Original Article

Role of Metformin, Sodium-Glucose Cotransporter-2 (SGLT2) Inhibitors, Glucagon-Like Peptide-1 (GLP-1) Receptor Agonists, and Orlistat based Multidrug Therapy in Glycemic Control, Weight Loss, and Euglycemia in Diabesity: A Real-World Experience

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Abstract

Background: This study evaluated the real-world weight loss and glycemic outcomes of multidrug therapy (MDT) according to various combinations of metformin, sodium-glucose cotransporter -2 inhibitor (SGLT2i), glucagon-like peptide-1 receptor analogs (GLP1a), and orlistat in diabesity. **Methods:** Data retrospectively captured from medical records of 2 different centers in New Delhi for patients >35 years-age having prediabetes/diabetes and on at least any one of the 4 above medications with >6-months follow-up was analyzed. **Results:** In total, 5,336 patient records were screened; 2,442 with prediabetes/diabetes were considered; 1,509 patients who fulfilled all criteria were analyzed. Use of metformin, SGLT2i, sulfonylureas, DPP4i, pioglitazone, orlistat, and GLP1a was 85.35%, 74.95%, 68.32%, 60%, 39.16%, 9.08%, and 4.17%, respectively. However, 365, 970, and 104 patients were on one of 4 concerned medications (Group-1; 24.18%), dual MDT (Group-2; 64.28%), and triple/quadruple MDT (Group-3; 6.89%). Metformin with SGLT2i was most commonly used dual MDT (94.12%). Analysis according to weight-loss quartiles from 558 patients showed 6.9 kg weight-loss in the highest quartile. People losing maximum weight were significantly younger; had higher use of metformin, SGLT2i, GLP1, orlistat, and lower pioglitazone use; greatest HbA1c reduction (–1.3 vs. –0.3; quartile-1 vs. quartile –4; $P < 0.001$); and significantly higher occurrence of HbA1c<5.7% (16.8% vs. 6.29%; quartile-1 vs. 4; $P < 0.001$). Patients in Group-3 had the highest baseline BMI and maximum weight loss with highest number of patients with HbA1c<5.7% (19.44% vs. 10.34%; Group-3 vs. Group-1; $P < 0.001$). **Conclusion:** Greater weight loss with HbA1c reduction along with a greater number of patients attaining HbA1c <5.7% highlights that MDT is the way forward to tackle diabesity in India.

Keywords: Diabesity, diabetes reversal, GLP1 receptor agonists, metformin, orlistat, SGLT2 inhibitors, weight loss

Introduction

Diabetes along with obesity has become a global pandemic and is of special concern in India, which is often considered as the diabetes capital of the globe.[1] The exponential increase in the burden of obesity, especially in the young population is driving the diabetes epidemic in India. Hence, it is not surprising that prediabetes and diabetes onset in India is nearly 2 decades earlier than in the western world.[2,3] It is especially concerning

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that not only is the onset of diabetes earlier in Indians, it tends to have a more aggressive phenotype as evidenced by the highest global rates of prediabetes to diabetes progression (14–18% p.a. in India in contrast to 2.5% p.a. in USA and 6% p.a. in Finland), greater insulin resistance, systemic inflammation, beta cell dysfunction, and onset at a lower body mass index.[1,3]

Recent studies have also demonstrated the importance of weight loss in not only ensuring better glycemic control in type-2 diabetes (T2DM) but also in diabetes reversal.[3] Various criteria have been used to define diabetes reversal. Diabetes reversal has been traditionally defined as HbA1c<6% [42.1 mmol/mol] and being off all anti-diabetes medications for >2 months.[4] A huge basket of pharmacotherapy is currently available for the management of diabetes (488 different drugs; 70 different genericcompounds).[5] However, among them, only metformin, sodium-glucose co-transporter -2 inhibitors (SGLT2i), and glucagon-like peptide-1 receptor analog (GLP1a) have been reported to be associated with mild weight loss.[6] Orlistat is also approved and available in India, as an anti-obesity medication. Topiramate-phentermine and bupropion-naltrexone fixed-dose combinations are not available in India. In spite, the large volume of literature available regarding the mild weight losing properties of each of the above 4 drugs when used alone, data on their impact on weight loss and glycemic control when used in different combinations is scant.[6,7] Multi-drug therapy (MDT) has become the standard for managing different disorders including tuberculosis, leprosy, hypertension, and diabetes.[8] Hence, the aim of this study was to evaluate the real-world efficacy on weight loss and glycemic outcomes of MDT according to a different combination of metformin, SGLT2i, GLP1a, and orlistat in the management of diabesity in India.

