# TO DETERMINE THE FREQUENCY OF HYPOGLYCAEMIA IN DIABETIC PATIENTS TAKING ORAL HYPOGLYCAEMIC DRUGS/ INSULIN

[1]**Dr. Syed Farasat Ali Shah, **[2]**Dr. Eesha Noor, **[3]**Dr. Ifaza Tariq**
[1]PIMS Islamabad
[2]DHQ, Hospital Jhelum
[3]Holy Family Hospital Rawalpindi

**Abstract:**

*Background:* *The risk of severe hypoglycemia is greatly increased in subjects having old age, renal failure, hepatic failure and pregnancy. The overall prevalence is 2–3%, and the lifetime risk is around 15%.*

*Objective: To determine the frequency of hypoglycemia in diabetic subjects taking oral hypoglycemic agents/ Insulin therapy.*

*Method: This cross-sectional study includes 250 out/in patient type 2 diabetic subjects visiting to Pakistan Institute of Medical Sciences that is a tertiary care hospital from 06-12-2013 to 06-06-2014. Subjects of both genders, age more than 12 years, diagnosed case of type 2 diabetes mellitus (including subjects admitted to emergency department or emergency room) using insulin/oral hypoglycemic agents were included. Subjects were categorized between 12 to > 60 years of age groups. Non-Probability Consecutive sampling technique was used. Sample size was calculated by using WHO (World Health Organization) sample size calculator. Baseline characteristics and other detailed information was obtained by using electronic questionnaire. Once stabilizing the subjects were asked about hypoglycemic episodes by inquiring about the hypoglycemic symptoms.*

*Result: Total of 250 subjects having Type 2 diabetes, taking oral hypoglycemic agents/insulin were included in this study. Mean age of study subjects was 46.02 ± 34 years. Male gender was predominant compared to females. Out of 250 subject's frequencies of hypoglycemia was seen in 60(24%) subjects taking oral hypoglycemic agents or insulin. Results indicate 34(56.6%) subjects have hypoglycemia in more than 50 years of age. Total of 104(41.6%) subjects were taking insulin only, 63 (25%) oral hypoglycemic agents and 83(33.3%) both oral hypoglycemic agents and insulin Lantus (Glargine). On the basis of types of insulin Premix 70/30 insulin was used in 60% of subjects. After comparing oral hypoglycemic agents most of the subjects 53.30% were observed taking Glibenclamide.*

*Conclusion: This study concludes that high frequency of hypoglycemia not associated with increased mortality risk but may be a marker of disease burden. Hypoglycemic episodes can be prevented by keeping the lowest possible dose of insulin or oral hypoglycemic agents (or using shortest acting oral hypoglycemic agents) or by proper counseling of subjects about lifestyle management and making the subjects aware about hypoglycemic symptoms.*

**Key Words:** *Diabetes mellitus, hypoglycemia, oral hypoglycemic agents/ Insulin*

**\*Corresponding Author:**
**Dr. Syed Farasat Ali Shah,**
*PIMS Islamabad*

QR code

## INTRODUCTION:

According to International Diabetes Federation (IDF), 425 million people in all over the world are suffering from diabetes mellitus.[1] As reported earlier, incidences of both type of diabetes are increasing throughout the world but, the prevalence of type 2 diabetes is rising much more rapidly.[2] It occurs because of aging of the population, increasing obesity and low activity levels. One of the most important complications of diabetes mellitus is hypoglycemia which mainly leads to neuroglycopenic symptoms and sometime death of the subject.[3] Risk factors of severe hypoglycemia were observed in subjects having old age, renal failure, hepatic failure and pregnancy.[4] Type 2 diabetes with poor control is also associated with microvascular, macrovascular, and neuropathic complications.[5]

In hypoglycemia the brain becomes neuroglycopenic and promote secretion of epinephrine and nor epinephrine along with glucagon which in turn have relevant cardiovascular effects by producing quick response. This situation mainly occurs with no symptoms. Type of diabetes play a key role in the frequency of severe hypoglycemic events. As estimated for type 1 diabetes one and three events per subject-year and for type 2 diabetes 0.4 and 0.7 events.[6] The value can also be three in type 2 diabetes. In previous study, the rate of major hypoglycemic episodes in oral hypoglycemic agents group and in insulin treated group was 1.7% and 1.8% was observed.[7]

