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Efficacy of Fixed-dose Combination of Dapagliflozin and Sitagliptin in Type 2 Diabetes Mellitus Using Continuous Glucose Monitoring: A Real-world Study in India

Supratik Bhattacharyya [a++*], Sameer Muchhala [b#] and Kunal Jhaveri [b†]

[a] SKN Diabetes and Endocrine Centre, 18, George Road, Naihati, Near SBI Naihati Branch, North 24 Parganas – 743165, West Bengal, India.
[b] Medical Affairs, Zydus Lifesciences Limited, Mumbai, Maharashtra, India.

Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a progressive disease with multifactorial aetiology. Metformin monotherapy is commonly used as the initial treatment, but is often inadequate in achieving optimal glycaemic control, necessitating the need of second and third-line

[++] Consultant Endocrinologist;
[#] GM;
[†] DGM;
**Corresponding author: E-mail: dr_supratik@yahoo.co.uk;*

therapies. Fixed dose combination (FDC) of dapagliflozin and sitagliptin in Indian setting is gaining popularity. Time-in-target has become a useful blood glucose indicator that goes "beyond HbA1c" to understand glycaemic control in people with diabetes better.

Aims and Objectives: To assess the efficacy of a FDC of dapagliflozin and sitagliptin in Indian T2DM patients.

Materials and Methods: This was a single-arm, single-centre, real-world study. Twenty-eight consented T2DM patients age >18 years, either sex, not hospitalized, and estimated glomerular filtration rate >60 ml/min/1.73m^2 were administered a continuous glucose monitoring system (CGMS) (Freestyle Libre Pro). Once daily fixed-dose combination (FDC) of dapagliflozin (10mg) and sitagliptin (100mg) was given along with CGMS administration on a background of existing therapy for those who were not to target for glycemic parameters. Since the FDC reaches at its peak concentration after 3-4 days of administration, the efficacy of FDC was considered from 5th day. Hence the baseline was calculated taking the mean of first 4 days after FDC administration. Patients' characteristics, including age (years), sex, weight (kg), body mass index (kg/m^2), estimated glycated haemoglobin (%), history of oral hypoglycaemic agents, and dose of insulin were recorded. For efficacy assessment, average daily glucose (ADG), time in target (TIT), time below target (TBT), and time above target (TAT) were recorded at baseline.) and end of the study (day 15th of CGMS administration) from the daily glucose summary of Freestyle Libre Pro CGMS. The percentage improvement of each efficacy parameters were assessed.

Results: A statistically significant improvement (p<0.05) in ADG (19.41% decrease), TIT (34.47% increase), and TAT (31.13% decrease) was observed, whereas TBT was increased by 29.23%; which was statistically non-significant. Mean age (n=28), weight (n=23), body mass index (n=19) and estimated HbA1c (n=19) was 56.70±9.8 years, 64.67±9.52 Kg, 24.99±4.23 Kg/m^2 and 6.84±1.63 % respectively. The majority were on triple drug (n=14; 50%) therapy before CGMS administration than dual (n=5; 17.9%) and monotherapy (2; 7.1%). Fifteen (53.8%) were on insulin with a mean insulin dose of 16.40 IU.

Conclusion: Once daily FDC of dapagliflozin and sitagliptin in Indian T2DM patients significantly improves AGD, TIT, and TAT at the end of 15 days.

Keywords: Fixed-dose combination; time-in-target; time-above-target; time-below-target; continuous glucose monitoring system.

1. INTRODUCTION

The global spread of diabetes in adults persists to be one of the fastest rising health challenges. International Diabetes Federation(IDF) states that the number of diabetic patients will rise to 643 million by 2030 and 783 million by 2045 around the world [1)]. According to recent statistics (2019) compiled by IDF, it has been observed that India and other South Asian countries exhibit a higher prevalence of diabetes, with an anticipated surge to 134 million by 2045 from 77 million in 2019 [2]. Approximately 25 million individuals are classified as prediabetic, indicating a higher likelihood of developing diabetes in the near future [3].