Methods

Data were retrospectively captured from the electronic medical record (EMR) database of 2 different centers in New Delhi. The duration of the study was from August 2017 to December 2018. The institutional ethics committee had approved this retrospective EMR based study. The American Diabetes Association 2016 guideline was followed for managing all patients with metabolic syndrome (prediabetes and type-2 diabetes) at both the centers. Patients with metabolic syndrome more than 35 years of age were considered for the study. Patients with prediabetes or diabetes on at least any one of the 4 medications in focus (metformin, SGLT2i, GLP1a, or orlistat; either alone or as a part of MDT) were included in the study. Patients with associated severe chronic co-morbid states such as chronic liver, renal , and cardiac diseases were excluded. In addition, patients with a history of hospital admission in the last 6 months were also excluded. Incomplete records were excluded from the analysis. Details of other anti-diabetes medications being used as per standard care were noted. All patients had dedicated sessions with a dietician for half an hour during their initial visit and were counseled regarding low carbohydrate hypo-caloric diet. Patients with at least 6 months follow-up data available (glycemic and body weight outcomes) were included in the study. The entire flow of patient recruitment has been elaborated in Figure 1. Data for the following variables were collected at baseline and after 6 months of follow-up (height, weight, fasting glucose, 2 h postprandial glucose, and HbA1c). In addition, data were collected on hemoglobin, renal function status (creatinine), and lipid-parameters (LDL-C and triglycerides). Because pioglitazone and sulfonylureas are antidiabetic medications known to be associated with weight gain, we specifically recorded what percent of patients were receiving these drugs.

Statistical analysis

The extracted data were manually entered into a pre-coded MS excel sheet. Data analysis was done using the Statistical Package for Social Sciences (SPSS) version 20.0, IBM, USA. Normality of the distribution of variables was assessed using the Kolmogorov-Smirnov test. All normally distributed variables expressed as mean ± standard deviation; all non-normally distributed variables expressed

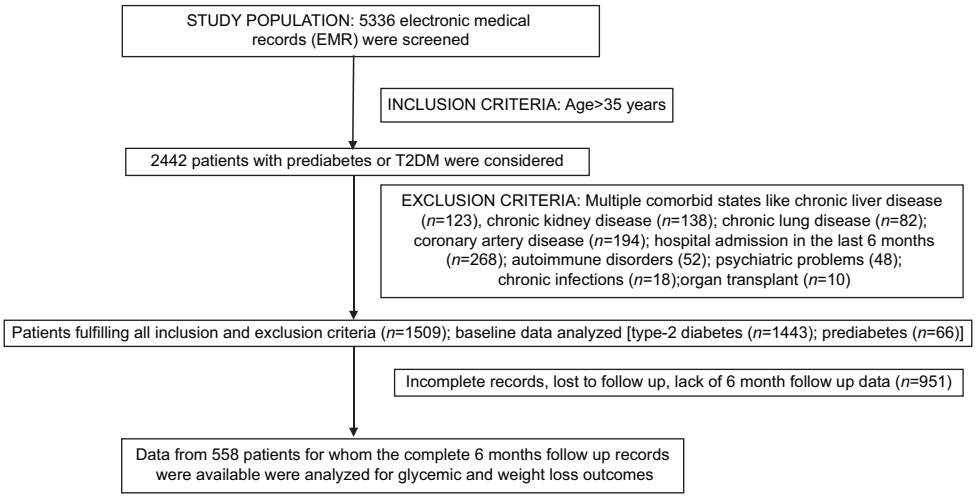

Figure 1: Flowchart elaborating the study protocol and flow of patients

as median [25th – 75th percentile]. Independent t test and Wilcoxon rank-sum test were done for normally distributed and skewed variables, respectively. Chi-square tests were used for categorical variables. $P < 0.05$ considered statistically significant.

Results

A total of 5,336 patient records were screened (male: female = 1649:2010) having mean age, weight, and BMI of 51.8 ± 15.45 years, 72.35 ± 23.3 kg, and 27.74 ± 6.35 kg/m^2, respectively. Using the BMI based obesity diagnostic criteria for south Asians,[9] 60.53% (n = 3229) and 8.76% (n = 468) patients in our population were obese (25–34.9 kg/m^2) or morbidly obese (> =35 kg/m^2). However, 14.52% patients (n = 775) were overweight (23–24.9 kg/m^2). Normal BMI (18.5–22.9 kg/m^2) was documented in only 13.77% patients (n = 735). Moreover, 129 patients (2.4%) were underweight (BMI <18.5 kg/m^2). The prevalence of hypertension in this cohort was 37.06% (n = 1978). In total, 2,442 patients with prediabetes or diabetes were considered for this study of which data from 1,509 patients [type-2 diabetes (n = 1443); prediabetes (n = 66] who fulfilled the initial inclusion criteria have been elaborated in Tables 1 and 2. The occurrence of obesity was significantly higher in the study cohort patients (n = 1509; 29.63 ± 5.67 kg/m^2; $P < 0.001$) than all the patients coming to the center for treatment (n = 5336; 27.74 ± 6.35 kg/m^2) [Table 1].

