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Impact of Multidrug Therapy and Co-Morbidities on Treatment Outcomes in T2DM Patients at GP Clinics: A Clinico-Epidemiological Study

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Abstract

Background: T2DM is already a global menace creating new management challenges every day. Although thought to be a super speciality subject, majority of the T2DM patients end up being treated by general physicians. But GPs have their own limitations in managing this condition which is hardly ever addressed by national & international management guidelines. Hence this study was undertaken to evaluate the various factors affecting T2DM management outcomes at GP clinics. **Material and Methods:** A sample of 153 T2DM patients were selected by applying various inclusion and exclusion criteria and data was collected with help of a predesigned case record form. Then the data was evaluated using statistical methods like descriptive analysis and multinomial logistic regression to see the impact of various factors like multidrug therapy, co-morbidities, patient's demography, ADR etc on treatment outcomes. **Results:** The mean BMI of the patients was 26.93±3.62 kg/meter2 of whhome Around majority (90 & 70, 58.8% & 45.8%) people were having fasting & post prandial hyperglycemia with blood sugar level more than 126 & 200 respectively. HBA1C level was more than 7mg% in around 69(45.1%) people. Patients treated with sulfonylureas and a combination of sulfonylureas/metformin/DPP4 inhibitors did show statistically significant better glycemic outcome (OR, 8.237; 95% CI, 1.786-37.985) & (OR, 2.862; 95% CI, 1.349-6.069). Hypertension had a negative impact on glycemic outcome (OR, 0.191; 95% CI, 0.79-0.464). Patients taking a combination of metformin/sulfonylureas/SGLT-2I have shown significantly less glycemic control (OR, 0.039;95% CI, 0.008-0.183). The group taking a combination therapy of metformin & sulfonylureas have shown significantly worst BP control over others (OR, 0.114; 95% CI, 0.025-0.529) and those treated with metformin/sulfonylureas/SGLT-2I have shown the best BP outcomes (OR, 5.527; 95% CI, 2.012-15.183). **Conclusion:** Patients treated with newer drugs like SGLT-2 inhibitors have been seen to be less efficacious in glycemic control as compared to traditional drugs, while more efficacious in preventing cardiovascular morbidities in GP setups. Co-morbidities like hypertension had a significant negative impact on treatment outcomes. This study indicates further studies on anti-diabetic drugs and a detailed comparative analysis to establish a better treatment hierarchy in T2DM management.

Keywords: T2DM, multidrug therapy, treatment inertia, GP clinic, glycemic outcome.

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Introduction

Type 2 diabetes mellitus is a highly heterogeneous, polygenic, multi-factorial, progressive disease characterized by inherited and acquired insulin resistance along with qualitative or quantitative insulin secretion disturbances.[1,2] Approximately 463 million adults aged 20–79 year are having diabetes worldwide which represents 9.3% of the world's population while 374 million (around 7.5%) adults are pre-diabetic.[3] The prevalence of diabetes in India is expected to rise from around 8.8% to 11.4% by 2045 while approximately 60% of diabetes cases are going undiagnosed in south-east Asian population.[4]

The problem with T2DM is not only its rising prevalence but also difficulty in its management with achievement of glycemic control only in around 53-62% of patients according to large studies like GUIDANCE (N = 7597) and PANORAMA (N = 5817), which is clearly sub-optimal, leading to development of deadly diabetic complications.[5] There are numerous barriers in management of T2DM, such as patient-level, healthcare system level & Physician-level barriers.[6] The most important barrier among them appears to be at Physician level who fail to effectively intensify the treatment as and when needed.[6]

Diabetes being such a common disease, it is almost impossible for all patients to get treatment & care from super specialists & vast majority of them are being managed by general practitioners (GP) which usually are not up to the mark.[7] Primary causes of inadequate diabetic management at GP or primary physicians level are time constraints, competing demands, lack of knowledge, barriers to access help from allied health professionals, ineffective remunerations, variations in guideline recommendations along with wrong perceptions to side effects leading to treatment inertia.[7,8]

T2DM management guidelines primarily in low & middle income countries like India are largely inadequate in terms of applicability, clarity, and dissemination plan as well as socioeconomic and ethical-legal points of view with narrower spectrums of T2DM clinical care.[9] Hence a detailed study was undertaken to collect evidence of impact of various prescription patterns, multidrug therapy and other external factors on T2DM management outcome at the level of general practitioners.

