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ASSESSMENT OF FREQUENCY OF HYPOGLYCEMIA DUE TO METFORMIN THERAPY IN PATIENTS WITH TYPE-2 DIABETES MELLITUS, POLYCYSTIC OVARIAN DISEASE - A PROSPECTIVE OBSERVATIONAL STUDY

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Hypoglycemia, Metformin, Diabetes, Polycystic Ovarian Disease

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ABSTRACT

OBJECTIVE: To evaluate the incidence of hypoglycemia in metformin users in diabetic and PCOD patients. **METHODS**: Patients with Diabetes who are taking metformin alone(n=160) and polycystic ovarian disease who are euglycemic taking metformin (n=160) are recruited for the study. They were given a questionnaire regarding hypoglycemic symptoms. They were asked to fill the questionnaire based on the symptoms they experienced while taking metformin. Data were collected and analysed by using descriptive analysis, severity assessment and WHO causality assessment scale. **RESULTS** : PCOD patients taking metformin showed higher occurrence of hypoglycemic symptoms than Diabetic patients,whereas severity of hypoglycemia was more in Diabetic patients. **CONCLUSION :** This study provided an evidence that metformin causes hypoglycemia irrespective of the glycemic status of the patients.

1.0 INTRODUCTION

Hypoglycemia is the one of the most important adverse effect of anti-diabetic drugs. It can cause severe morbidity and even sudden death. It is a true medical emergency which require immediate recognition and treatment to prevent vital organ damage [1].

The symptoms depends on the severity and duration of hypoglycemia like behavior changes, neurological damage, cardiovascular complication leading to seizure or coma [1].

The immediate response to hypoglycemia is decrease in insulin secretion followed by increased release of glucagon and epinephrine causing increase glucose production and hyperglycemia [1,2].

Frequent bouts of hypoglycemia causes decrease release of glucagon and epinephrine leading to Hypoglycemia Associated Autonomic Failure (HAAF). This causes a clinical syndrome of defective glucose counter-regulation and unawareness of hypoglycemia due to attenuation of autonomic response which leads to vicious cycle of recurrent hypoglycemia [1,3,4]

Metformin, a biguanide, derived from plant galega officinalis[5] is the most commonly used oral hypoglycemic agent to treat type-II diabetes, as the first line treatment[6],as monotherapy and in combination for type II diabetes[7].

Metformin has been shown to delay the progression of diabetes in patients with impaired glucose tolerance [7,8].

Metformin is also used in the treatment of polycystic ovarian disease, for treatment of infertility as it improves ovulation and regulates menstrual cycle by reducing circulating androgens[7,9 10,].

The major mechanism of metformin is by reducing hepatic glucose production and increasing peripheral glucose uptake by activating AMP dependent protein kinase (AMP Kinase)[7,11].

Metformin does not affect insulin release[11]. Therefore, it has been claimed to cause less hypoglycemia [7] which varied between 0% to 21% only[12]. Strenous physical activity or fasting increases the risk of hypoglycemia[12].Metformin has little effect on blood glucose level in normoglycemic state[7,13]. Incidence of hypoglycemia caused by metformin in type II diabetes and polycystic ovarian disease patient has not been documented so far, even though many patients experiences the effect of hypoglycemia which affects the quality of life.

Therefore, we conducted an observational study to find out the exact incidence of hypoglycemia among users of metformin in type-II diabetes and polycystic ovarian disease

2.0 METHODOLOGY

This study was done to assess the occurrence of hypoglycemia in patients receiving metformin in type-II diabetes and polycystic ovarian disease patients.

2.1 STUDY DESIGN

This was a prospective observational study done in two groups of patients attending as outpatient receiving metformin.

2.2 STUDY CENTRE

Patients who are attending the Department of Diabetology, Rajiv Gandhi Govt. General Hospital, Chennai, Institute of Obstetrics and Gynecology, Chennai and RSRM lying in Hospital, Chennai.