Metformin (85.35%) was the most commonly used medication in the study cohort followed by SGLT2i (74.95%), sulfonylureas (68.32%), and DPP4i (60.00%) [Table 1]. A significant percentage of patients were on pioglitazone (39.16%) [Table 1]. Only 4.17% patients were of GLP1a [Table 1]. We analyzed the data focusing on clinical usage patterns of the 4 medications, which have been linked with weight loss viz. metformin, SGLT2i, GLP1a, and orlistat in different combinations. Of the 1,509 patients in this study, 70 patients were on medical nutrition therapy, 365 patients were on one of the 4 medications under focus (Group-1; 24.18%), 970 patients were in dual MDT group (any 2 of the 4 medications under focus; Group-2; 64.28%), and 104 patients were in triple/quadruple MDT group (Group-3; 6.89%). In absolute numbers, these translate to 88 patients on triple MDT and 16 patients on quadruple MDT [Table 2]. Among the different dual MDT combinations, metformin with SGLT2i was the most commonly used dual MDT constituting 94.12% of all patients receiving dual MDT [Table 2].

The 6-month follow-up data were available from 558 patients [T2DM (n = 541); prediabetes (n = 17)], which has been elaborated in Table 3. Because the number of people with prediabetes was too small (n = 17), they have not been analyzed separately. In Table 3, the baseline clinical and treatment parameters have been elaborated according to the quartiles of weight loss at the end of 6 months follow-up. 125 patients in quartile-1 lost a median of 6.9 kg weight in contrast to 143 patients in quartile-4 who gained a median of 1.8 kg weight at 6 months follow-up [Table 3].There was no significant difference in the distribution of people with diabetes or prediabetes across the 4 quartiles [Table 3]. People who lost weight were significantly younger [Table 3]. Our study showed that people who lost the greatest weight (quartile-1) had the highest BMI at baseline (35.51 ± 6.29 kg/m^2) and had significantly higher use of metformin, SGLT2i, GLP1, and orlistat, along with significantly lower use of pioglitazone. Patients on 3 or more of the 4 medications under focus (triple/quadruple MDT; Group-3; n = 72) had a greater median weight loss of 4 kg as compared to a weight loss of only 0.5 kg who were on one of the 4 medications under focus (Group-1; n = 114) [Table 4]. Patients in Group-3 (triple/quadruple MDT)

Table 1: Baseline clinical, biochemical, and pharmacologic profile of patients in this study

Parameter	Patient profile
Total number of patients	1509
Prediabetes: Type-2 diabetes	66:1443
Age (years)	50.95±13.49
Male:Female	790:719
BMI (kg/m^2) baseline	29.63±5.67
HbA1c (%) baseline	8.01±2.01 [64 mmol/mol]
Hypothyroidism	252 (16.69%)
Hyperthyroidism	8 (0.01%)
Metformin	1288 (85.35%)
Sulfonylureas	
Total	1031 (68.32%)
Glimepiride	915
Gliclazide	105
Others	11
DPP4i	
Total	906 (60.00%)
Teneligliptin	521
Sitagliptin	167
Vildagliptin	67
Saxagliptin	108
Linagliptin	43
SGLT2i	
Total	1131 (74.95%)
Dapagliflozin-10 mg	303
Empagliflozin-25 mg	302
Canagliflozin-100 mg	255
Canagliflozin-300 mg	271
Alpha glucosidase inhibitors	158 (10.47%)
Pioglitazone	591 (39.16%)
GLP1a	
Total	63 (4.17%)
Dulaglutide	45
Liraglutide	18
Orlistat	211 (13.98%)
Basal insulin	213 (14.11%)
Short acting insulin	161 (10.66%)

All normally distributed variables expressed as mean±standard deviation; all categorical variables have been expressed as absolute numbers (percentage)

Table 2: Profile of multi-drug therapy used in clinical practice for managing diabesity

Type of drug therapy combinations used	Type-2 diabetes ($n=1443$)	Prediabetes ($n=66$)
No drug (only on MNT)	67	3
Single drug	316	49
Metformin only	229	17
Orlistat only	65	32
SGLT2i	22	-
Dual drug combinations	956	14
Metformin+ Orlistat	11	14
Metformin+ SGLT2i	913	-
SGLT2i + Orlistat	32	-
Triple drug combinations	88	-
Metformin+SGLT2i + Orlistat	41	-
Metformin+SGLT2i+GLP1a	47	-
Quadruple drug combination (Meformin+SGLT2i+GLI1a+Orlistat)	16	-