Aims and Objectives:

The aim of this study is to provide evidence about the impact of multidrug therapy and other external factors on the clinical outcome of T2DM management at GP clinics.[10]

Material and Methods

Study design:

The retrospective observational study was carried out on diagnosed T2DM patients with duration of 5 years & taking anti-diabetic treatment at GP clinics for more than one year. Data was collected over a period of six months from January 2021 to june 2021 with help of a data extraction form/case record form. Finally the glycemic, co-morbidity, ADR and complication outcomes were evaluated for all treatment

Target group[11]

Inclusion criteria[12]

- Patients with age more than 18 years
- Diagnosed cases of T2DM with 4-6 years of disease duration
- Patients having at-least two prescription fills for one of the above mentioned OADs or combinations continuously for last one year
- Patients who have maintained documents like prescriptions/laboratory reports/EMRs/self-monitoring data of BP, Blood sugar level etc in a recorded format of file or e-file for at-least last one year

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Exclusion criteria[12]

- Type-1 and any other form of diabetes
- Pregnancy during study period
- Patients with pre-existing serious diabetic complications like renal failure, diabetic foot with amputation etc

153 Patients who satisfied above criteria and had received their treatment at GP clinics for one of the following OADs were included in the study:

- Sulfonylureas (e.g. glibenclamide, glimpiride);
- Biguanides (e.g. metformin),
- Thiazolidinedione's (e.g. pioglitazone)
- Disaccharides inhibitors (e.g. voglibose)
- Dipeptidyl peptidase-4 inhibitor (e.g. sitagliptin)
- SGLT2 inhibitors (e.g. empagliflozin)
- Patients on combination therapy.

Sample size:

A sample of 153 patients were included in our study with consideration of inclusion and exclusions criteria as mentioned above. Sample size was calculated with the help of previous similar studies & using the formula $n=1.962 \times p(1-p)/d2$, where prevalence(p) = 9%, absolute error of precision(d) = 5% & confidence interval of 95%. Due to lack of data regarding percentage of diabetic population attending GP clinics, the prevalence of T2DM in India is used for sample size calculation which is approximately 9%.[13,14]

Procedures[15]

Patient consent were taken before data extraction with the help of a consent form and the privacy and confidentiality were strictly maintained.

A case record form was used to extract the data like the body weight (kg), systolic and diastolic blood pressure (mmHg), blood glucose levels (mg/dL), HbA1c (%), serum urea/creatinine along with treatment summary & incidences of adverse events from the data obtained over last consecutive outpatient visits (at-least two), patients self-monitored & recorded blood glucose and blood pressure data etc for last one year and were evaluated in different treatment groups.

Different demographic data like age, gender, weight, height, BMI, duration of disease, family history, socio-economic status, qualification, addiction history & history of adverse effects were measured and studied for having any impact on efficacy & safety outcomes of different treatment groups. Targets for different treatment outcomes were set like HBA1C<7, FBS<126, PPBS<200, BP< 130/80 etc and people below that target were considered controlled and above were uncontrolled. (16,17) Presence of various micro & macro vascular complications were recorded with the help of the documents maintained by the patients & evaluation outcomes at GP clinics.

Finally, all the parameters were analyzed.

Statistical analysis[15]

Descriptive statistics (frequency and percentages) was used to summarize the categorical variables and multiple logistic regression was used to calculate the adjusted odds ratio, which was further utilized to evaluate the relative efficacy & safety profile of the people in different treatment groups along with establishing the impact of other factors like demography and comorbidities on treatment outcomes.

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Confidence interval was taken as 95% and P value less than 0.05 was considered as statistically significant.