Hypoglycemia in type 2 subjects can compromise clinical outcomes with delayed initiation of insulin and non-adherence to insulin treatment. Hypoglycemic events also occur due to a comparative excess use of medication (in particular, insulin).[8] In most of type 2 diabetic subject lifestyle modifications are followed with first-line oral metformin to maintain glycemic control. But, to achieve and maintain good glycemic control Type 2 diabetics eventually require therapy intensification. American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) also recommends treatment by second oral agent as initiation of basal insulin, or a glucagon-like peptide-1 receptor agonist to achieve glycated hemoglobin (A1C) targets instead of non-insulin therapy at maximum tolerated dose over 3 months.[9]

The rationale of this study was to determine the frequency of hypoglycemic in type 2 diabetic subjects using insulin or oral hypoglycemic agents (or using shortest acting oral hypoglycemic agents) by proper counseling of patients.

## METHOD:

This Cross-sectional study was conducted at in/out patient department of General Medicine, Pakistan Institute of Medical Sciences Islamabad from 06 December 2013 to 06 May 2014. Total of 250 subjects were included in the study. Non-Probability Consecutive Sampling technique was used. Sample size was calculated by using WHO (World Health Organization) sample size calculator (where Confidence level=95%, Absolute precision 10%, Population proportion 1.4/1.8%). The subjects of both genders, age more than 12 years, diagnosed case of diabetes mellitus (including subjects admitted to emergency department or emergency room) using insulin/oral hypoglycemic agents were included. Subjects were categorized between 12 to > 60 years of age groups with the 10 years difference. Subjects with excessive alcoholism, hepatic, renal or cardiac failure were excluded on the basis of history examination, history of liver function test and renal function test and no such recorded symptoms. Addison's disease (was diagnosed by taking history from the subjects and asking whether he is taking steroids or not), Insulinoma, (Diagnosed by Whipple triad), Quinine therapy, Salicylates poisoning and Insulin/insulin secretagogue were also excluded.

All subjects fulfilling the inclusion criteria were enrolled for study. After receiving subjects in outpatient department, in emergency department or in emergency room subjects are initially resuscitated after checking plasma glucose by glucometer. This plasma reading was obtained to reconfirm the subjects and not recorded. Along with baseline demographic characteristics detailed information regarding education, family status and awareness about hypoglycemia were obtained using electronic questionnaire. Once stabilizing the subjects were asked about hypoglycemic episodes by inquiring about the hypoglycemic symptoms. He/she were asked about hypoglycemic episodes and how they manage these episodes of hypoglycemia. In subjects with hypoglycemia duration of diabetes was also recorded. Subjects were categorized into three main categories: subjects taking insulin only, taking oral hypoglycemic agents and taking both oral hypoglycemic agents and insulin. They were further categorized on the basis of types of insulin and types of oral hypoglycemic agents.

Diabetes Mellitus is defined as, a Fasting Plasma Glucose <7.0 mmol/L (126 mg/dL), or >11.1 mmol/L (200 mg/dL) 2 hours post prandial or an HbA1C >6.5% (according to American Diabetes Association) warrant the diagnosis of Diabetes Mellitus. Random plasma glucose concentration >11.1 mmol/L (200

mg/dL) accompanied by classic symptoms of DM (polyuria, polydipsia, weight loss) is sufficient for the diagnosis of Diabetes mellitus.[10] Hypoglycemia is considered as plasma glucose <70 mg/dl (3.9mmol/l).[11]This may also occur in absence of warning symptoms of hypoglycemia which normally occurs at lower plasma glucose level <60mg/dl (3mmol/l).

**Statistical Analysis**
The data was analyzed by using statistical package for social sciences (SPSS) software version 16. Descriptive statistics were calculated for all variables like age, gender and plasma glucose level. Frequency and percentage were presented for qualitative variables like sex, plasma sugar level.

