Clinical Inertia

An Old Barrier in the Way of Effective Management of Diabetes?

Clinical inertia

Despite recent advances in medical care with well-defined therapeutic targets, availability of effective therapies and extensive dissemination of practice guidelines, healthcare providers and patients often fail to take appropriate medical intervention at appropriate time. Achieving glycaemic control early in diabetes management is central to reducing the risk of long-term secondary complications[1] and associated morbidity and mortality. For many patients with diabetes, maintaining adequate metabolic control is still a challenge with significant proportion (80%) of patients not being able to meet the therapeutic target of glycosylated haemoglobin (HbA_{1c}) <7%[2]. Despite the advances in diabetes care in the past 2-3 decades with well-defined therapeutic targets[3,4], availability of effective therapies and extensive dissemination of practice guidelines[3,5], initiation of appropriate medical intervention is often delayed[6] in patients with diabetes. The failure to achieve therapeutic targets in patients with diabetes, points to a phenomenon known as 'clinical inertia' which is defined as "failure to initiate or advance therapy in a patient who is not at the evidence-based therapeutic goal" (Figure 1)[7].

> **ADA recommended targets[3]**
> HbA_{1c} <7%
> Systolic blood pressure <130 mm Hg
> Diastolic blood pressure <80 mm Hg
> LDL-cholesterol <100 mg/dL

Due to the progressive nature of diabetes, over time physiologic insulin response and beta-cell function continue to deteriorate in presence of elevated blood glucose levels, even in patients with good glycaemic control. Consequently, in many patients insulin therapy becomes essential, regardless of intensification with oral anti-diabetic drugs (OADs). It is estimated that up to 60% of patients with diabetes will require insulin in the first 6-10 years after initial diagnosis or even earlier in patients with long-standing undetected diabetes[8].

In patients starting insulin therapy, the simplicity of basal insulin (once or twice daily) in combination with OADs makes it the choice of first-line insulin therapy[9]. However, this regimen cannot control post-prandial hyperglycaemia. Instead, premixed insulin demonstrates better glycaemic control over basal insulin, as it comprises of both intermediate and rapid-acting components, addressing basal and post-prandial insulin needs.
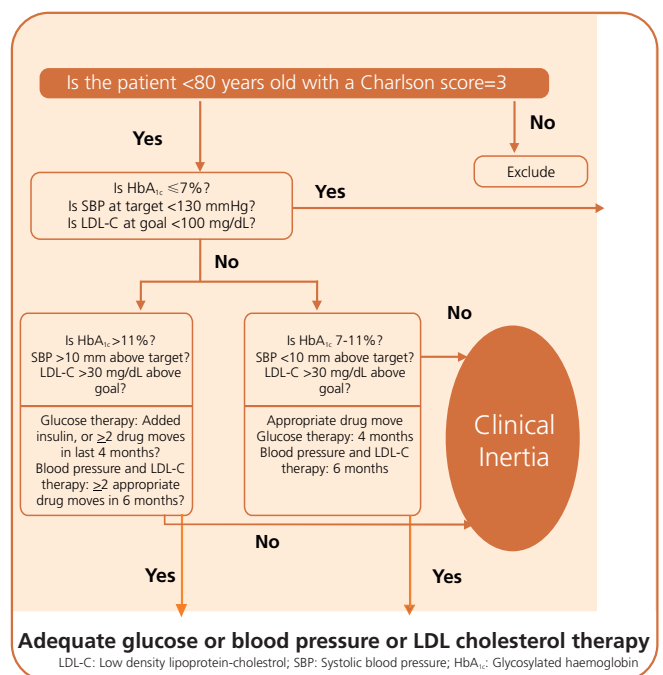

Figure1: Algorithm to identify clinical inertia[7]

LDL-C: Low density lipoprotein-cholestrol; SBP: Systolic blood pressure; HbA_{1c}: Glycosylated haemoglobin

Factors associated with clinical inertia

Propagation of clinical inertia in diabetes care is a result of number of multifactorial, interactive situations among patients, providers, and healthcare systems, and by the available treatment options themselves[10]; a combination of these is more likely to delay the initiation or advancement of effective, evidence-based therapy. To study the patient- and physician-related causes of delay in insulin initiation and intensification and improve outcomes of diabetes care, two multinational studies were initiated by Novo Nordisk.

novo nordisk®

Diabetes Attitudes, Wishes, and Needs (DAWN™) study is a collaborative program initiated in partnership with International Diabetes Federation (IDF) and an international expert advisory panel in 2001[11]. The interview-based study was designed to identify a broad set of psychosocial challenges faced by patients with diabetes, physicians and nurses and help address the issues arising from these findings. The Global Attitudes of Patients and Physicians in Insulin Therapy (GAPP™) survey[12] assessed the barriers and challenges experienced with insulin self-management in patients and physicians from 8 countries.