Results

A total of 153 patients were observed at GP clinics on an outpatient basis. It was seen that majority were from urban background (86, 56.2%). More male patients were enrolled (87, 56.9%) & majority of the people belonged to middle class from socio economic point of view (125, 81.7%). Most of the people were educated with minimum qualification of 10+ (117, 76.5%). Around 65% of the patients were having a positive family history of T2DM with majority having it in 1st degree relatives (81, 52.9%) and a minority in 2nd & 3rd degree relatives (19, 12.4%). Most of the people had no addiction history (113, 73.9%) & no major adverse effects seen in majority of patients taking anti-diabetic medications (86, 56.2%). The most common adverse effects that were observed were gastrointestinal (52, 34.6%) and hypoglycemia (14, 9.2%). [Table 1, Figure1]

Table 1: Clinocodemographic data(categorical)

Patient details		**Frequency**	**Percentage (%)**
Place	Rural	67	43.8
	Urban	86	56.2
Gender	Female	66	43.1
	Male	87	56.9
Socio economic status	High	9	5.9
	Middle	125	81.7
	Low	19	12.4
qualification	Post Matric	117	76.5
	Under Matric	36	23.5
Family history of T2DM	No History	53	34.6
	Yes Second Degree	19	12.4
	Yes First Degree	81	52.9
Addiction history	No	113	73.9
	Yes	40	26.1
ADR history	No	86	56.2
	GI side effects	53	34.6
	Hypoglycemia	14	9.2
	Total	153	100.0

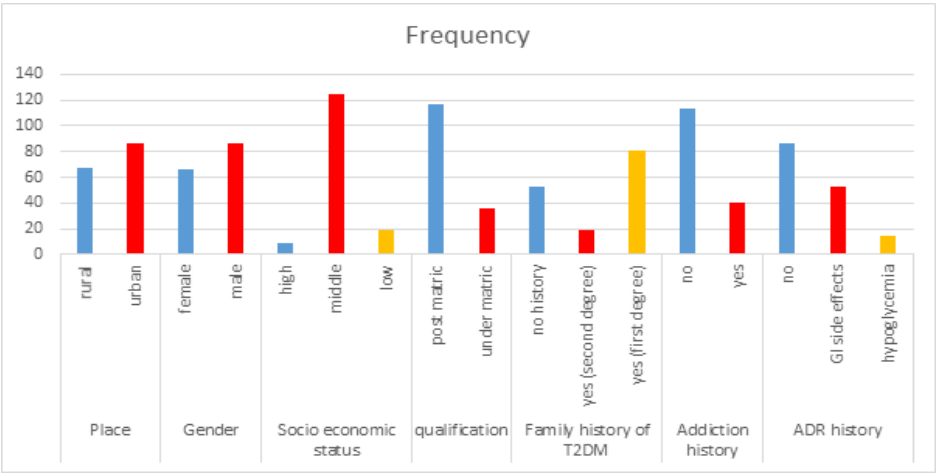

Figure 1: ?

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The mean age of the patients in our study was 57.31±8.38 yrs, where people from the age of 33 year to 72 years were enrolled. People with a duration of disease between 4-6 years were taken with a mean age of 5.16±0.81 years. Average weight of the study population was 68.84±7.15 kg and average height was 1.6±0.1 meters. The mean BMI of the patients was 26.93±3.62 kg/meter^2 which ranged from 19.14 to 33.78 kg/meter^2. [Table 2]

Table 2: Clinicodemographic data (continuous)

Patient details	Range	Mean±Std. Deviation
Age in years	33 - 72	57.31±8.38
Duration of disease in years	4 - 6	5.16±0.81
Body weight in KG	49 - 81	68.84±7.15
Height In meter	1.40 - 1.80	1.60±0.4
Body Mass Index in kg/mtr^2	19.14 - 33.78	26.93±3.62

Around (90 & 70, 58.8% & 45.8%) people of our study population were having fasting & post prandial hyperglycemia with blood sugar level more than 126 & 200 respectively. HBA1C level was more than 7mg% in around (69, 45.1%) people of different treatment group. Serum creatinine & blood pressure were also above control level in 10.5% & 54.9% of the population. [Table 3, Figure 2]

Table 3: Laboratory outcomes

Mean values of lab data of last one year		Frequency	Percentage (%)
FBS (mg/dl)	Less than 126	63	41.2
	More than or equal to 126	90	58.8
PPBS (mg/dl)	Less than 200	83	54.2
	More than or equal to 200	70	45.8
HBA1C (mg %)	Less than 7	84	54.9
	More than or equal to 7	69	45.1
Serum creatinine	Normal	137	89.5
	Above normal	16	10.5
Blood Pressure	Controlled	69	45.1
	Uncontrolled	84	54.9
	Total	153	100.0