Type 2 diabetes mellitus (T2DM), a progressive metabolic disorder, includes an array of disorders caused by the combination of diverse interaction of hereditary and other risk factors [4, 5]. In order to decrease the progression and complications associated with T2DM, better glycaemic control is requisite [6]. A plethora of drugs are available for clinical use to maintain euglycemia like biguanides, sulfonylureas, α-glucosidase inhibitors, dipeptidyl peptidase-4 (DPP4) inhibitors, sodium glucose transporter 2 (SGLT2) inhibitors, meglitinides and thiazolidinediones [5,7]. Since a majority of these medications are effective initially but are inefficient in maintaining normoglycemia over time as monotherapies, necessitate the use of multiple or combined antihyperglycemic drugs [7,8]. For patients who have not achieved glycaemic control with metformin or oral monotherapy, various combinations of medications, such as thiazolidinedione or acarbose, sulfonylurea plus metformin, or metformin plus thiazolidinedione or acarbose, have successfully lowered blood glucose levels. Moreover, research indicates that a fixed dose combination (FDC) therapy, which combines oral anti-diabetic drugs with different mechanisms of action, is effective in managing blood sugar levels [7, 9].

In India, FDCs are often advised by clinicians to patients recently diagnosed with T2DM. This treatment approach reduces pill intake, decreases the risk of adverse effects, is

inexpensive, and has strong patient compliance, thus contributing to better efficacy. The FDC of dapagliflozin and sitagliptin is becoming increasingly popular in India [10]. Dapagliflozin, a SGLT2 inhibitor, decreases glucose reabsorption by increasing excretion via urine, thus lowering the blood glucose level.(5)Another oral anti-diabetic, Sitagliptin, an orally active DPP-4 inhibitor, promotes insulin secretion in hyperglycaemic patients by elevating the levels of glucagon-like peptide-1(GLP-1) and incretin hormone, thereby inhibiting glucagon secretion, reducing HbA1c and fasting as well as postprandial glucose levels [11]. Prior preclinical and clinical studies have validated the synergistic efficacy of dapagliflozin and sitagliptin on insulin resistance [7,12] Since most of these clinical studies were conducted in Chinese, Japanese and European populations, the benefits of FDC of dapagliflozin and sitagliptin in the Indian population are indistinct [12,13].

The HbA1c analysis, a gold standard for assessing glycaemic control, which measures the average blood glucose level for past 3 months, is influenced by various other factors, apart from glucose concentration, and often does not accurately reflect glycaemic control. Hence, diabetologists across the globe emphasize on redirecting the focus from HbA1c alone to a more glucose-centric and patient-centric metric [14]. Continuous glucose monitoring (CGM) offers the benefit of measuring interstitial glucose levels every 5-15 minutes, allowing for a thorough 24-hour glycaemic profile, better identification of nocturnal and asymptomatic hypoglycaemia, and pattern recognition following each treatment intervention [15]. Time-in-Target (TIT) is an effective blood glucose metric that extends beyond HbA1 and provides a more comprehensive understanding of glycaemic control and variations in individuals with diabetes [14].

TIT is a simple statistic that indicates the proportion of time that a person's blood sugar level stays within the recommended target range [16]. Complementing TIT in CGM, the amount of time spent below and above the target range are the important metrics for assessing glycaemic control. Time below target (TBT) refers to the amount of time that glucose levels are below a specified target range, while time above target (TAT) is the time that glucose levels are above the target range. TIT, TBT, and TAT together provide a comprehensive assessment of glycaemic control over time and can identify patterns in glucose levels that may be missed by looking only at average glucose levels or HbA1c [17].

Therefore, the present study aims to assess the real-world efficacy of FDC of dapagliflozin and sitagliptin in Indian T2DM population using TIT as a preferred metric of CGM.

2. MATERIALS AND METHODS

2.1 Study Design and Participants Enrolment

This is a retrospective, single-arm, single-centre, real-world study conducted at SKN Diabetes and Endocrine Centre, North 24 Parganas, West Bengal. Twenty-eight consented patients suitable for T2DM treatment were enrolled in this study. Adult patients, either gender aged more than 18years of age with T2DM were included. The above selected non-hospitalized patients with estimated glomerular filtration rate (eGFR)> 60 ml/min/1.73m^2 were administered a continuous glucose monitoring system (CGMS) (Freestyle Libre Pro). Patients' characteristics, including age (years), sex, weight (kg), body mass index (kg/m^2), glycated haemoglobin (%), number of oral hypoglycaemic agents, and dose of insulin were recorded. The individuals below 18 years of age or prediabetic or with type 1 diabetes or pregnant women or with estimated GFR< 60 ml/min/1.73 m^2 were excluded from the study.