Drugs which have been considered to have weight losing properties in this study include metformin, SGLT2i, GLP1a, and orlistat. This table focuses on the number of patients on different combinations of these medications, with or without other medications for the management of diabetes; sodium-glucose cotransporter-2 inhibitor, GLP1a: Glucagon-like peptide receptor-1 antagonists; no drug implies that the patient is not on metformin, orlistat, GLP1a or SGLT2i but is on other anti-diabetes medications. One drug implies that the patient is on one of the 4 concerned medications; 2 drugs implies that the patient is on any 2 of the 4 concerned medications (metformin, orlistat, GLP1a, or SGLT2i); MNT: Medical nutrition therapy

were significantly more obese as compared to Group-1 (BMI 33.61 ± 7.3 vs. 28.39 ± 4.8 kg/m^2) [Table 4].

People who lost the greatest weight also had the greatest reduction in HbA1c (–1.3 vs. –0.3 in quartile-1 and quartile-4, respectively; $P < 0.001$) [Table 3]. It must be highlighted that the degree of weight loss was independent of baseline HbA1c of the patients, which was comparable across all the 4 quartiles [Table 3]. A total of 46 patients were documented to have an HbA1c<5.7% at 6 months of follow-up. Patients who attained HbA1c<5.7% has a median duration of diabetes of 2.0 [1.37–3] years as compared to 4.0 [2.0–6.0] years for patients who could not attain an HbA1c<5.7% ($P = 0.006$). In addition, patients in quartile-1 (maximum weight loss) had the greatest number of patients achieving HbA1c<5.7% (16.8% vs. 6.29% in quartile-1 and 4, respectively; $P < 0.001$) [Table 3]. Of the 558 patients with 6 months follow-up data, 541 patients were on one or more of the 4 medications under focus in this study viz. metformin, SGLT2i, GLP1, and orlistat [Table 4]. However, 17 patients were not on any of the 4 concerned medications. The greater reduction in body weight among patients in Group-3 was accompanied by a greater number of patients achieving HbA1c<5.7% (19.44% vs. 10.34% in Group-3 vs. Group-1; $P < 0.001$) [Table 4]. It is important to highlight that this greater benefit of triple or quadruple MDT on weight loss and better glycemic control happened in spite of comparable baseline HbA1c in Group-3 as compared to Group-1 [Table 4].

Moreover, 558 patients (36.97%) had 6-month follow-up data from the initial 1,509 patients, implying an overall dropout/lost to follow-up of 63.03%. Large dropouts/lost to follow-up always remain a concern in real-world studies and is a major limitation of this study. The drop out/lost to follow-up rates in one drug (Group-1), dual MDT (Group-2), and triple/quadruple MDT groups were 68.22% (249/365 patients), 63.81% (619/970 patients), and 30.7% (32/104 patients) respectively.

Patients on sulfonylureas and pioglitazone had a significantly lower baseline BMI than those not on sulfonylureas and pioglitazone [Tables 5 and 6]. Patients on sulfonylureas and pioglitazone had marginally less weight loss at 6 months of follow-up as compared to those not on these medications, which was statistically not significant [Tables 5 and 6]. Patients on sulfonylureas and pioglitazone had a higher baseline HbA1c. The fall in Hba1c at 6 months of follow-up was significantly greater in patients on sulfonylureas than those who were not on sulfonylureas [Table 5]. However, similar trends were not seen in patients on pioglitazone as compared to those not on pioglitazone [Table 6].

There were 36 reports (6.45%) of mild self-limiting hypoglycemia, 19 reports (3.4%) of mild lower genital infection, 3 severe hypoglycemia (0.01%) needing visit to the emergency department of the hospital, and 1 report of severe arthralgia. There were no reports of fractures, amputations, euglycemic ketosis, or any hypersensitivity reactions.

Discussion

Studies have consistently demonstrated that weight loss is associated with increased life expectancy in people living with type-2 diabetes, with a weight loss of 15 kg or more linked with high chances of diabetes reversal.[10-12] Different authors and societies have suggested a different definition for diabetes remission. The American Diabetes Association (ADA) consensus group suggested partial remission of diabetes as HbA <6.5% [<48 mmol/mol] and fasting blood glucose 5.6–6.9 mmol/L without antidiabetes drugs (time not specified).[9] ADA and Buchwald *et al*. (systematic review in post-metabolic surgery patients) defined complete remission was defined as HbA1c<6% [<42 mmol/mol] and fasting blood glucose <5.6 mmol/L without antidiabetes drugs (time not specified).[9,13] It is interesting to consider that these cut-offs continue to be higher than Hba1c<5.7% [38.8 mmol/mol], which is defined as normoglycemia. Increased risk of hypoglycemia with low HbA1c, especially when using certain classes of drugs remains a challenge to achieving normoglycemic HbA1c values.