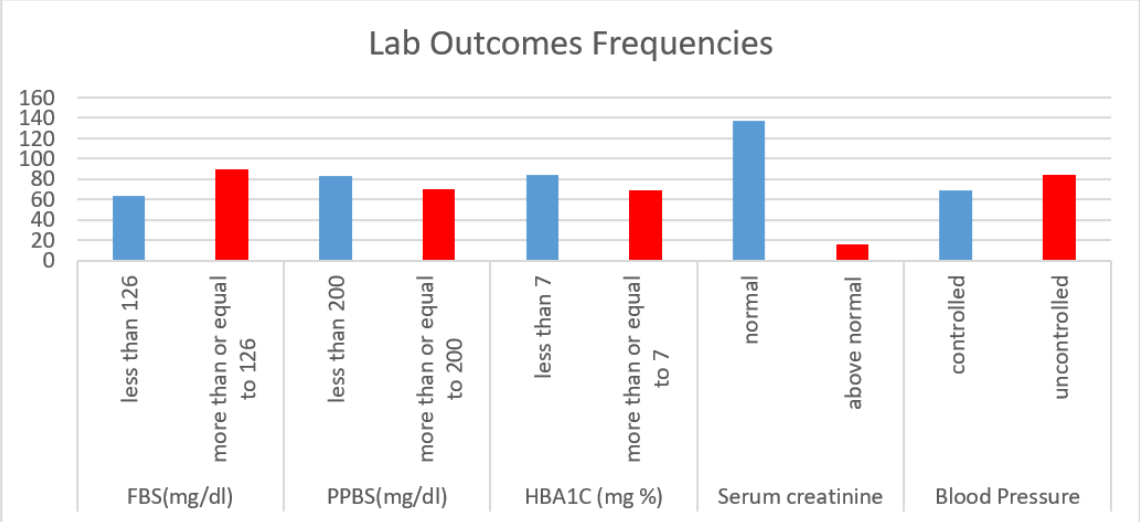

Figure 2: ?

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In our study, multiple co-morbidities were also recorded along with T2DM. Around 114(74.5%) people were having hypertension, 94(61.4%) were having dyslipidemia and 48(31.4%) people were overweight or obese. While hypertension had a negative impact on glycemic outcome (OR, 0.191; 95% CI, 0.79-0.464) for HBA1C being less than 7, obesity had an opposite effect (OR, 6.204; 95% CI, 2.539-15.164). Rest of the co-morbidities had no statistically significant impact on HBA1C level. [Table 4, Figure 3]

Table 4: Comorbidities

Comorbidities		**Frequency**	**Percentage (%)**
Hypertension	Yes	114	74.5
	No	39	25.5
Dyslipidemia	Yes	94	61.4
	No	59	38.6
Obesity	Yes	48	31.4
	No	105	68.6
	Total	153	100.0

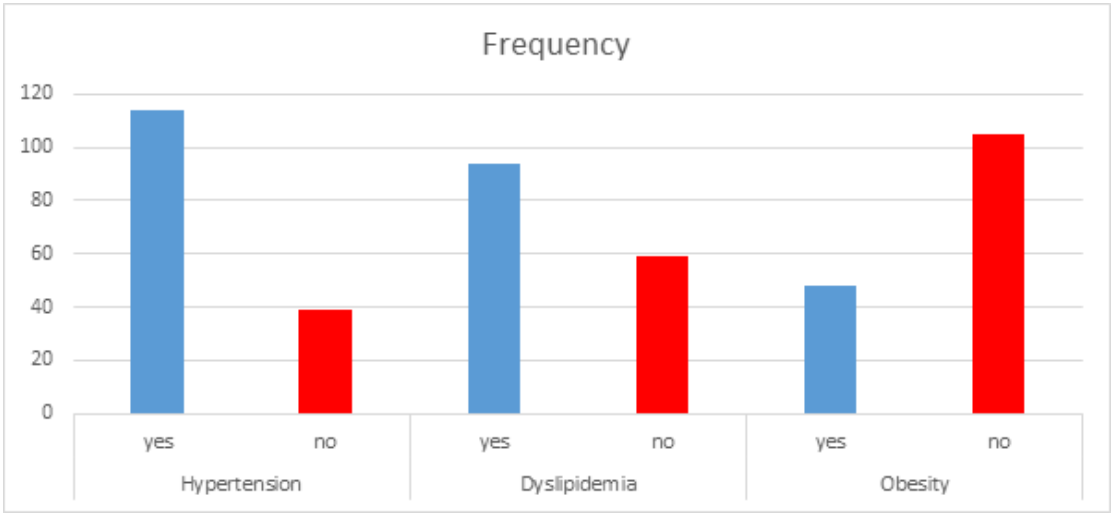

Figure 3: ?