2.2 Procedure

The administration of the FDC of dapagliflozin and sitagliptin commenced simultaneously with the use of CGMS on Day 1 on a background of existing therapy for those who were not to target for glycemic parameters. The average values of the first four days, corresponding to the peak concentration of the FDC attained after 3-4 days of administration, were designated as the baseline. All the patients were given once daily dose of dapagliflozin(10mg) and sitagliptin (100mg) for 15 days.

2.3 Outcomes

For efficacy assessment, average daily glucose (ADG), TIT, TBT, and TAT were recorded at baseline. The baseline was determined based on the average of the first four days when the concentration of the FDC reached its peak. At the end of the study, i.e., day $15^{th}$of CGMS administration, change in the values of

parameters were recorded from the daily glucose summary of Freestyle Libre Pro CGMS. The percentage improvement of each efficacy parameter was also assessed.

2.4 Statistical Analysis

The data collected were pooled in a Microsoft Excel spreadsheet and then transferred for statistical calculations to SPSS version 25. The primary endpoint was reported with two-sided 95% CIs, calculated using paired t-test. A *p*-value of <0.05 is considered statistically significant.

3. RESULTS

3.1 Patients Demographic

Among 28 patients 60.7 % were males and 39.2 % were females. They were aged between 31-74 years. The mean body weight of 23 patients was 64.67±9.52 Kg. The body mass index and HbA1c of 19 patients is mentioned in Table 1 along with other characteristics of enrolled patients. The above are enrolled patients were previously on different therapies, the description of therapies is depicted in Table 2.

14 patients who received triple therapy were administered with the combination of anti-diabetic agents like Metformin, Repaglinide, and Voglibose (*n*=1); Glimepiride, Metformin, and Pioglitazone (*n*=13). Patients on dual therapy received Glimepiride and Metformin (*n*=5), while 2 patients on monotherapy were administered metformin (*n*=1) and insulin (*n*=1). The 15 patients on insulin therapy received Glargine: Degludec, and Aspart (Mean insulin dose= 16.40 IU).

3.2 Outcomes

At the end of the study, i.e., at the15th day of CGM, there was a decrease in ADG by 32.94mg/dl, TIT was increased by 14.03 %, and TAT decreased by 16.17%. All the above-mentioned parameters showed a statistically significant improvement (p<0.05). The study evaluated the percentage improvement in these parameters from baseline to the 15th day, and the overall changes are as follows: a 19.41% decrease in AGD, a 34.47% increase in TIT, and a 31.13% decrease in TAT. Although TBT increased by 2.13% showing an improvement of 29.23% from baseline, it was statistically non-significant. The efficacy assessment at the end of the study is indicated in Table 3 and Fig 1.

During this study, FDC of dapagliflozin and sitagliptin was well tolerated. Adverse events and side effects like daytime and nocturnal hypoglycemia were negligible.

Table 1. Baseline demographics data

Parameters	Values
Total Patients: n (%)	28 (100)
Male	17 (60.71)
Female	11 (39.28)
Age (years) (mean ± SD)	56.70±9.8
Weight(kg) (mean ± SD)	64.67±9.52
BMI (kg/m^2) (mean ± SD)	24.99±4.23
HbA1c (%) (mean ± SD)	6.84±1.63
Status of patients	
Ambulatory	All
Hospitalized	None

Note: BMI: Body Mass Index; HbA1: % Glycated Haemoglobin

Table 2. Distribution of patients on anti-diabetic agents before study intervention

Therapy	Patients, n (%)
Monotherapy	2(7.1%)
Dual therapy	5(17.9%)
Triple therapy	14 (50%)
Insulin	15 (53.8%)

Table 3. Efficacy assessment from daily glucose summary of freestyle libre pro CGMS

Parameters	Baseline *	End of the study *	Mean difference	Improvement	*p*-value
ADG (mg/dL)	169.71±66.41	136.77±38.42	-32.94	-19.41% -	0.032
TIT (%)	40.73±28.62	54.77±34.24	14.03	34.47%	0.017
TBT (%)	7.32±8.53	9.46±20.00	2.13	29.23%	0.998
TAT (%)	51.94±34.27	35.77±32.93	-16.17	-31.13%	0.001

