

## PATTERN OF SWITCH THERAPY FROM INSULIN TO ORAL HYPOGLYCEMIC AGENTS IN INPATIENTS WITH TYPE 2 DIABETES MELLITUS AT A TERTIARY CARE HOSPITAL MANDYA: A RECORD BASED DESCRIPTIVE STUDY

Vishwas A. T. L.<sup>1\*</sup>, Jeena Sara Joy<sup>2</sup>, Pranoy S. Sankar<sup>3</sup>, Ajisha K. V.<sup>4</sup> and Agna K.<sup>5</sup>

<sup>1</sup>Assistant Professor, Department of Pharmacy Practice, Bharathi College of Pharmacy, Bharathinagara – 571422.

<sup>2</sup>Principal investigator, Pharm D, Department of Pharmacy practice, Bharathi College of Pharmacy, Bharathinagara, Mandya, Karnataka, India- 571422.

<sup>3,4,5</sup>Pharm D, Department of Pharmacy practice, Bharathi College of Pharmacy, Bharathinagara, Mandya, Karnataka, India- 571422.

\*Corresponding Author: Dr. Vishwas A. T. L.

Assistant Professor, Department of Pharmacy Practice, Bharathi College of Pharmacy, Bharathinagara, Mandya, Karnataka, India – 571422.

Article Received on 08/09/2022

Article Revised on 28/09/2022

Article Accepted on 18/10/2022

### ABSTRACT

**Background:** Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. We aimed to determine the feasibility of substituting oral hypoglycemic agents for insulin injection therapy in patients with Type 2 Diabetes Mellitus. **Objective:** To describe the switch therapy from insulin preparation to oral hypo glycaemic agents. **Methodology:** This was a record based descriptive study on TYPE 2 DM cases of patients admitted in the department of General Medicine at MIMS, Mandya. **Result:** Among the 135 cases, Majority of patient Females (51.72%) are more admitting TYPE 2 DM in hospital. The majority of patients belong to the category of age 60-69 years (34.84%). The most preferred insulin preparation among patients was Human Actrapid (54.08%). Biguanides were the most commonly prescribed class of drugs during switch therapy which is prescribed in (95.55%) prescriptions. While doing switch therapy tablet Metformin was the most preferable drug of choice (58.51%). Chi-square test was applied to check the relationship between types of oral hypoglycemic agents and blood glucose level we found that the calculated value was found to be 25.939 which was less than the expected tabular value 32.67. Hence, there exists a relationship between these variables. **Conclusion:** Our study concludes that, mostly female patients suffered from TYPE 2 DM. Switch therapy was done in MIMS hospital Mandya when the blood glucose level is controllable. Biguanides was the commonly prescribed class of oral hypoglycemic agents. The most preferable drug for switch therapy was found to be Metformin.

**KEYWORDS:** Biguanides, Switch Therapy, TYPE 2 DM, Metformin, Insulin, Hypoglycemia.

### INTRODUCTION

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. Type2DM is (formerly called non-insulin dependent, adult-onset) results from the bodies ineffective use of insulin.<sup>[1]</sup> The number of people with type 2 DM is increasing in every country with 80 of people with DM living in low- and middle-income countries. DM caused 4.6 million deaths in 2011. It is estimated that 439 million people would have type 2 DM by the year 2030.<sup>[2]</sup>

Insulin is usually needed when diabetes is diagnosed in the context of an acute medical event causing acute metabolic deterioration, or in case of surgery or any

other invasive procedure, temporarily or for longer term. Some oral agents may be contraindicated in these situations, and insulin may be used to provide rapid and reliable control of the metabolic disturbance. The preparations may be long acting, intermediate acting and short acting.<sup>[3]</sup>

Metformin, the only biguanide presently available for use, is an insulin sensitizer. Hypoglycaemia has been commonly seen in non-fasting patients taking metformin.<sup>[4]</sup> The major classes of oral antidiabetic medications include biguanides, sulfonylureas, meglitinide, thiazolidinedione (TZD), dipeptidyl peptidase 4 (DPP-4) inhibitors, sodium-glucose cotransporter (SGLT2) inhibitors, and  $\alpha$ -glucosidase inhibitors. If the HbA1C level rises to 7.5% while on

medication or if the initial HbA1C is  $\geq 9\%$ , combination therapy with two oral agents, or with insulin, may be considered.<sup>[5]</sup>

