Current trends in the pharmacological treatment of diabetic complications in a tertiary care setting

Benita Lisa Baji, Tasmiya K, Saraswathy GR*, Ann Mary Swaroop, Maheswari Eswaran, Viswam Subeesh

Department of Pharmacy Practice, Faculty of Pharmacy, Ramaiah University of Applied Sciences, Bangalore-560054, Karnataka, India

ABSTRACT

Type 2 Diabetes Mellitus (DM) is a condition primarily defined by the level of hyperglycemia giving rise to the risk of microvascular and macrovascular complications. It is associated with reduced life expectancy, significant morbidity and diminished quality of life. The aim of the study was to assess the prevalence and prescribing pattern in Type 2 DM and its complications in a tertiary care hospital. It was a prospective observational study carried out among 200 patients for 6 months in a tertiary care hospital. Patient's details were collected from case sheets and entered into data collection form. Hyperglycemia was managed with insulin (75.5%) due to its proven effectiveness; oral hypoglycemic agents (OHA) (24.5%) were prescribed to a limited extent. For diabetic nephropathy, beta-blockers (43%) were the highest prescribed. Pregabalin was mostly prescribed (35.8%) in diabetic neuropathy. The diabetic foot was commonly managed with clindamycin (61.5%), but treatment differed based on cultural sensitivity. Ischemic heart disease (IHD) was found to be the most prevalent complication in our study setting (41.5%). Macrovascular complications were managed with antihypertensives, diuretics, antianginals, anticoagulants, antiplatelets and antihyperlipidemics. The association of risk factors with diabetic retinopathy and IHD with duration of DM and HbA1c was statistically significant (p=0.007, p=0.05; p=0.007,p=0.004 respectively) Prescribing trend of drugs was based on the severity of complication, associated comorbid conditions and presently existing evidence to promote the rational use of drugs.

* Corresponding Author

Name: Dr Saraswathy GR
Phone: +91-08123230400
Email: saraswathypradish@gmail.com

INTRODUCTION

According to the International Diabetes Federation, 415 million adults have diabetes globally. By 2040 diabetic population will rise to 642 million. In 2015, 9.3% of adults aged 20-79 years was estimated to be living with diabetes. Over half (52.1%) of these are undiagnosed, 61.6% live in cities, and 90.2% live in low or middle-income countries. The western Pacific region is home to 36.9% of the total number of people with diabetes in the world (IDF 2017).

Type 2 Diabetes mellitus (T2DM) is a condition primarily characterized by high blood sugar levels, increased insulin resistance and relative lack of insulin. Uncontrolled Diabetes Mellitus (DM) gives rise to the risk of microvascular complications like retinopathy, nephropathy, neuropathy and macrovascular complications like ischemic heart disease, stroke and peripheral vascular disease resulting in poor quality of life (WHO 2008). Mohan *et al.,* (2013), has concluded that the prevalence of neuropathy was the most common complication followed by cardiovascular (23.6%),

renal (21.1%), ophthalmic (16.6%) and foot ulcer (5.1%) (Mohan *et al.,* 2013).

Poor glycemic control is more commonly seen in developing countries which lead to prolonged hospitalisation, increased mortality and morbidity. Maintaining optimal glycemic control is one of the major goals of the therapy. DM management includes the employment of both non-pharmacological and pharmacological therapy of which insulin plays a prominent role. The requirement of insulin depends on the balance between insulin secretion and insulin resistance (Ogbera *et al.,* 2012). The current anti-diabetic drugs are proven to be effective in a maximum number of cases, but a lot of factors such as adherence, disease knowledge, lifestyle modification, and cost of medication contribute to glycemic control (Haghighatpanah M *et al.,* 2016).

The clinical pharmacist can play an important role by screening patients at high risk, assessing their health status, checking adherence to standards of care, educating patients and monitoring outcomes (Huri Z *et al.,*2013). Although the diabetes management guidelines have been updated regularly, variations in the overall treatment of diabetes and changes in the diabetes management of each patient remain unclear (Fujibayashi *et al.,* 2016). The objective of our study was to provide an insight into current prescribing practices as there are limited studies focused in our setting.