2.3 STUDY DURATION

This study was carried out from march 2013 to September 2013.

2.4 STUDY SUBJECTS

Patients attending diabetic OPD of RGGH and gynecology OPD of IOG,RSRM ,Chennai.

2.5 SAMPLE SIZE

Sample size is 320. 160 Patients in each group

2.6 SELECTION CRITERIA

INCLUSION CRITERIA

Age between 18- 80 years Patients of both gender Patients who are willing to participate in the study

Patients who have type-2 diabetes mellitus taking metformin alone for more than one month with no other illness

Patients who are taking metformin for more than one month for PCOD with normal blood glucose level and no other illness

EXCLUSION CRITERIA

Patients who are taking other anti-diabetic drugs along with metformin.

Patients who are taking other medications for polycystic ovarian disease.

Patients having PCOD with increased blood glucose level.

2.7 STUDY PROCEDURE

Study was started after obtaining the approval and clearance from institutional ethical committee(No. 23042013). Informed consent and information sheet written in the regional language was shown to each patient and who are willing to participate in the study,sign their forms.

Questionnaire regarding hypoglycemic symptoms was prepared in regional language was given to the patients and asked to fill the columns.

2.8 EVALUATION

The collected data were analysed by WHO causality assessment scale and ADR severity assessment was done.

3.0 OBSERVATION AND RESULTS

Total of 320 patients were enrolled, and 160 in each group were analysed. Descriptive statistics were used for data analysis.

1.AGE DISTRIBUTION

IN PCOD

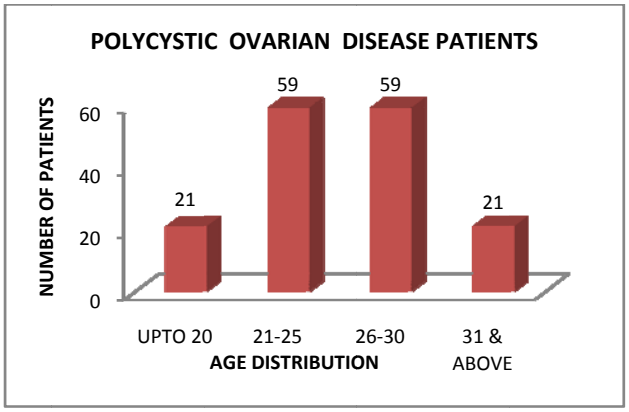

Figure-1 shows the age distribution in PCOD patients

IN DIABETES

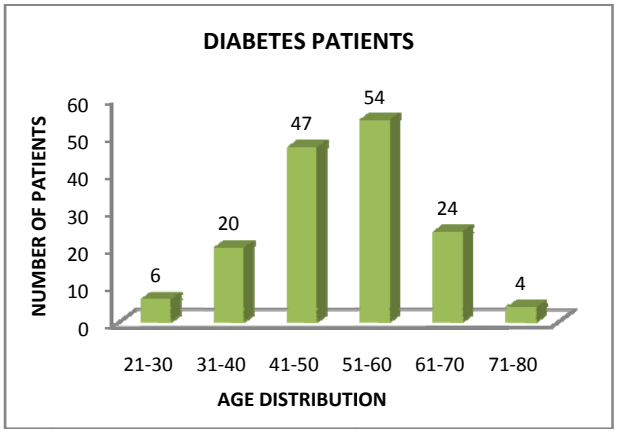

Figure-2 shows the age distribution in Diabetic patients

2.OCCURRENCE OF ADVERSE DRUG REACTION

IN PCOD

Occurrence of ADR	Number of patients	Percentage
Patients with ADR	157	98%
Patients without ADR	3	2%

Table-1 shows number of patients with adverse drug reaction

IN DIABETES

Occurrence of ADR	Number of patients	Percentage
Patients with ADR	150	94%
Patients without ADR	10	6%