Combination of insulin and metformin is indeed associated with better glycaemic control, fewer hypoglycaemic events, and less weight gain than treatment with insulin alone. Therefore, metformin should be continued when patients are initiated on insulin therapy.<sup>[6]</sup> The psychological insulin resistance includes fear of hypoglycaemia, weight gain and fear for injections. Consequently, it could be expected that insulin therapy may have negative effects on psychological outcomes and well-being.<sup>7</sup> One-third of insulin taking patients who are prescribed insulin do not become ongoing users and almost 60% of patients miss injections, with 20% missing doses on a regular basis. Challenges to insulin therapy may present an even greater hurdle in clinical practice settings that are not specialized in intensive diabetes care or where educational resources are limited.<sup>[8]</sup>

Among different types of insulin preparations which is the common type of insulin preparations prescribed in general medicine department. Commonly diabetic patients managed with oral hypoglycaemic agents. After admitting to hospital due to elevated plasma glucose switched into insulin and then to same oral hypoglycaemic agents with or without combination therapy. To study whether there are any problems happened at the time of switch therapy.

So, the aim of our study is to evaluate the feasibility of switch therapy from insulin to oral hypoglycemic agents in patients suffering from type 2 diabetes mellitus.

### Objectives

- To evaluate the practice of switch therapy from subcutaneous to oral for type 2 diabetes mellitus in MIMS Tertiary Care Teaching Hospital, Mandya.
- To analyse the switch therapy done in type2 diabetes mellitus, evaluation of common drugs used during switch therapy, drugs prescribed for other co-morbidities

### MATERIALS AND METHODS

**Study design:** Record Based Study.

**Study period:** Patient records from January 2018 till the sample size reached is collected within the time period of 6 months since getting the approval from ethical committee.

**Table 1: Distribution of patients based on gender.**

Sr. No.	Category	Number of patients	Percentage
1	Male	65	48.28%
2	Female	70	51.72%

**Study population:** Patients who were treated for type 2 DM in general medicine department.

**Sample size:**  $132 \cong 135$  patients

Formula =  $4pq/L^2$

$p=9\%$ ,  $q=100-p$ ,  $L= 5\%$

$p$ =The prevalence of diabetes in India = $9\%$ <sup>(10)</sup>

Calculation

$4 \times 9(91)/5^2 = 132 \cong 135$

**Sampling method:** Convenience sampling.

### Inclusion criteria

- Diabetes mellitus patients who were treated in general medicine department and switch therapy was done.
- Age above 18 years who are admitted to MIMS with complaints of Type 2 diabetes mellitus.

### Exclusion criteria

- Incomplete data.
- Patient who are taking insulin.

### Method of data collection (Study tools)

The patients who are treated for type2 DM and switch therapy is done in general medicine department MIMS Mandya.

Following information will be collected

- Socio-demographic details like name, age, sex.
- Details of patients who were suffered from type2 DM.
- Details on insulin conversion from subcutaneous to oral.

**Analysis:** Data will be entered in MS Excel Worksheet and Descriptive statistics like percentage, mean etc will be used.

### RESULTS AND DISCUSSION

This is a record based retrospective study was conducted at MIMS tertiary care teaching hospital, Mandya. A total of 135 patient's case records in medical record room at MIMS were enrolled in the study based on inclusion and exclusion criteria. The demographic details such as age, sex, etc and treatment details from the patient's case records were recorded in a suitably designed patient profile form.

### Distribution based on gender

Total 135 patients were included during the study period. Table 1 provides the Gender distribution of the patients. The numbers of females, 70(51.72%) was more compared to the numbers of males, 65(48.28%). (Table1).

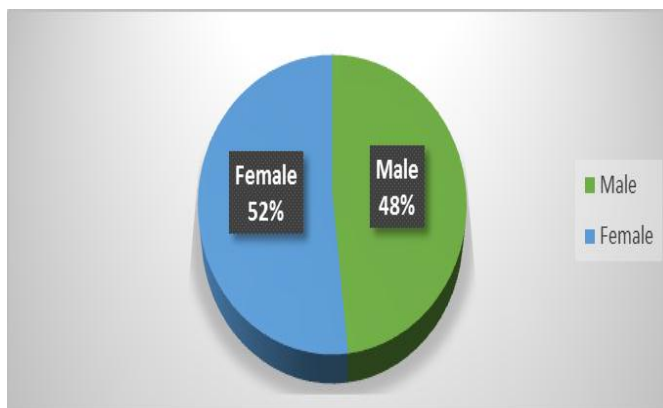


Figure 1: Distribution of patients based on gender.