**RESULTS**
Table 1 describes the general characteristic of study subjects. Total of 250 subjects having Type 2 diabetes, taking oral hypoglycemic agents/insulin were included in this study. The mean age of study subjects was $46.02 \pm 34$ years ranging from 12 to 80 years. The male gender was predominant with 142 (56.8%) proportion compared to females who were 108 (43.2%) in the current study. Most of the study participants belong to low class family 170 (68%). Similarly, most of the subjects were illiterate 54 (21.6%) and having primary level of education 78 (31.2%). Subjects with secondary, Intermediate, Graduation and Post-Graduation were 38 (15.2%), 33 (13.20%), 32(12.8%) and 15(6%) respectively.
Results show that 179(71.7%) study subjects were not aware about the hypoglycemic symptoms despite of many visits to various doctors while 71(29.3%) subjects know about the hypoglycemic symptoms. Frequency of hypoglycemia was seen in 60(24%) subjects taking oral hypoglycemic agents or insulin while hypoglycemia was not observed in remaining 190(76%) subjects. Similarly, prevalence of hypoglycemia was more in subjects having diabetes mellitus of less than six years 43(71.6%) while the prevalence of hypoglycemia was less common in subjects having diabetes mellitus of more than six years 17(28.4%).

Table 2 discuss hypoglycemic subjects with age category. As per age category subjects were categorized from 12 to > 60 years of age groups. Almost 129 (51.6%) of the subjects were more than 50 years of age while 121 (48.4%) of the subjects were less than 50 years of age. Hypoglycemia was more common in old age people, as results indicate 34(56.6%) subjects have hypoglycemia in more than 50 years of age. Significant results were also observed in 21-30 years of age group.

Table 3 shows the subjects with hypoglycemia associated with various types of treatment. Total of 104(41.6%) hypoglycemic subjects were taking insulin only, 63 (25%) oral hypoglycemic agents and 83(33.3%) both oral hypoglycemic agents and insulin Lantus (Glargine). On the basis of types of insulin Premix 70/30 insulin was used in 60% of subjects and Regular insulin in 32% while very low percentage (8%) of subjects taking Glargine (Lantus). After comparing oral hypoglycemic agents most of the subjects 53.30% were observed taking Glibenclamide, 13.30% Gliclazide, 26.60% Glimepirides and 6.60% Glipizide.

**Table 1: Baseline characteristics of study subjects**

| General characteristics | Total number of subjects (%) | P-value |
|---|---|---|
| Age (years) | $46.02 \pm 34$ | |
| Male | 142 (56.8%) | |
| Female | 108 (43.2%) | |
| **Family income** | | |
| Low income Families (< Rs.5000) | 170 (68%) | p< 0.0005 |
| High income Families (> Rs.5000) | 80 (32%) | |
| **Education** | | |
| Illiterate | 54(21.6%) | p= 0.0003 |
| Primary | 78(31.2%) | p< 0.0005 |
| Secondary | 38(15.2%) | |
| Intermediate | 33(13.2%) | |
| Graduation | 32(12.8%) | |
| Post-Graduation | 15(6%) | |
| **Awareness about hypoglycemia** | | |
| Yes | 71(29.30%) | |
| no | 179(71.77%) | |
| **Frequency of hypoglycemia** | | |
| Yes | 60(24%) | p=0.0001 |
| No | 190(76%) | |
| **Duration of Diabetes Mellitus** | **Patients with Hypoglycemia** | |
| 1-3 years | 24 (40%) | |
| 4-6 years | 19 (31.6 %) | p= 0.0003 |
| 7-10 years | 11 (18.3 %) | |
| > 10 years | 6 (10 %) | |

**Table 2 Number of patients having hypoglycemia with age category**

| Age categories (years) | Total number of subjects (%) (n = 250) | Number of patients having hypoglycemia (n =60) | P-value |
|---|---|---|---|
| 12 to 20 | 0 (0%) | 0 (0%) | |
| 21 to 30 | 20 (8%) | 18(30%) | |
| 31 to 40 | 35 (14%) | 2(3.3%) | p= 0.005 |
| 41 to 50 | 66 (26.4%) | 6(10%) | |
| 51 and 60 | 55 (22%) | 12(20%) | |
| Above 60 years | 74 (29.6%) | 22(36.6%) | |

**Table 3: Subjects with hypoglycemia associated with various types of treatment**

| Hypoglycemia associated with various types of treatment | Total no. of subjects with treatment | |
|---|---|---|
| Insulin | 104(41.60%) | |
| OHAs | 63(25.00%) | p= 0.001 |
| OHAs + LANTUS | 83(33.30%) | |
| **Hypoglycemia with different types of Insulin** | | |
| Regular Insulin | 80(32.00%) | |
| Premix 70/30 | 150(60.00%) | |
| Glargine/Detemer | 20(8.00%) | |
| **Hypoglycemia with different types of OHAs** | | |
| Glibenclamide | 135(54.00%) | |
| Gliclazide | 35(14.00%) | |
| Glimepiride | 65(26.00%) | |
| Glipizide | 15(6.00%) | |

