IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 17, Issue 3 Ver. 2 March. (2018), PP 35-40
www.iosrjournals.org

Pharmacoepidemiology of Macrovascular and Microvascular Complications in Type 2 Diabetes Mellitus Patients

Venkateswarlu Konuru[1], T.Rama Mohan Reddy[2]
Department of Pharmacy, Research Scholar[1]MewarUniversity,Chittorgarh, Rajasthan,
Research Supervisor[2], MewarUniversity,Chittorgarh, Rajasthan.
Corresponding Author:Venkateswarlu Konuru

Abstract:
Background Work: *Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia; is associated with abnormalities in carbohydrates, fat, and protein metabolism; and results in chronic complications including microvascular, macrovascular, and neuropathic disorders. Researchers have shown that as a result of these complications, the quality of life (QOL) of patients with type-2 DM is remarkably lower than the QOL of general population and also somewhat lower than patients with other chronic disease. Most complications are preventable and a key strategy is metabolic control through of diet, exercise, and medication*
Methodology: *This study was a prospective observational study which was conducted over a period of one year among type-2 diabetic patients attended at out-patient department of Diabetes Center the patients were reviewed on daily bases those are within the study inclusion criteria enrolled into study. Collected all relevant information from the patient's case sheets, laboratory reports, patients care taker, treatment charts and other resources.Calculate the prescribed daily dose and compare it with the Defined Daily Dose.*
Results and Discussion: *Out of 509 patients nearly 324 (63.65%) were associated with macrovascular complications like hypertension, Ischemic heart disease and Hyperlipidemia and 185 (36.34%) were associated with microvascular complications like Neuropathy, Nephropathy and Retinopathy. In 186 hypertensive patients a total of 317 antihypertensive drugs were prescribed. The average use of antihypertensive drugs per prescription was 1.70. For Ischemic Heart Disease Aspirin is often given at higher doses than defined dose as well as clopidogrel. PDD:DDD for aspirin and clopidogrel was 1.66 and 1.33 respectively. The average uses of dyslipidemia drugs per prescription were 1.71. In 185 patients a total 248 microvascular complications were identified. Microvascular complications occur due to the damage of small blood vessels. Damage of nerves due to diabetes is known as diabetic neuropathy 122 (65.94%).Nephropathy, where kidney enlarges in size, which follows the increase in glomerular filtration rate (GFR), but as the disease advances it decreases 78 (42.16%).Losartan were given mostly followed by torsemide and Ramipril. In 122 patients with Neuropathy a total of 375 drugs were prescribed, with an average of 3.07 drugs per prescription and are as follows.*
Conclusion:*This study was conducted to decrease prevalence of disease, through creating awareness about drug treatment and diabetic complications.Among the various complications,macrovascular complications caused major threat and among macrovascular complications, Hyperlipidemia and hypertension are major causes.*

Keywords:*Diabetes mellitus, Macrovascular, Microvascular, complications.*

Date of Submission: 13-02-2018 Date of acceptance: 07-03-2018

I. Introduction

According to WHO(World Health Organization)2006, Diabetes mellitus is defined as metabolic disorder of multiple etiology characterized by chronic hyperglycemia with disturbances of carbohydrate, protein and fat metabolism resulting from defect in insulin secretion, insulin action or both [1].

Diabetes mellitus is a group of metabolic disorders characterized by hyperglycemia; is associated with abnormalities in carbohydrates, fat, and protein metabolism; and results in chronic complications including microvascular, macrovascular, and neuropathic disorders [2]The effects of diabetes mellitus include long-term damage, dysfunction and failure of various organs. This is also having characteristic symptoms like thirsty, polyuria, blurring of vision and weight loss. The long term complications include retinopathy with potential blindness, nephropathy with kidney failure and neuropathy with risk of foot ulcers, amputation, and Charcot joint and sexual dysfunction (American Diabetes Association (ADA), 2013). Macrovascular event is responsible for 75% of deaths in patients having type-2 DM. Multiple risk factors are responsible for developing type-2 DM, which include family history, obesity, habitual physical activity, race or ethnicity, previously identified impaired glucose tolerance or impaired fasting glucose, hypertension, high density lipoprotein cholesterol and

triglyceride[3]. Researchers have shown that as a result of these complications, the quality of life (QOL) of patients with type-2 DM is remarkably lower than the QOL of general population and also somewhat lower than patients with other chronic disease. Most complications are preventable and a key strategy is metabolic control through of diet, exercise, and medication [4].

