Neonatal and Pediatric Medicine
ISSN: 2572-4983
Kumar, Neonat Pediatr Med 2023, 9:10
Case Report
Open Access

A Long-term Retrospective Real-World Evidence to Understand the Pattern of Insulin Prescription in Patients with Type 2 Diabetes (T2d) - Insulinitiation Study

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Abstract

Background: Rationale use of insulin and oral anti-diabetic medications (OADs) improves glycaemic control.

Aims and objective: Evaluate the efficacy and prescription pattern of anti-diabetic medications in achieving glycaemic control among people attending a tertiary care centre in India.

Materials and methods: This cross-sectional observational study was conducted on people with diabetes (PwD) over 9 years. Demographic profiles, anthropometry, biochemical parameters [HbA1c, fasting blood plasma glucose (FPG) and post-prandial glucose (PPG)], insulin types and doses, and OADs prescriptions were recorded at baseline (2011) and, 2015 and 2019.

Results: Among 647 PwDs majority were males (75.9% in 2011, 71.3% in 2015 and 67.7% in 2019), with T2DM (214 in 2011, 214 in 2015 and 209 in 2019), and BMI >25 kg/m2. Subjects' group with "diabetes under control" (FPG <130 mg/dL, PPG <180 mg/dL, and HbA1c <7%) were comparable [13 subjects (5.9%) in 2011, 16 subjects (7.0%) in 2015, 14 subjects (6.0%) in 2019]. The number of subjects in "uncontrolled diabetes" group (FPG >130 mg/dL, PPG >180 mg/dL, and HbA1c >7%) decreased significantly ($p<0.05$) from baseline over years of monitoring [100 subjects (45.6%) in 2011, 112 subjects (50.9%) in 2015, 72 subjects (34.1%) in 2019s. Sub-group analysis revealed increase in insulin prescriptions (30 folds) with further titration. 20 units of basal insulin prescribed at study initiation increased to 39.9 ± 15.7 in 2015 and maintained at 36.7 ± 10.5 in 2019. Doses of Bolus and premixed insulin increased from 20.93 ± 9.6 and 41.85 ± 14.6 at baseline to 21.8 ± 13.6 and 43.1 ± 9.8 in 2015 and titrated to 43.1 ± 9.8 and 39.63 ± 10.8, respectively by 2019. SGLT-2i and DPP-4i prescriptions increased significantly ($p<0.05$) from 2011 to 2019, though total OADs remained same.

Conclusion: The proportion of subjects with uncontrolled diabetes decreased significantly over the study, which can be attributed to the shifting trend of increased insulin prescription or insulinization, leading to better glycaemic control.

Keywords: Extensive comorbidities; Anti-diabetic medications; Glycaemic level; Capillary plasma; Controlled diabetes; Treatment outcomes

Introduction

Glycaemic control is the primary objective of quality diabetes care. The American Diabetes Association (ADA) recommends glycated haemoglobin (A1C), pre-prandial and peak postprandial capillary plasma glucose measurements for glycaemic assessment. Intensive diabetes treatment effectively delays the development and progression of long-term complications in insulin-dependent diabetes mellitus. Maintaining glycated haemoglobin levels below 7% lowers the risk of cardiovascular events in type 2 diabetes. Immediate intensive glucose control may be necessary to prevent irremediable diabetes-related complications and mortality, while a less stringent goal should be considered for subjects at high risk of hypoglycaemia, geriatric subjects, and ones with limited life expectancy or extensive comorbidities. Therefore, the greatest number of complications will be averted by taking subjects from uncontrolled/ poorly controlled to optimal/ good glycaemic control [1].

The rate of glycaemia management is poor among people with diabetes (PwD) in India. Among three-fourths of the PwD under anti-diabetic medications, nearly half could achieve optimal glycaemic control. The real-world burden of uncontrolled diabetes may be as high as 76.6%. Poorly controlled diabetes is a major determinant of macro and micro-vascular complications of diabetes [2].