MATERIALS AND METHODS

Study design: It was a prospective observational study conducted for six months to analyse the prescribing pattern of Type 2 DM and to identify the strength of the relation between a different variable and the risk of diabetic complications. The study was conducted in the age group above 18 years, and patients with diabetic complications were included. Gestational diabetics were excluded from the study.

Ethical approval: The study was approved by the Institutional ethics committee of M.S Ramaiah Medical College, Bangalore, Karnataka, India.

Sample size: the Sample size was calculated based on the previous study in which the prevalence of neuropathy was found to be 15% with an absolute precision of 5% and a confidence level of 95%. The minimum sample size was estimated to be 196.

Study procedure: This study was conducted among the diabetic population in order to assess the prescribing trends and prevalence of diabetic complications in a tertiary care setting. The study was initiated after obtaining ethical clearance. Informed consent was taken from the study participants. Data were collected from patient's

case notes, laboratory investigation reports, medication charts and by conducting medication history interview. Patient`s previous medical records and prescriptions were considered as an additional source. Data were further summarized into data collection form.

Statistical analysis: The statistical software SPSS 20.0 was used for data analysis. There was a correlation between the risk factors and diabetic complications which was studied using Pearson's $\chi 2$ test or Fisher's exact test. The threshold for significance was set at $p < 0.05$. The strength of the relationship between each variable and risk of diabetic complications was evaluated by the bivariate logistic regression model. Variables with an odds ratio (OR) > 1 and p <0.05 were considered significant risk factors for diabetic complications.
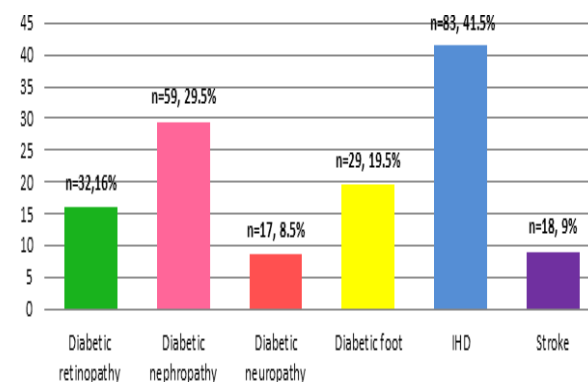
RESULTS

Figure 1: Prevalence of diabetic complications

A total of 200 patients with type 2 diabetes mellitus were enrolled for the study out of which 65.5% were male, and 34.5% were female. The complications of the study population were found to be 83(41.5%) were having IHD, diabetic nephropathy was found in 59(29.5%), diabetic foot in 29(19.5%) patients, diabetic retinopathy was seen in 32(16%), stroke was observed in 18(9%) and diabetic neuropathy was diagnosed in 17(8.5%). [Figure 1] The demographics and association of risks were studied. There was a positive association for increasing age with diabetic neuropathy and diabetic foot [Table 1]. Statistically significant association was observed between diabetic retinopathy and longer duration of diabetes as well as HbA1c (p= 0.007; p= 0.05 respectively), similarly these factors were associated with IHD 83(41.5%) with (p=0.007; p= 0.004 respectively) [Table 2].

Use of insulin was highly preferred due to ease of administration. Patients with poor glycemic control were prescribed with insulin as well as OHAs. Compared to all other complications, in IHD alpha-glucosidase inhibitor 2(9.52%) and OHA combination 3(3.61%) were prescribed [Table 3].

Table 1: Demographic characteristics of patients in diabetic complications

Complications	Age		P value	Sex		P value
	<65	>65		female	Male	
	n (%)			n (%)		
Diabetic neuropathy	12 (70.6%)	5 (29.4%)	0.024	8(47.1%)	9 (52.9%)	0.255
Diabetic retinopathy	7 (43.8%)	9 (56.2%)	0.95	7(43.8%)	9 (56.2%)	0.417
Diabetic foot	12 (30.8%)	27(69.2%)	0.04	13(33.3%)	26(66.7%)	0.864
Diabetic nephropathy	29 (49.2%)	30(50.8%)	0.39	16(27.1%)	43(72.9%)	0.03
Ischemic heart disease	36 (43.4%)	47(56.6%)	0.787	26(31.3%)	57(68.7%)	0.426
Stroke	10 (55.6%)	8(44.4%)	0.322	11(61.1%)	7(38.9%)	0.013