Nearly 10-15% of patients suffers from type-1 diabetes .It usually occurs in younger population, below 30 years of age. Occurring of type-1 diabetes is very high in girls between 10-12 years of age and boys between 12-14years of age.Type-2 diabetes occurs mainly in older population >40 years of age. Most commonly occur in 55 years of age [5].According to World Health Organization (WHO), there are 31.7million people in India were affected by diabetes during the year 2000 which may further rise to 79.4million by the year 2030.There are 171 million people in the world with diabetes in the year 2000 and it has estimated to increase 366 million by 2030 [1].

Defined Daily Dose (DDD) is the average of the maintenance dose per day which is used as a comparable unit. Prescribed daily dose (PDD) is not always equal to DDD. They both are a rough estimate of drug utilization. The primary outcome of the study is to calculate the PDD and secondary outcome of the study is to compare the PDD with DDD (WHO defined daily dose) and also to identify the commonly prescribed anticoagulants in various indications [6]. The target of this study is to identify common complications in type-2 diabetic patients, to identify commonly used or prescribed medications to manage complications and calculate the prescribed daily dose and compare it with the Defined Daily Dose.

II. Methodology

This study was a prospective observational study which was conducted over a period of one year among type-2 diabetic patients attendedat out-patient department of Diabetes Center the patients were reviewed on daily bases those are within the study inclusion criteria like type-2 Diabetic patients of both Genders, Patients of more than or equal to 20 years of age and type-2 Diabetic patients having at leastone diabetic complication were enrolled into study and Gestational Diabetes and Patients with Type-1 Diabetes were excluded from the study. Collected all relevant information from the patient's case sheets, laboratory reports, patients care taker, treatment charts and other resources. All the collected information documented properly by previously design data collection form which contain patient demographic details like age, sex, education and address, Past medical history and present medical condition, comorbid conditions, laboratory findings like hemogram, serum biochemistry, blood pressure, lipid profile and radiological findings- Vascular test, ECG, Foot examination, Fundus examination, CT, MRI, Micral test, Neuropathy and list of medication were used for complication, duration, dose and frequency of medication also to calculate the PDD. For each and every drug, defined daily dose is defined by the WHO collaborating center for Drug Statistics and Methodology as the assumed average maintenance adult dose per day for its main indication. Therefore, DDD is an international unit serving for regional and international comparisons. DDD is assumed average maintenance dose per day for a drug which is used for its main indication only in adults. It is a unit of measurement and does not correspond to PDD. Individual dosage regimen will differ based on patient groups, age and weight hence they differ from DDD [7].
Prescribed daily dose (PDD) is defined as the average dose prescribed according to a representative sample of prescriptions. It is important to relate the PDD to the diagnosis on which the dosage is based. The PDD will give the average daily amount of a drug that is actually prescribed. When there is a substantial difference between the PDD and the defined daily dose (DDD), it is important to take this into consideration when evaluating and interpreting drug utilization figures, particularly in terms of morbidity

III. Results

During the study period total 2000 patients were reviewed. Among them, total number of 509 patients was enrolled into the study. Among which 237 (46.56%) patients were men and 272 (53.43%) were females respectively. The average age of patients was 54.43+ 07.34, the average age of male patients was 56.34 + 06.35 and female patients was 52.52 + 08.34 (T- Value -5.96, P-Value less than 0.0001 confidence interval at 95% -05.07 to -02.56) statistically provedthat female are likely to develop at early age than male.