Table-2 shows number of patients with adverse drug reaction

3.PATTERN OF ADVERSE DRUG REACTION

IN PCOD

Sl. No	Name of the ADR	No of Patients	Percentage
1	Intense Hunger	118	22
2	Tremors	61	11
3	Weakness	83	15
4	Light Headedness	23	4
5	Sweating	38	7
6	Headache	35	6
7	Giddiness	95	18
8	Palpitation	26	5
9	Anxiousness	42	8
10	Night mares	20	4

Table-3 shows the different symptoms of hypoglycemia due to metformin

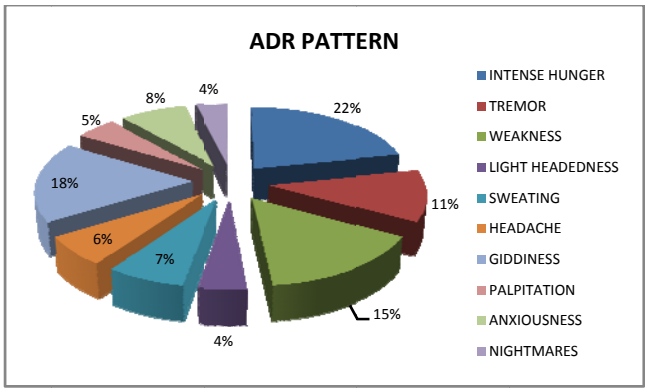

Figure-3 shows the pattern of symptoms of hypoglycemia.

IN DIABETES

Sl. No	Name of the ADR	No of patients	Percentage
1	Intense Hunger	102	14
2	Tremors	76	10
3	Weakness	88	12
4	Lightheadedness	64	8
5	Sweating	71	9
6	Headache	56	7
7	Giddiness	110	15
8	Palpitation	62	8
9	Anxiousness	96	13
10	Nightmares	30	4

Table-4 shows the different symptoms of hypoglycemia due to metformin.

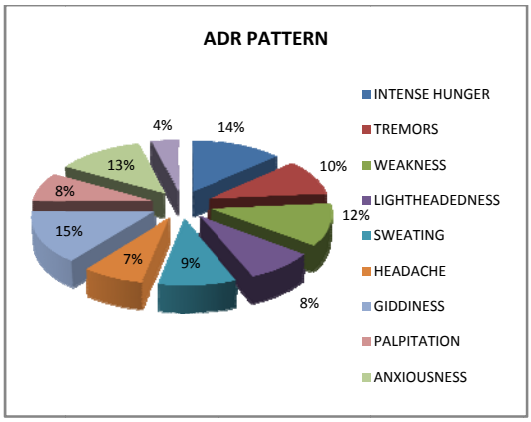

Figure-4 shows the pattern of symptoms of hypoglycemia in Diabetic patients.

4.WHO CAUSALITY ASSESSMENT

IN PCOD

Assessment Category	No. of patients	Percentage
Certain	0	0
Probable	95	18
Possible	446	82

Table-5 shows the causality assessment of ADR.

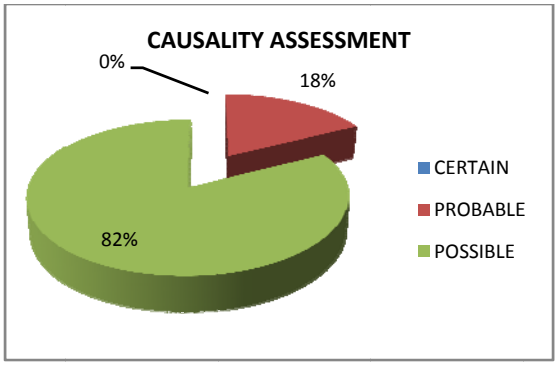

Figure-5 shows the causality assessment of ADR

IN DIABETES

Assessment Category	No. of patients	Percentage
Certain	0	0
Probable	110	15
Possible	645	85