Limited access to anti-diabetic medications, higher number of medications, prolonged duration of diabetes (14), poor knowledge about glucose control, and a sedentary and unhealthy lifestyle are the common causes of suboptimal diabetes control in the Indian subcontinent. Clinical inertia is another important parameter associated with difficulty in attaining the target glycaemic level. A more early and selective addition of insulin could facilitate achieving and maintaining eu-glycaemia [3].

Most subjects need pharmacotherapy for diabetes management. Mono-therapy with an oral anti-diabetic drug (OAD) is started concomitantly with intensive lifestyle management. PwD not adequately managed with a non-insulin regimen, or symptomatic hyperglycaemic subjects require insulin initiation. Uncontrolled diabetes leads to a

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Received: 26-Sep-2023, Manuscript No.NNP-23-99249; **Editor assigned:** 29-Sep-2023, Pre-QC No.NNP-23-99249 (PQ); **Reviewed:** 13-Oct-2023, QC No.NNP-23-99249; **Revised:** 18-Oct-2023, Manuscript No.NNP-23-99249 (R); **Published:** 25-Oct-2023, DOI: 10.4172/2572-4983.1000361

Citation: Kumar S (2023) A Long-term Retrospective Real-World Evidence to Understand the Pattern of Insulin Prescription in Patients with Type 2 Diabetes (T2d) - Insulinitiation Study. Neonat Pediatr Med 9: 361.

progressive decline in beta cell function, mandating insulin as the most acceptable natural choice. Diabetes care should be optimized by escalating pharmacotherapy, including the timely introduction of insulin, whenever required [4].

Analysis of the temporal trends in prescribing anti-diabetic medications is key to identifying putative factors influencing diabetes management. Hence, this study was planned to evaluate the efficacy and prescription pattern of anti-diabetic medications in managing glycaemic control in people attending a tertiary care centre in India [5].

Materials and Methods

This cross-sectional observational study was conducted at a tertiary care centre in Mumbai, India. PwD prescribed insulin or oral anti-diabetic medications (OADs) were included in the study. Baseline parameters were recorded at the initial visit in 2011. The subjects were examined for assessment of height, weight, and body mass index (BMI), blood pressure (BP). In addition, biochemical parameters, including HbA1c, fasting blood plasma glucose (FPG) and post-prandial glucose (PPG), comorbidities, insulin types and doses, and anti-diabetic medications prescription were recorded. The same parameters were analysed at intervals of 4 years in 2015 and then in 2019 to observe the trend in drug prescription and efficacy of the medications [6].

A descriptive analysis of glycaemic control was performed to assess the efficacy of different drug regimens. Samples for the glycaemic assessment were collected after at least 10-12 hours of overnight fasting. Samples for post-prandial plasma glucose were collected after 2 hours from the time of starting breakfast, after the subjects took their usual medicines. Glycaemic targets were defined as A1C<7.0% (53 mmol/mol), pre-prandial capillary plasma glucose 80–130 mg/dL (4.4–7.2 mmol/L), and peak postprandial capillary plasma glucose <180 mg/dL (10.0 mmol/L).1 Statistical analysis was done using Statistical Package for the Social Sciences version (Chicago: SPSS Inc) software to identify the proportion of PwD achieving optimal glucose target. A chi-square test was performed to examine associations between variables. P-value < 0.05 was considered statistically significant. The study was conducted after getting informed consent. The study was approved by the Institutional Ethical Committee [7].

Results

Baseline data

This study included 647 subjects, out of which 216 subjects with a mean age 52.3 ± 12.3 years were reported in 2011, 220 subjects were assessed in 2015 with a mean age 52.0 ± 12.7 years and 211 subjects with an average age 54.5 ± 12.4 years were evaluated in 2019 [8]. The cohort was predominantly male; 75.9% in 2011, 71.3% in 2015, 67.7% in 2019. 214 subjects were type 2 diabetic (T2DM) and 1 patient was type 1 diabetic (T1DM) in the 2011 cohort, 214 subjects were T2DM and 1 patient was T1DM in the 2015 cohort, and 209 T2DM subjects and 1 patient of T1DM was included in the 2019 cohort (Table 1).