Barriers to insulin use

Patient barriers

In India, awareness of diabetes in the general population is low[18,19] and even amongst patients with diabetes, 50-65% take at least 2 or more years to realise that diabetes is a life-long condition[11] indicating low patient-physician communication.

Non-adherence to therapy by patients is one of the most significant factors contributing to clinical inertia[20]. Noncompliance to medication is an independent risk factor (hazard ratio: 1.58) for all-cause mortality in patients taking insulin[21]. Physicians intensify treatment (53% greater odds) in patients highly adherent to medication than patients with low medication adherence[20]. In addition to concerns on therapeutic side-effects related to hypoglycaemia (45%) and weight gain (55%)[11], patients with diabetes on insulin therapy expressed several psychosocial factors for intentional skipping of insulin therapy.

Psychological barriers to clinical inertia[11]

- Self-blame upon initiation of insulin therapy
- Low belief on insulin efficacy and social stigma
- Fear of needles and anxiety of insulin treatment
- Lack of awareness of natural progression of diabetes
- Available in vials and syringes

Other factors like medication costs, concern for family and financial future, patient's emotional well-being, religious fasting, and poor knowledge of updated care process might contribute to non-adherence to insulin therapy. Financial constraint is a major contributor to clinical inertia in initiation and adherence to insulin

therapy in patients with limited social resources (lower education/occupation and unmarried), rural residency, and diabetes complications. In 2009, the median annual healthcare cost associated with diabetes in India was INR 30,361[22] which is approximately thrice that in 2005 (INR 10,000)[23]. In India, 23.4% of patients with diabetes suffered from depression[24] and expressed shock, guilt, anxiety, anger and depression upon diagnosis, indicating a negative attitude to diabetes[11]. The patient reported reasons for intentional insulin skipping[25] were:

T2DM patients

- Injection related pain or embarrassment
- Need to plan daily activities around insulin
- Interference to daily activities with dosing schedule
- Burden of insulin injections

T1DM patients

- Number of daily insulin injections
- Need to follow a healthy diet
- Interference to daily activities with dosing schedule
- Stigma to take injections at school

Physician barriers

Physician barriers exist in delaying initiation or intensification of insulin therapy based on their perceptions[6]; viz., insulin therapy may not be effective, may result in weight gain, increase the risk of hypoglycaemia, is inconvenient and painful for patients and will result in patient dissatisfaction[26,27]. Figure 2 depicts patient-physician perception towards insulin therapy and common reasons attributing to omission/non-adherence to insulin therapy[6].
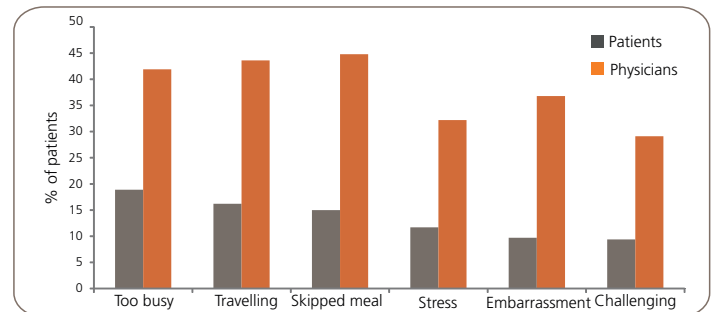

Figure 2: Patient and physician reported reasons* for insulin omission/non-adherence
*respondents were asked to select top three reasons; data are % of respondents choosing a reason as one of the three

Physicians from India delay insulin initiation until patients with diabetes reach HbA$_{1c}$ >9%, longer than physicians from any other country[26] in the DAWN study.

novo nordisk®

Physician and general practitioner (US and UK) cited reasons for clinical inertia include: HbA_{1c} >7% associated with patient's diet and lifestyle[10,32], perception of significant hyperglycaemia as mild[33] concerns about OADs, comorbidities, polypharmacy[32,33] presuming patient's non-adherence to recommended treatment plan and overestimation of self-adherence to guidelines[10].

Patient and physician barriers to insulin initiation: Review of surveys

Despite the unsurpassed efficacy of insulin in the management of diabetes and advances in diabetes care, both patients and physicians have concerns in initiating insulin therapy. Although hypoglycaemia and weight gain are the most frequent reasons for clinical inertia, studies on physicians and patients from different parts of the world revealed diverse opinions for failing to start insulin therapy in patients with diabetes.