**Data are expressed as mean ± standard deviation; p<0.05 is considered statistically significant. ADG, average daily glucose; TIT, time in target; TBT, time below target; TAT, time above target*

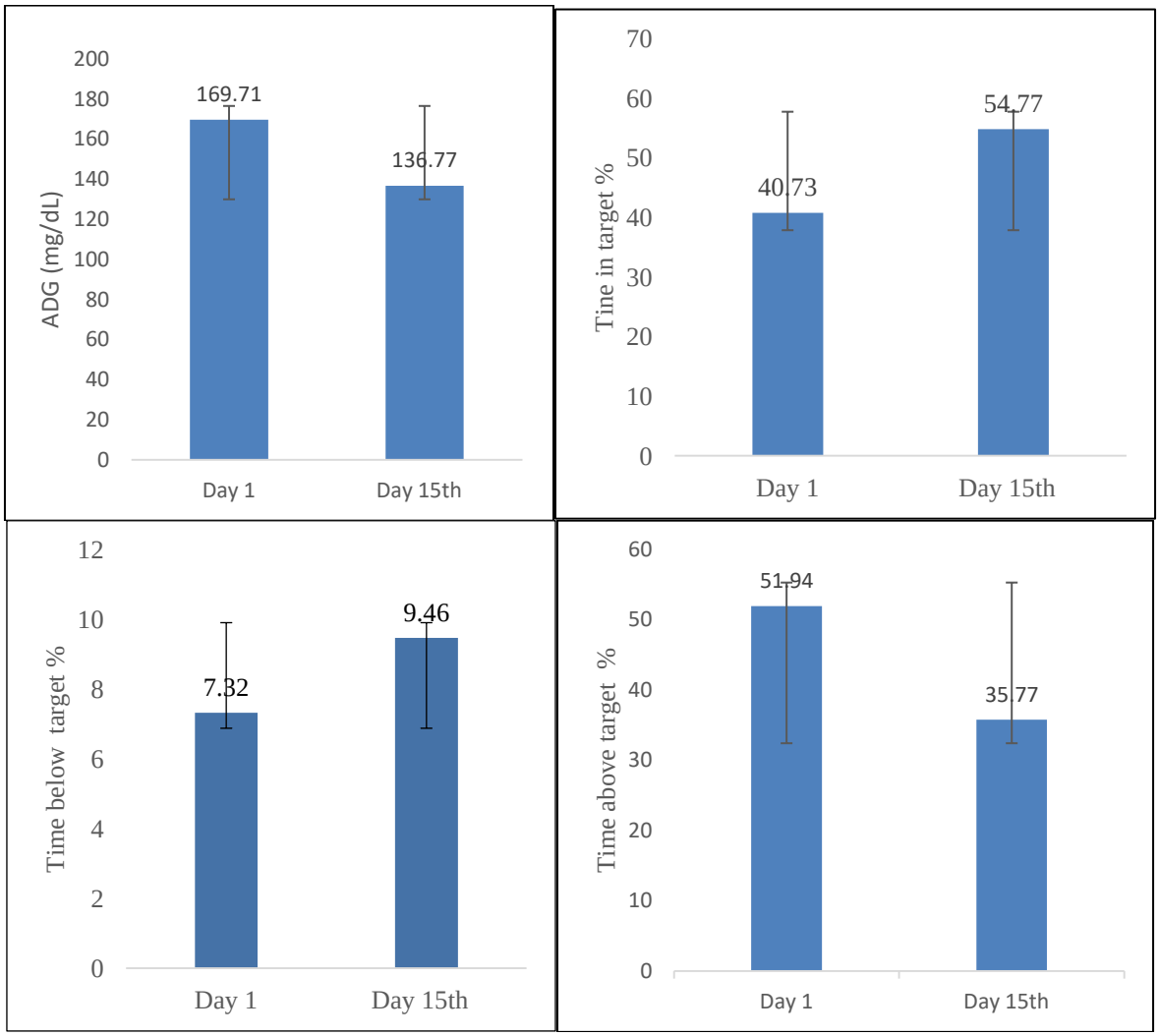

Fig. 1. Change in Average Daily Glucose, Time-in-target, Time-below-target, Time-above-target after the administration of FDC. Data are expressed as mean ± standard deviation; *p*<0.05 was considered statistically significant

