the study had CKD as primary risk factor for severe hypoglycaemia. These results are comparable with the present study where primary risk factor was also identified as CKD .CKD and Diabetes are major hazardous factors for hypoglycemia but are not important predictors of mortality in the present study.

According to Chici Pratiwi et al study, the most common risk factor observed for hypoglycemia is Kidney disease which is consistent with the present study. In Kathleen. F. Fischer[5] et al study the most common hazardous factors identified for hypoglycemia are Diabetes which accounted for 45% and CKD was the next most common cause of hypoglycemia in non-diabetic patients. Common hazardous findings identified in our present study are Diabetes and CKD.Kidney disease forms a major hazardous factor for hypoglycemia in Diabetes patients. Findings are consistent with S.G.Bruderer et al[6] study in which study risk factors for severe hypoglycemia were Insulin treatment, Kidney disease and increasing age. The commonest hazardous factors associated with low blood sugar levels in our study are Kidney disease , Diabetes on therapy and acute liver injury. In Diabetes patients presented with hypoglycemia most common associated factor for hypoglycemia is kidney disease

Conclusions

Hypoglycemia needs to be investigated thoroughly to know the causative factor and should be treated appropriately. Renal failure, Congestive heart failure, and Sepsis are precipitating factors for hypoglycemia in diabetes patients. Common causative factors for hypoglycemia in non-diabetic patients are Renal failure, Sepsis, and Alcoholic hepatitis. Hypoglycemia in T2DM patients due to OHA/Insulin food mismatch is mild in absence of organ failure. In this study alcohol was an important causative factor for hypoglycemia.

References

1. Abdelhafiz, Bailey C, Eng Loo B, Sinclair A. Hypoglycaemic symptoms and hypoglycaemia threshold in older people with diabetes-A patient perspective. *The journal of nutrition, health & aging*. 2013;17(10):899-902.
2. Shilo S et al.Hypoglycemia in hospitalized non diabetic older patients.*J Am Geriatric Society* . 1998 Aug ;46(8):978-82
3. Jeon J, Kim S, Kim H, Kim D, Lee K, Lee J et al. Risk factors of severe hypoglycemia requiring medical assistance and

neurological sequelae in patients with diabetes. *Medicine*. 2016;95(47):e5365.

4. Alexander Turchin et al .Hypoglycemia and clinical outcomes in patients with diabetes mellitus hospitalized in general wards. *Diabetes Care* 2009; Jul 32 (7): 1153-1157.
5. Kathleen F Fisher et al.Hypoglycemia in hospitalized patients; *NEJM* ; 1986;315:1245-1250.
6. S.G .Bruderer et al .Incidence and risk factors for severe hypoglycemia in treated type 2 diabetes mellitus patients in UK.*Diabetes, Obesity and Metabolism*;2014 ; volm.16;issue 9:801-811.
7. Cryer PE . The barrier of hypoglycemia in Diabetes. *Diabetes* 2008;57:3 3169-3176
8. Cryer PE.Hypoglycemia in Diabetes: Pathophysiology, prevalence and prevention. Association,2009 Alexandria, VA:American Diabetes
9. Campbell IW.Dead in bed syndrome : a new manifestation of nocturnal hypoglycemia ? *Diabet Med* 1991; 8 : 3-4
10. Borsch –Johnsen K, Helweg- Larsen K.Sudden death and human insulin: is there a link ? *Diabetes Med* 1993; 10:255-9
11. Stumvoll M,Meyer C,Mitrakou A et al.Importance of kidney in carbohydrate metabolism.*Med Hypotheses* 1999;52:363-366
12. Haviv YS,Sharkia M ,Safadi R. Hypoglycemia in patients with renal failure *Ren Fail* 2000;22:219-223.
13. Laitinen T, Lyyra-Laitinen T et al. Electrocardiographic alterations during hyperinsulinemic hypoglycemia in healthy subjects. *Ann Noninvasive Electrocardiol*. 2008;13:97–105
14. Gill GV, Woodward A, et al Cardiac arrhythmia and nocturnal hypoglycaemia in type 1 diabetes: The ‘dead in bed’ syndrome revisited. *Diabetologia*. 2009;52:42–5.
15. Galloway PJ, Thomson GA, Fisher BM, Semple CG. Insulin induced hypoglycemia induced a rise in C-reactive protein. *Diabetes Care*. 2000; 23:861–2.
16. Fisher BM, Hepburn DA, Smith JG, Frier BM. Responses of peripheral blood cells to acute insulin-induced hypoglycaemia in humans: Effect of alphaadrenergic blockade. *Horm Metab Res Suppl*.1992;26:109–10
17. Sommerfield AJ, Wilkinson IB, Webb DJ, Frier BM. Vessel wall stiffness in type 1 diabetes and the central hemodynamic effects of acute hypoglycemia. *Am J Physiol Endocrinol Metab*. 2007; 293:E1274–9.
18. Maclaren NK,Valman HB,Levin B.Alcohol induced hypoglycaemia in Childhood. *BMJ*.1970;1:278-280
19. Marks V,Teale JD,Drug induced hypoglycaemia. *Endocr, met.Clin. North.Am* 1999; 28:555-577
20. Whipple AO. The surgical therapy of hyperinsulinism. *J.Int.Chir* 1938;3:237-276.

Conflict of Interest: Nil Source of support: Nil