The Translating Research Into Action for Diabetes (TRIAD) study was conducted in USA in poorly controlled, insulin-naïve and insulin-eligible T2DM patients who were primary adherent or non-adherent to insulin therapy[34]. Patients with similar clinical profile visiting hospital in Taiwan were interviewed on perceived barriers to insulin initiation[35]. Similarly, focus group discussions between patients and physicians in Singapore[36], interviews and focus groups of healthcare professionals (HCPs) from Malaysia[37] have revealed interesting reasons on barriers to insulin initiation. The patients responses observed in these surveys are enlisted in Table 1. The studies supplement the data from the DAWN and GAPP studies.

Healthcare system in India

Inadequate diabetes care professionals, equipment, treatment protocols, and standards for healthcare facilities contribute to clinical inertia in the management of diabetes. Moreover, legal requirement of practice of evidence-based guidelines, disparity in access to healthcare based on socio-economic status, urban-rural residence, healthcare systems and practices also contribute to clinical inertia. In addition, lower levels of awareness of diabetes, its risk factors, associated complications and methods to improve health among patients with diabetes delay and/or cause poor adherence to insulin therapy. Medication non-adherence is a result of: focus on acute healthcare services, lack of pricing control[38], uncertainty about the availability diabetes care supplies in public healthcare facilities at rural settings[39], increased indirect expenditure[40], etc. Disparities in distribution of qualified healthcare workforce contributes to clinical inertia through restriction in access to quality diabetes care[41] in Madhya Pradesh, 75.6% healthcare workforce is in private sector, and 80% of it is concentrated in urban areas.

Overcoming clinical inertia in diabetes management

It's not only essential to improve therapeutic adherence in patients through standard initiatives but also apply provider-directed strategies and improve certain components of healthcare process to overcome clinical inertia in diabetes management and achieve effective glycaemic control and improved quality of life. The observed clinical inertia due to patients, physicians, and the healthcare system can be overcome with strategies aimed at:

a) Efficacy and safety of antidiabetic drugs

b) Convenience and lifestyle of patient

c) Patient and physician education on diabetes care

d) Healthcare system

Efficacy and safety

Following failure to achieve glycaemic control with lifestyle changes and OADs, initiation of insulin therapy is the next step. To overcome clinical inertia due to multiple insulin injections a smooth, relatively flat, 24-hour basal insulin supply, protracted basal insulin levels, with longer duration of action, once daily administration and minimal intra-patient variability can be prescribed to patients with diabetes[42]. However, use of basal insulin is limited by the lack of provision for prandial insulin[43]. Hence, premix insulin is the preferred insulin of choice.

Premix insulin[44]
- Simple to start
- Option to intensify with same insulin
- Coverage of FPG and post-prandial plasma glucose
- Improves HbA_{1c}
- Twice daily injection
- Low risk of hypoglycaemia and weight gain
- Available in vials and insulin delivery devices

Location	Study population	Patient barriers
USA[34], (N=69)	Insulin-naïve, insulin-eligible patients with T2DM non-adherent to insulin	Misconceptions about insulin risk, plans to improve on diet and exercise, negative impact on social life and job, sense of personal failure, injection phobia, hypoglycaemia concerns, HCPs inadequately explaining risks/benefits
Malaysia[35], (N=38)	HCPs providing diabetes care to patients from different ethnicities	Culture-specific religious purity of insulin, preferred use of complementary medicine, perceived lethality and stigma of insulin therapy, fear of side effects, lack of knowledge and self-efficacy, negative influence from family members
Singapore[36], (N=11)	Patients with T2DM	Refusal to accept insulin therapy, perception as social stigma, inconvenient mode of treatment or punishment for failure, needle phobia, fear of side-effects
Taiwan[37], (N=15)	Patients who refused insulin treatment	Reluctance of physicians, misconceptions about insulin risk, low adaptation capacity, needle phobia, psychological resistance

Table 1: Surveys from different countries reporting barriers to insulin initiation

novo nordisk®

The usage of premix insulin is quite high in some parts of the world and represented about 40% of the world market in human insulin, in the year 2000[45]. Use of premixed insulin has been advocated by several guidelines. The American Association of Clinical Endocrinologists, IDF and Indian Council of Medical Research[4] diabetes treatment guidelines recommend use of premix insulin twice a day in patients with elevated HbA_{1c}. Evidence also suggest that premix insulin may be used as an option in primary care[46-48].

> ### Evidence for use of premix insulin in primary care[46-48]
>
> - Addition of premix insulin to OADs: effective in achieving HbA_{1c} targets (60% patients), than adding basal insulin (40% patients) in patients with T2DM[46]
> - Similar efficacy of premix insulin therapy with basal bolus therapy in HbA_{1c} reduction (-1.23% and -1.56%, respectively), in insulin naïve patients[47]
> - Similar safety profiles (major and minor hypoglycaemic episodes) of premixed insulin compared to bolus aspart[48]

Effective insulin regimens with low risk of hypoglycaemia and weight gain can lead to increased patient adherence and decreased clinical inertia. Physicians expressed a wish for an insulin regimen with sustained efficacy capable of compensating for missed or delayed doses, and indicated their willingness to manage diabetes aggressively if not for concern about hypoglycaemia (75.5%)[6] in the GAPP™ study. Thus, customizable, patient-centric options are important in improving adherence to insulin.