Diabetic patients with comorbid conditions

Out of 509 patients nearly 324 (63.65%) were associated with macrovascular complications like hypertension, Ischemic heart disease and Hyperlipidemia and 185 (36.34%) were associated with microvascular complications like Neuropathy, Nephropathy and Retinopathy.

Details of macrovascular diabetic complications

Macrovascular complications which are associated with diabetes are Hypertension 186 (57.40%), which is more predominate followed by Ischemic heart disease 71(21.91%) and Hyperlipidemia154 (47.53%) respectively.

Table 1: Patients were distributed according to diabetes complications

Complications/ No. of Patients (Percentage)	Disease	No. of Patients (Percentage)	Total No. of drugs prescribed	Average No. of drugs per prescription
Macrovascular 324 (63.65)	Hypertension	186 (57.40)	317	1.70
	Ischemic heart disease	71 (21.91)	71	1
	Hyperlipidemia	154 (47.53)	264	1.71
Microvascular 185 (36.34)	Nephropathy	78(42.16)	78	1
	Neuropathy	122(65.94)	375	3.07
	Retinopathy	48(25.94)		

Drug therapy of DM patients with HTN

In 186 hypertensive patients a total of 317 antihypertensive drugs were prescribed. The average use of antihypertensive drugs per prescription was 1.70 and are as follows

Most commonly prescribed combination therapy of drugs for treating hypertension were Olmesartan and hydrochlorthiazide 148 (46.68%) followed by telmisartan and hydrochlorthiazide 18(5.67%) which are angiotensin receptor blockers and thiazides diuretics. Monotherapy of drugs are telmisartan56 (17.66%) followed by losartan 55 (17.35%) angiotensin receptor blockers are prescribed more. Metaprolol30 (9.46%) beta-blocker, Amlodipine 5(1.57%) calcium channel blocker, Ramipril 3(0.94%) &Enalapril2 (0.63%) which are angiotensinogen converting enzyme are prescribed.The treatment have analyzed that the class of angiotensin receptor blocker along with thiazides diuretic are prescribed most commonly. PDD:DDD for Olmesartan+Hydrochlorthiazidewas 1. Telmisartan and Losartan are the next efficient drugs at 18% and 17% respectively prescribed for this population. Telmisartan is prescribed 1.5 times more than the defined dose while Losartan is prescribed low than the defined dose. PDD: DDD for Telmisartan and Losartan was 1.5 and 0.7 respectively. Metoprolol has being prescribed for 9% of the population 3 times less than the defined dose. PDD: DDD for metoprolol was 0.33. Telmisartan + Hydrochlorthiazide combination and amlodipine take about 5% and 1% of population prescribed at the same dose as the defined doses. PDD: DDD for TEL+HCT and amlodipine was 1 and 1 respectively. Enalapril and ramipril are rarely used in this population at slightly higher doses than defined doses. PDD: DDD for enalapril and ramipril was 1.25 and 1.4 respectively.

Drug therapy of DM patients with IHD

Most commonly prescribed drugs are in the class of anti-platelets are Aspirin 26 (36.61%) was given to the patients with ischemic heart disease followed by clopidogrel 24 (33.80%). A combination of aspirin and clopidogrel 21 (29.57%) were given to coronary heart disease patients, which shows synergistic effect. Aspirin is often given at higher doses than defined dose as well as clopidogrel. PDD:DDD for aspirin and clopidogrel was 1.66 and 1.33 respectively.

Drug therapy of DM patients with Hyperlipidemia

In 154 Hyperlipidemia patients a total of 264 dyslipidemia drugs were prescribed. The average uses of dyslipidemia drugs per prescription were 1.71 and are as follows. Patients with elevated total cholesterol or LDL cholesterol were given Atorvastatin 102 (38.63%). Atorvastatin + Fenofibrate were given to patients with elevated triglycerides and LDL levels 90 (34.09%), Rosuvastatin 56 (21.21%) were given to reduce LDL. Combination therapy was given more rarely. Rosuvastatin and fenofibrate 16 (06.06%) were given to the patients with both elevated triglyceride and reduce LDL. PDD:DDD of atorvastatin was 1.75 and rosuvastatin PDD:DDD of Rosuvastatin was 0.75.

