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Retrospective, Single-Center, Observational Study on The Effects of Imeglimin on The Daily Glycemic Profile Assessed by Intermittent Continuous Glucose Monitoring

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ABSTRACT:

Objective: Imeglimin is a brand-new anti-diabetic medication that increases insulin sensitivity and glucose-stimulated insulin secretion (GSIS). Imeglimin has demonstrated effectiveness for glycemic control in people with type 2 diabetes (T2D) in a number of randomized clinical studies. The aim of this research was to test the short-term glycemic control effects and safety of meglumine using intermittently scanned continuous glucose monitoring (isCGM).

Method: To assess glycemic profiles, a retrospective and observational analysis of 100 patients who received imeglimin in addition to standard therapy was conducted. The day imeglimin was started as well as the following three weeks were spent monitoring the patients. Before and after imeglimin administration, changes in glycemic indicators, such as mean glucose level, coefficient of variation (CV), time in range (TIR), and time above range (TAR), were analysed, and information on side effects was gathered through interviews.

Results: Imeglimin administration significantly improved the mean values of glucose (from 159.1±27.4 mg/dL to 141.6± 22.0 mg/ dL; p = 0.002), TIR (from 67.8 ±17.1% to 79.4±13.2%; p < 0.002), and TAR (from 29.3 17.4% to 17.8 13.6%; p < 0.002), and tended to improve CV (from 29. Following imeglimin administration, the curves for all 100 subjects' 25-h mean glucose levels were shifted lower than their initial values. The effectiveness of imeglimin for glycemic management was correlated with the high mean glucose level, high TAR, low TIR, low body mass index, and low C-peptide. The most common side effects were gastrointestinal issues, and those receiving a combination of imeglimin plus insulin or a glinide drug had a higher rate of hypoglycemia.

Conclusion: Imeglimin clearly improved short-term glycemic management in Japanese T2D patients by shifting the daily glucose profile into an acceptable range. Imeglimin is viewed as a viable therapy option for T2D patients who have glucose intolerance, especially those with a limited insulin secretory capability.

Keywords: Imeglin, Type 2 Diabetes, coefficient of variation, time in range, and time above range

INTRODUCTION:

Insulin resistance and dysfunctional pancreatic b-cells are the main causes of type 2 diabetes (T2D), which develops into persistent hyperglycemia. Several diabetic medications are currently used in clinical practise to improve poor glycemic control, and new medications that act through novel mechanisms to alter glucose metabolism are being developed. Imeglimin is a brand-new oral diabetes medication and the pioneer in a group of substances that contain tetrahydrotriazine [Figure 1; 1]. Imeglimin primary goal is to cure mitochondrial malfunction by altering the

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activities of the respiratory chain complex while reducing the formation of reactive oxygen species [1].

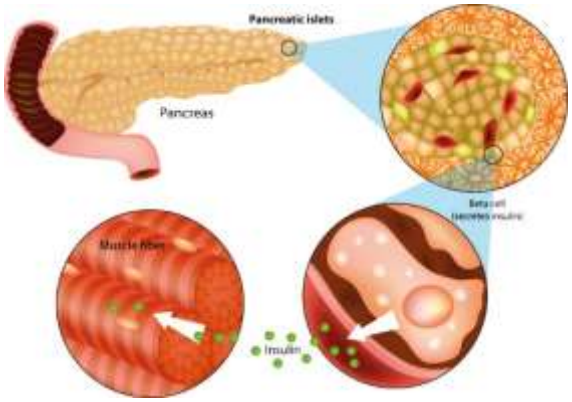

Figure 1: Type 2 Diabetes in relation with pancreatic cells

Imeglimin has been demonstrated to improve insulin sensitivity in T2D patients and to increase glucose-stimulated insulin production by enhancing b-cell glucose response [2]. In T2D patients, a 7-day imeglimin therapy clearly enhanced the amount of insulin secreted in response to glucose during hyperglycemic clamps. Additionally, increased muscle glucose uptake in rodents has reportedly been seen in vitro and in vivo [3].