Recommendations for best practices in injection techniques

The DAWN study elucidated the reasons for resistance to insulin therapy among patients and providers[26]. Often the reluctance among patients is psychological and physician's attitudes and beliefs are also associated in the clinical inertia. The first Indian insulin injection technique guideline has been developed by the Forum for Injection Technique (FIT) in India[49]. This guideline has been adapted from the Third Injection Technique workshop in AthenNs (TITAN)[50]. This guideline provides good injection techniques and evidence-based recommendations to assist the physicians and patients towards achieving optimal glycaemic control.

Pre-injection assessment: Physicians should make a thorough clinical, sociocultural, and environmental assessment before prescribing insulin therapy in patients.

Pre-injection counseling: In order to overcome the clinical inertia, physicians should provide a sense of control over their treatment plan and usage of devices to patients (children, adolescents, adults). This will improve the acceptance of patients to a prescribed therapeutic regimen. For adult population the guideline recommends to "educate all newly-diagnosed patients about the course of diabetes and the need to start insulin therapy (A3)".

Injection storage: In order to increase the shelf-life of the injections "specific storage guidelines given by the manufacturer should be followed (A1); insulin pens and vials not in use are to be refrigerated at a temperature of 4-8 °C, but not frozen (A1); if insulin is frozen, it should be discarded (A1); insulin should be stored in a cool and dark place at room temperature (15-25 °C) and discarded 30 days after initial use or as per manufacturers instruction; and insulin should be kept out of reach of children (A1)". While travelling by air or road, special attention should be paid for storage of insulin.

Device selection and use: Special attention should be paid both by the HCP and patient towards selection and use of right insulin delivery device (pen or syringe and vial), right syringe, needle size and needle strength. Prior to injection, the patient must verify expiration date and the dose, and if the correct type of insulin is being prepared for injection (A1); the choice of injection device, needle length, gauge, and type of insulin syringe should be emphasised into the prescription (A1); and the insulin bottle should be examined to ensure that there are no changes in insulin.

Use of insulin pens for injection is advantageous over syringe and vial due to shorter needle size, safety and tolerability. In obese patients, studies have reported equal efficacy, safety/tolerability of shorter needles (4-5 mm) in comparison to longer ones (A1). Adults do not require the lifting of a skin fold, particularly for 4 mm needles (A1). A needle of 4 mm length is considered to be safe and efficacious in patients of all age groups (A1). The safest needle for children appears to be the 4 mm pen needle (A1).

Injection site: Insulin is often injected through subcutaneous, intravenous, intravenous infusion and intramuscular routes to achieve optimal glycaemic control. So choosing of injection site along with cleaning of infection site to use of skin folds and injection angle should be taken into consideration by the HCPs.

Injection techniques: Syringe is a primary injecting device used in India, so to inject insulin this guideline recommends that "insulin vial should be taken out of refrigerator 30 minutes prior to injection to ensure that the insulin is at room temperature. Make sure that it is not expired and the bottle is not damaged (A1); if using cloudy insulin, inspect for any changes, i.e. clumping, frosting, or precipitation and ensure that the insulin is uniformly mixed by rolling the vial between palms (A3)".

This guideline also provides recommendations on various topics such as mixing of insulin, device preparation for injecting insulin, injection-meal time gap, lipohypertrophy, disposal of injecting material and patient and physician education.

Convenience and lifestyle

Initiation of insulin therapy is more challenging for a physician, as it requires changes in patient's lifestyle and adherence to new patterns of thought and behaviour. In most cases, it is associated with negative impact on quality of life and low rates of adherence[25]. Patient barriers of pain, fear due to injection and embarrassment to inject in public can be addressed with the help of latest pen devices. Smaller and narrower NovoFine® 32-gauge tip 6 mm needles (p<0.0001) are associated with less frightening (p<0.05), less painful (p<0.01), and less frequent bleeding and bruising (p<0.001) as compared with Micro Fine Plus 31-gauge 5 mm needles[52]. A large post-marketing observational study that evaluated

novo nordisk®

treatment satisfaction with NovoPen® 4 over other delivery devices in insulin-treated and insulin-naïve patients reported a significant preference for NovoPen® 4 over other insulin devices for ease of use and learning that potentially led to improved acceptance of and compliance with prescribed insulin therapy[53] (Figure 3).