**DISCUSSION:**

Low plasma sugars can be scary. In this study, frequency of hypoglycemia was seen in 24% subjects. Most of the cases were seen in less than six years of duration of diabetes in 50 or more than 50 years of age groups. In type 2 diabetes occurrence of hypoglycemia may not be considered as common as hypoglycemia in type 1 diabetes previously, but misleading information may have caused this misperception.[12] Some studies have disregarded the ageing effects by selecting middle-aged subjects with type 2 diabetes to focus hypoglycemic symptoms.[13] Similar to current study significant associations between older age and risk of severe hypoglycemia were observed in previous study. The scarcity of elderly people is concerning because at this age-group symptom are frequently obscure which result in improper treatment.[14]

Regardless of age groups, rate of hypoglycemia was greater in women than in men studied previously but in this study no such detail was recorded is the limitation of this study. No detail of fasting plasma glucose and random plasma glucose obtained are also the limitation of this study. Further observations of current study show that most of the subjects were taking insulin only as compare to oral hypoglycemic agents and both oral hypoglycemic agents and insulin Lantus (Glargine). Previously, in type 2 diabetes hypoglycemia risk are potential to intensify with the increasing use of insulin.[15] The risk of hypoglycemia in both types of diabetes should also be focused with the rise in the need of insulin therapy. Another study demonstrated that physicians often delay insulin initiation.[16] Hence, future studies are required for appropriate strategies to overcome these physician barriers.

On the basis of types of insulin, Premix 70/30 insulin was most commonly used in this study as compare to regular Insulin and Glargine (Lantus). But previous study shows that starting treatment by insulin adding glargine also known as basal insulin once a day with treatment of glimepiride plus metformin results to produce good effects as compare to initiating premix 70/30 injections twice a day and ending oral antidiabetic drugs (OADs) in subjects with type 2 diabetes.[17] The data on hypoglycemia in subjects receiving insulin other than glargine and switching to insulin glargine should further elaborate which would include comprehensive results of effectiveness and safety.

As studied previously that oral hypoglycemic medications can cause hypoglycemia. By comparing oral hypoglycemic agents in this study most of the subjects were using Glibenclamide as compare to Gliclazide, Glimepiride and Glipizide. However, similar to previous study hypoglycemia is more prevalent in subjects taking glibenclamide. But previous studies of counterregulatory responses to hypoglycemia when treatment given by diet or oral medicine also indicate the releasing effects of counterregulatory hormone occur at higher plasma glucose levels in subjects with type 2 diabetes as compare to nondiabetic subjects (control) and type 1 diabetic subjects.[18] Similarly, incidence of hypoglycemic symptoms was increasing significantly in subjects treated with glyburide than in subjects treated with gliclazide or chlorpropamide.[19] Subjects

on sulfonylureas and meglitinides have the highest incidence of hypoglycemia because of their pharmacological action of increasing insulin secretion.[20]

This study concludes that high frequency of hypoglycemia not associated with increased mortality risk but may be a marker of disease burden. Hypoglycemic episodes can be prevented by keeping the lowest possible dose of insulin or oral hypoglycemic agents (or using shortest acting oral hypoglycemic agents) or by proper counseling of subjects about lifestyle management and making the subjects aware about hypoglycemic symptoms.

**REFERENCES:**

1. Available at: IDF diabetes atlas - 2017 Atlas, www.diabetesatlas.org/resources/2017-atlas.html [Last reviewed on 2-2-2018].

2. Available at: WHO | Diabetes - World Health Organization, www.who.int/mediacentre/factsheets/fs312/en/ [Last accessed at 13-2-18].

3. Kassem MA, Durda MA, Stoicea N, Cavus O, Sahin L, Rogers B. The Impact of Bariatric Surgery on Type 2 Diabetes Mellitus and the Management of Hypoglycemic Events. Frontiers in endocrinology. 2017 Mar 1;8:37.

4. Leonard CE, Han X, Brensinger CM, Bilker WB, Cardillo S, Flory JH, Hennessy S. Comparative risk of serious hypoglycemia with oral antidiabetic monotherapy: A retrospective cohort study. Pharmacoepidemiology and drug safety. 2018 Jan 1;27(1):9-18.