Details of microvascular diabetic complications.

In 185 patients a total 248 microvascular complications were identified. Microvascular complications occur due to the damage of small blood vessels.Damage of nerves due to diabetes is known as diabetic neuropathy 122 (65.94%).Nephropathy, where kidney enlarges in size, which follows the increase in glomerular filtration rate (GFR), but as the disease advances it decreases 78 (42.16%).Diabetic Retinopathy affects the eyes, risk of developing diabetic retinopathy 48(25.94%) or other microvascular complications of diabetes depends on both the duration and the severity of hyperglycemia.

Drug therapy of DM patients with Nephropathy

Class of drugs such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers and diuretics were given in diabetic nephropathy. Losartan 44 (56.41%) were given mostly followed by torsemide 19 (24.35%) and Ramipril 15 (19.23%). Losartan was prescribed in 56.41% of the population at dose lower than defined dose which has being efficient enough. PDD: DDD for Losartan was 0.70. Torsemide was prescribed in 24% of population and prescribed at half of the defined dose. PDD: DDD of Torsemide was 0.5. Ramipril was prescribed in 19% of the population at higher doses than defined dose. PDD: DDD for Ramipril was 1.5.

Table 2: Drug utilization in macrovascular complications

Complication Associated with Diabetes	Drugs Used	Total No. of drugs prescribed	PDD	DDD	PDD :DDD
Hypertension	Losartan	55 (17.35)	35	50	0.7
	Telmisartan	56 (17.66)	60	40	1.5
	Metaprolol	30 (09.46)	50	150	0.3
	Olmesartan + hydrochlorthiazide	148 (46.68)	20 +12.5	20 +12.5	1
	Telmisartan + hydrochlorthiazide	18 (05.67)	40 +12.5	40 +12.5	1
	Amlodipine	5 (01.57)	7.5	5	1.5
	Enalapril	2 (00.63)	12.5	10	1.25
	Ramipril	3 (00.94)	3.5	2.5	1.4
	Total	**317**			
Ischemic heart disease	Aspirin	26 (36.61)	125	75	1.66
	Clopidogrel	24 (33.80)	100	75	1.33
	Aspirin + Clopidogrel	21 (29.57)			
	Total	**71**			
Hyperlipidemia	Atorvastatin	102 (38.63)	35	20	1.75
	Atorvastatin + Fenofibrate	90 (34.09)			
	Rosuvastatin	56 (21.21)	7.5	10	0.75
	Rosuvastatin + Fenofibrate	16 (06.06)			
	Total	**264**			

Drug therapy of DM patients with Neuropathy

In 122 patients with Neuropathy a total of 375 drugs were prescribed, with an average of 3.07 drugs per prescription and are as follows.In diabetic neuropathy neuroprotective drugs were prescribed more Amitriptyline107(28.53%) followed by pregabalin79 (21.06%),Pregabalin + Vitamin B12 68 (18.13), Clonazepam 54 (14.40%) which is a sedative, beta-histine42 (11.20%) an anti-vertigo drug and Acyclopram +Clonazepam 25 (06.66).