Advantages of pens over syringes and vials[54,55]

- Improved acceptability and adherence to injections[54]

- Better convenience in insulin delivery, discreet to use

- Increased portability, ease of use and dosing accuracy

- Simpler to use for special populations: children and adolescents, pregnant women and older adults

Figure 3: NovoPen® 4

Education

Clinical inertia due to lack of awareness of evidence-based guidelines and updated knowledge of therapeutic processes can be overcome by structured education programs such as continuing medical education and workshops for practicing physicians[56] and paramedical personnel. Educating physicians that new forms of insulin reduce the risk of hypoglycaemia and integrate more easily into patient's lifestyles can help reduce anxiety of initiating insulin injection. Patient awareness of strategies to prevent, recognise, and treat hypoglycaemia and the benefits of linking therapy with timely and routine blood glucose monitoring (BGM) can improve diabetes care outcomes.

The impact of educational interventions is clear from previous studies. Educational interventions carried out on dietary modification, improving physical activity, and knowledge improvement showed reduced FPG levels in 25% adults with T2DM in a resource-poor village of Tamil Nadu[57].

Another multinational study found that educational intervention was associated with improved glycaemic control, insulin use, self-care performance and lower rate of chronic complications[58] in patients with diabetes.

Patients with self-management and diabetes-related psychosocial problems receiving intensive diabetes education program[61], showed improvements in HbA_{1c} levels (p<0.01), psychosocial issues (p<0.001) and reduction in mean diabetes-related costs to half (p=0.001). Similarly, better medication adherence and better glycaemic control (HbA_{1c} #6.5%, p <0.05) were found to be associated with patients' knowledge about diabetes[62]. Interactive small-group education methods have also showed improved glycaemic control (6.7% vs. 6.4%, p<0.001) than conventional education[63].

Suggestions on response to patient's concerns about insulin therapy

Educating patients on all aspects of therapy, including ways to overcome inertia in insulin initiation and adherence can be accomplished by the treating physician. Patient's non-adherence to insulin therapy might not be due to choice but the constraints that T2DM places on their lifestyle. By providing awareness on therapy and possibilities to enhance the flexibility of therapy, adherence to insulin injections can be improved. Patient education should address their knowledge regarding insulin therapy, concerns and perceived barriers to insulin therapy, providing solutions through collaborative goal setting and continued support[64]. The suggestions on response to patient's concern about insulin therapy have been listed in Table 2[65].

Healthcare system

Public healthcare systems should be designed to achieve and maintain evidence-based goals of diabetes management at affordable cost to the largely needy population of India. Targeting healthcare benefits, including essential medicines and treatment, to socio-economically backward strata of the population can improve access and adherence to therapy. Schemes such as Community Health Insurance and Rashtriya Swasthya Bima Yojana[66] have the potential to improve access to hospital care, even for vulnerable sections of the community-the poorest, individuals with pre-existing conditions like diabetes and hypertension[66,67]. Information technology-based

Barrier	Physician strategies to address patient concerns
Sense of loss of control over one's life	• Counsel patients that he or she can manage diabetes and take control of life by following insulin regimen
Sense of personal failure	• Explain that insulin is required due to the natural progression of T2DM and not due to patient behaviour • During diagnosis, indicate the possibility of insulin use at a later stage of disease • Do not project insulin therapy as punishment or threat for non-compliance to diet, exercise, and medication
Belief that disease has worsened	• Explain that most patients will require insulin due to the progressive beta-cell failure • Explain that all patients experience beta-cell failure but at different rates • Describe that insulin therapy can improve glycaemic control at any point in treatment continuum
Perception that insulin is not effective	• Explain that proper use of insulin improves glycaemic control • Assure that insulin therapy improves symptoms, makes patient feel better and energetic
Injection-related anxiety	• Demonstrate that needles are small and very fine • Introduce user-friendly insulin pens • Assure patient that injections are less painful than finger sticks used for self-monitoring of blood glucose
Fear of weight gain	• Explain that some modern insulins can attenuate weight gain than others • To minimise weight gain and improve glycaemic control with insulin therapy, prescribe daily exercise
Fear of hypoglycaemia	• Explain that frequency of serious hypoglycaemia is rare • Long-acting, once-daily formulations cause less hypoglycaemia, especially nocturnal hypoglycaemia • Educate patient on symptoms of hypoglycaemia and it's treatment and preventive measures
Lack of confidence in ability to manage	• Long-acting insulins can be used at convenient timings like evening meal or at bedtime • Other insulins can be used at any time of the day, preferably at the same time of day • Insulin pens are easy to administer • Certified diabetes educators are available to assist on all aspect of insulin therapy
Concerns of family, work, and friends	• Explain patients that taking insulin should not affect their ability to work as long as treatment guidelines are observed. However, employers should be informed of their insulin therapy • Patients should ensure that people close to them are aware of all aspects about their disease management

Table 2: Strategies to address patients' concerns regarding the use of insulin (adapted from Peyrot et al[64])

interventions such as maintaining electronic medical records, using clinical decision support tools (e.g. algorithms, data prompts) can maximise the efficiency of time and data related issues affecting clinical inertia while enabling appropriate, evidence-based care[68] especially in low- and middle- income countries[69]. In addition, implementing and integrating a single chronic care model can help overcome clinical inertia by providing an appropriate strategy for treating different chronic conditions. For instance, training social health workers on broad spectrum of chronic diseases can reduce human resources required for each disease[62].