Finally all the treatment groups were evaluated for relative glycemic control and other treatment outcomes. Patients treated with sulfonylureas and a combination of sulfonylureas/metformin/DPP4 inhibitors did show statistically significant better glycemic outcome (OR, 8.237; 95% CI, 1.786-37.985) & (OR, 2.862; 95% CI, 1.349-6.069). Patients taking a combination of metformin/sulfonylureas/SGLT-2I have shown significantly less glycemic control (OR, 0.039;95% CI, 0.008-0.183). [Table 5, Figure 4]

Table 5: Glycemic outcome in different treatment groups (in terms of HBA1C level)

Treatment given	**N**	**n (HBA1C<7)**	**Odds ratio**	**CI(95%)**	**P-value**
Metformin	30	13	0.695	0.307-1.576	0.384
Sulfonylureas	17	15	8.237	1.786-37.985	0.007
Metformin+Sulfonylureas	17	9	0.845	0.299-2.385	0.751
Metformin+Sulfonylureas+DPP4I	57	40	2.862	1.349-6.069	0.006
Metformin+sulfonylureas+ disaccharidase	4	3	2.589	0.263-25.503	0.415
Metformin+sulfonylureas+SGLT2I	28	2	0.039	0.008-0.183	0.001

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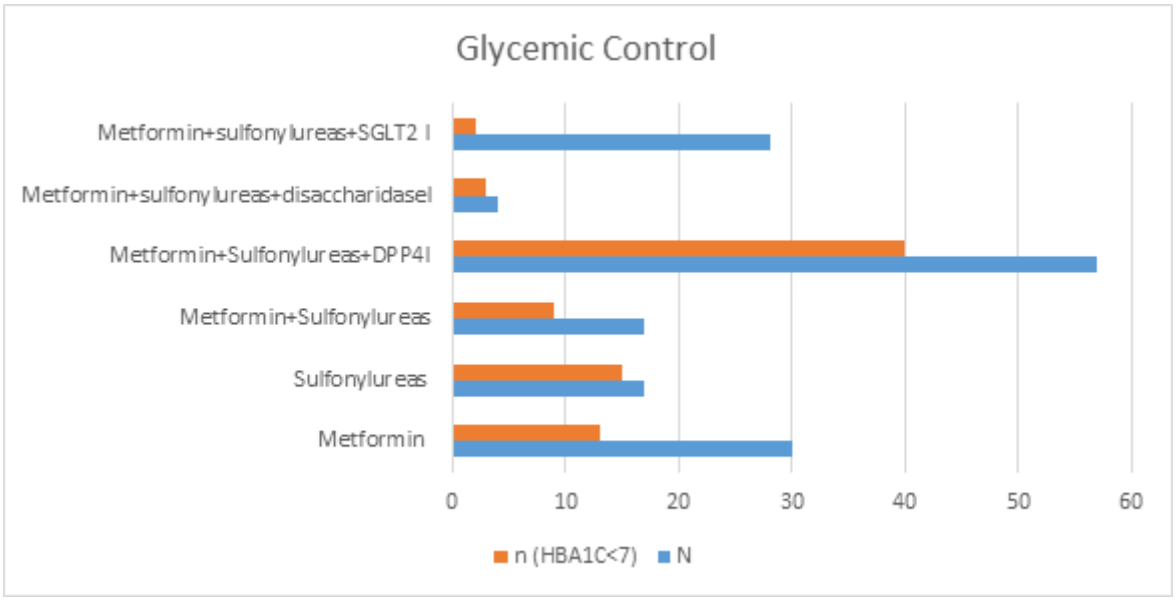

