ORIGINAL ARTICLE

Practical implementation of ADA/EASD consensus algorithm in patients with type 2 diabetes in Pakistan

Muhammad Imtiaz Hasan,[1] Wasim Amer,[2] Nabeea Junaid[3]

Abstract

Objective: To ascertain the effectiveness of implementing the American Diabetes Association/European Association for the Study of Diabetes 2009 consensus algorithm in achieving glycaemic control in patients with type 2 diabetes.

Methods: The prospective, observational, open label, product registry was conducted at 38 sites across 7 cities in Pakistan between July 2011 and February 2014. Uncontrolled type 2 diabetes patients were either initiated on or switched to insulin glargine from other basal insulin. Glycated haemoglobin and fasting blood glucose were measured at baseline, 3 and 6 months.

Results: Of the 307 patients, 166(54%) were males. At baseline, the overall mean age was 49.5 ± 8.7 years. Mean duration of diabetes was 7.1 ± 4.5 years. Both fasting blood glucose and glycated haemoglobin levels significantly reduced from baseline to 3 months to 6 months ($p<0.01$). At 6 months, 18(5.8%) patients reported 41 hypoglycaemic episodes of which 19(46.3%) were asymptomatic and 22(53.6%) were symptomatic. No severe hypoglycaemic episodes were reported.

Conclusion: Insulin initiation and titration as per American Diabetes Association/European Association for the Study of Diabetes guidelines helped in achieving glycaemic targets without increasing the risk of hypoglycaemia.

Keywords: Diabetes mellitus, Type 2, Glargine, Hypoglycaemia. (JPMA 68: 1304; 2018)

Introduction

Type 2 diabetes mellitus (T2DM) is a global public health crisis that presents a substantial economic burden the world over, chiefly in developing countries.[1] Pakistan has a 6.8% prevalence rate of T2DM in the age group of 20-79 years. The number of T2DM cases in this age group in Pakistan was 6.9 million in 2014 and is estimated to reach 11.4 million by 2030 in the absence of interventions.[2,3] According to the International Diabetes Federation, T2DM led to 87,548 deaths in Pakistan in 2013 and resulted in a mean healthcare per-person expenditure of 52.7 USD.[2] The mounting burden of T2DM and the awareness that meeting glycaemic targets can considerably decrease morbidity, have made effective treatment of hyperglycaemia imperative.[4]

Insulin is the most effective treatment in lowering glycaemia.[5] However, patients with T2DM are reluctant to initiate insulin due to a number of reasons, such as injection phobia, negative impact on work, concerns about long-term medication use, inconvenience, not believing insulin is needed etc.[6] In Pakistan particularly, misconceptions regarding insulin are common, and reluctance to initiate insulin is observed in physicians as well.[7] The results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study showed that physicians often believe that insulin should be delayed until 'absolutely necessary'.[8] As a result, there is a delay in treatment intensification with insulin and a sizeable chunk of T2DM population remains under sub-optimal glycaemic control for several years before insulin initiation.[9,10]

The American Diabetes Association/European Association for the Study of Diabetes (ADA/EASD) consensus algorithm introduces insulin therapy early in the treatment of T2DM with rapid intensification to achieve the target glycated haemoglobin (HbA1c) <7%.[11,12] However, the International Diabetes Management Practices Study, a disease registry conducted in patients with diabetes in Asia, Latin America, Africa and Eastern Europe, confirmed that there is a gap between treatment guidelines and practice.[13] Therefore, there is a need for studies that can assess the impact of the application of treatment algorithms like ADA/EASD consensus algorithm on glycaemic control in a real-world setting.

The current study was therefore planned to ascertain the effectiveness of implementing the ADA/EASD 2009 consensus algorithm (which was in force when the study was initiated) in achieving glycaemic control in patients

[1]Diabetic Institute of Pakistan, [2]Lahore Medical and Dental College, [3]Sanofi-Aventis Pakistan Ltd.