Table 2: Association of risk factors with diabetic complications

Complications	Duration		P value	HbA1c		P value
	<10 years	>10 years		Controlled	Uncontrolled	
	n (%)			n (%)		
Diabetic neuropathy	9(52.9%)	8 (47.1%)	0.169	1(5.9%)	16 (94.1%)	0.234
Diabetic retinopathy	1(6.2%)	15 (93.8%)	0.007	0	16 (100%)	0.05
Diabetic foot	11(28.2%)	28 (71.8%)	0.181	8 (20.5%)	31 (79.5%)	0.39
Diabetic nephropathy	24 40.7%)	35 (59.3%)	0.548	10 (16.9%)	49 (83.1%)	0.813
Ischemic heart disease	22(26.5%)	61(73.5%)	0.007	6 (7.2%)	77(92.8%)	0.004
Stroke	8(44.4%)	10 (55.6%)	0.523	5 (27.8%)	13 (72.2%)	0.153

Table 3: Use of antidiabetic drugs in patients with different diabetic complications

Anti diabetic drugs	Diabetic retinopathy	Diabetic nephropathy	Diabetic neuropathy	Diabetic foot	Ischemic heart disease	Stroke
n (%) of Insulin						
Ultrashort acting Insulin	-	1(6.6%)	-	-	4(7%)	-
Short acting insulin	11(47.8%)	23(51.11%)	5(50%)	14(48.27%)	30(52.63%)	11(73.33%)
Intermediate acting insulin	2(8.6%)	3(6.6%)	1(10%)	3(10.34%)	5(8.77%)	2(13.33%)
Premixed insulin	1(4.3%)	2(4.4%)	-	1(3.44%)	5(8.77%)	-
Long acting insulin	1(4.3%)	3(6.6%)	-	1(3.44%)	3(5.26%)	-
Insulin combination	8 (25%)	10 (16.9%)	4(23.52%)	10 (34.4%)	10 12.04%)	2(11.1%)
n (%) of OHAs						
Sulphonyl ureas	1(16.6%)	6(66.6%)	2(40%)	-	6 (28.57%)	1(25%)
Biguanides	3(50%)	2(22.2%)	3(60%)	4(80%)	8(38%)	3(75%)
DPP-4 inhibitors	1(16.6%)	1(11.1%)	-	1(20%)	2(9.52%)	-
Insulin + OHAs	3 (9.3%)	5 (8.4%)	2(2.76%)	5 (17.2%)	5 (6.02%)	-

Beta blockers were the favoured drug followed by calcium channel blockers compared to other antihypertensives. Among the antihyperlipidemic, use of statins in diabetic nephropathy and IHD was 20(33.9%); 39(47%) respectively. Aspirin was most commonly used in patients with stroke 8(44.4%) followed by IHD 25(30.1%). Enoxaparin was the frequently prescribed anticoagulant in stroke 7(38.9%) followed by in IHD 11(13. 3%). In Diabetic foot, the choice of antibiotics was based on

Table 4: Antihypertensive use in different diabetic complication

Antihypertensives	Diabetic nephropathy	Ischemic heart disease	Stroke
Beta-blockers	34(43%)	34(40.9%)	3(16.7%)
Angiotensin receptor antagonist	--	5 (6%)	1(5.6%)
Calcium channel blockers	9 (15%)	10(12.04%)	4 (22.2%)
Potassium-Sparing Diuretics	1(3.3%)	5(6%)	-
Loop Diuretics	20(66.6%)	16 (19.2%)	-
Osmotic Diuretics	-	-	1(5.6%)
Thiazide Diuretics	2(6.6%)	5 (6.02%)	1(5.6%)
2 drug combinations	12 (20.3%)	10 (12.04%)	2 (11.1%)
3 drug combinations	9 (15.2%)	16 (19.2%)	4 (22.2%)
Aspirin	17(28.5%)	25(30.1%)	8(44.4%)
Clopidogrel	5(8.5%)	6(7.2%)	1(5.6%)
Aspirin + Clopidogrel	4(6.8%)	27(32.5%)	2(11.1%)