**Categorization based on age**

In our study maximum numbers of patients were found in the age group of 60-69 years 47(34.84%) followed by 50-59 years 40(29.62%), >70years 27(20.00%), 40-49

years 12(08.88%) and minimum number of patients were found in the age group of 30-39 years 9(06.66%). (Table2).

Table 2: Categorization based on patients age.

Sr. no.	Age category	Number of patients	Percentage
1	30-39 years	9	06.66%
2	40-49 years	12	08.88%
3	50-59 years	40	29.62%
4	60-69 years	47	34.84%
5	>70 years	27	20.00%

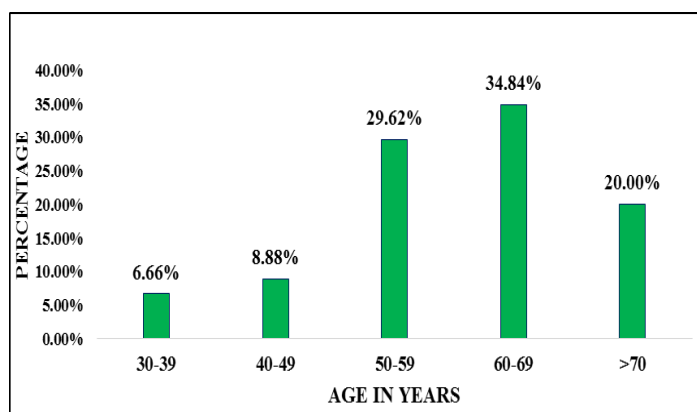


Figure 2: Categorization based on patients age.

**Type of insulin prescribed**

Among 135 patients there are two types of insulin preparations were found during the study. Most

commonly used insulin was found to be insulin Human Actrapid 73(54.08%) and Human Mixtard 62(45.92%). (Table 3).

Table 3: Types of insulin prescribed.

Sr. No.	Insulin preparation	Number of prescription prescribed	Percentage
1	Human mixtard	62	45.92%
2	Human actrapid	73	54.08%

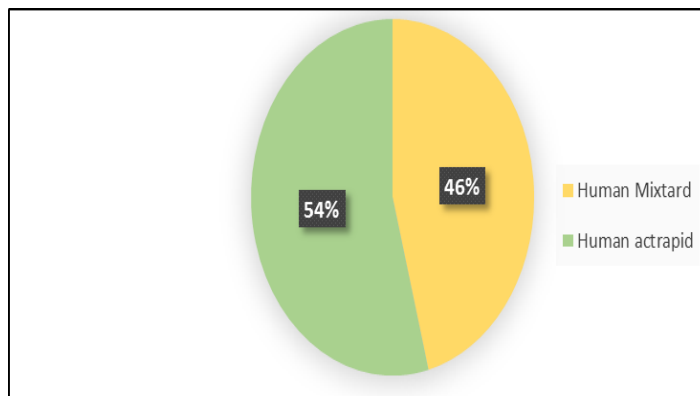


Figure 3: Types of insulin prescribed.

**Class of oral hypoglycemic drugs**

Different class of oral hypoglycemic agents was found during the study. The most common used drugs are coming under Biguanides 129(64.17%), and

Sulfonylureas 50(24.87%) followed by Dipeptidyl peptidase inhibitor 08(3.98%), Sodium glucose co-transporter inhibitor 02(0.99%), Thiazolidinediones 01(0.49%). (Table 4).

Table 4: Class of oral hypoglycemic agents given to patients.