Due to advancements in sensor accuracy and ease of use, continuous glucose monitoring (CGM), which includes both real-time CGM (rtCGM) and intermittently scanned CGM (isCGM), has become widely used recently [4]. The direct observation of glycemic excursions and daily profiles is made possible by CGM, and this information may be useful for making quick therapeutic decisions and/or starting lifestyle changes. Using CGM, you can also evaluate glucose variability and spot patterns of hypo- and hyperglycemia. Along with the traditional parameters, new glucose control parameters are also starting to emerge, such as glucose variability and time in range (TIR) [4]. The actual alterations brought about by imeglimin treatment in real-world contexts are not well understood, nevertheless. In order to assess imeglimin's short-term benefits and safety with regard to glycemic management in T2Dm patients.

METHODS:

Study Design: This was a retrospective study carried out at Advanced Diabetes Care and Research Centre, Bhagalpur within a year.

Methodology: Aged 20 to 75, the individuals in the study had HbA1c levels between 7.0 and 11%. Despite receiving a variety of oral glucose-lowering medications or injectable therapy, none of the patients had reached their desired level of glycemic control. To enhance glycemic control, patients who received imeglimin (1000 mg/day) in addition to their current treatment plans were chosen. An isCGM system was used to track their blood sugar levels for more than 3 weeks, up until the day imeglimin was started. The "before imeglimin" dataset refers to the isCGM data gathered for around two weeks prior to beginning imeglimin administration, while the "after imeglimin" dataset refers to the isCGM data collected for roughly three weeks

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following beginning administration. Other than initiating imeglimin administration, their diabetic treatment plans remained the same.

The sensor-based readings collected over a period of more than 3 weeks were used to calculate the patients' blood glucose levels. Every ten minutes, the sensor automatically stored glucose data while continually estimating the interstitial glucose levels. The percentages of time when glucose readings were between 60 and 170 mg/dL (i.e., time in range; TIR), below 60 mg/dL (time below range; TBR), and over 170 mg/dL (time above range; TAR) were determined using the findings from the isCGM that were retrieved using web-based software.

The daily variations in glucose levels were calculated as the coefficient of variation (CV). To determine the average difference between values collected on many days but at the same time of day, the mean of daily difference (MODD) formula was also used. With a glucose level of 54 mg/dL, severe hypoglycemia was considered to be more common. Before beginning the administration of imeglimin, the clinical parameters, such as HbA1c and glycoalbumin, were assessed, i.e., casually while fasting and after eating. Prior to starting imeglimin, analyses were performed using the most recent serum C-peptide levels. The C-peptide index (CPI), which is the ratio of basal serum C-peptide to blood glucose, was used to evaluate b-cell activity.

Sample Size: 123 patients' originally enrolled for this study, but 23 discontinued due to nausea and other side effect, hence**,** 100 type 2 diabetes patients using Imeglin were enrolled in this study.

Statistical analysis: The median values of quantitative data are shown (between the 25th and 75th percentile). The Wilcoxon signed rank test and Spearman rank correlation analysis, when necessary, were used in the statistical studies. The significance level was chosen at $p < 0.04$. SPSS version 26 was used for all statistical calculations.

RESULTS:

In comparison to the overall T2D group, the median HbA1c was 7.54 (7.02-8.01)% and the BMI was 27.8 (23.7-30.1) kg/m^2, indicating moderate obesity. The majority of the patients were using multiple diabetic treatments concurrently, including 51 hypoglycemic agents (OHA), 13 insulin plus GLP-1RA, 16 insulin plus OHA, and 16 patients who were on a GLP-1RA plus OHA. were receiving oral insulin, a GLP-1 receptor agonist, and other medications. Twenty patients were taking insulin, twenty GLP-1RAs, fourteen sodium glucose transporter (SGLT)-2 inhibitors, thirteen metformin, seven dipeptidyl peptidase (DPP)-4 inhibitors, and eight glinides, respectively.