Correspondence: Nabeea Junaid. Email: nabeea.junaid@sanofi.com

with T2DM in Pakistan. The primary objective was to determine the percentage of patients achieving HbA1c <7% at 6 months. Secondary objectives included evaluation of percentage of patients achieving HbA1c<7% at 3 months, HbA1c change from baseline to months 3 and 6, evolution of fasting blood glucose (FBG) determined by self-monitoring blood glucose (SMBG), insulin glargine (GLA) dosages at 3 and 6 months, number of hypoglycaemic episodes in the 4 weeks preceding inclusion in the study and during the registry and adverse events/serious adverse events (AEs/SAEs) occurring during the registry.

Subjects and Methods

This was a prospective, observational, open label, product registry conducted at 38 sites across 7 cities in Pakistan between July 2011 and February 2014. Since ethical review committee does not exist for majority of such clinics, administrative approval was taken from each participating clinic/investigator. Written informed consent was obtained from each subject.

Potential sites/investigators were selected based on convenience sampling from a list of qualified clinicians available from the database for diabetes portfolio at sanofi-aventis Pakistan limited. Investigators comprised 32 internists and 6 diabetologists practising in urban areas of Pakistan, having a suitable and loyal patient population.

Patient enrolment began in July 2011. Each selected investigator included 10 consecutive patients who met the study's eligibility criteria. Patients of either gender, ≥21 years of age, diagnosed with T2DM for at least 1 year, uncontrolled (HbA1c: 7%-10%), either insulin-naïve and in whom the physician had independently decided to initiate basal insulin after failure of metformin ± sulfonylurea (MET±SU) at maximum tolerated dose, or those already on basal insulin with MET±SU with FBG >130 mg/dL, were included. Patients on other oral anti-diabetic drugs (OADs), or unable/unwilling to perform SMBG and self-titrate insulin dose, or those who had a serious underlying illness or were hospitalised, and those pregnant or planning to conceive, were excluded.

The physician took the independent decision to initiate (or switch to) GLA as basal insulin therapy as part of the routine clinical care.

Step 1 of the treatment process was insulinisation with GLA. The GLA starting dosage was determined by the physician in insulin-naïve patients as well as in those who were switched from other basal insulin to GLA. The patient used GLA in the morning or evening but at the same time every day. According to the ADA/EASD consensus algorithm 2009,[11,12] the recommended starting daily dose of basal insulin is 10 units, or 0.2 unit/kg of body weight.

In step 2-, the insulin dosage of patients was titrated. According to the algorithm,[11,12] the insulin dose was increased by 2 units every 3 days until goals were met (e.g. until FBG was 70-130 mg/dL). If FBG was >180 mg/dL, dose of GLAwas increased by 4 units every 3 days. In the event of hypoglycaemia or FBG level <70 mg/dL, bedtime GLA dose was reduced by 4 units, or by 10% if >60 units. In order to support patients' self-titration, written instructions were provided to the patient on SMBG and how to titrate GLA. This titration scheme continued for the entire 6 months of the study until target goals were reached.

At 3 months, HbA1c was checked. If HbA1c was <7%, the regimen was continued. If HbA1c ≥7% and FBG was > target range, the GLA was up-titrated. And if FBG was within target range, one injection of rapid acting insulin was added before the main meal at the usual starting dose (~4 units)

The individual patient's goals were set by patient's physician. The physician was allowed to use his/her own regimen according to his/her standard practice of patient insulin dose titration.

The registry was conducted over 3 scheduled visits i.e. baseline (visit 1), 3 months (visit 2) and 6 months (visit 3) during which the HbA1C and FBG were measured. Glucometers (at baseline) and patient diaries (at baseline and 3 months) were provided by the study sponsor at all the sites. These were handed over to the patients by investigators for SMBG and self-titration of GLA dose. Data regarding demography, height, weight, vital signs, medical and surgical history, diabetes history, current anti-diabetic therapy (oral and/or insulin), concomitant medications, and hypoglycaemic episodes was collected on paper-based case report form.