Sr. no.	Class of drug	Number of prescription	Percentage
1	Biguanides	129	64.17%
2	Sulfonylureas	50	24.87%
3	Alpha glucosidase inhibitors	11	6.00%
4	Dipeptidyl peptidase inhibitor	08	3.98%
5	Sodium glucose co-transporter inhibitor	02	0.99%
6	Thiazolidinediones	01	0.49%

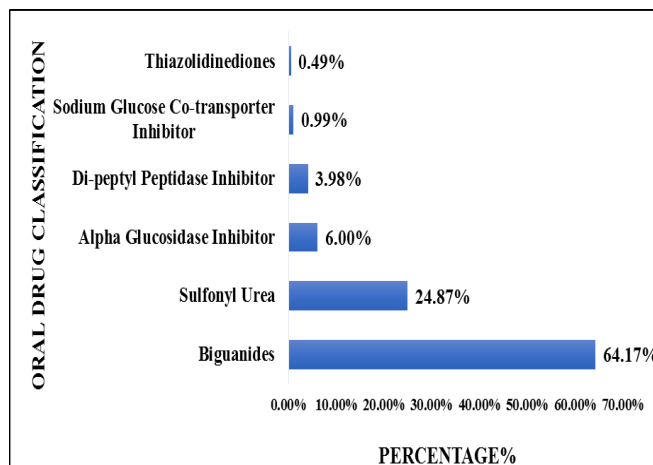


Figure 4: Class of oral hypoglycemic agents given to patients.

**List of oral hypoglycemic agents**

Different types of drugs which are used for the switch therapy, also combination of drugs also prescribed was found during the study. The most common drugs prescribed are Metformin 79 (58.51%), Metformin + Glimepiride 43(31.85%), followed by Metformin +

Vildagliptin04 (2.96%), Metformin + Glimepiride + Voglibose03 (2.22%), Voglibose03 (2.22%), Glimepiride02(1.48%), Metformin + Glimepiride + Pioglitazone 01(0.74%), Dapagliflozin 01(0.74%). (Table 5).

Table 5: Details of oral hypoglycemic drugs.

Sr. no.	Name of oral hypoglycemic agents	Number of prescriptions	Percentage
1	Metformin	79	58.51%
2	Glimepiride	02	1.48%
3	Voglibose	03	2.22%
4	Dapagliflozin	01	0.74%
5	Metformin + glimepiride	43	31.85%
6	Metformin + glimepiride + voglibose	03	2.22%
7	Metformin + vildagliptin	04	2.96%
8	Metformin + glimepiride + pioglitazone	01	0.74%

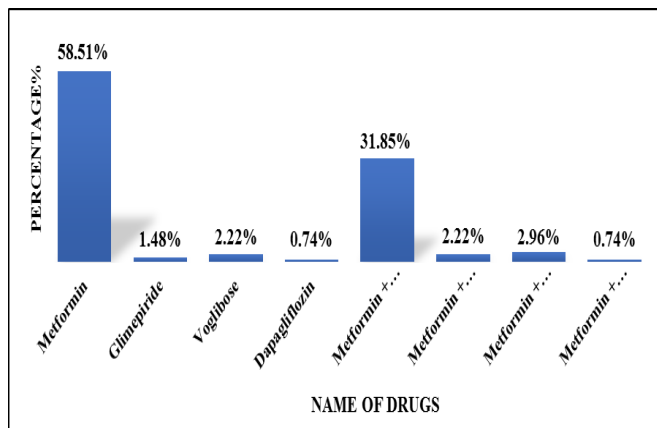


Figure 5: Details of oral hypoglycemic drugs.

**Conversion from human actrapid to oral hypoglycemic agents**

Total of 73 patients they used Human actrapid and they converted to oral hypoglycemic agents, which includes combination drugs also. Most common prescribed drug

are metformin 40 (49.38%), metformin + glimepiride 30(37.03%), followed by metformin + glimepiride + voglibose 4(4.93%), metformin + vildagliptin 4(4.93%), voglibose 02(2.50%), glimepiride 1(1.23%). (Table 6).

Table 6: Switch from Human actrapid to oral hypoglycemic agents.

Sr. no.	Insulin preparation	Oral hypoclycemic agents	Number of prescription	Percentage%
1	Human actrapid	Metformin	40	49.38%
		Glimepiride	01	1.23%
		Metformin + glimepiride	30	37.03%
		Metformin + glimepiride + voglibose	04	4.93%
		Voglibose	02	2.50%
		Metformin + vildagliptin	04	4.93%