References

1. Gaede P, Lund-Andersen H, Parving HH, *et al.* Effect of a multifactorial intervention on mortality in type 2 diabetes. *N Engl J Med.* 2008;358(6):580-591.

2. Mohan V, Seshiah V, Sahay BK, *et al.* Current status of management of diabetes and glycaemic control in India: Preliminary results from the Diab Care India 2011 study. *Diabetes.* 2012;61:A645-A677.

3. American Diabetes Association. Standards of medical care in diabetes-2013. *Diabetes Care.* 2013;36 Suppl 1:S11-66.

4. http://icmr.nic.in/guidelines_diabetes/section4.pdf. Accessed Mar 18, 2013.

5. Moses A. Indian insulin guidelines: a year later and the road ahead. *J Assoc Physicians India.* 2011;59 Suppl:23-24.

6. Peyrot M, Barnett AH, Meneghini LF, *et al.* Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study. *Diabet Med.* 2012;29(5):682-689.

7. Phillips LS, Branch WT, Cook CB, *et al.* Clinical Inertia. *Ann Intern Med.* 2001;135(9):825-834.

8. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352(9131):837-853.

9. Nathan DM, Buse JB, Davidson MB, *et al.* Medical management of hyperglycemia in type 2 diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. *Diabetes Care.* 2009;32(1):193-203.

10. Triplitt C. Improving Treatment Success Rates for Type 2 Diabetes: Recommendations for a Changing Environment. *Am J Manag Care.* 2010;16:S195-S200.

11. Data on File. Diabetes Attitudes Wishes and Needs (DAWN) study. 2001.

12. Data on file. The Global Attitudes of Patients and Physicians in Insulin Therapy (GAPP) survey. 17-11-2010.

13. http://www.idf.org/diabetesatlas/5e/the-global-burden. Accessed Mar 18, 2013.

14. Sharma SK, Seshiah V, Sahay BK, *et al.* Baseline characteristics of the IMPROVE control study population: A study to evaluate the effectiveness of a standardized healthcare professionals training program. *Indian J Endocr Metab.* 2012;16(Suppl 2):S471-S473.

15. Zhang P, Zhang X, Brown J, *et al.* Global healthcare expenditure on diabetes for 2010 and 2030. *Diabetes Res Clin Pract.* 2010;87(3):293-301.

16. Vasan SK, Pittard AE, Abraham J, *et al.* Cause-specific mortality in diabetes: retrospective hospital based data from south India. *J Diabetes.* 2012;4(1):47-54.

17. Nam S, Chesla C, Stotts NA, *et al.* Barriers to diabetes management: patient and provider factors. *Diabetes Res Clin Pract.* 2011;93(1):1-9.

18. Mohan D, Raj D, Shanthirani CS, *et al.* Awareness and knowledge of diabetes in Chennai- the Chennai Urban Rural Epidemiology Study [CURES-9]. *J Assoc Physicians India.* 2005;53:283-287.

19. Singh A, Milton PE, Nanaiah A, *et al.* Awareness and attitude toward diabetes in the rural population of Arunachal Pradesh, Northeast India. *Indian J Endocrinol Metab.* 2012;16(Suppl 1):S83-S86.

20. Grant R, Adams AS, Trinacty CM, *et al.* Relationship between patient medication adherence and subsequent clinical inertia in type 2 diabetes glycemic management. *Diabetes Care.* 2007;30(4):807-812.

21. Currie CJ, Peyrot M, Morgan CL, *et al.* The impact of treatment noncompliance on mortality in people with type 2 diabetes. *Diabetes Care.* 2012;35(6):1279-1284.

22. Tharkar S, Devarajan A, Kumpatla S, *et al.* The socio-economics of diabetes from a developing country: a population based cost of illness study. *Diabetes Res Clin Pract.* 2010;89(3):334-340.

23. Ramachandran A, Ramachandran S, Snehalatha C, *et al.* Increasing expenditure on health care incurred by diabetic subjects in a developing country: a study from India. *Diabetes Care.* 2007;30(2):252-256.

24. Poongothai S, Anjana RM, Pradeepa R, *et al.* Association of depression with complications of type 2 diabetes the Chennai Urban Rural Epidemiology Study

(CURES- 102). *J Assoc Physicians India*. 2011;59:644-648.