Mean BMI for the entire study cohort was above the normal cut-off of 25 kg/m^2. Average BMI was 27.34 ± 4.4 28 kg/m^2 in the 2011 sample, 27.67 ± 5.6 28 kg/m^2 in the 2015 group, and 27.5 ± 5.8 28 kg/m^2 in the 2019 population [9]. Mean SBP and DBP values were 137.5 ± 13.9 mm Hg and 88.1 ± 12.2 mm Hg in the 2011 sample, 137.1 ± 14 mm and 87.3 ± 8.8 mm in the 2015 group, and 139.4 ± 10.5 mm and 84.2 ± 9.3 mm in the 2019 population, respectively (Table 2).

Glycaemic control

HbA1C level <7% requires less stringent glycaemic management. (22) In our study, the proportion of this subset of subjects was similar through 2011 to 2019. 40 subjects (18.51%) had HbA1C < 7% in 2011, 42 (19%) in 2015, and 44 (20%) in 2019. On the other hand, HbA1C level above 7% must be managed with two or more anti-diabetic medications or injectable [10]. (22) We observed a higher proportion of subjects with HbA1C between 7-10 % in 2015 than in 2011, while the 2019 subset was similar to 2015. Sixty-three (28.76%) of the study population had HbA1C between 7 -10% in 2011, 94 (42.7%) in 2015, and 87 (41.2%) in 2019. Early introduction of insulin should be considered when HbA1C is above 10%. (22) Thirty-one subjects (14.15%) had HbA1C level >10% in 2011, 30 (13.6%) in 2015, and 35 (16.5%) in 2019, which was comparable throughout the study period. Subjects were initiated on insulin with an average HbA1C of 8.9 ± 2% in

Data	2011	2015	2019
No of patients	216	220	211
Age (Years)	52.3±12.3	52.0±12.7	54.5±12.4
18-40 41-59 60-79 ≥ 80	33 (15.3%) 103(47.7%) 73 (33.8%) 2 (0.9%)	37 (16%) 112 (51%) 66 (30%) 3 (1.3%)	27 (12.7%) 113 (53.5%) 72 (34.1%) 2 (0.9%)
Male / Female	164 (75.9%) / 52 (24.1%)	157 (71.3%) / 62 (28.1%)	143 (67.7%) /58 (32.3%)
Type of DM (2/1)	214/1	214 / 6	209/1

Table 1: Baseline demography of the study population - The demographic profile of the subjects was similar throughout the study period. Patient population was predominantly male and most had type 2 diabetes.

Data	2011	2015	2019
Height (M)	1.58±0.09	1.65±0.1	1.66±0.1
Weight (Kg)	72.9±14.6	75.4±16	73.8±16.6
BMI (kg/m^2)	27.34±4.4	27.67±5.6	27.5±5.8
SBP (mmHg)	137.5±13.9	137.1±14	139.4±10.5
DBP (mmHg)	88.1±12.2	87.3±8.8	84.2±9.3

Table 2: Anthropometric profile of the study population - Most subjects had BMI above the normal cutoff of 25 kg/m^2, and systolic and diastolic blood pressure above 120/80 mm Hg.

2011, 9.0 ± 1.8% in 2015, and 8.7 ± 1.7% in 2019 (Table 3).

Average FPG was 103.8 ± 13.2 mg/dL, 157.0 ± 69 mg/dL, and 151.8 ± 63 mg/dL in 2011, 2015, and 2019, respectively. While mean PPG was 139.1 ± 31.1 mg/dL, 220.1 ± 94 mg/dL, and 219.1 ± 87 mg/dL in 2011, 2015 and 2019, respectively [11]. Average FPG in the subjects started with insulin was comparable throughout the study (mean FPG was 168.7 ± 68.7 mg/dL in 2011, 190 ± 88 mg/dL in 2015, and 159 ± 80 mg/dL in 2019). The mean PPG was higher in the 2015 subjects initiated on insulin than the 2011 subjects, while the 2019 group initiated on insulin had average PPG similar to the 2015 group. The mean PPG in the insulin-initiated population was 245.9 ± 103.3 mg/dL in 2011, 250 ± 112 mg/dL in 2015 and 241 ± 100 mg/dL in 2019.