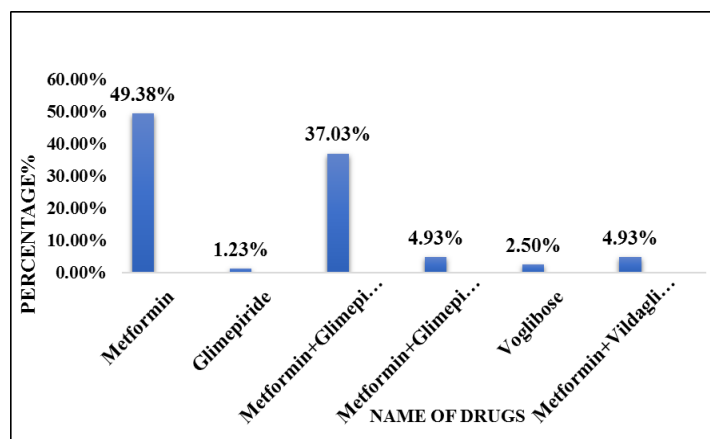


Figure 6: Switch from human actrapid to oral hypoglycemic agents.

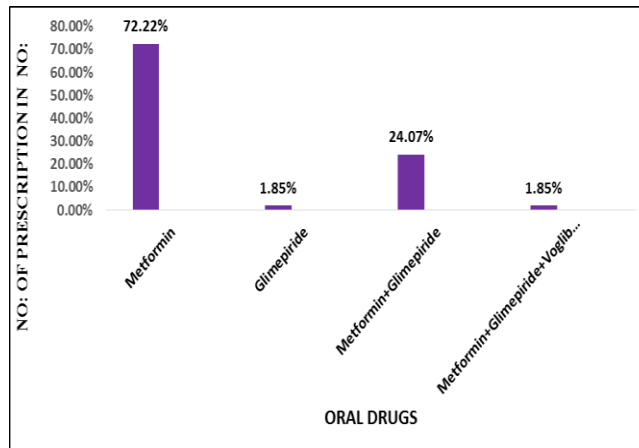
**Patients details on human mixtard to oral hypoglycemic agents**

Switch therapy done from insulin Human Mixtard to several drugs was found during study, which includes

combination drugs also. Most common prescribed drug are Metformin 39(72.22%), Metformin + Glimepiride 13 (24.07%), followed by, Metformin + Glimepiride + Voglibose 1(1.85%), Glimepiride 1(1.85%). (Table7).

*Table7: Switch from human mixtard to oral hypoglycemic agents.*

Sr. No.	Insulin preparation	Oral hypoglycemic agents	Number of prescription	Percentage
1	Human mixtard	Metformin	39	72.22%
		Glimepiride	1	1.85%
		Metformin + glimepiride	13	24.08%
		Metformin + glimepiride + voglibose	1	1.85%



*Figure 7: Conversion from human mixtard to oral hypoglycemic agents.*

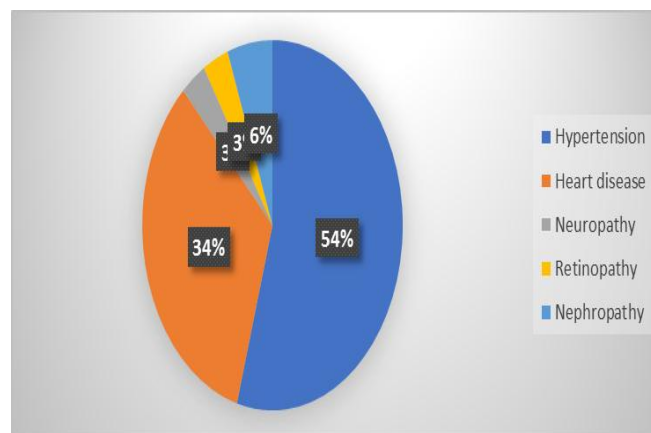
**Details on complications of diabetic mellitus**

Patients who were admitted in the hospital was found different types of complications. The common complication found among 135patients are Hypertension

68(54.40%), Heart disease 42(33.60%), Neuropathy 4(3.20%), Retinopathy 4(3.20%), Nephropathy 7(5.60%). (Table8).