The study population consisted of all patients who were enrolled and had signed an informed consent with at least one assessment. The safety population consisted of all patients included in the registry.

Considering the most stringent hypothesis from statistical point of view (that at least 50% of insulin-naïve patients would reach HbA1c<7%), assuming an error of 5.5% and a 95% confidence level, a total sample size of 318 patients was worked out. Factoring in a 25% dropout rate, a total number of 400 subjects were required.

Descriptive analyses were performed for all variables in this study. Frequency and percentages were used for categorical variables and mean±standard deviation (SD) for continuous variables. Paired t-test was used to compare the mean change/improvement of HbA1c, FBG and GLA dose in comparison to the baseline. The P-P and Q-Q plot was used to assess the normality of HbA1c, FBG and GLA dose at baseline. The data was approximately normally distributed. Statistical analyses were performed using SPSS 18.

Results

Against the target of 400 subjects, 372(93%) patients were recruited. Of them, 65(17.4%) patients were excluded. Final sample size stood at 307(82.5%) (Figure).

Of the total, 166(54%) subjects were male. The overall mean age was 49.5±8.7 years and the mean duration of diabetes was 7.1±4.5 years. Baseline HbA1c and FBG were 8.8%±0.7% and 170.8±38.1 mg/dL, respectively (Table-1).

Of the 307 patients, 289(94%) were insulin-naïve; 230(74.9%) were on combination of MET+SU; 30(9.8%) on MET;22(7.2%) on SU; 18(5.9%) on basal insulin; and 18(5.8%) patients were on a combination of basal insulin and OADs.

GLA vials were provided to 53(17.3%) patients and SoloStar® pen to 254(82.7%). At baseline, GLA+MET+SU combination was prescribed to 186(60.5%) subjects, followed by GLA+MET to 73(23.7%). The most commonly prescribed combination across the study period was GLA+MET+SU which increased from the baseline to visits 2 and 3, while GLA+SU combination declined over the same period, and GLA+MET combination was the most effective, followed by GLA+MET+SU (Table-2).

Table-1: Baseline characteristics.

Baseline characteristics	N=307
Age (years)	49.5 ± 8.7
Male, n (%)	166 (54.1)
Systolic BP (mmHg)	131.1 ± 13.8
Diastolic BP (mmHg)	83.2 ± 7.6
Heart rate (beats/min)	79.5 ± 7.7
Weight (kg)	77.7 ± 12.6
Height (cm)	163.5 ± 11.1
BMI (kg/m^2)	29.4 ± 6.1
HbA1c (%)	8.8 ± 0.7
FBG (mg/dL)	170.8 ± 38.1
Mean duration of diabetes (years)	7.1 ± 4.5
Median duration of diabetes (years); Median (range)	6 (2-25)
Family history of diabetes, n (%)	196 (63.8)

BP: Blood pressure.
BMI: Body mass index.
FBG: Fasting blood glucose.
ITT: Intention to treat.

Table-2: Therapeutic management, effectiveness and safety parameters.

	ITT population		
Therapy	Baseline* (N=307) n (%)	3 month visit (N=217) n(%)	6 month visit (N=179) n(%)
GLA + MET	73 (23.7)	51 (23.5)	41(22.9)
GLA + SU	29 (9.4)	13 (5.9)	5 (2.8)
GLA + MET + SU	186 (60.5)	136 (62.6)	112 (62.6)
GLA	19 (6.1)	15 (6.9)	12 (6.7)
GLA+ MET + Other OADs	-	-	2 (1.1)
GLA + MET + Rapid insulin	-	-	2 (1.1)
GLA + MET + SU + Other OADs	-	-	1 (0.6)
Missing information	0	2 (0.9)	4 (2.2)

