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ORIGINAL ARTICLE

Pattern of Loss of Glycemic Control in Indian Type 2 Diabetes Patients: An Observational Study

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Aim: *The aim of the study was to determine pattern of loss of glycemic control in Indian type 2 diabetes patients.*

Methods: *An observational registry, the study included 64 type 2 diabetes patients, divided in four groups based on baseline HbA1c values: group 1 (<6.5%, n = 17), 2 (6.5-6.9%, n = 11), 3 (7.0-7.9%, n = 21), 4 (e" 8%, n = 15). Using continuous glucose monitoring system patients' 24-hours glucose profiles were obtained over 3 consecutive days. Mean glucose values were compared between groups for post-prandial(08:00 AM to 11:59 PM, or time from breakfast to midnight), morning (05:31 AM to 07:59 AM or time from early dawn up to breakfast)and nocturnal fasting period (00:00 AM to 05:30 AM or time from midnight to early dawn) and within each group across these periods, using ANOVA, followed by Bonferroni's post-hoc test.*

Results: *Mean age of patients was 52.95 years (SD =11.02) and 65.62% were male. Mean duration of diabetes in study population was 7.52 years (SD = 7.09).*

Between HbA1c 6.5 and 7.9 the groups did not differ significantly during any of the study periods. With HbA1c e" 8, significant differences in glycemic control affecting various periods became apparent. While for postprandial period significant differences were noted between group 4 and each of groups 1, 2 and 3 (p <0.0001), for morning and nocturnal periods only group 1 and 4 were significantly different (p=0.0251 and 0.0071, respectively). Within group comparison showed similar glucose values for three study periods till HbA1c 6.9; while significantly higher values in postprandial period compared to morning or nocturnal (p=0.0111 and 0.0056 for groups 3 and 4 respectively) were noted once HbA1c was e" 7.

Discussion and conclusions: *Daily glycemic excursions in Indian type 2 diabetes patients become more evident with worsening diabetes. Excursions in postprandial glucose values were statistically significant with even narrow differences in HbA1c values while excursions in morning and nocturnal glucose values required wide difference between HbA1c values, indicating that with worsening diabetes once the HbA1c reached the value of 7 and above, postprandial glycemic control was more vulnerable to deterioration as compared to morning or nocturnal glycemic control.*

Introduction

It has been postulated in literature that in type 2 diabetes postprandial glycemic control deteriorates before deterioration of fasting glycemic control[1, 2]. Various studies have supported such postulation and it has been observed that in type 2 diabetes deterioration of glycemic control progressed from postprandial to fasting period with worsening diabetes in a step-wise fashion: the first step involved a loss of postprandial glycemic control; the intermediary step involved deterioration of glycemic control during the morning pre and post-breakfast periods, corresponding to the dawn and extended dawn phenomena; the final step involved loss of glycemic control during the nocturnal fasting period, resulting in fasting hyperglycemia[3, 4].

Although these findings offer insight into the evolution of type 2 diabetes and are of potential significance in guiding the choice of anti-diabetic therapy, it remains to be established whether the loss in postprandial and fasting glycemic control occurs in parallel or sequentially. Furthermore, there is dearth of similar data in Indian population and the pattern of loss of postprandial and fasting glycemic control with worsening diabetes amongst Indian patients has hither to remained unexplored.

Objective

The objective of the study was to determine the pattern of loss of postprandial and fasting glycemic control in Indian type 2 diabetes patients and to evaluate if such loss occurred in parallel or sequentially in the evolution of type 2 diabetes.

Materials and Methods

Study design and centre

The study was designed as an open-label, non-randomized, observational disease registry. Patients coming for routine visit to their diabetologist were recruited from a private diabetic clinic in India, under supervision of the principal investigator.

Study subjects

Adult patients (>18 years of age) diagnosed with type 2 diabetes mellitus on diet alone or diet plus different individual or combinations of oral hypoglycemic agents (OHA) having a constant diet and / or drug regimen for at least 3 months were included in the study, after taking their written informed consent. Prior to inclusion each patient provided their written informed consent to study participation by signing a data release consent form. Patients diagnosed with type 1 diabetes, participating in other clinical trial and pregnant and lactating females were excluded from the study. Patients treated with steroids within last 3 months, patients having history of acute intercurrent illness in past 3 months, hospitalized patients and patients with severe hepatic and renal disease were not included in the study. Also, patients treated with alpha-glucosidase inhibitors or glinides were excluded from the study to avoid any bias in the interpretation of postprandial glucose excursions.