25. Peyrot M, Rubin RR, Kruger DF, *et al*. Correlates of insulin injection omission. *Diabetes Care*. 2010;33(2):240-245.

26. Peyrot M, Rubin RR, Lauritzen T, *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(11):2673-2679.

27. Rubin RR, Peyrot M. Factors associated with physician perceptions of and willingness to recommend inhaled insulin. *Curr Med Res Opin*. 2011;27:(2)285-294.

28. Joshi SR, Das AK, Vijay VJ, Mohan V. Challenges in diabetes care in India: sheer numbers, lack of awareness and inadequate control. J *Assoc Physicians India*. 2008;56:443-450.

29. Hasan H, Zodpey S, Saraf A. Diabetologist's perspective on practice of evidence based diabetes management in India. *Diabetes Res Clin Pract*. 2012;95(2):189-193.

30. Data on File. Action Asia: Indian country session summary. 29-10-2011.

31. Desai A, Tandon N. Challenges in prevention and management of diabetes mellitus and metabolic syndrome in India. *Curr Sci*. 2009;97(3):356-366.

32. Marrett E, Zhang Q, Kanitscheider C, *et al*. Physician reasons for nonpharma-cologic treatment of hyperglycemia in older patients newly diagnosed with type 2 diabetes mellitus. *Diabetes Ther*. 2012;3(1):5.

33. Zhang Q, Marrett E, Jameson K, *et al*. Reasons given by general practitioners for non-treatment decisions in younger and older patients with newly diagnosed type 2 diabetes mellitus in the United Kingdom: a survey study. BMC *Endocr Disord*. 2011;11:17.

34. Karter AJ, Subramanian U, Saha C, *et al*. Barriers to insulin initiation: the translating research into action for diabetes insulin starts project. *Diabetes Care*. 2010;33(4):733-735.

35. Lee YK, Lee PY, Ng CJ. A qualitative study on healthcare professionals' perceived barriers to insulin initiation in a multi-ethnic population. *BMC Fam Pract*. 2012;13:28.

36. Tan AM, Muthusamy L, Ng CC, *et al*. Initiation of insulin for type 2 diabetes mellitus patients: what are the issues? A qualitative study. *Singapore Med J*. 2011;52(11):801-809.

37. Chen KW, Tseng HM, Huang YY, *et al*. The Barriers to Initiating Insulin Therapy among People with Type 2 Diabetes in Taiwan - A Qualitative Study. *J Diabetes Metab*. 2012;3(5):1-4.

38. Venkataraman K, Kannan AT, Mohan V. Challenges in diabetes management with particular reference to India. *Int J Diabetes Dev Ctries*. 2009;29(3):103-109.

39. http://cdsco.nic.in/National%20List%20of%20Essential%20Medicine-%20final%20copy.pdf. Accessed Mar 18, 2013.

40. Rao SK, Nundy M, Dua AS. Delivery of health services in the private sector. Financing and delivery of health care services in India. National Commission on Macroeconomics and Health–Background papers. Ministry of Health and Family Welfare. Government of India. 2005:89–124.

41. De Costa A, Diwan V. 'Where is the public health sector?': Public and private sector healthcare provision in Madhya Pradesh, India. *Health Policy*. 2007;84(2-3):269–276.

42. Heise T, Pieber TR. Towards peakless, reproducible and long-acting insulins. An assessment of the basal analogues based on isoglycaemic clamp studies. *Diabetes Obes Metab*. 2007;9(5):648–659.

43. Monnier L, Lapinski H, Colette C. Contributions of fasting and postprandial plasma glucose increments to the overall diurnal hyperglycemia of type 2 diabetic patients: variations with increasing levels of HbA_{1c}. *Diabetes Care*. 2003;26(3):881–885.

44. Indian National Consensus Group. Premix Insulin: Initiation and Continuation Guidelines for Management of Diabetes in Primary Care. *J Assoc Physicians India*. 2009;57 Suppl:42-46.

45. Turner HE, Matthews DR. The use of fixed-mixture insulins in clinical practice. *Eur J Clin Pharmacol*. 2000;56(1):19-25.

46. Raskin P, Allen E, Hollander P, *et al*. Initiating insulin therapy in type 2 diabetes: a comparison of biphasic and basal insulin analogs. *Diabetes Care*. 2005;28(2):260-5.

47. Liebl A, Prusty V, Valensi P, *et al*. Ten years of experience with biphasic insulin aspart 30: from drug development to the latest clinical findings. *Drugs*. 2012;72:1495-520.

48. Shanmugasundar G, Bhansali A, Walia R, *et al*. Comparison of thrice daily biphasic human insulin (30/70) versus basal detemir & bolus aspart in patients with poorly controlled type 2 diabetes mellitus - a pilot study. *Indian J Med Res*. 2012;135:78-83.