Effectiveness parameters*

	ITT population		
	Baseline (N=307)	3 month visit (N=217)	6 month visit (N=179)
HbA1c<7%, n (%)	0(0)	23(10.6)	57(31.8)
HbA1c (%), mean (±SD)	8.8 (± 0.7)	7.9 (± 0.9)	7.4 (± 1.0)
FBG mg/dL, mean (±SD)	170.8 (± 38.1)	136.9 (± 38.1)	123.4 (± 36.0)
GLA dosage, mean (±SD)	15.9 (±5.5)	25.5 (±9.6)	29.8 (±12.1)

Safety parameters

	Hypoglycaemic episodes ITT population		
	Total (N=307)	3 month visit (N=217)	6 month visit (N=179)
Patients reporting hypoglycaemia, n	18	8	10
Hypoglycaemic Episodes	41	23	18
Asymptomatic	19	11	8
Symptomatic	22	12	10

GLA: Insulin glargine.
SU: Sulfonylurea.
MET: Metformin.
ITT: Intention to treat.
FBG: Fasting blood glucose.
*After prescription or switching to GLA.
+p <0.01 for all comparison between baseline and 3 Month visit, baseline and 6 Month visit; and 3 Month visit compared to 6 Month for all glycaemic parameters.

Mean HbA1c values declined from the baseline and the drop was significant (p<0.01). Target HbA1c<7% was achieved by 23 of the 217(10.6%) patients at 3 months, and 57 of 179 patients (31.8%) at 6 months. A significant decline was observed in mean FBG from baseline to 6 months (p<0.01).