SGLT2i and GLP1a MDT make sense because of their ability to reduce HbA1c by different mechanisms, independent cardiovascular risk reduction effects (through hemodynamic effects for SGLT2i; anti-atherogenic/anti-inflammatory mechanisms for GLP1a), nephroprotective effects (macroalbuminuria reduction, decreasing the time for doubling of serum creatinine, and slowing time to end-stage

Table 3: Baseline clinical and treatment parameters as per weight loss outcomes after 6 months of follow-up

Parameter	Weight Change Quartiles (kg) (*n*=558)*				*P*
	Quartile-1	Quartile-2	Quartile-3	Quartile-4	
	-6.9 kg [-31.3 to-4 kg]	-3.0 kg [-4.0 to -1.45 kg]	-0.6 kg [-1.45 to+0.4 kg]	+1.8 kg [0.4 to 11.1 kg]	
	n=125	*n*=154	*n*=136	*n*=143	
Age (years)	48.45±13.26	51.91±11.84	51.8±12.62	46.51±14.33	**0.001**
Sex (Male:Female)	71:54	83:71	72:64	103:40	**0.030**
Diabetes:Prediabetes	123:2	151:3	133:3	134:9	0.108
Duration of diagnosis[#]	3.0 [2.0-4.5]	3.2 [2.0-6.0]	4.0 [2.0-6.0]	3.0 [2.0-5.0]	0.620
BMI (kg/m^2)	35.51±6.29	30.84±5.76	29.03±5.12	29.88±5.51	**<0.001**
SBP (mm of Hg)	134.86±18.39	130.32±18.45	133.39±21.26	129.16±23.77	0.096
DBP (mm of Hg)	83.42±9.91	80.46±9.38	80.22±10.82	80.57±12.51	0.063
Weight (kg)	94.1 [84.2 - 109.05]	80.95 [71.0 -91.95]	74.2 [67.0 - 81.95]	75.0 [65.8 - 85.7]	**<0.001**
Percent weight loss at 6 months (%)	-6.99 [-9.28 - -5.54]	-3.44 [-4.26 - -2.83]	-0.80 [-1.26 - -0.25]	2.43 [1.26 - 5.47]	**<0.001**
HbA1c (%)*	6.98 [6.0 - 9.03]	7.71 [6.37 - 9.42]	7.6 [6.88-9.2]	7.35 [6.3 - 8.9]	0.218
HbA1c at 6 months (%)*	6.0 [5.3 - 7.2]	7.0 [6.1 - 8.0]	7.2 [6.32 -8.17]	7.0 [5.95 - 8.05]	**<0.001**
Δ HbA1c (%)*	-1.30 [-1.95 - -0.5]	-0.7 [-1.5 - 0.1]	-0.6 [-1.07 - 0.0]	-0.3 [-1.0 - 0.25]	**0.029**
HbA1c<5.7% at 6 months	21 (16.8%)	11 (7.14%)	5 (3.37%)	9 (6.29%)	**<0.001**
Creatinine (mg/dl)	0.85±0.31	0.88±0.32	0.89±0.28	0.82±0.25	0.622
Hemoglobin (gm/dl)	13.57±2.1	12.48±1.98	12.10±2.65	12.46±1.97	0.063
LDL-C (mg/dl)*	103.5 [82.75 - 120.5]	108 [81.75 - 135.25]	104 [88.0-148.0]	102.5 [84.5 - 128.25]	0.639
Triglycerides (mg/dl)*	160 [116.5 - 219.5]	180.5 [131.25 - 249]	179 [128-256]	196 [122-322]	0.459
Hypothyroidism	30	19	13	37	**0.031**
Metformin	106	132	125	111	**0.011**
SGLT2i	117	137	107	95	**<0.001**
Dapagliflozin-10 mg	13	17	21	20	0.550
Empagliflozin-25 mg	8	33	21	21	**0.006**
Canagliflozin-100 mg	4	21	27	10	**<0.001**
Canagliflozin-300 mg	92	66	38	44	**<0.001**
GLP1a	30	14	7	5	**<0.001**
Liragultide	9	2	4	2	**0.016**
Dulaglutide	21	12	3	3	**<0.001**
Orlistat	19	9	4	26	**<0.001**
Pioglitazone	26	52	67	40	**<0.001**
Alpha-glucosidase inhibitors	20	22	13	10	0.072
Sulfonylureas	75	106	113	72	**<0.001**
Basal insulin	17	28	24	20	0.617
Short acting insulin	13	19	18	18	0.911