Table-6 shows the causality assessment of ADR

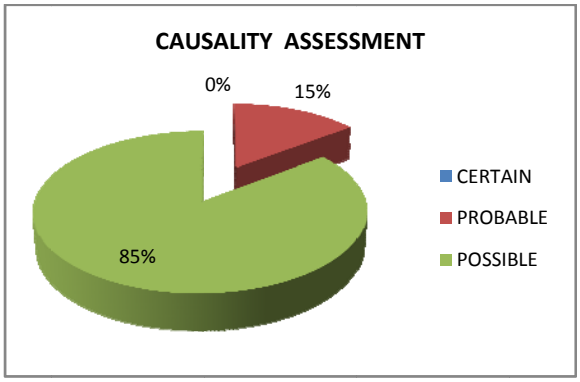

Figure-6 shows the causality assessment of ADR

5.SEVERITY ASSESSMENT

IN PCOD

Assessment Category	No. of patients	Percentage
Mild	106	66
Moderate	50	31
Severe	4	3

Table-7 shows the Severity assessment of hypoglycemic symptoms

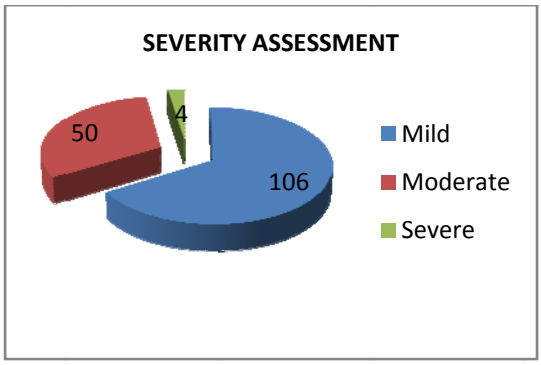

Figure-7 shows the Severity assessment of hypoglycemic symptoms.

IN DIABETES

Assessment Category	No. of patients	Percentage
Mild	60	38
Moderate	69	43
Severe	31	19

Table-8 shows the severity assessment of hypoglycemic symptoms

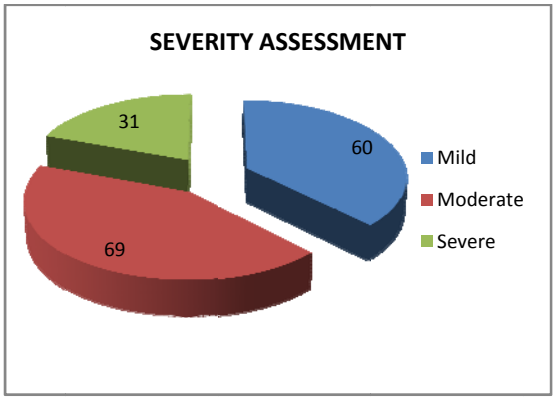

Figure-8 shows the causality assessment of hypoglycemic symptoms.

4.0 DISCUSSION

The incidence and severity of hypoglycemia due to metformin has been assessed in two groups of patients namely type-2 Diabetes mellitus and PCOD with normal blood sugar level.

In type-II Diabetes, 94% patients reported symptoms of hypoglycemia whereas 6% doesn't have any symptoms of hypoglycemia. Around 38% had mild, 43% had moderate and 19% had severe degree of hypoglycemia.

In patients with polycystic ovarian disease, 98% of patients had symptoms of hypoglycemia. out of which 66% had mild,33% had moderate and 3% had severe degree of hypoglycemia.

The standard textbooks say that metformin monotherapy does not cause hypoglycemia[13] in euglycemic patients. Hypoglycemia due to metformin was reported only in association with strenuous physical activity and fasting[12]. In this study the incidence of hypoglycemia was more in euglycemic patients (PCOD patients) under normal condition than in type-II diabetes.

The severity of hypoglycemia was more in type-II diabetes (19%) than in PCOD patients (3%).Recurrent attacks of hypoglycemia can cause severe morbidity and even death due to myocardial infarction or cerebrovascular disease[1].Therefore, the physicians and the patients should be aware of this adverse effect while using oral hypoglycemic agents.