At baseline, the mean starting daily dose of GLA was

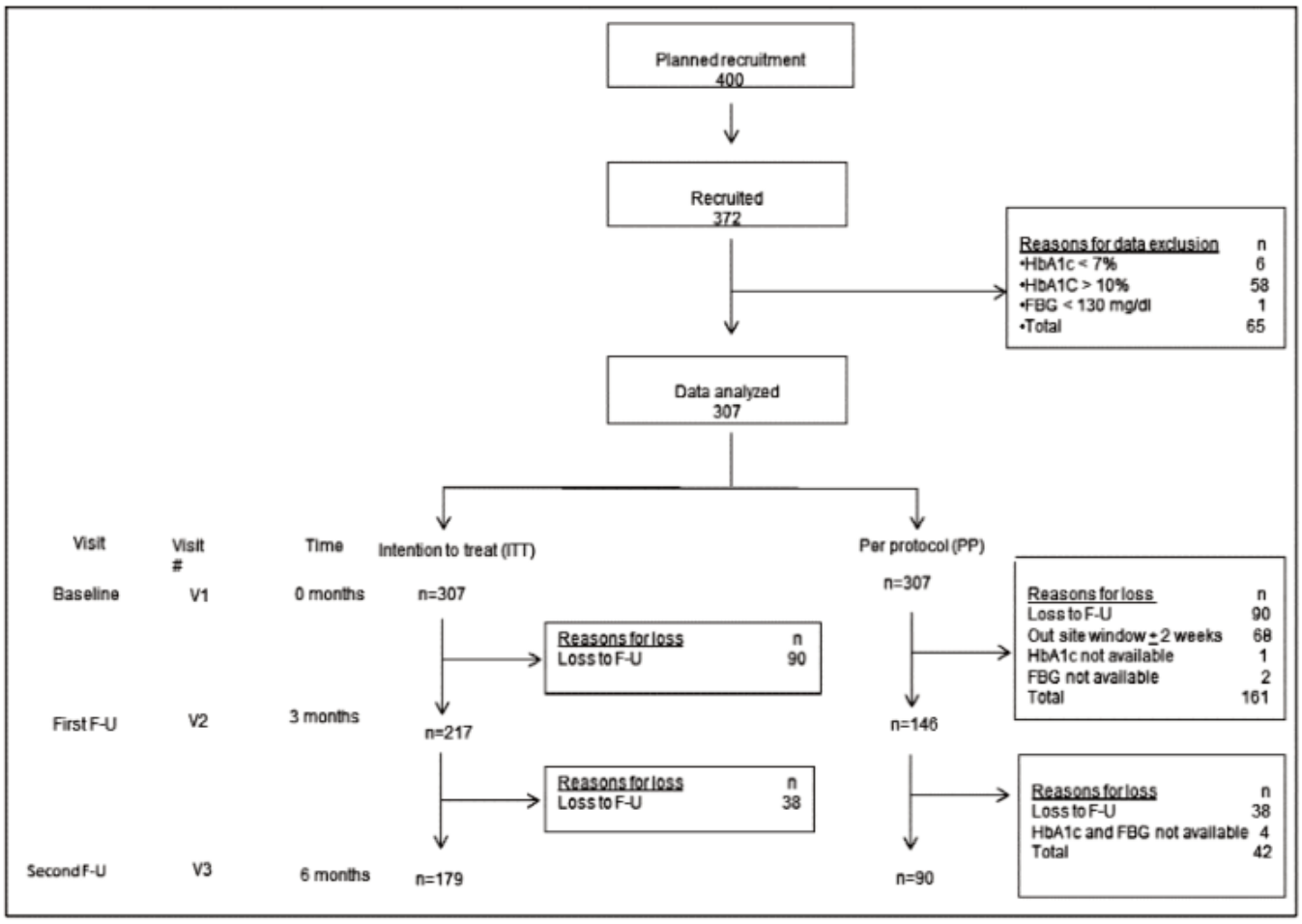

Figure: Patient disposition.

15.9±5.5 U. Dose of >10U was prescribed in 238(77.4%) patients. The maximum daily dose prescribed was 34U.

At 3 months, a significant up-titration by almost 10Uwas observed (p<0.01). At 6 months, patients up-titrated GLA by a mean of 13.8±11.2 U.

By the end of 6 months, 18(5.8%) patients reported 41 hypoglycaemic episodes of which 19(46.3%) were asymptomatic and 22(53.6%) were symptomatic. No severe hypoglycaemic episodes were reported.

There were two severe adverse events (SAEs); 1(50%) sudden death and 1(50%) hyperglycaemic event.

Mean body weight increased from 77.7±12.6 to 78.2±11.5 kg) (p=0.04).

Discussion

The study results show that timely initiation and appropriate titration of insulin as per the ADA/EASD consensus algorithm[11,12] achieves good glycaemic control in uncontrolled T2DM patients. There was a significant decline in HbA1c and FBG within 3 months of treatment with GLA, with further reductions at 6 months. There was a significant up-titration in GLA dosage. Hypoglycaemia was of a non-severe nature requiring no hospitalisation. Weight-gain was limited and only two SAEs were reported.

The timing of insulin initiation is critical in the management of T2DM, and a delay in insulin initiation may result in disease progression and an increased risk of complications.[14,15] Early insulin initiation is associated with several benefits such as attainment of near-normal FBG, easier achievement of therapy goals and their maintenance for many years, and safety with respect to cardiovascular risk and tumour genesis.[16] Despite uncontrolled diabetes, and a mean diabetes duration of 7.1±4.5 years at baseline, 94% patients were insulin-naïve. Initiation of GLA or switching from other basal insulin to GLA in the study patients resulted in statistically and clinically significant reductions in

mean HbA1c levels after 6 months of treatment.

At the end of the 6-month study period, 31.8% patients achieved HbA1c <7%. The results were consistent with another study in Asian population (including Pakistani population), where one-third of patients reached the ADA/EASD 2015 consensus HbA1c target of <7%.[17]

In our study, FBG reduced significantly after 6 months of treatment. In the Outcome Reduction with an Initial Glargine Intervention (ORIGIN) study, conducted in Canada to evaluate the cardiovascular risk reduction and glycaemic control in patients aged above 50 years, more than 75% patients (mean duration of diabetes: 5.5±6.1years) treated with GLA achieved an FBG level of <108 mg/dL. The study also demonstrated that early insulin therapy with GLA achieves and maintains near-normal FBG and HbA1c levels for more than 6 years.[18] Thus addition of GLA improves and maintains long-term glycaemic control in patients uncontrolled on OADs alone or in combination with other basal insulin.