Normality of the variable distribution calculated using Kolmogorov- Smirnov test; All normally distributed variables expressed as mean±standard deviation; all non-normally distributed variables expressed as median [25th – 75th percentile]; *P*<0.05 considered statistically significant; Δ HbA1c: HbA1c at 6 months – HbA1c at baseline; sodium-glucose cotransporter-2 inhibitor, GLP1a: Glucagon-like peptide receptor-1 antagonists; BMI: Body mass index; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; LDL-C: Low density lipoprotein cholesterol; HbA1c: Glycated hemoglobin; [#]: Duration of diagnosis (in years) as told by the patient; *these 558 patients are comprised of 541 patients with T2DM and 17 patients with prediabetes. All *P* values which were less than 0.05 (statistically significant) were marked in bold

renal disease) with added benefits of weight-reducing properties.[7] The DURATION-8 trial demonstrated that over a period of 52 weeks, the combination of SGLT-2i (dapagliflozin) and GLP1a (exenatide QW) was associated with a greater reduction in HbA1c, weight, and blood pressure than either drug alone.[14] Orlistat has been shown to have good weight loss property in patients with diabetes on metformin and other oral diabetes medications.[15,16] In our study, patients with prediabetes were either on only MNT or received metformin and/or orlistat. Metformin and SGLT2i MDT have been extensively studied in the medical literature. A recent report from Australia has suggested that early use of dapagliflozin-metformin MDT may be more cost-effective and improve long-term outcomes in Australians with T2DM.[17] Dapagliflozin-metformin dual therapy or triple-drug therapy when saxagliptin was added to the regimen has been reported to be associated with a 1 years reduction in HbA1c and body weight by –0.82 to –1.2% and –3.2 to –3.5 kg.[18] Similar results have been documented with canagliflozin and empagliflozin based dual/triple MDT (metformin with SGLT2i with DPP4i).[19,20]

Table 4: Clinical profile and body weight outcomes according to the number of drugs used for managing diabetes, which have weight losing properties

Parameter	Total patients (n=541)			P
	One drug (Group-1) (n=116)	Two drugs (Group-2) (n=351)	Three or more drugs (Group-3) (n=72)	
Age (years)	49.36±14.75	53.24±12.8	38.03±10.88	**<0.001**
Sex (Male:Female)	47:69	187:164	42:30	**0.022**
Baseline BMI (kg/m^2)	28.39±4.8	28.58±4.93	33.61±7.3	**<0.001**
Baseline Weight (kg)*	72.95 [60.85-83.9]	80.0 [71.0-91.0]	100 [89.08-113.7]	**<0.001**
Weight at 6 months (kg)*	71.20 [61-84]	78.0 [70.0 - 89.0]	95 [88.0 - 109.5]	**<0.001**
Weight loss (kg)*	-0.5 [-2.8- 1.37]	-1.7 [-3.9 - 0.0]	-4.0 [-7.0 - 0.0]	**<0.001**
Percent weight loss at 6 months	-0.76 [-3.61 - 1.97]	-2.3 [-4.39 - 0.00]	-4.03 [-6.9 -0.00]	**<0.001**
HbA1c (%)*	6.8 [6.0 -8.1]	8.1 [6.9-9.8]	6.7 [5.9 - 7.17]	**<0.001**
HbA1c at 6 months (%)	6.45 [5.98-7.35]	7.2 [6.27-8.3]	5.9 [4.9 - 7.0]	**<0.001**
Δ HbA1c (%)*	-0.5 [-0.97 -0.17]	-0.6 [-1.83 - 0.0]	-0.7 [-1.4 - 0.2]	0.148
HbA1c<5.7% at 6 months	12 (10.34%)	14 (3.98%)	14 (19.44%)	**<0.001**
Pioglitazone	36 (31.03%)	142 (40.45%)	3 (4.16%)	**<0.001**

Normality of the variable distribution calculated using Kolmogorov-Smirnov test; All normally distributed variables expressed as mean±standard deviation; *all non-normally distributed variables expressed as median [25th – 75th percentile]; P<0.05 considered statistically significant; Δ HbA1c: HbA1c at 6 months – HbA1c at baseline; drugs which have been considered to have weight losing properties in this study include metformin, SGLT2i, GLP1a, and orlistat; SGLT2i: Sodium-glucose cotransporter-2 inhibitor, GLP1a: Glucagon-like peptide receptor-1 antagonists; no drug implies that the patient is not on metformin, orlistat, GLP1a or SGLT2i but is on other anti-diabetes medications. One drug implies that the patient is on one of the 4 concerned medications; 2 drugs implies that the patient is on any 2 of the 4 concerned medications (metformin, orlistat, GLP1a, or SGLT2i); 6 month follow-up data were available from 558 patients; 17 of these 558 patients were not on metformin, orlistat, GLP1a, or SGLT2i and hence excluded from this table; $^{\#}$: Duration of diagnosis (in years) as told by the patient. All P values which were less than 0.05 (statistically significant) were marked in bold

Table 5: Clinical profile and body weight outcomes in type-2 diabetes patients on sulfonylureas as compared to those not on sulfonylureas (n=541)