Proportion of subjects with controlled diabetes was comparable throughout the study duration. Thirteen (5.9%) subjects had diabetes under control [defined as FPG (<120 mg/dL), PPG (<180 mg/dL), and HbA1c (<7%)] in 2011, 16 (7%) in 2015, and 14 (6%) in 2019. In addition, uncontrolled diabetes [defined as FPG (>130 mg/dL), PPG (>180 mg/dL), and HbA1c (>7%)] demonstrated a decreasing prevalence trend with 156 (45.6%) subjects 2011, 112 (50.9%) subjects in 2015, and 72 (34.1%) in 2019 (Figure 1), showing subjects achieving a better glycaemic control over the period [12].

No significant differences were observed in other biochemical parameters (SGOT, SGPT, creatinine, eGFR, uric acid, LDL-C, HDL-C, triglycerides, cholesterol, T3, T4, and haemoglobin) in the overall treated population.

Prescription pattern

Sub-group analysis of data revealed a significant increase in insulin prescriptions from 2011 to 2015 (30 folds), along with dose titrations. 20 units of basal insulin were prescribed at the study initiation, which increased to 39.9 ± 15.7 units in 2015 and was maintained at 36.7 ± 10.5 units at the end of the study, possible showing the need for up titrating the insulin dose to achieve better hyperglycaemic control [13]. Doses of Bolus and premixed insulin also marginally increased from 20.93 ± 9.6 units and 41.85 ± 14.6 units at baseline to 21.8 ± 13.6 units and 43.1 ± 9.8 units, respectively in 2015. Bolus insulin was titrated to a dose of 43.1 ± 9.8 units and premix insulin at 39.63 ± 10.8 units by the end of the study (Table 4).

Among the OADs, SUs and metformin were the most prescribed. 170 PwD were on SUs and 145 PwD were on metformin in 2011. In 2015, a similar number of metformin and SUs were dispensed (171 of metformin and 172 of SUs). While in 2019 more metformin (155) was prescribed than SUs (138). Significant difference was observed in the prescription of newer OADs like DPP4i and SGLT2i, which demonstrated significant increase from 2015 to 2019. 34 DPP4i were prescribed in 2011 which increased marginally to 41 in 2015 and significantly to 111 in 2019. Similarly, SGLT2i prescriptions increased from 2 to 37 in 2015 and 66 in 2019. Though the number of OADs prescribed were comparable throughout the study period (Table 5).

Discussion

Maintaining optimal blood glucose is crucial in preventing the onset and progression of diabetic complications. Resorting to effective glucose-lowering medications optimizes glycaemic control. In the present study, we observed a significant decrease in the proportion of

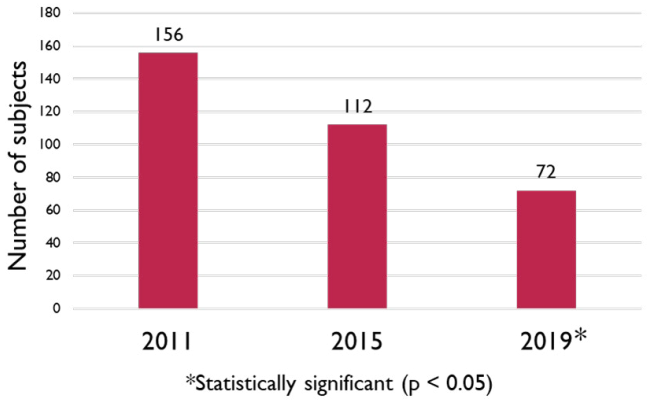

Figure 1: Number of subjects with uncontrolled diabetes throughout the study - In 2019, significantly fewer subjects was seen with un-controlled glycaemic conditions.