49. Kalra S, Megallaa MH, Jawad F. Patient-centered care in diabetology: From eminence-based, to evidence-based, to end user-based medicine. *Indian J Endocr Metab*. 2012;16:871-872.

50. Frid A, Hirsch L, Gaspar R, *et al*. New injection recommendations for patients with diabetes. *Diabetes Metab*. 2010;36 Suppl 2:S3-S18.

51. Kalra S, Megallaa MH, Jawad F. Patient-centered care in diabetology: From eminence-based, to evidence-based, to end user-based medicine. *Indian J Endocr Metab*. 2012;16:871-872.

52. Davis SN, Wei W, Garg S. Clinical impact of initiating insulin glargine therapy with disposable pen versus vial in patients with type 2 diabetes mellitus in a managed care setting. *Endocr Pract*. 2011;17(6):845-852.

53. Hansen B, Lilleøre SK, Ter-Borch G. Needle with a novel attachment versus conventional screw-thread needles: a preference and usability test among adults with diabetes and impaired manual dexterity. *Diabetes Technol Ther*. 2011;13(5):579-585.

54. Iwanaga M, Kamoi K. Patient perceptions of injection pain and anxiety: a comparison of NovoFine 32-gauge tip 6mm and Micro Fine Plus 31-gauge 5 mm needles. *Diabetes Technol Ther*. 2009;11(2):81-86.

55. Israël-Bultman H, Hyllested-Winge J, Kolaczynski M, *et al*. Comparison of preference for NovoPen(®) 4 with previous insulin pen treatments after 12 weeks in adult patients with type 1 and type 2 diabetes: a multicentre observational study. *Clin Ther*. 2011;33(3):346-57.

56. Murugesan N, Shobana R, Snehalatha C, *et al*. Immediate impact of a diabetes training programme for primary care physicians an endeavour for national capacity building for diabetes management in India. *Diabetes Res Clin Pract*. 2009;83:140-144.

57. Balagopal P, Kamalamma N, Patel TG, *et al*. A community-based diabetes prevention and management education program in a rural village in India. *Diabetes Care*. 2008;31:1097-1104.

58. Gagliardino JJ, Aschner P, Baik SH, *et al*. Patients' education, and its impact on care outcomes, resource consumption and working conditions: data from the International Diabetes Management Practices Study (IDMPS). *Diabetes Metab*. 2012;38(2):128-134.

59. Soundarya M, Asha A, Mohan V. Role of a diabetes educator in the management of diabetes. *Int J Diab Dev Countries*. 2004;24:65-68.

60. Kesavadev J, Shankar A, Pillai PB, *et al*. Cost-effective use of telemedicine and self-monitoring of blood glucose via Diabetes Tele Management System (DTMS) to achieve target glycosylated hemoglobin values without serious symptomatic hypoglycemia in 1,000 subjects with type 2 diabetes mellitus a retrospective study. *Diabetes Technol Ther*. 2012;14(9):772-776.

61. Keers JC, Groen H, Sluiter WJ, *et al*. Cost and benefits of a multidisciplinary intensive diabetes education programme. *J Eval Clin Pract*. 2005;11(3):293-303.

62. Al-Qazaz HKh, Sulaiman SA, Hassali MA, *et al*. Diabetes knowledge, medication adherence and glycemic control among patients with type 2 diabetes. *Int J Clin Pharm*. 2011;33(6):1028-1035.

63. Choi MJ, Yoo SH, Kim KR, *et al*. Effect on Glycemic, Blood Pressure, and Lipid Control according to Education Types. *Diabetes Metab J*. 2011;35(6):580-586.

64. Petznick AM. Identifying and addressing barriers to insulin acceptance and adherence in patients with type 2 diabetes mellitus. *J Am Osteopath Assoc*. 2013;113(4 Suppl 2):S6-S16.

65. Peyrot M, Rubin RR, Khunti K. Addressing barriers to initiation of insulin in patients with type 2 diabetes. *Prim Care Diabetes*. 2010;4(suppl 1):S11-S18.

66. http://rsby.gov.in. Last accessed on June 10, 2013.

67. Devadasan N, Criel B, Van Damme W, *et al*. Community health insurance in Gudalur, India, increases access to hospital care. *Health Policy Plan*. 2010;25(2):145-154.

68. Varroud-Vial M. Improving diabetes management with electronic medical records. *Diabetes Metab*. 2011;37 Suppl 4:S48-S52.

69. Ali MK, Shah S, Tandon N. Review of electronic decision-support tools for diabetes care: a viable option for low- and middle-income countries? *J Diabetes Sci Technol*. 2011;5(3):553-570.

---

novo nordisk®