Parameter	Patients on sulfonylureas (n=376)	Patients not on sulfonylureas (n=165)	P
Age (years)	53.82±10.32	42.73±13.92	**<0.001**
Sex (Male:Female)	194:182	83:82	0.872
Baseline BMI (kg/m^2)	30.36±5.79	33.22±6.33	**<0.001**
Baseline Weight (kg)*	78.2 [68.7 - 88.95]	88.1 [73.6 - 104]	**<0.001**
Weight at 6 months (kg)*	76.0 [67.0-86.0]	86 [72.75 -100]	**<0.001**
Weight loss (kg)*	-1.4 [-3.6 - 0.0]	-2.2 [-4.45 - 1.01]	0.702
Percent weight loss at 6 months	-1.91 [-4.38 - 0.0]	-2.76 [-4.89 -1.36]	0.502
HbA1c (%)*	8.25 [7.19 -9.8]	6.0 [5.8-6.7]	**<0.001**
HbA1c at 6 months (%)*	7.3 [6.7 -8.4]	5.9 [5.3- 6.3]	**0.001**
Δ HbA1c (%)*	-0.7 [-1.8 - 0.0]	-0.5 [-1.0 - 0.2]	**0.028**
HbA1c<5.7%at 6 months	7	35	**<0.001**

BMI: Body mass index; *all non-normally distributed variables expressed as median [25th – 75th percentile]; P<0.05 considered statistically significant. All P values which were less than 0.05 (statistically significant) were marked in bold

Our study highlights the extremely concerning trend of a high prevalence of obesity in urban Indians. In our study, in a cohort of 5,336 patients, an overwhelming majority of 83.81% patients were overweight to obese. Another recent study from New Delhi reported similar high rates of obesity of 71.5% in a cohort of 1,473 patients.[21] The CARRS study in a population screening of 5,365 individuals from New Delhi revealed a very high prevalence of prediabetes/diabetes of 72.7%.[22] Obesity is an independent predictor of increased cardiovascular events and worsens all end-organ damage associated with diabetes.[23] The prevalence of obesity in an apparently healthy population in India has increased exponentially in the last 30 years and varies from 11.8% to 31.3%.[24] The disproportionately higher trends of use of SGLT2i among the patients in our cohort than the general practice trends in India[6] may be explained by the significantly higher occurrence of obesity and morbid obesity in our patients, where SGLT2i would do both the job of glycemic control along with mild weight loss. Insulin use was low in our cohort of patients (10–14%). This may be because we excluded sick and morbid patients from the study, who are more likely to use insulin. In addition, this is in accordance with previous data from India, which have showed delayed insulin initiation in clinical practice.[6]

This is the first-real world study from India to highlight the importance of weight loss in ensuring good glycemic control. Patients who lost the greatest amount of body weight had

Table 6: Clinical profile and body weight outcomes in type-2 diabetes patients on pioglitazone as compared to those not on pioglitazone (*n*=541)

Parameter	Patients on pioglitazone (*n*=185)	Patients not on pioglitazone (*n*=356)	*P*
Age (years)	54.35±10.65	48.39±13.07	**<0.001**
Sex (Male:Female)	96:89	180:176	0.512
Baseline BMI (kg/m^2)	28.62±5.26	32.59±6.07	**<0.001**
Baseline Weight (kg)*	73.6 [65.4 -82.1]	84.25 [73.1 - 98.75]	**<0.001**
Weight at 6 months (kg)*	73.0 [63.0 - 80.45]	83 [72 - 94.9]	**<0.001**
Weight loss (kg)*	-1.0 [-3.0 - 0.0]	-2.05 [-4.4 - 0.48]	0.054
Percent weight loss at 6 months	-1.47 [-3.85 - 0.0]	-2.75 [-4.92 -0.58]	0.355
HbA1c (%)*	8.8 [7.3 - 9.9]	7.1 [6.0 -8.2]	**<0.001**
HbA1c at 6 months (%)*	7.4 [6.9 -8.75]	6.4 [5.8 -7.5]	**<0.001**
Δ HbA1c (%)*	-0.77 [-1.83 - -0.1]	-0.5 [-1.4 - 0.1]	0.356
HbA1c<5.7%at 6 months	2	41	**<0.001**