4. DISCUSSION

In this study, the efficacy of FDC of dapagliflozin and sitagliptin was assessed using TIT as the preferred metric. This being one such study in India to assess the efficacy of FDC of dapagliflozin and sitagliptin using CGM instead of HbA1c in the Indian population. Growing evidence suggests that HbA1c alone is insufficient for accurately assessing one's diabetes management [14,18]. Although the HbA1c test is considered the gold standard for

assessing blood sugar levels, it may not accurately reflect glycaemic control, as it does not account for short-term blood sugar fluctuations, hypoglycaemia, hyperglycaemia, and other factors, including the patient's glycated haemoglobin, which can affect the prediction of chronic complications. With technological advancements, CGM provides additional information about the glucose profile that helps with crucial decision-making of initiation and optimization of treatments through measuring TIT. Since TIT has gained significant research attention, setting the goal value is essential for a new measure like TIT to be more broadly recognized in clinical practice [18,19]. The International consensus recommends the integration of CGM in standards of care and provides a threshold for the TIT for different diabetic patients across the globe. American Diabetes Association (ADA) revealed, a TIT of 50% within the range of 70-180 mg/dL is linked to an average HbA1c level of approximately 8%, but the actual HbA1c range can vary from 6.6% to 9.2%. Furthermore, the same study showed that for every 10% increase in TIT within this range, there is a corresponding decrease of 0.6% in HbA1c. For the Indian population, it has been demonstrated that a TIT of more than 70% correlates to an HbA1c level of less than 7.5%.[20]. The increase in the TIT while reducing the TBT is considered the primary glycaemic goal to achieve effective and safe glucose control [21].

In the present study, the ADG for the 28 patients was 169.71±66.41 mg/dL at day 5 (considered as day 1). After treatment with the FDC, the average ADG decreased and was statistically significant (p<0.05) by 19.41% to 136.77±38.42 mg/dL. The results presented here indicated the FDC of dapagliflozin and sitagliptin significantly improved the glycaemic control of T2DM patients. The unique mechanism of dapagliflozin involves inhibiting SGLT2, which is independent of pancreatic beta cells' insulin secretion ability making it a suitable option for a diverse range of patients at various stages of type 2 diabetes, including those in advanced stages of the disease with a severely impaired beta-cell function who are already taking one or more oral anti-hyperglycaemic agents [22]. Previous pre-clinical and clinical research has established the aforementioned fact that dapagliflozin enhances glucose homeostasis in diabetics. Additionally, dapagliflozin has been shown to lower glucose levels and provide additional benefits, such as reducing body weight (including abdominal adiposity), blood pressure, and serum uric acid, all of which are independent markers of cardiovascular risk [23]. On the other hand, sitagliptin has also been used as a combination therapy with metformin, pioglitazone, to improve glycaemic control [24]. Brazg et al., 2007 conducted one of the initial studies that examined sitagliptin as an add-on therapy to metformin in patients with inadequate glycaemic control. This short-term study demonstrated that the addition of sitagliptin enhanced efficacy and did not result in any additional adverse events in comparison to metformin monotherapy [25]. Also, Sitagliptin has the potential to hinder the increase in endogenous glucose production by inhibiting glucagon secretion, elevating the levels of GLP-1 and stimulating insulin secretion in hyperglycaemic patients. Combining sitagliptin and dapagliflozin helps in maintaining glucose homeostasis and allows individuals with type 2 diabetes to achieve their glycaemic targets [26].

Jabbour *et al*.,2014 demonstrated that a 12-week course of treatment with dapagliflozin and sitagliptin resulted in improved blood glucose control compared to baseline, which may be attributed to an improvement in insulin resistance. In a randomized trial, the effectiveness and safety of dapagliflozin 10mg (n=225) as an add-on therapy to sitagliptin 100mg with or without metformin were compared to a placebo (n=226) in patients with poorly controlled T2D (mean baseline HbA1c 7.9%). After 24 weeks, adding dapagliflozin provided additional clinical benefits with a significant reduction in HbA1c (-0.5% *vs*. 0% with placebo) and body weight (-2.1kg *vs*. -0.3 kg). When added to sitagliptin alone or to sitagliptin plus metformin, dapagliflozin significantly decreased HbA1c *vs.* placebo (placebo-subtracted, -0.6% and -0.4%, respectively; both p<0.0001). The benefits of glucose control and weight reduction seen at week 24 were maintained through week 48, and fewer patients receiving dapagliflozin were discontinued or rescued for failing to achieve glycaemic targets compared to those on a placebo [22].