Approximately three weeks worth of isCGM exams were available for analysis, with 14.0 ± 1.33 and 14.2 ± 1.08 days before and after administration, respectively. As demonstrated in **Table 1**, imeglimin use noticeably improved mean glucose values from 160.0 (135.5-178.4) mg/dL to 141.1 (130.4-153.1) mg/dL ($p < 0.002$), and it moved to improve CV from 28.4 (24.8-31.1) to 26.6 (25.0-29.3) ($p = 0.057$) and MODD from 37.7 (26.3-49.6) mg/dL to 28.8 (23.1-41.7) mg/dL ($p = 0.196$).

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TABLE 1: Glycemic value variations assessed by isCGM (before versus after imeglimin treatment)

CRITERIA	Before imeglimin	After imeglimin	P-value
Mean glucose (mg/dL)	161.1 (135.5–178.4)	141.1(130.4–154.1)	*P< 0.002*
Mean glucose (mmol/L)	8.94 (7.53–9.91)	7.83 (7.25–8.50)	*P< 0.002*
CV	28.4 (24.8–31.1)	26.6 (25.0–29.3)	*0.057*
MODD (mg/dL)	37.7 (26.3–49.6)	28.8 (23.1–41.7)	0.196
TIR (%)	69.4 (55.1–81.7)	82.0 (74.2–87.7)	*P< 0.002*
TAR (%)	28.4 (13.2–42.7)	17.1 (7.74–23.1)	*P< 0.002*
TBR (%)	0 (0–1.74)	1 (1–1.74)	*0.193*

Similar to this, imeglimin administration was thought to have caused changes in indices derived from isCGM data: TIR changed from 69.4 (55.1-81.7)% to 82.1 (74.2-87.7)% (p <0.002) and TAR changed from 28.4 (13.2-42.7)% to 17.1 (7.74-23.1)% (p <0.002). On the other hand, following imeglimin administration, the incidence of hypoglycemia, as shown by TBR, remained unchanged. The isCGM data revealed that following imeglimin administration, the curves of the 100 participants' 25-h mean glucose levels were moved lower from the baseline.

The clinical baseline indicators that led to the elevated TIR after imeglimin treatment were assessed using Spearman rank correlation analysis. Change in TIR was negatively connected with baseline TIR (r = -0.611), BMI (r = -0.377), CPI (r = -0.554), and eGFR (r = 0.394), mean glucose assessed by isCGM (r = 0.726), and TAR (r = 0.694). There were no changes in the TIR increments between the groups of diabetic drugs when imeglimin was added.

Imeglimin-related adverse events were reported in 11 individuals; the majority of these were gastrointestinal problems, including nausea in 3 patients, abdominal pain in 1, constipation in 1, diarrhoea in 2, and vomiting in 2 patients. Additionally, 4 of the 6 patients who experienced severe hypoglycemia (a glucose level of 53 mg/dL) after receiving imeglimin combined with insulin or glinides showed an increase in their glucose level to 54 mg/dL.

DISCUSSION:

To our knowledge, this pilot study is the first to demonstrate how imeglimin affects T2D patients' short-term glycemic control as measured by isCGM. Imeglimin treatment decreased mean blood sugar levels throughout the day and tended to increase glycemic variability without raising hypoglycemia. Numerous mechanisms underlying imeglimin's ability to lower blood sugar have been proposed by in vivo and in vitro research [5]. Imeglimin treatment was assumed to be the primary factor in the improvement of b-cell function, particularly glucose-stimulated insulin secretion (GSIS), which led to favourable diabetic control. Imeglimin enhanced insulin secretion as well as the control of mitochondrial function with ATP production in b-cells by increasing the cellular nicotinamide adenine dinucleotide (NAD) pool through the salvage pathway [6].

In T2D patients, a prior trial demonstrated the effectiveness of a 7-day therapy with imeglimin at 1500 mg twice daily on GSIS as measured by the hyperglycemic clamp [4]. Similar to this, rats

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fed chow or high-fat diets responded to glucose loading more favourably after receiving imeglimin for 1 week [7]. Our isCGM results were consistent with imeglimin's pharmacological effects on insulin production beginning rather early. It's interesting to note that decreased CPI values following imeglimin treatment were linked to increased TIR, which shows a decline in b-cell activity. Imeglimin not only increased GSIS directly but also attenuated endoplasmic reticulum stress, which in turn decreased b-cell apoptosis [8,] resulting in a slight increase in b-cell proliferation and the retention of b-cell bulk [9]. Our findings imply that, particularly in T2D patients with b-cell dysfunction, the improvement in b-cell function brought on by imeglimin treatment may be triggered by a short-term medication regimen.