Among three concomitant regimens viz. MET, MET+SU, and SU, included in the current study, MET+SU was the most commonly prescribed combination at baseline and throughout the study. MET was the second most commonly prescribed medication at baseline. Greatest glycaemic benefits, including reductions in HbA1c and achievement of glycaemic goals, along with lowest weight-gain and lowest incidence of hypoglycaemia, are observed in patients receiving MET only prior to the initiation of GLA.[19] In our study as well, highest percentage of the patients (39%) achieving HbA1c <7% was observed in patients on combination of GLA+MET. This data thus supports the inclusion of GLA earlier in the treatment of the disease and its use as second-line therapy to MET in the ADA/EASD algorithm.[11,12] Patients receiving GLA+MET+SU were the second highest group in terms of percentage of the patients achieving HbA1c <7%. A similar pattern was observed in another study where proportion of study participants who achieved HbA1c <7% was the greatest for those treated with GLA+MET, followed by GLA+MET+SU, and then GLA+SU.[20]

Adverse effects of insulin therapy, including hypoglycaemia and weight-gain, which are a major concern for physicians and patients, often influence the decision to initiate insulin.[21] In our study, hypoglycaemic episodes were of non-severe nature and were manageable requiring no hospitalisation. Considering that low insulin doses may decrease the risk of hypoglycaemia, early insulinisation achieves a better glycaemic control with lesser insulin dosage and thereby reduces the frequency of hypoglycaemic events.[22,23] Despite up-titration of insulin dosage observed in this study (which resulted in a significant reduction in HbA1c), the GLA dosage administered was relatively lesser than that seen in another study in Indian population.[24] Further, as seen in the First Basal Insulin Evaluation (FINE) Asia study, a lower mean basal insulin dose is required to achieve HbA1c reduction in Asian patients compared to Western population.[17] In addition to timely insulin therapy and relatively low insulin doses, strategies to reduce the risk of hypoglycaemia such as SMBG and patient education regarding self-management that were employed in the study may have prevented serious/severe hypoglycaemia.

Treatment with GLA in initiation or switch from another basal insulin resulted in a slight but significant weight-gain (+0.6kg; p=0.04). However, this weight-gain though statistically significant may not be clinically relevant. An insulin-associated weight-gain could be further limited by adopting an approach to reduce insulin dosage by increasing insulin sensitivity through diet and exercise.[25]

Considering that this product registry was conducted at 38 sites across 7 cities in Pakistan, the findings can be extrapolated to the urban population of Pakistan, seeking specialised care for diabetes. The results may also be applicable to the urban Indian subcontinent where there are similarities in population in terms of diet, exercise, genetics and healthcare services. However, the targeted sample size could not be achieved. Newer OAD molecules have been introduced since the time the study was conducted, while this study was limited to patients on GLA with MET and SU. Further, this study included patients with HbA1c 7%-10%. In real-life situation, there are many patients with HbA1c beyond this range, thus limiting the extrapolation of these results to patients with HbA1c>10%. The rate of loss to follow-up in this study was high. These patients could have had a different trend in terms of glycaemic control.

Conclusion

The findings further substantiated the available evidence indicating that timely insulin initiation and titration can help in achieving good glycaemic control. Adherence to diabetes management guidelines by treatment intensification (basal insulin initiation or switch) significantly improved glycaemic control within six months with no additional risk of serious/severe hypoglycaemia.