From this study, we have found that metformin causes hypoglycemia irrespective of glycemic state of the individual, which should be documented in standard textbooks and the patients should be informed about the symptoms of hypoglycemia whenever metformin is prescribed.

5.0 CONCLUSION

From this observational study, we have concluded that metformin causes various degrees of hypoglycemia in both diabetic and euglycemic (PCOD) patients.

Hypoglycemia is one of the most important cause of sudden death in Diabetes. Since Diabetes[14] and PCOD[15] are stress related disease,frequent attacks of hypoglycemia can worsen the disease inspite of treatment.

Therefore, awareness should be created regarding the consequences of recurrent attacks of hypoglycemia among the physicians and patients.

Hypoglycemia can be prevented by life style modification, timely food and early recognition of symptoms while using metformin.

REFERENCES

[1] Gita Shafiee,, Mohammadreza Mohajeri-Tehrani, Mohammad Pajouhi and Bagher Larijani: The importance of hypoglycemia in diabetic patients, Journal of Diabetes & Metabolic Disorders 2012,11:17 page 1- 7.

[2] Cryer PE: Hypoglycemia ,functional brain failure, and brain death.J Clin Invest 2007,117:868-870.

[3] Cryer PE: Diverse causes of hypoglycemia-associated autonomic failure in diabetes.N Engl J Med 2004,350:2272-2279.

[4] Dagogo-Jack SE, Craft S, Cryer PE:Hypoglycemia-associated autonomic failure in insulin-dependent diabetes.Recent antecedent hypoglycemia reduces autonomic responses to,symptoms of, and defense against subsequent hypoglycemia.J Clin Invest 1993, 91: 819-828

[5] Stephanie A.Amiel and Melanie J.Davies: Oxford Textbook of endocrinology and Diabetes 2nd edition , page no 1783.

[6] Jolien de Jager, Adriaan Kooy, Phillppe Lehert, Michiel G Wulffele, Jan van der Kolk, Daniel Bets, Joop Verburg, Ab J M Donker, Coen D A Stehouwer:Long term treatment with metformin in patients with type 2diabetes and risk of vitamin B-12 deficiency: randomized placebo controlled trial:BMJ 2010:340:c2181 page1-7

[7] Brunton LL, Chabner BA, and Knollmann BC,Goodman and Gilman's The Pharmacological Basis of Therapeutics, 12 th Edition page no-1258

[8] Diabetes Prevention Program Research Group: REDUCTION IN THE INCIDENCE OF TYPE 2 DIABETES WITH LIFESTYLE INTERVENTION OR METFORMIN. N Engl J Med, Vol.346, No.6 page no 393-403

[9] Tahira Dar, Sidra Batool, Khawaja Tahir Mahmood, Fatima Amin: Benefits of Metformin in Polycystic Ovarian Syndrome. International Journal of Pharmaceutical Sciences, Vol.3 (1),2011,118-124.

[10] BB Tripathy: Research society for the study of Diabetes in india (RSSDI) Text book of DIABETES MELLITUS 2nd edition page no-531.]

[11] K D TRIPATHI : Essentials of Medical Pharmacology, 7th Edition, page no-275.

[12] Bodmer M, Meier C, Krahenbuhl S, jick SS, Meier CR: Metformin, sulfonylureas, or other antidiabetes Drugs and the risk of lactic acidosis or hypoglycaemia. Diabetes care Vol.31 (11),2008, 2086-2091

[13] Joslin's Diabetes Mellites 14th Edition page no 698-699.

[14] Richard S Surwit, Mark S Schneider, Mark N Feinglos: Stress and Diabetes Mellitus: Diabetic Care, Vol 15 (10), 1992, 1413-1421.

[15] PG Sundararaman, Shweta, GR Sridhar: Psychosocial Aspects of Women with Polycystic Ovary Syndrome from South India: JAPI, Vol 56, 2008, 945-948