*Table 8: Details on complications of diabetic mellitus.*

Sr. No.	Name of complications	Number of prescription	Percentage
1	Hypertension	68	54.40%
2	Heart disease	42	33.60%
3	Neuropathy	4	3.20%
4	Retinopathy	4	3.20%
5	Nephropathy	7	5.60%



*Figure 8: Details on complications of diabetic mellitus.*

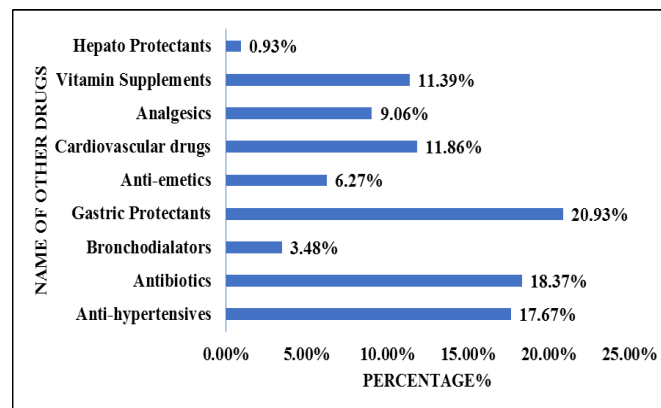
**Drugs prescribed for comorbidity condition**

Patients who were admitted in the hospital was found different types of comorbidity conditions and several drugs also prescribed. The most common drug prescribed in total number of 135 prescription are Gastric protectants 90(20.93%), Antibiotics 79(18.37%),

Antihypertensives 76(17.67%), Cardiovascular Drugs 51(11.86%), Vitamin supplements 49(11.39%), Analgesics 39(9.06%), Anti emetics 27(6.27%), Bronchodilators 15(3.48%), Hepato Protectants 04(0.93%). (Table9).

**Table 9: Total number of drugs prescribed for different types of comorbidities.**

Sr. No.	Class of drug	Number of prescription	Percentage
1	Anti-hypertensives	76	17.67%
2	Antibiotics	79	18.37%
3	Bronchodilators	15	3.48%
4	Gastric protectants	90	20.93%
5	Anti-emetics	27	6.27%
6	Cardiovascular drugs	51	11.86%
7	Analgesics	39	9.06%
8	Vitamin supplements	49	11.39%
9	Hepato protectants	04	0.93%



**Figure 9: Total number of drugs prescribed for different types of comorbidities**

**Relationship between types of oral hypoglycemic Agents and Blood glucose level**

A relationship exists between type of oral hypoglycemic agents and blood glucose level since the calculated chi-square value (25.939) was found to be less than the expected table value (32.67). The degree of freedom was

found to be 21 and the P value was 0.05. Hence our study rejects the null hypothesis and accepts the alternative hypothesis value (32.67). The degree of freedom was found to be 21 and the P value was 0.05. Hence our study rejects the null hypothesis and accepts the alternative hypothesis. (Table10).

**Table10: Relationship between oral hypoglycemic Drugs and Blood glucose.**

Sr. No.	Name of drugs	Blood glucose level				Chi square value
		<140mg/dl	140-160mg/dl	161-180mg/dl	<200mg/dl	
1	Metformin	28	15	19	23	25.939
2	Glimipiride	0	0	1	1	
3	Voglibose	0	1	2	1	
4	Dapagliflozin	0	1	0	0	
5	Metformin + glimepiride	8	11	12	5	
6	Metformin + glimepiride + voglibose	0	1	2	0	
7	Metformin + vildagliptin	0	1	1	2	
8	Metformin + glimepiride + pioglitazone	0	0	1	0	

**CONCLUSION**

Our study concludes that, most of the patients who were admitted for Type 2 DM were mostly females compared to males. After the analysis of our data, we found that the

switch therapy was doing to suitable patients in MIMS teaching hospital and it was found that human actrapid is the mostly prescribed insulin preparation and drugs coming under biguanides which are preferred most

during switch therapy. The drug metformin is the most preferred drug of choice during switch therapy. Chi-square test was applied to check the relationship between types of oral hypoglycemic agents and blood glucose level. The calculated value was less than the tabular value and hence, we concluded that a relationship exists between the variables. Clinical pharmacist along with physician plays an important role in switching from insulin preparation to oral hypoglycemic agents. Clinical pharmacist needs to review the condition of patients to find out the suitable time for switch therapy in patients with TYPE 2 DM.

#### ACKNOWLEDGEMENT

We are very thankful to our Director Dr. T. Tamizh Mani and Principal Dr. Balasubramanian T M and also Head of the Department of Pharmacy Practice Dr. Suresha B S. Bharathi College of Pharmacy, Bharathinagara for their suggestions and advice. We would like to thank Dr. Vinay M, Member secretary, MIMS hospital for supporting us to conduct this research. Finally, our deepest gratitude goes to MIMS staffs, who helped and allowed us in collecting and gathering data.