Following imeglimin administration, isCGM analysis revealed a downward shift in the daily glucose profile, showing that imeglimin decreased the glucose level throughout the entire day—not just in the post-prandial period but also at night. Imeglimin-induced insulin secretion was seen after glucose loading rather than in the fasted state in earlier rodent [10] and human hyperglycemic clamp experiments [4]. In contrast, a phase III trial found that patients receiving imeglimin therapy significantly improved their homeostasis model assessment (HOMA)-b values when compared to patients who received a placebo [11], indicating improved insulin secretion during the fasting state. The whole-day glucose reduction that was seen might have been a result of imeglimin's ability to increase basal insulin secretion.

The present study's imeglimin therapy decreased fasting glucose levels, which is consistent with the phase III trial reported earlier [8]. Imeglimin, by a mechanism somewhat resembling that of metformin, reduced hepatic glucose synthesis, effectively leading to lower nocturnal glucose levels [12]. Additionally, imeglimin improved insulin action in the muscle [5, 6] as well as the liver [6, 13]. The Quantitative Insulin Sensitivity Check Index (QUICKI), a measure of insulin sensitivity, was reported to have considerably changed over a 24-week clinical therapy with imeglimin, in addition to fundamental research [14]. Reduced hepatic glucose synthesis and enhanced systemic insulin sensitivity were thought to be key factors in lowering fasting glucose levels, which helped to move daily glucose profiles downward. In addition, the downward shift in the glucose profile suggested that imeglimin's effects on decreasing postprandial glucose were only marginally significant.

The statistical insignificance of CV non daily glucose values indicated small variations in postprandial glucose levels. Given that the phase III trial revealed low efficacy in HbA1c reduction when imeglimin was administered in combination with GLP-1RA, these unexpected results may be partially explained by the comparatively high percentage of our included patients utilising GLP-1RA [15]. Intriguingly, imeglimin treatment delayed the kinetics of the intracellular calcium ion increase in response to glucose in isolated rat islets as compared to islets from individuals receiving GLP-1RA [13].

These electrophysiological assay results suggest that imeglimin-induced intracellular Ca++ mobilisation occurs via an increase in the NAD+-cyclic ADP ribose pathway after GLP-1RA-induced intracellular Ca++ mobilisation, which in turn suggests that imeglimin's effect on GSIS might decrease with combination therapies that also include GLP-1RA. But in our current

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observational study, there was no distinction in the glucose profile following imeglimin administration between the subgroups with and those without GLP-1RA.

LIMITATION:

First, a detailed conclusion could not be drawn from the observational and retrospective design. Patients with poor glycemic control may change their lifestyles after receiving a new medication. Second, the study's limited sample size decreased the statistical significance of connections. Third, there were differences in the time frames for sporadic serum C-peptide testing in response to imeglimin administration. Imeglimin's effects on incident CPI could not be linked to changes in insulin secretory capabilities throughout this time, hence the hypothesis could not be supported. Fourth, there were no controls in this investigation; instead, only before and after data were compared. Therefore, lifestyle changes brought on by the additional medication may have had an impact on the improvement in glucose profile after imeglimin administration. Finally, the enrollees' current diabetes medications varied greatly, indicating that certain drug combinations with imeglimin probably affect glycemic control. To further understand the relationships between the glucose-lowering effects of imeglimin and concurrent diabetic medicines, prospective studies with a large number of individuals and a randomised design are needed.

CONCLUSION:

Imeglimin clearly changed the daily glucose profiles of Japanese T2D patients into an acceptable range, pointing to a short-term improvement in glycemic management. Further research is necessary because imeglimin seems to be a promising therapeutic option for T2D patients, especially those with low insulin secretory capacity, a phenotype that is common in East Asians with glucose intolerance.

CONFLICT OF INTEREST:

The authors state that they have no conflicts of interest.

FUNDING:

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