A total 64 patients fulfilling the above selection criteria were included in the study. At baseline, patients were assigned to one of four groups based on their Hb A1C values: group 1 (Hb A1C <6.5%) – 17 patients; group 2 (HbA1C 6.5-6.9%) – 11 patients; group 3 (Hb A1C 7.0-7.9%) – 21 patients and group 4 (Hb A1C e" 8%) – 15 patients. The sample size calculation as well as distribution of patients in four unequal sized groups was based on data from published literature [4] and considering alpha of 0.05 and power of 80%. The rationale for selection of these different groups was based on the fact that Hb A1C goals for type 2 diabetes patients have been set at <6.5% by the International Diabetes Federation [5], at 7% by the American Diabetes Association[6]and until 2002 8% was the Hb A1C threshold value selected by American Diabetes Association for additional therapeutic intervention[7].

Study duration

The study spanned over a period of 9 months, from January 2008 (first patient enrolled) to October 2008 (last patient completed).

Study procedures

In all enrolled patients, 24 hours continuous glucose profiles were obtained using a second generation Medtronic Minimed continuous glucose monitoring system (CGMS)[8]. This device measured the subcutaneous interstitial glucose concentration on an ambulatory basis over a period of 3 consecutive days. The CGMS sensor was inserted on day 0 at the out patients clinic of the principal investigator and removed at the end of day 3. The patients were instructed to maintain their usual diet and therapy regimen and not to modify meal timings over the 3-day period of continuous monitoring. The CGMS machine was programmed to give one reading at every 5 minutes interval throughout the 3 days period. The CGMS data were downloaded on a computer for analysis and evaluation of glucose profiles of enrolled patients.

For the purpose of analysis of glucose profiles, three time frames were defined: the postprandial state was defined as time from 08:00 AM to 11:59 PM (time from breakfast to midnight); the morning state, representing the dawn phenomenon was defined as time from 05:31 AM to 07:59 AM (time from early dawn up to breakfast) and the nocturnal fasting period was defined as time from 00:00 AM to 05:30 AM (time from midnight to early dawn). In each of the four groups, the glucose values obtained from the CGMS data were averaged for the three periods.

Statistical analysis

Data were tested for normality using Shapiro-Wilk test which indicated glucose values followed normal distribution in the study population. In order to assess presence or absence of any specific pattern or sequence in loss of glycemic control of the enrolled patients, we first averaged the CGMS readings for individual patient separately over three periods of our interest (i.e., postprandial, morning and nocturnal fasting periods), then calculated the mean glucose value for each of the four groups over these three phases.

For one patient in group 3, CGMS readings were not available for any of the three phases while for one patient in group 4, readings were not available for morning and nocturnal phases. For each of the four Hb A1C groups data were represented as mean ± standard deviation (SD) for each of the three time frames.

Between group comparisonsin mean glucose values over each of the three periods were made using ANOVA. Similarly, ANOVA was also used to compare mean glucose values between the three periods within each of the four study groups. For ANOVA, a two-tailed alpha of 0.05 was assumed and any statistically significant difference noted in ANOVA was followed by Bonferroni's post hoc testing.

All statistical tests were carried out using SAS software version 9.2 (SAS institute, Carry, NC).

Results

Out of total 64 enrolled patients, 42 (65.62%) were male while 22 (34.37%) were females. Mean age of enrolled patients was 52.95 years with a standard deviation (SD) of 11.02 years. Mean weight, height and waist circumference of enrolled patients were 73.62 kg (SD = 13.48), 165.16 cm (SD = 8.60) and 93.56 cm (SD = 11.06) respectively. Six of the enrolled patients (9.37%) were smoker while rest was non-smoker; mean systolic blood pressure (SBP) was 133.46 mm Hg (SD = 10.55) and mean diastolic blood

Table-1: Baseline demography and disease profile of enrolled patients

	Group 1	Group 2	Group 3	Group 4	Total
Hb A1C (%)	<6.5	6.5-6.9	7.0-7.9	e"8	—
Patients (n)	17	11	21	15	64
Age (years)*	54.18 ±12.85	54.09±11.13	54.29±10.84	48.87±8.83	52.95±11.02
M/F ratio	13/4	8/3	11/10	10/5	42/22
Weight (kilograms)*	68.68±9.78	69.75±9.29	75.40±16.11	79.57±13.86	73.62±13.48
Height (centimeters)*	164.29±7.82	164.64±8.37	164.33±8.83	167.67±9.62	165.16±8.60
Waist Circumference (centimeters)*	88.29±14.62	91.82±5.58	94.43±7.81	99.60±10.96	93.56±11.06
SBP (mmHg)*	130.00±8.66	130.91±8.31	136.10±11.34	135.33±11.87	133.46±10.55
DBP (mmHg)*	82.71±4.69	81.45±4.66	83.14±5.28	81.60±4.85	82.41±4.89
Smoker/non-smoker ratio	2/15	1/10	1/20	2/13	6/58
Diabetes duration (years)*	7.94±8.22	7.82±8.11	7.05±6.74	7.47±6.05	7.52±7.09
Patients with diabetic neuropathy (n)	0	0	2	0	2
Patients with CAD (n)	1	0	0	0	1
Patients with hypertension(n)	7	6	12	6	31
Patients with dyslipidemia(n)	5	7	11	9	32
Patients on OHA therapy(n)	14	10	20	14	58

* Data are mean ± standard deviation.