#### Conflict of interest

The authors declared no conflict of interest.

#### REFERENCE

- World health organization : Diabetes mellitus : WHO Tech Rep, 2021 ; 10: 727.[Last exist on 2022 april 23]
- Abdulfatai B Olokoba, Olusegun A Obateru, Lateefat B. Olokoba. Type 2 Diabetes Mellitus: A Review of Current Trends. Oman Medical Journal, 2012; 27 (4): 269-273.
- Philip HomeMatthew Riddle, William T. Cefalu, Clifford J. Bailey, Reinhard G, et al, Insulin Therapy in People with Type 2 Diabetes: Opportunities and Challenges? Diabetes Care, 2014; 37: 1499–1508.
- Arun Chaudhury, Chitharanjan Duvoor, Vijaya Sena Reddy Dendi, Shashank Kraleti, et al, Clinical Review of Antidiabetic Drugs: Implications for Type 2 Diabetes Mellitus Management. Frontier Endoscopy journal, 2017; 8 (6): 1-12.
- Ying Zhang, Yi-juan Xie, Dong-dong Meng, Hao-hang Zhang, Hui Chen and En Liu. Clinical study of treatment switching from premixed insulin to basal insulin combined with oral hypoglycemic drugs in patients with type, 2014; 2: 13.
- Gyuri Kim, Yong-ho Lee, Eun Seok Kang, Bong-Soo Cha, Hyun Chul Lee, and Byung-Wan Lee. Characteristics Predictive for a Successful Switch from Insulin Analogue Therapy to Oral Hypoglycemic Agents in Patients with Type 2 Diabetes. Open access Journal, 2016; 6(37): 323-329.
- Nils Ekström, Ann-Marie Svensson, Mervete Miftaraj, Karolina Andersson Sundell, Cederhol et al. Durability of oral hypoglycemic agents in drug naïve patients with type 2 diabetes: report from the Swedish National Diabetes Register (NDR). Open access journal, 2015; 3(1): 28-48.
- Philip Raskin, Elsie Allen, Priscilla Hollander, Andrew Lewin, Obert A. Gabbay Peter Hu, et al. Initiating Insulin Therapy in Type 2 Diabetes. Diabetes care journal, 2005; 28(2): 260-265
- Mir Iftikhar Bashir, Md Faruque Pathan, Syed Abbas Raza, Jamal Ahmad, et al. Role of oral hypoglycemic agents in the management of type 2 diabetes mellitus during Ramadan. Indian Journal of Endocrinology and Metabolism, 2012; 16(4): 503-507.
- Pradeepa, Rajendra Mohan, Viswanathan: Epidemiology of type 2 diabetes in india. Indian journal of Ophthalmology. November, 2021; 69: 2932-2938.
- Ranjith Unnikrishnan, Rajendra Pradeepa, Shashank R Joshi, Viswanathan mohan: Type2 Diabetes: Demystifying the Global Epidemic. Perspectives in journals, 2017; 66(6): 1432–1442.
- Dr. Lusiana Manoa, Dr Kennar Briand, Dr Villaroya Bong, Dr Arbin Marbibi, Dr Andre Mark Durand, Dr Jose Tana, et al, Diabetes Management Guidelines. Ministry Of Health Republic of Marshall Islands, 2016; 12: 1-63.
- Hodish: Insulin therapy for type 2 diabetes – are we there yet the d-Nav story, Clinical Diabetes and Endocrinology, 2018; 4: 8.
- Ewan R. Pearson, Isabelle Flechtner, Pål R. Njølstad, Maciej T. Malecki, Sarah E. Flanagan, Brian Larkin, et al, Switching from Insulin to Oral Sulfonylureas in Patients with Diabetes Due to Kir6.2 Mutations. The new england journal of medicine, 2006; 355: 467-77.
- Dawn D, De witt, Irl b harsh: Outpatient insulin therapy in Type1, Type2 Diabetes Mellitus, Jama journal, 2003; 289: 2254-2264.
- Anne Meike Boels, Guy Rutten, Frits Cleveringa, Mariëlle van Avendonk and RimkVos: Insulin Therapy in Type 2 Diabetes Is Associated with Barriers to Activity and Worse Health Status: A Cross-Sectional Study in Primary Care, Frontiers in endocrinology, 2021; 57325: 1-12.
- Irajheydari, Vida Radi, Sara Razmjou and AfsanehAmiri: Chronic complications of diabetes mellitus in newly diagnosed patients, International Journal of Diabetes Mellitus, 2010; 2(1): 61-63.
- Josephine M Forbes and Mark E Cooper, Mechanism of diabetic complications. Physiological Reviews, 2013; 93(1): 9-16.
- Maskey r, Shakya DR, Sharma SK, Karki P and Lavaju P: Diabetes mellitus related complications in outpatient clinic of tertiary care hospital. Journal of college medical science-Nepal, 2011; 7(2): 9-16.
- Grace C Davey, Swapnil B Patil, Aonghus o loughlin and Timothy o Brien: Mesenchymal Stem Cell based Treatment for Microvascular and secondary complications of Diabetes mellitus. Frontiers in Endocrinology, 2014; 5: 1-16.