BMI: Body mass index; *all non-normally distributed variables expressed as median [25th – 75th percentile]; *P*<0.05 considered statistically significant. All *P* values which were less than 0.05 (statistically significant) were marked in bold

the highest reduction in HbA1c (–1.3% HbA1c reduction in patients who lost 6.9 kg body weight as compared to only –0.3% HbA1c reduction in patients who gained 1.8 kg weight; quartile-1 vs. quartile-4) [Table 3]. Our study showed that people who were more obese to start with and who were younger were more likely to lose a greater amount of body weight. Younger people with a lesser duration of diabetes also had greater chances of attaining HbA1c<5.7%. An HbA1c of <5.7% (normoglycemia) was documented in a total of 46 patients in this study (8.24%). Although normoglycemia was attained, this cannot be considered as diabetes remission as the patients were continuing their medications. The Look AHEAD study, which focused on intensive lifestyle interventions, reported 11.5% diabetes remission at 12 months of follow-up.[25] In contrast, the Scottish Care Information Diabetes database, which includes data from every patient in Scotland, documented 0.1% remission of type-2 diabetes (245/254,208) (March 2017).[12]

This study highlights the importance of combining low carbohydrate hypocaloric diet with MDT in contributing to both weight loss and glycemic control in patients with diabesity. Patients who were on triple/quadruple MDT had significantly higher weight reduction, associated with a greater percentage of patients achieving HbA1c<5.7% (19.44%) than those who were on dual MDT (3.98%) or on only one of the 4 concerned medications (10.34%) [Table 4]. The disproportionately lower number of patients achieving HbA1c<5.7% in dual MDT group may be explained by the significantly higher baseline HbA1c in that group [Table 4]. It must be realized that patients on triple/quadruple MDT were not matched to those on dual MDT or on one of the 4 concerned medications. Patients on triple/quadruple MDT were significantly more obese to start with, which would also have contributed to the greater weight loss. It is likely that people who are more obese are more likely to get one or more of diabetes medications, which are associated with weight loss. This is a limitation of real-world study, where one has no control over patient recruitment and treatment allocation. Strength of this study includes the focus on therapeutic lifestyle interventions in routine clinical practice. All patients during their first visit to the department had a dedicated session of 30 min with the dietician who discussed and motivated the patient to follow a low calorie, low carbohydrate diet. Importance of daily physical activity was equally reinforced in all patients.

Both the use of sulfonylureas and pioglitazone was associated with a blunting effect on weight loss at 6 months of follow-up. However, this effect was marginal and statistically not significant. Both these drugs were used at a relatively lower BMI in clinical practice and in the setting of significantly higher baseline HbA1c. Insulin/needle-prick phobia among the patients may explain the greater use of different oral anti-diabetes agents in different permutations and combinations in clinical practice in India.[6] Use of GLP1a was very low in this study. High costs associated with GLP1a use, predominantly out of pocket health care expenditure, coupled with needle-prick phobia may have contributed to low use of GLP1a in our population.

We have tried to analyze the concerns with long-term compliance with MDT for weight loss and glycemic control. Greater number of medications in MDT would not only increase the cost of therapy, but is theoretically likely to increase the chances of side effects, which would have an adverse impact on long-term compliance. This study had an overall lost to follow-up rate of 63.03%. It must be realized dropouts here just imply that the patient did not come back to the same center for follow-up. It does not imply the cessation of treatment. The patient would have continued treatment at some other center or may have relocated. Finally, lost to follow-up always remain a concern in real-world studies, where the data has been collected retrospectively, the data recording may have been incomplete, the authors have no control over the flow of patients over a period of time, and patients have no incentive to come back to follow-up. However, it is interesting to note that from an overall lost to follow-up rates of 63.03% in this study; the lost to follow-up rates in patients on single drug, dual MDT, and triple MDT groups were 68.22%, 63.81%, and 30.7%, respectively, highlighting that the progressive increase in the number of

medications in the MDT was associated with a significantly lower and not increased drop-out in the real-world scenario. These data were assuring in terms of side effects with increasing number of medications in MDT. A lesser lost to follow-up with greater number of medications in MDT for diabesity may be owing to the greater weight loss, better glycemic control, along with possibly no increase in major side effects, which would result in greater patient satisfaction and hence better treatment compliance and return to follow-up. However, dedicated patient satisfaction data were not collected, which remains a limitation. However, it is also likely that because patients on triple/quadruple MDT were more obese to start with, they may have been more motivated to lose weight, also contributing to lesser dropouts over the 6 months period.

To summarize, it may be said that this study provides encouraging real-world data on the use of therapeutic lifestyle interventions with metformin, SGLT2i, GLP1, and orlistat together in different combinations for managing diabesity. Not only does MDT result in greater weight loss and glycemic control, patient dropout is also lower. Further studies in a larger cohort of patients, having longer follow-up duration, in different ethnic groups are warranted. MDT according to metformin, SGLT2i, GLP1a, and orlistat along with medical nutrition therapy may be the way forward to aggressively tackle the problem of diabesity in India.

Authors's contribution

The study was planned by DD and SG. Data extraction was done by RJ, RM, and SG. Data analysis was done by DD, DK. and SK. All authors contributed equally to the manuscript preparation.

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Conflicts of interest

There are no conflicts of interest.

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