5. Gedebjerg A, Almdal TP, Berencsi K, Rungby J, Nielsen JS, Witte DR, Friborg S, Brandslund I, Vaag A, Beck-Nielsen H, Sørensen HT. Prevalence of micro-and macrovascular diabetes complications at time of type 2 diabetes diagnosis and associated clinical characteristics: A cross-sectional baseline study of 6958 patients in the Danish DD2 cohort. Journal of diabetes and its complications. 2018 Jan 1;32(1):34-40.

6. Mohan V, Kalra S, Kesavadev J, Singh K, Kumar A, Unnikrishnan UG, Chawla M. Consensus on Initiation and Intensification of Premix Insulin in Type 2 Diabetes Management. Journal of the Association of Physicians of India. 2017; 65:59-73.

7. King P, Peacock I, Donnelly R. The UK Prospective Diabetes Study (UKPDS): clinical and therapeutic implications for type 2 diabetes. British journal of clinical pharmacology. 1999 Nov 1;48(5):643-8.

8. Dalal MR, Kazemi M, Ye F, Xie L. Hypoglycemia after initiation of basal insulin in patients with type 2 diabetes in the United States: implications for treatment discontinuation and healthcare costs and utilization. Advances in therapy. 2017 Sep 1;34(9):2083-92.

9. Inzucchi SE, Bergenstal RM, Buse JB, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015; 38:140–9.

10. Ansong K. The Management of Type 2 Diabetes Mellitus: Compliance, Barriers and Effect on Glycaemic Control of Adult Outpatients in Sunyani Municipality, Brong Ahafo Region-Ghana (Doctoral dissertation).

11. American Diabetes Association. 6. Glycemic Targets: Standards of Medical Care in Diabetes—2018. Diabetes care. 2018 Jan 1;41(Supplement 1):S55-64.

12. Nicola N. Zammitt, MRCP, Brian M. Frier, MD. Hypoglycemia in Type 2 Diabetes, Pathophysiology, frequency, and effects of different treatment modalities. Diabetes Care 2005 Dec; 28(12): 2948-2961. doi.org/10.2337/diacare. 28.12.2948.

13. Abdelhafiz, A. H., & Sinclair, A. J. (2013). Management of Type 2 Diabetes in Older People. Diabetes Therapy, 4(1), 13–26. doi.org/10.1007/s13300-013-0020-4.

14. Abdelhafiz, A. H., Rodríguez-Mañas, L., Morley, J. E., & Sinclair, A. J. (2015). Hypoglycemia in Older People - A Less Well Recognized Risk Factor for Frailty. Aging and Disease, 6(2), 156–167. http://doi.org/10.14336/AD.2014.0330

15. Shafiee, G., Mohajeri-Tehrani, M., Pajouhi, M., & Larijani, B. (2012). The importance of hypoglycemia in diabetic patients. Journal of Diabetes and Metabolic Disorders, 11, 17. http://doi.org/10.1186/2251-6581-11-17.

16. Ishii, H., Iwamoto, Y., & Tajima, N. (2012). An Exploration of Barriers to Insulin Initiation for Physicians in Japan: Findings from the Diabetes Attitudes, Wishes and Needs (DAWN) JAPAN Study. PLoS ONE, 7(6), e36361. http://doi.org/10.1371/journal.pone.0036361

17. Hans U. Janka, Gerd Plewe, Matthew C. Riddle, Christine Kliebe-Frisch, Matthias A. Schweitzer, Hannele Yki-Järvinen. Comparison of Basal Insulin Added to Oral Agents Versus Twice-Daily Premixed Insulin as Initial Insulin Therapy for Type 2 Diabetes. Diabetes Care Feb 2005, 28 (2) 254-259; DOI: 10.2337/diacare.28.2.254

18. Sprague, J. E., & Arbeláez, A. M. (2011). Glucose Counterregulatory Responses to Hypoglycemia. Pediatric Endocrinology Reviews: PER, 9(1), 463–475.

19.Basit, A., Riaz, M., & Fawwad, A. (2012). Glimepiride: evidence-based facts, trends, and observations. Vascular Health and Risk Management, 8, 463–472. http://doi.org/10.2147/HIV.S33194.

20.Sola, D., Rossi, L., Schianca, G. P. C., Maffioli, P., Bigliocca, M., Mella, R., … Derosa, G. (2015). Sulfonylureas and their use in clinical practice. Archives of Medical Science: AMS, 11(4), 840–848. http://doi.org/10.5114/aoms.2015.53304