SBP=Systolic Blood Pressure, DBP=Diastolic Blood Pressure; CAD=Coronary Artery Disease; OHA=Oral Hypoglycemic Agents

pressure (DBP) was 82.41 mm Hg (SD = 4.89). Mean duration of diabetes in the study population was 7.52 years (SD = 7.09). The group-wise distribution of these variables is shown in Table 1. Except for the fact that mean waist circumference in group 4 was significantly higher compared to group 1, no other statistically significant difference was noted between the four groups in terms of age, sex distribution, weight, height, SBP, DB, smoking habitand duration of diabetes at baseline.

At baseline, 2 of the enrolled patients had diabetic neuropathy and 1 had coronary artery disease as diabetic late complication, while 31 patients had hypertension and 32 patients had dyslipidemia as co-morbidity. Fifty eight of the enrolled patients (90.62%) were on OHA therapy (monotherapy or as combination of more than one agent) while 6 (9.38%)) were not taking any OHA therapy.

Figures 1-4 represents CGMS graph patterns for one randomly selected patient from each of the four study groups (thus four graphs for four patients). For each patient,reading of 3 days are represented with different colors. Although the graphs are not indicative of group mean values, they roughly represent the CGMS graph pattern in the respective group. It is evident from Figures 1 to 4 that the glucose values go on increasing as we move from group 1 to 4, indicating worsening glycemic control, as could be expected. Also, it was noted that the glycemic excursions, were minimum in group 1, producing a more or less flat graph, and went on increasing with maximum excursion in group 4, indicating, glycemic excursions become more and more evident with worsening of diabetes.

Table 2 below presents a summary ofCGMS glucose values in each of the four study group over the three periods:

As evident from Table 2, between group comparison showed statistically significant differences (ANOVA p-values <0.0001, 0.0251 and 0.0071 for postprandial, morning and nocturnal periods respectively) for all three study periods.After applying Bonferroni's post hoc test, it was found that for all three periods, no significant difference existed between groups 1 versus 2, 2 versus 3 and 3 versus 1. This means, between HbA1c values below 6.5 till 7.9 the groups did not differ significantly from each other in terms of glycemic control during any of the three study periods.

However, once HbA1c reached the value 8 and above, significant differences in glycemic control affecting various periods became apparent. Using Bonferroni's post hoc test statistically significant differenceswere notedonly between groups 1 and group 4 for both morning and nocturnal periods. However, for postprandial period statistically significant differences were noted between group 4 and all other groups (i.e., group 4 versus each of groups 1, 2, and 3). This indicates that postprandial glycemic control is more vulnerable to the effects of worsening diabetes (indicated by increasing HbA1c values) and hence, postprandial glucose values in group 4 are significantly higher compared to all other groups, even though the HbA1c values in some of these groups (group 3 and 4, for example) were very close. On the contrary, morning and nocturnal glucose values seemed less vulnerable to the effects of worsening diabetes, and statistically significant deterioration in glycemic control in these phases were observed only when HbA1c values were widely different (below 6.5 versus 8 and above) and not between groups with narrow difference in HbA1c values (for example groups 4 versus 3 or 4 versus 2).

Table 2: Glucose values for post-prandial, morningand nocturnal periods

	Group 1 (HbA1c <6.5%)	Group 2 (HbA1c 6.5-6.9%)	Group 3 (HbA1c7.0-7.9%)	Group 4 (HbA1c ≥ 8%)	ANOVA p-value@
Post-prandial	132.63±19.95	156.10±29.43	158.80±29.49	191.19±40.44	<0.0001*
Morning	120.23±26.87	127.18±33.00	140.97±30.61	154.69±39.46	0.0251*
Nocturnal	117.64±29.45	129.44±31.94	131.99±27.16	156.24±31.70	0.0071*
ANOVA p-value $	0.1648	0.0921	0.0111*	0.0056*	—

All values mean ± standard deviation

Post-prandial - time from breakfast (8:00 am) to midnight (11:59 pm); morning time from 5:31 am up to breakfast (7:59 am); nocturnal - time from midnight (00:00 am) to 5:30 am.