Data	2011	2015	2019
HbA1c (%) <7 7-10 >10	6.4±0.4/ (8.9±2) 40 (18.51%) 63 (28.76%) 31 (14.15%)	8.37±1.8 / (9.0±1.8) 42 (19%) 94 (42.7%) 30 (13.6%)	8.35±1.9 / (8.7±1.7) 44 (20%) 87 (41.2%) 35 (16.5%)
FPG (mg/dL)	103.8±13.2/ (168.7±68.7)	157.0±69 / (190±88)	151.8±63 / (159±80)
PPG (mg/dL)	139.1±31.1/ (245.9±103.3)	220.1±94 / (250±112)	219.1±87 / (241±100)
Controlled: FPG (<120 mg/dL) PPG (<180 mg/dL) HbA1c (<7%)	13 (5.9%)	16 (7%)	14 (6%)
Uncontrolled: FPG (>120 mg/dL) PPG (>180 mg/dL) HbA1c (>7%)	156 (45.6%)	112 (50.9%)	72 (34.1%)

Blue data is for Insulin initiated patients

Table 3: Glycemic parameters of the study population – Subject's group with "diabetes under control" was comparable through the years, while lesser subjects were seen with un-controlled glycaemic conditions over years of monitoring.

Data	2011		2015		2019	
	Number	Dose	Number	Dose	Number	Dose
BASAL	1	20	15	39.9±15.7	8	36.7±10.5
BOLUS	42	20.93±9.6	51	21.8±13.6	47	43.1±9.8
PREMIX	60	41.85±14.6	51	43.1±9.8	61	39.63±10.8

Table 4: Prescription trend of insulin - The prescription of basal and bolus insulin increased from 2011 to 2015 and was maintained in 2019. Premix insulin prescription was comparable throughout the study.

Data	2011		2015		2019	
	Number	Dose	Number	Dose	Number	Dose
METFORMIN	145	1210±518.12	171	1049±284	155	990±287
SUs	170		172		138	
DPP4 inhib	**34**		**41**		**111***	
SGLT2 inhib	**2**		**37**		**66***	
TZDS	9		1		2	

SUs: Sulphonylurea; DPP4 inhib: Dipeptidyl peptidase 4 inhibitors; SGLT2 inhib: Sodium-glucose co-transporter-2 (SGLT-2) inhibitors; TZDs: Thiazolidinediones

Table 5: Prescription pattern of OADs - Prescription of DPP4i and SGLT2i increased significantly throughout the study.

subjects with uncontrolled diabetes over the period of time. By 2019, 34.1% of subjects had suboptimal glucose levels compared to 50.9% in 2015. This is much lower than the high uncontrolled glycaemia rate reported by other Indian population based studies [14]. Our results indicate improved treatment outcomes which might be partly attributable to the appropriate and timely prescription pattern of the anti-diabetic medications.

A shift in trend occurred in the prescribed insulin regimen over the 8-years study period. The utilization of basal insulin increased from 1 subject in 2011 to 15 subjects in 2015 and was maintained at 18 subjects in 2019. Bolus insulin also exhibited a similar pattern. Other Indian studies have reported similar frequent insulin prescriptions. Premixed insulin is perceived as the most suited insulin in the Indian population having persistent glycaemic variability. Nevertheless, to combat the high overnight glycaemic burden, initiation with basal insulin is an effective proven strategy. The ability to attain the glycaemic target from a relatively high HbA1c with basal insulin only is significant. The flexibility of dose titration with basal insulin translates into an improved treatment outcomes.

Based on our results, a likely correlation between the frequency of insulin prescription and its regular dose titration helped achieving target glycaemic control. A similar declining trend in suboptimal diabetes has been observed following insulin initiation. The Improve study observed a need for timely and appropriately intensive insulin-based therapy to combat poor glycaemic control in the Indian cohort.