Figure 4: glycemic outcome in different treatment groups (in terms of HBA1C level)

Among patients with hypertension as a comorbidity, the group taking a combination therapy of metformin & sulfonylureas have shown significantly worst BP control over others (OR, 0.114; 95% CI, 0.025-0.529) and those treated with metformin/sulfonylureas/SGLT-2I have shown the best BP outcomes (OR, 5.527; 95% CI, 2.012-15.183). [Table 6, Figure 5]

Table 6: Blood pressure outcome in different treatment groups (in MM/HG)

Treatment given	N	n BP<130/80 MM of HG	Odds ratio	CI(95%)	P-value
Metformin	30	9	0.489	0.205-1.166	0.107
Sulfonylureas	17	9	1.438	0.520-3.977	0.484
Metformin+Sulfonylureas	17	2	0.114	0.025-0.529	0.006
Metformin+Sulfonylureas+DPP4I	57	28	0.997	0.487-2.043	0.994
Metformin+sulfonylureas+ disaccharidaseI	4	3	3.590	0.365-35.324	0.273
Metformin+sulfonylureas+SGLT2I	28	19	5.527	2.012-15.183	0.001

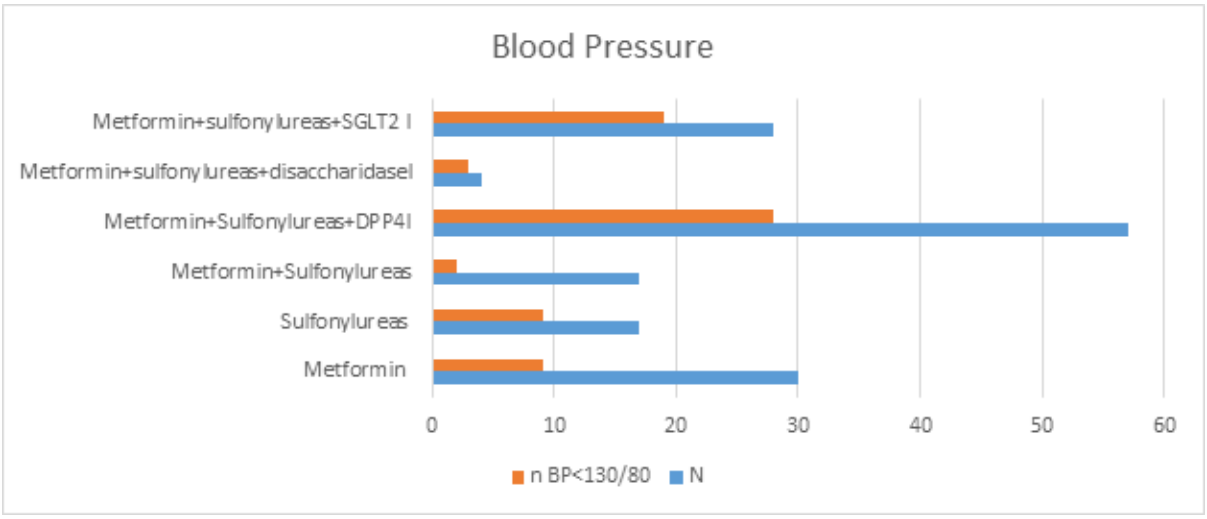

Figure 5: Blood pressure outcome in different treatment groups (in MM/HG)

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Discussion

The present study found that most of the patients that attended a GP clinic belong to urban background. This might be due to the location and the accessibility of a GP clinic catering to diabetic patients in an urban setup and a higher level of awareness about the disease in urban population.[18] More male patients were enrolled in the study than females indicating a possibility that women face multiple personal, sociocultural, health system, economic, psychological, and geographical barriers in accessing type 2 diabetes care.[19] People from middle & low socio-economic class were more affected by the disease as compared their high socio economic status peers. This might be due to exposure of a combination of risk factors like genetic predisposition, poor diet quality, lack of physical activity, stress & smoking etc.[20] Enrolment of more qualified people in the study possibly indicated more awareness about the disease and its complications in qualified people.