21. Micheal J Fowler: Microvascular and Macrovascular Complications of diabetes. *Clinical Diabetes*, 2008; 26(2): 77-82.
22. Alia Ali, Farrukhiqbal, AzeemTaj, Zafariqbal, Muhammed Joher Amin, and Qasimzafariqbal. Prevalance of Microvascular Complications in Newly Diagnosed patients With Type 2 Diabetes. *Pakistan Journal of Medical Science*, 2013; 29(4): 899-902.
23. Takashi Okamoto, Lisa Okamoto, Micheal P Lisanti, Mashrio Akishita: Switch to oral hypoglycemic agent therapy from insulin injection in patients with type 2 diabetes. *Geriatrics&Gerontology International*, 2008; (11): 218-226.
24. Ewan R Person, Isabelle Flechtner, Pal R Njolstad, Maciej T. Malecki, Sarah E, et al: Switching from insulin to oral sulfonylureas in patients with Diabetes Due to Kir6.2 Mutations. *N Engl j Med*, 2006; 355: 467-477.
25. Elizabeth m Vaughan, Jennette P Moreno, David Hyman, Tzu-An Chen and John p Foreyt: Efficacy of oral versus insulin therapy for newly diagnosed diabetes in low-income settings. *Arch Gen Intern Med*, 2017; 1(2): 17-22.
26. Michiel G Wulffele, Adriaan kooy, Philippe Lehert, Daniel Bets, Jeles C Ogterop, Bob Borger van der Burg, et al, Combination of Insulin and Metformin in the Treatment of Type 2 Diabetes. *Diabetes Care*, 2002; 25(12): 2133-2140.
27. Bianca Hemmingsen, Louise Lundby christenen, Jorn Wettersev, Allan Vaag, Christian Gluud, Soren S Lund, et al, Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systemic review of randomised clinical trial with meta-analyses and trial sequential analyses. *Thebmj*, 2012; 344: 12-25.
28. Bartolomeo, Lorenzati, Chiara Zucco, Sara Miglietta, Federico Lamberti and Graziella Bruno. Oral Hypoglycemic Drugs: Pathophysiological Basis of Their Mechanism of Action. *mdpi Journal*, 2010; 3: 3005-3020.
29. Sherly Jacob, Mohamed Aly Morsy, Anroop Nair: An overview on the insulin preparations and Devices. *Indian journal of Pharmaceutical Education and Research*, 2018; 52(4): 550-557.
30. Giovanni Corrao, Matteo Monzio, Raffaella Ronco, Luca Merlino, Stefano Ciardullo, Gianluca Perseghin, et al, is switching from oral antidiabetic Therapy to Insulin Associated with an Increased Fracture Risk. *Clinical Orthopaedics and Related Research*, 2019; 478: 992-1003.
31. Silvio Inzucchi, Richard Bergenstal, Vivian Fonseca, Edwerd Gregg. *Diagnosis and Classification of Diabetes Mellitus: Diabetes Care*, 2010; 62-68.
32. Laura Di Magno, Fiorella Di Pastena, Rosa Bordone, Sonia Coni and Gianluca Canettieri. The Mechanism of Action of Biguanides: A New Answer to a complex question: *mdpi Journals*, 2022; 2-32.