Table 3: Drug utilization in microvascular complications

Complication Associated with Diabetes	Drugs Used	Total No. of drugs prescribed	PDD	DDD	PDD :DDD
Nephropathy	Ramipril	15 (19.23)	3.75	2.5	1.5
	Losartan	44 (56.41)	35.26	50	0.70
	Torsemide	19 (24.35)	10	15	0.5
	Total	**78**			
Neuropathy	Amitriptyline	107 (28.53)	100	75	1.33
	Pregabalin	79 (21.06)	500	300	1.66
	Pregabalin+Vitamin B12	68 (18.13)			
	Clonazepam	54 (14.40)	4	8	0.5
	β-histine	42 (11.20)	20	24	0.83
	Acyclopram + Clonazepam	25 (06.66)			
	Total	**375**			

IV. Discussion

In this study, Diabetes Mellitus associated comorbid conditions were analyzed and managed by the treatment. Type-2 DM is a complex, heterogeneous, polygenic metabolic syndrome where the body fails to produce enough insulin which is required for our body, characterized by abnormal homeostasis. The burden of DM is sever with macrovascular complications like HTN, peripheral vascular disease, atherosclerosis and microvascular complications like nephropathy, neuropathy, retinopathy of the disease. Result of ageing, increasing obesity and decreasing physical activity, the global incidence of prevalence of DM exploding.

In this study, total number of 509 Type-2 Diabetes Mellitus patients prescriptions was included, were females (53.43%) are higher than males (46.56%) same as percentage of females were more than men when compared with the previous study. In generally elder patients are at a greater risk of developing Type-2 Diabetes Mellitus.

Diabetes complications are major life threatening, which leads to morbidity and mortality. Patients with long duration of Diabetes are at high risk of developing complications. Various Macrovascular complications including Hypertension, Hyperlipidemia, and Ischemic heart disease, cardiovascular complications cause major threat. In this study there were total number of 509 patients prescriptions were enrolled. Macrovascular complications are found to be in more percentage (63.65%) when compared to Microvascular complications (36.34%). Among Macrovascular complications, Hypertension was accounted for 57.40% of the total complications in diabetes patients, highest percentage of complications followed by Hyperlipidemia. Same results were obtained by previous studies (Upadhyay D K, *et al*., 2007 and Kannan*et al*., 2011).

ARB's and thiazides diuretics are given in combination for treating HTN followed by ARB's.Patients with elevated total cholesterol or LDL cholesterol were given Atorvastatin. Fenofibrates were given to patients with elevated triglycerides. Rosuvastatin were given to reduce HDL. Statins, HMG CoA reductase inhibitors many acts on abnormal lipid levels and atherosclerotic plaque stabilizing effect. Aspirin, an anti-platelet drug used to treat patients with co-existing IHD. Clopidogrel was given to patients with acid peptic disease. Combination therapy of aspirin and clopidogrel given to patients with coronary artery disease. Ramipril, Aspirin and Atorvastatin were given to patients with associated HTN, IHD and Hyperlipidemia.

Microvascular complications which include neuropathy, nephropathy and retinopathy. Out of patients prescriptions, Microvascular complications were found to be 185 patients the percentage of patients who are diagnosed with diabetic nephropathy are, diabetic neuropathy, diabetic retinopathy are found. Among these complications diabetic neuropathy was higher when compared to diabetic nephropathy and diabetic retinopathy. Hence diabetic neuropathy is more common in south India regions. When compared with study (NahidAli,*et al*., 2011) diabetic nephropathy is more may be due to life style, food habits etc.

In treatment of diabetic neuropathy Neuroprotective agents like pregabalin and Clonazepam. In treatment of diabetic nephropathy ARB's are most commonly prescribed drugsfollowed by diuretics.

V. Conclusion

In this study, Diabetes Mellitus associated comorbid conditions were analyzed and managed by the treatment. This study shows the drug utilization pattern of co-morbidities among type-2 diabetic patients which were conducted in out-patient department.In this study females were more affected than males**.** Out of 509 patients nearly 324 (63.65%) were associated with macrovascular complications like hypertension, Ischemic heart disease and Hyperlipidemia and 185 (36.34%) were associated with microvascular complications like Neuropathy, Nephropathy and Retinopathy. In 186 hypertensive patients a total of 317 antihypertensive drugs were prescribed. The average use of antihypertensive drugs per prescription was 1.70 and are as follows, most commonly prescribed combination therapy of drugs for treating hypertension were Olmesartan and hydrochlorthiazide and enalapril and ramipril are rarely used in this population at slightly higher doses than defined doses. PDD: DDD for enalapril and ramipril was 1.25 and 1.4 respectively.For Ischemic Heart Disease Aspirin is often given at higher doses than defined dose as well as clopidogrel. PDD:DDD for aspirin and clopidogrel was 1.66 and 1.33 respectively.In 154 Hyperlipidemia patients a total of 264 dyslipidemia drugs were prescribed. The average uses of dyslipidemia drugs per prescription were 1.71.