A higher proportion of diabetic patients having a positive family history strongly suggests it to be a very important risk factor for development of the disease.[21] Around 35% of the treated population reported minor ADRs like GI side effects wile around 9% reported major side effects like hypoglycemia which has potentially high chance of hospitalization for management. Although producing multiple ADRs, the potential benefit of all the treatment protocols significantly out-weigh their risk. Incidence of ADRs may be attributed to multiple factors like polygenic variability, inter-ethnic variability, Clinical, anthropometric, and environmental factors such as age, sex, weight, concomitant use of other drugs etc.[22]

The average age being between 55 to 60 years starting from as low as 33 years old people being affected by T2DM is a clear warning of the risk shifting towards younger population. This hazardous trend can be attributed to multiple factors such as increase in prevalence of obesity among youth.[23] People with a disease duration between 4-6 years with a mean duration of 5.16±0.81 have been enrolled in the study to minimize multiple confounders and establish relative equilibrium in the study population. It's an well-established fact that high BMI is a risk factors not only for development of pre-diabetes and diabetes but also for development of multiple complications of T2DM with increased tendency of hemoglobin to be glycated which is re-established in our study with average BMI of around 27(overweight) of the study population.[24]

Multiple co-morbidities were observed in the diabetes patients of our study population and we recorded the important ones which have possible impact on diabetes treatment and complication outcomes. In our study population around 114(74.5%) people were having hypertension as a comorbidity and the treatment outcome in this subset of population was relatively bad with lesser propensity of good glycemic control. This outcome can be explained by the possible worsening of pathophysiology due to added oxidative stress, inflammation and fibrosis caused by hypertension in diabetic patients which not only affects glycemic outcome, but also exaggerates cardiovascular risk which already is high in diabetic patients.[25] In contrary to the well-established fact that obesity does worsen glycemic outcomes, in our study obese patients had a better glycemic control than their lean counter parts.[26] This kind of finding is hard to be explained scientifically, but some possible other factors such as higher level of awareness & concern in obese patients and their family members, the higher level of treatment inertia for intensification in lean diabetic patients among GPs due to fear of adverse effect like hypoglycemia etc might have contributed to such finding.[27,28]

When different treatment groups were compared for with each other, patients treated with sulfonylureas/metformin/DPP4I did show a significantly better glycemic outcome as compared to Group-B. This finding is in line with the fact that sulfonylureas & biguanides are still the most efficacious anti-diabetic drugs with HBA1C lowering efficacy upto 1-2 % which is comparable to insulin therapy, and DPP4 inhibitors can act synergistically with them

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to lower blood glucose level & even increases the risk of hypoglycemia.[29,30] But due to the recommendations of newer guidelines and proposed theory of initiation of treatment with combination therapy, physicians usually combine other drugs with first line drug to achieve target glycaemia far before reaching the higher recommended doses of metformin.[31,32] In our study population, the most common treatment and combination regimen was of sulfonylureas/metformin/DPP4I. The possible reasons behind bad glycemic outcome in the treatment group containing SGLT2 inhibitors are, consideration of these drugs as second or third line drugs hence their use only in uncontrolled or treatment failure diabetic patients as a combination therapy, higher level of inertia among general practitioners for these drugs and consideration of them as only a last option as they are new, less treatment compliance by the patients due to increased incidences of urinary and genital infections etc.[33,34]

Limitations:

Various limitations might have restricted the study outcome such as lower sample size, less diversification of study populations, dependency on patient documents for data collection, various possible biases such as recall bias etc. we believe further such studies can be helpful in designing population based T2DM treatment guidelines which can be of immense help to primary care physicians.

Conclusion

Our study strongly suggests that, the drugs used in T2DM might have different long-term outcomes with respect to complications, ADRs, co-morbidity out comes etc. In our study, we found biguanides, sulfonylureas, DPP-4 inhibitors to be very good blood glucose lowering agents, while SGLT-2 inhibitors have possible cardio & nephro protective properties. General physicians have significant treatment inertia, more so with newer agents like SGLT-2 inhibitors. Co-morbidities like hypertension might have negative impact on diabetes outcome indicating their prompt treatment. Majority patients in GP clinics are not reaching glycemic target, which prompts the need of rigorous training of GPs and awareness of patients. Further studies are needed to evaluate the comparative efficacy and safety outcomes of all antidiabetic medications with respect to complications, co-morbidities, ADR etc along with glycemic control in long term treatment.

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