Acknowledgments: We would like to thank the patients in the study and the following participating physicians who recruited patients: Amir Latif, Gujranwala; Aslam Pervaiz, Karachi; Amir Kamal, Karachi; Aamir Shoukat, Faisalabad; Ammar Kaleem, Gujranwala; Aziz ur Rahman, Lahore; Arshad

Mehmood, Lahore; Aslam Khan Marwat, Rawalpindi; Asim Anwar, Lahore; Aslam Memon, Karachi; Bilal bin Younas, Lahore; Fareeduddin, Karachi; Farrukh Iqbal, Lahore; Ghulam Murtaza, Rawalpindi; Ghazala Khalid, Lahore; Hassan A Bokhari, Faisalabad; Imtiaz Hassan, Lahore; Imitaz Malik, Lahore; Iqbal Batavia, Karachi; K.M. Yahya, Faisalabad; M. Haneef Nagra, Faisalabad; M. Iqbal Methani, Karachi; Mian Naeem, Gujranwala; M. Mujeeb Khan, Rawalpindi; Mairajuddin Nizami, Hyderabad; M. Majid, Karachi; Muhammad Asalm Khan, Rawalpindi; Nadeem Youaf, Rawalpindi; Naila Masood, Hyderabad; Nadeem-ul-Islam, Rawalpindi; Naveed Aslam, Gujranwala; Noman Khursheed, Faisalabad; Pirbho Mal Makhji, Sukkur; Saleem Quershi, Rawalpindi; Tahir Rasool, Lahore; Tariq Adnan, Karachi; Wasim Aamer, Lahore; and Zahid Yaseen Hashmi, Faisalabad.

We also acknowledge the assistance of Iqbal Mujtaba from Sanofi (Pakistan) for performing statistical analysis, and Dr. Alina Gomes and Anahita Gouri for editorial assistance.

Disclaimer: None.

Conflict of Interest: One of the authors was employed by sanofi-aventis Pakistan limited.

Source of Funding: sanofi-aventis Pakistan limited.