Insulin offers a physiological, stringent, and consistent control of glycaemic variables. With disease progression, achieving target glycaemic control becomes difficult with OADs in subjects with uncontrolled diabetes, and most subjects eventually require insulin initiation. For subjects susceptible to glycaemic variability, the most preferred method of prolonged glycaemic control is insulin initiation with basal insulin or once-daily / twice-daily premixed insulin, either as mono-therapy or combined with OADs. Growing utilization of long-acting insulin may reflect a growing awareness of the patient benefits and value in managing PwD.

Basal insulin like insulin degludec (IDeg), an ultra-long-acting insulin analogue, provides a flat and stable glucose-lowering profile exceeding 30 hours with less inter-patient variability. In particular, insulin degludec allows a soluble co-formulation with prandial insulin as part. This combination (IDegAsp) offers 24-hour basal insulin coverage with additional mealtime insulin leading to sustained glycaemic control. Compared to other basal and dual action insulin, the simpler formulation of IDeg and IDegAsp provide an effective and safe dose adjustment/ reduction in persons shifting from other basal insulin's.

In addition to the standard treatment of insulin therapy and metformin, SGLT2 inhibitors and DPP4 inhibitors have gained substantial use during the last decade. Das et al (2021) found that among number of anti-diabetic medicines, metformin (37%) and lispromix (41%) were the most commonly prescribed mono-therapy. In our study, among the OADs, metformin was most prescribed, followed by sulphonylureas (SUs), similar to previous studies in Indian PwD. However, their prescription decreased throughout the study, along with a gradual yet significant increase in prescriptions of DPP-4i and SGLT-2i. The total number of OADs prescribed was similar from the beginning to the end of the study. Unlike other studies, our study documented the prescription transition from conventional to newer OADs. This variation could be because the pharmacotherapy for diabetes has changed significantly in the last few years owing to advent to newer and more effective drugs.

In routine clinical practice, combination therapy is initiated if the patient does not achieve glycaemic target in 3-6 months and if over time, the glycaemic variability persists thereafter, then a third OAD or insulin is added. In subjects with high HbA1C levels, such an approach may lead to unnecessary delays in the advancement of appropriate therapy to attain glycaemic control. An ineffective and suboptimal response to OADs may go undetected for extended periods of time increasing the likelihood of gluco-toxicity, and progression of complications. Early addition of basal insulin offers an effective strategy to improve treatment responses in uncontrolled glycaemic. Introduction of a long-acting or an intermediate-acting or premix /co-formulation insulin to an oral agent regimen is a way represents an effective step toward providing near-physiological insulin replacement. After basal insulin therapy is initiated, individual dose titration will allow subjects to achieve and maintain individual glycaemic goals. Treatment regimens that approach physiological insulin secretion by addressing basal and prandial insulin requirements may improve subjects' quality of life.

In terms of clinical care, we observed an increasing trend of insulin prescriptions with number of OADs prescriptions similar over the study duration. A shift towards newer OAD prescription was observed. The proportion of uncontrolled diabetics reduced significantly, indicating that the anti-diabetic medication prescription pattern of our study was effective in addressing glycaemic variability in the study population.

Limitations of the Study

The present study has certain limitations. This study being a cross-sectional study, only the anti-diabetics agents prescribed at that particular time were recorded and the same patient population was not followed up through the years.

Conclusion

Despite pharmacological advancements, glycaemic control in India remains poor. Identifying drug prescription patterns provides valuable insights in managing the significant public health concern of uncontrolled diabetes. We observed an increase in insulin prescriptions over an 8-year study period, a greater number of newer OADs prescriptions, with an unchanged number of total OADs prescribed. A significant decrease in the proportion of uncontrolled PwD was also observed over time. This shift in the trend of insulin prescription could be the major attributable factor for optimal glycaemic control in our study. Thus, insulinitiation could be an effective strategy for achieving optimal glycaemic control in subjects with uncontrolled diabetes. Understanding recent drug prescription and glycaemic control trends offers newer insights into devising personalized care in diabetes management.

Acknowledgement

None

Conflict of Interest

None

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