Table 5: Results of logistic regression analysis of risk factors of Diabetic complications

Covariant	Pearson correlation	p-value	Odds ratio	95%Confidence interval		p-value
				Lower	Upper	
Duration of diabetes	7.317	0.007	1.796	1.182	4.155	0.013
Poor Adherence	6.326	0.012	0.924	1.161	5.467	0.019
Uncontrolled HbA1c	8.121	0.004	1.287	1.388	9.451	0.009

cultural sensitivity as well as the severity of infection while primary management was done with antibiotics such as clindamycin 24(61.5%) [Table 4]. Pregabalin was highly favoured 6(35.8%) in diabetic neuropathy. Even though gabapentin 2(11.8%) was least preferred it is also proven to be effective in the management of neuropathic pain. The diabetic patients reported a relationship between the severity of disease and risk factors (Duration of diabetes P=0.007, poor adherence P=0.012 and uncontrolled HbA1c P=0.004). The risk factors associated with diabetic complications which were analysed by bivariate logistic regression were found to be duration of diabetes (OR = 1.796, 95% CI: 1.182-4.155, P=0.019, poor adherence (OR = 0.924, 95% CI: 1.161-5.467, P=0.019) and uncontrolled HbA1c (OR = 1.287,95% CI: 1.388-9.451, P= 0.009) [Table 5]

DISCUSSION

A prospective observational study was conducted among 200 patients to analyse the prescribing pattern of Type 2 DM and to identify the strength of the relation between a different variable and the risk of diabetic complications. Due to limited studies concerning the microvascular and macrovascular complications in the southern part of India this study was conducted to record different complications and the influence of various risk factors on the same. Almost half of the study population had IHD which is contradictory to the study conducted by Agrawal *et al.,* (2004) that showed 1323(32.5%) subjects had nephropathy which was the major complication in their study whereas IHD was found only in 780(19.2%) subjects (Agarwal RP *et al.,* 2004).

In the study population, it was noted that diabetic patients who were on insulin therapy used insulin in varying combinations with oral OHAs. Short-acting insulin was used in half of the patients with IHD. Among OHAs, metformin was the first-line agent in the diabetic foot as it increases insulin sensitivity, reduces HbA1c by 1.0–2.0% and has less hypoglycemic episodes. Glimepiride was used in one among three patients who were on sulphonylurea. Metformin was rarely prescribed in diabetic nephropathy as it declines renal function. A study conducted by Quazi *et al.,* (2013) had similar results with glimepiride being more commonly prescribed in diabetic nephropathy (Shahir AQ *et al.,* 2013).

Our study was in accordance to American Diabetes Association (ADA) guidelines and patients with any level of macular edema, severe non-proliferative or any proliferative diabetic retinopathy were referred to an ophthalmologist who is knowledgeable and experienced in the management of diabetic retinopathy. In diabetic nephropathy use of ACE inhibitors or ARB therapy, in achieving blood pressure control is a subject of debate. Diuretics, calcium channel blockers, and beta blockers can be used as add-on therapy to achieve blood pressure goals in patients treated with maximum doses of ACE inhibitors or ARBs or as alternate therapy in rare individuals unable to tolerate ACE inhibitors and ARBs.

According to Rajan *et al.,* (2013) Gabapentinoids (Gabapentin and Pregabalin) are the frequently

used anticonvulsants in neuropathic pain (Rajan RS *et al.,* 2014). In this investigation, pregabalin 6(35.8%), gabapentin 2(11.8%) and the combination of these two drugs 5(29.4%) were commonly prescribed. In the diabetic foot, proper debridement is essential to reduce the risk of infection. Further infection control was achieved with antibiotics like clindamycin. Another study conducted by Ali *et al.,* (2009) states ceftriaxone as the highly preferred drug which is contrary to our study (Ali N *et al.,* 2009). But the outcome of infection control hasn't measured as it was not a part of our study.