References

1. Hu FB. Globalization of diabetes: the role of diet, lifestyle, and genes. Diabetes Care. 2011; 34: 1249-57.
2. International Diabetes Federation. International Diabetes Federation Middle East and North Africa [Online] 2014 [Cited 2015 April 27]. Available from URL: http://www.idf.org/membership/mena/pakistan.
3. Whiting DR, Guariguata L, Weil C, Shaw J. IDF diabetes atlas: global estimates of the prevalence of diabetes for 2011 and 2030. Diabetes Res Clin Pract. 2011; 94:311-21.
4. Abubakari BB, Ibrahim MM, Mutawakilu I, Porrata-Maury C, Alvarez VR, Triana MH, et al. Ma-Pi 2 macrobiotic diet intervention during 21 days in adults with type 2 diabetes mellitus, Ghana 2011. Inter Med Inside. 2014; 2:1-9.
5. Nathan DM, Buse JB, Davidson MB, Heine RJ, Holman RR, Sherwin R, et al. Management of hyperglycemia in type 2 diabetes: A consensus algorithm for the initiation and adjustment of therapy a consensus statement from the American Diabetes Association and the European Association for the study of diabetes. Diabetes Care. 2006; 29: 1963-72.
6. Karter AJ, Subramanian U, Saha C, Crosson JC, Parker MM, Swain BE, et al. Barriers to Insulin Initiation The Translating Research Into Action for Diabetes Insulin Starts Project. Diabetes Care. 2010; 33:733-5.
7. Ahmed U, Junaidi B, Ali A, Akhter O, Salahuddin M, Akhter J. Barriers in initiating insulin therapy in a South Asian Muslim community. Diabet Med. 2010; 27:169-74.
8. Peyrot M, Rubin RR, Lauritzen T, Skovlund SE, Snoek FJ, Matthews DR, et al. Resistance to insulin therapy among patients and providers results of the cross-national Diabetes Attitudes, Wishes, and Needs (DAWN) study. Diabetes Care. 2005; 28: 2673-9.
9. Khattab M, Khader YS, Al-Khawaldeh A, Ajlouni K. Factors associated with poor glycemic control among patients with type 2 diabetes. J Diabetes Complications. 2010; 24: 84-9.
10. Khunti K, Wolden ML, Thorsted BL, Andersen M, Davies MJ. Clinical Inertia in People With Type 2 Diabetes A retrospective cohort study of more than 80,000 people. Diabetes Care. 2013; 36: 3411-7.
11. Garber AJ, Abrahamson MJ, Barzilay JI, Blonde L, Bloomgarden ZT, Bush MA, et al. American Association of Clinical Endocrinologists' comprehensive diabetes management algorithm 2013 consensus statement. Endocr Pract. 2013; 19:1-48.
12. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2015; 38:140-9.
13. Chan JC, Gagliardino JJ, Baik SH, Chantelot J-M, Ferreira SR, Hancu N, et al. Multifaceted determinants for achieving glycemic control the International Diabetes Management Practice Study (IDMPS). Diabetes Care. 2009; 32:227-33.
14. Goodall G, Sarpong EM, Hayes C, Valentine WJ. The consequences of delaying insulin initiation in UK type 2 diabetes patients failing oral hyperglycaemic agents: a modelling study. BMC Endocr Disord. 2009; 9: 19.
15. Owens DR. Clinical evidence for the earlier initiation of insulin therapy in type 2 diabetes. Diabetes Technol Ther. 2013; 15: 776-85.
16. Raz I, Mosenzon O. Early Insulinization to Prevent Diabetes Progression. Diabetes Care. 2013; 36: S190-S7.
17. TSAI ST, Pathan F, Ji L, Yeung VTF, Chadha M, Suastika K, et al. First insulinization with basal insulin in patients with Type 2 diabetes in a real world setting in Asia. J Diabetes. 2011; 3: 208-16.
18. ORIGIN Trial Investigators, Gerstein HC, Bosch J, Dagenais GR, Díaz R, Jung H, et al. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med. 2012; 367: 319.
19. Fonseca V, Gill J, Zhou R, Leahy J. An analysis of early insulin glargine added to metformin with or without sulfonylurea: impact on glycaemic control and hypoglycaemia. Diabetes Obes Metab. 2011; 13: 814-22.
20. Owens DR, Traylor L, Dain M-P, Landgraf W. Efficacy and safety of basal insulin glargine 12 and 24 weeks after initiation in persons with type 2 diabetes: A pooled analysis of data from treatment arms of 15 treat-to-target randomised controlled trials. Diabetes Res Clin Pract. 2014; 106:264-74.
21. Polonsky WH, Jackson RA. What's so tough about taking insulin? Addressing the problem of psychological insulin resistance in type 2 diabetes. Clin Diabetes. 2004; 22: 147-50.
22. Childs BP, Grothe JM, Greenleaf PJ. Strategies to limit the effect of hypoglycemia on diabetes control: identifying and reducing the risks. Clin Diabetes. 2012; 30: 28-33.
23. Kim SS, Kim IJ, Kim YK, Yoon KH, Son HY, Park SW, et al. Duration of diabetes and effectiveness of insulin in the management of insulin-naïve Korean patients uncontrolled on oral antidiabetic drugs: a sub-analysis of the MOdaliTy of Insulin treatment eValuation (MOTIV) registry results. Acta Diabetol. 2014; 51: 655-61.
24. Agarwal S, Singh B, Wadhwa R. Study of optimal basal insulin glargine dose requirement in Indian population as an add on therapy to oral hypoglycaemic agents to achieve target fasting blood glucose levels. J Indian Med Assoc. 2013; 111: 626-8.
25. Russell Jones D, Khan R. Insulin associated weight gain in diabetes-causes, effects and coping strategies. Diabetes Obes Metab. 2007; 9:799-812.