Also, Shamana et al. 2020 conducted a study utilizing CGM data to evaluate changes in HbA1c, insulin resistance, anti-diabetic medication use, and other ambulatory glucose profile metrics over a 90-day period. The study analysed mean TBT and TIT values over the 90-day period and found that an increase in TIT, even as little as 5%, and a decrease in TBT were associated with fewer complications due to diabetes [27].

In addition to the improvement in ADG, in the present study the FDC treatment also led to significant changes in TIT, which increased from 40.73±28.62% to 54.77±34.24% (overall improvement of 34.47%, $p<0.05$). The study results compliments the goal set by the ADA, which includes the description of and the use of CGM report as part of its standard of care (SOC) since 2020 [20]. According to the ADA, a TIT of glucose level between 70 to 180 mg/dL should be greater than 70% [28] For patients below 25 years of age, the TIT should be >60 % and for older patients, >50% TIT is recommended. Since, in this study, the age of patients varied (mean= 56.70±9.8 years), the TIT (54.77 ±34.24%) achieves the general target of >50%. Our results correspond to the prior results published by Beck *et al*.,2017 where 158 patients having T2DM with a mean age of 60 years showed a TIT between 55- 60% [29].Thus, our results, in line with the above-mentioned studies, conclude that increase in TIT reflected better glycaemic control by the FDC of dapagliflozin and sitagliptin.

The second important metric of CGM, TAT, is divided into two levels of hyperglycaemia (as per the 2019 consensus), where level 1 (blood glucose level between 180-250 mg/dL) alerts patients to continuously monitor their glucose levels, and level 2 (blood glucose level above 250mg/dL) urges them to take immediate action. In this study, TAT decreased from 51.94±34.27% to 35.77±32.93%, showing an overall improvement of 31.13% ($p=0.001$). The 16.17% decrease in TAT after the administration of FDC supports the effectiveness of dapagliflozin and sitagliptin in improving blood glucose levels in people with T2DM. This improvement further suggests that the FDC decreased the risk of hyperglycaemia by decreasing the TAT [21, 27].

Similarly, the international consensus also subdivides TBT into two levels of hypoglycaemia. Level 1 TBT (blood glucose level between 54-70 mg/dL) is considered an alarm clock that raises awareness of individuals at risk of developing hypoglycaemia, while level 2 (blood glucose level below 54mg/dL) requires immediate attention as the patient is already hypoglycaemic. In this study, TBT increased from 7.32±8.53% to 9.46±20.00%, but the change was non-significant statistically [21, 27].

Altogether, this single-centre, single-arm real-world study highlighted the effectiveness of once-daily FDC of dapagliflozin and sitagliptin in T2DM patients in Indian population. The administration of CGM (Freestyle Libre Pro) was integral to acquire glycaemic data that identified the patterns of hyper- and hypoglycaemia, which provides detailed assessment in comparison to a gold standard like HbA1c. Additionally, CGM parameters like ADG, TIT, and TAT showed a significant improvement at the end of the study compared to baseline, when patients were previously on triple, dual, mono, and insulin therapy. However, to substantiate these results a larger sample size needs to be evaluated for defining target parameters regarding diabetes therapy.

5. CONCLUSION

The treatment of T2DM does not have a singular approach, but the ultimate objective is to maintain glycaemic targets over time to decrease the possibility of acute and chronic complications. The present study indicates that once daily administration of FDC of dapagliflozin and sitagliptin in Indian T2DM patients significantly improved glycaemic parameters like, AGD, TIT, and TAT at the end of 15 days.

ETHICAL APPROVAL

In view of the retrospective nature of the study, the procedures performed were part of the routine care. Therefore, the ethical approval was not applied to any Ethics Committee.

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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