IHD contributed to about 41.5% of the observed complications. Upon logistic regression analysis, it was evident that there is a linear increase in the prevalence of IHD with various risk factors like increased duration of diabetes, poor medication adherence and uncontrolled HbA1c whereas a study conducted by Mohan *et al.,* (1995) exhibited an association only with increasing duration of diabetes (Hewitt J *et al.,* 2012). Patients with type 2 DM have an increased prevalence of lipid abnormalities, contributing to their high risk of cardiovascular diseases (Mohan V *et al.,* 1995). Use of statins (47%) was seen as a part of prophylactic therapy.

CONCLUSION

There was a growing trend in the utilization of insulin for the management of complications associated with diabetes mellitus. Our study demonstrated a greater tendency of prescribing metformin over the other OHAs. Patient-specific factors like medication non-adherence exerted a negative influence on the achievement of optimal glycemic control. This study also highlights the prevalence of diabetic complications at a tertiary care setting.

CONFLICTS OF INTEREST

The authors have no conflict of interests to declare regarding the publication of this paper.

REFERENCES

Agrawal, R.P., Ranka, M., Beniwal, R., Sharma, S., Purohit, V.P., Kochar, D.K. and Kothari, R.P., Prevalence of micro and macrovascular complications in type 2 diabetes and their risk factors. Age, 50, 2004, pp.12-4.

Ali, N., Rehman, S., Imran, M., Hussian, I., Shehbaz, N., Jamshed, H., Hayat, A., Khan, S. and Anwar, M., The in-practice prescribing pattern for antibiotics in the management of diabetic foot: Needs much more to be done! Journal of Young Pharmacists, 2009, 1(4), p.375.

Fujibayashi, K., Hayashi, M., Yokokawa, H. and Naito, T., Changes in antidiabetic prescription patterns and indicators of diabetic control among 200,000 patients over 13 years at a single institution in Japan. Diabetology & metabolic syndrome, 2016, 8(1), p.72.

Haghighatpanah, M., Thunga, G., Jha, A., Study on prescribing pattern of anti-diabetic drugs among type 2 diabetes patients with complication in south Indian teaching hospital. Asian J Pharm Clin Res, 2016, 9(1), p.194-197

Hewitt, J., Castilla Guerra, L., Fernández-Moreno, M.D.C. and Sierra, C. Diabetes and stroke prevention: a review. Stroke research and treatment, 2012.

Huri, Z., and Wee, F., Drug-related problems in type 2 diabetes patients with hypertension: a cross-sectional retrospective study. BMC Endocrine Disorder, 2013, 13(2), p. 1-12.

International Diabetes Federation. IDF Diabetes Atlas – 7th edition, Available: http://www.diabetesatlas.org [Accessed: 8 Aug 2017]

Mohan, V. and Premalatha, G., Ischaemic heart disease in south Indian NIDDM patients-A clinic-based study on 6597 NIDDM patients. International Journal of Diabetes in Developing Countries, 1995, 15, pp.64-9.

Mohan, V., Shah, S. and Saboo, B., Current glycemic status and diabetes-related complications among type 2 diabetes patients in India: data from the A1chieve study. The Journal of the Association of Physicians of India, 2013, 61(1 Suppl), pp.12-5.

Ogbera, A.O., and Kuku, S.F., Insulin use, prescription patterns, regimens and costs. -A narrative from a developing country. Diabetology & metabolic syndrome, 2012, 4(1), p.50.

Rajan, R S., Gray, L D., George, E., Painful diabetic neuropathy*.* Continuing Education in Anaesthesia Critical Care & Pain, 2014,14(5), p 230-235.

Shahir, A.Q., Kauser, S., Dharmender, G. and Ahmad, A.N., Prescribing patterns of antidiabetic

medications in a tertiary care teaching hospital, Bareilly, UP, India. J Pharm Sci Innov, 2, 2013, pp.41-6.

World Health Organization (2008). Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia, Available: http://www.who.int/diabetes/publications/Def initionanddiagnosisofdiabetes_new.pdf [Accessed: 8 Aug 2017].