* Statistically significant by ANOVA; for Bonferroni's post hoc test results please refer to text

@ Between group comparison over each of three periods

$ Comparison between three periods within each group

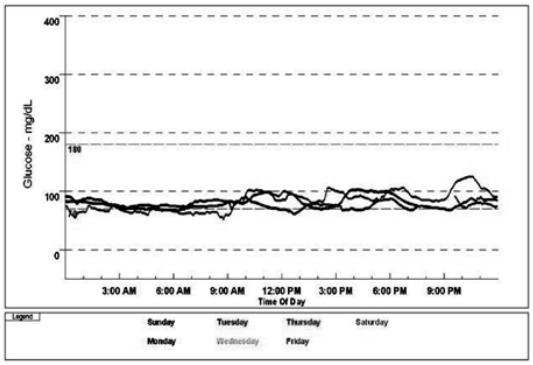

Figure 1. Three Day Plot of CGMS Values for One Randomly Selected Patient in Group 1

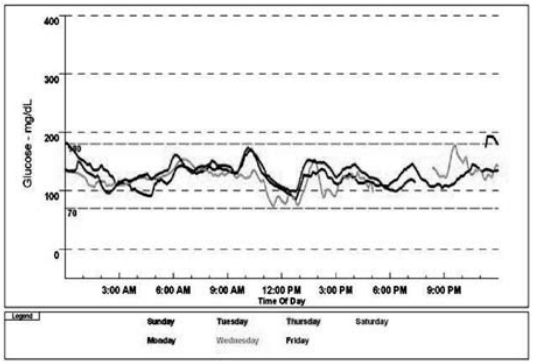

Figure 2. Three Day Plot of CGMS Values for One Randomly Selected Patient in Group 2

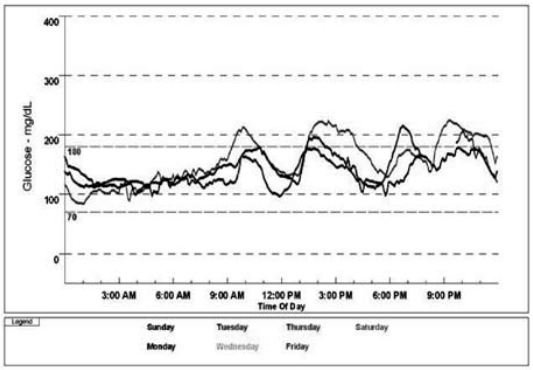

Figure 3. Three Day Plot of CGMS Values for One Randomly Selected Patient in Group 3

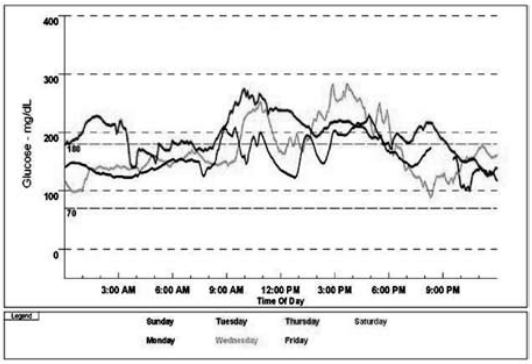

Figure 4. Three Day Plot of CGMS Values for One Randomly Selected Patient in Group 4

Further, as per Table 2, when HbA1c values were in the range of less than 6.5 till 6.9 (groups 1 and 2) glucose values across postprandial, morning and nocturnal periods were similar, without any statistically significant difference (ANOVA p-values 0.1648 and 0.0921, respectively). However, once HbA1c reached the value of 7and above (groups 3 and 4) statistically significant difference in glucose values were observed between the three study periods (ANOVA p-values 0.0111 and 0.0056 for groups 3 and 4 respectively). After applying Bonferroni's post hoc test it was found that for both group 3 and 4, postprandial glucose values were significantly higher compared to morning or nocturnal values. These data further underscore the fact that with worsening diabetes, postprandial glycemic control is more vulnerable to deterioration compared to morning or nocturnal glycemic control.

Conclusion

Our study demonstrated that daily glycemic excursions become more evident with worsening diabetes. Our study also demonstrated that excursions in postprandial glucose values in Indian type 2 diabetes patients were statistically significant with even narrow differences in HbA1c values while excursions in morning and nocturnal glucose values required wide difference between HbA1c values.

Although our study was not able to establish an exact sequence of deterioration of glycemic control as demonstrated by Monnier et al[4], we found that with worsening diabetes once the HbA1c reached the value of 7 and above, postprandial glycemic control was more vulnerable to deterioration as compared to morning or nocturnal glycemic control.

Further studies involving larger and more heterogeneous population, spread across the world are required to confirm if these findings could be generalized for all type 2 diabetes patients and also to establish if there is a sequence in deterioration of morning and nocturnal glycemic control, as shown by Monnier et al

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"Thousands of candles can be lighted from a single candle, and the life of the candle will not be shortened. Happiness never decreases by being shared."

— Buddha