In 185 patients a total 248 microvascular complications were identified. Microvascular complications occur due to the damage of small blood vessels. Damage of nerves due to diabetes is known as diabetic neuropathy 122 (65.94%).Nephropathy, where kidney enlarges in size, which follows the increase in glomerular filtration rate (GFR), but as the disease advances it decreases 78 (42.16%).Diabetic Retinopathy affects the eyes, risk of developing diabetic retinopathy 48 (25.94%) or other microvascular complications of diabetes depends on both the duration and the severity of hyperglycemia.Class of drugs such as angiotensin converting enzyme inhibitors, angiotensin receptor blockers and diuretics were given in diabetic nephropathy. Losartan were given mostly followed by torsemideand Ramipril. In 122 patients with Neuropathy a total of 375 drugs were prescribed, with an average of 3.07 drugs per prescription and are as follows.This study was conducted to decrease prevalence of disease, through creating awareness about drug treatment and diabetic

complications.Among the various complications,macrovascular complications caused major threat and among macrovascular complications, Hyperlipidemia and hypertension are major causes.

References

1. E. Etuk, S.A. Isezuo, A. Chika, J. Aknuche and M. Ali, Prescription pattern of anti-hypertensive drugs in a tertiary health institution in Nigeria, Annals of African medicine, volume 7, No. 3, 2008; pg. no 128-132.
2. Brain L. Strom, Stephen E. Kimmel, Text book of Pharmacoepidemiology, University of Pennsylvania, Philadelphia, USA.
3. Leon shargel, Alan H. Mutnick, Paul F. Souney, Larry N. Swanson, Comprehensive pharmacy review, 7th edition, pg. no 1165-1193, 850-870, Lippincott Williams and Wilkins.
4. Joseph T. Dipiro, Barbara G. Wells, Terry L. Schwinghammer, Cecily V. Dipiro, Pharmacotherapy, A pathophysiologic approach, 8th edition, pg. no 217-236, 116-135, McGraw Hill.
5. Chowdhury NA, Hayee MA, Alam N, Study of complications in hypertensive patients having irregular treatment, Bangladesh medical research council bulletin, 1993, Dec 19 (3): 86-93.
6. TasneemSandozi, Vamsi Krishna Emani, Survey of Prescription pattern of antihypertensive drugs in hypertensives and hypertension associated diabetics, International Journal of Pharma and Biosciences, Volume 1, Issue 1, Oct-Dec 2010.
7. Jaana Lindstrom and JaakkoTuomilehto. The Diabetes Risk Score: A Practical Tool to Predict Type 2 Diabetes Risk. Diabetes Care 2003; 26(3): 725-729.
8. Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: Diagnosis and classification of diabetes mellitus. Geneva, World Health Organization, 1999 (WHO/NCD/NCS/99.2).
9. Iraj H, Vida R, Sara R, Afsaneh A. Chronic complications of diabetes mellitus in newly diagnosed patients. International Journal of Diabetes Mellitus 2010; 2: 61-63.
10. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, Paciorek CJ et al. National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2.7 million participants. *Lancet*, 2011, 378(9785):31–40.

Venkateswarlu Konuru. Pharmacoepidemiology Of Macrovascular And Microvascular Complications In Type 2 Diabetes Mellitus Patients." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS), vol. 17, no. 3, 2018, pp. 35-40.