

Review Article

Refractory diabetes : a 5D approach

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This communication shares a simple and pragmatic approach to evaluate and to defect refractory diabetes which does not “respond” to insulin. The 5D rubric offers a mnemonic based best treatment practices in the easiest way to remember and follow. This communication improves upon earlier publications, and describes the 5 D approach to managing diabetes that cannot be controlled by ‘high’ doses of insulin and adequate pharmacotherapy. This approach will help health care professionals in choosing best treatment regimen and converting most ‘refractory’ patients to responsive ones.

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Key words : 5D approach, Refractory diabetes, diabetes, high doses insulin, insulin therapy.

Diabetes is a global challenge today¹. Insulin is most effective, and perhaps the most important drug used for the management of diabetes. However, many persons with diabetes experience poor control in spite of using insulin. The causes may be multifactorial in such patients. Such patients present a clinical challenge for diabetes care professionals, who find it difficult to motivate them to continue insulin therapy². This leads to suboptimal outcomes in the affected individual, and fuels misconceptions and hearsay against diabetes in the society

Clinical Aids :

Persons who are unable to achieve satisfactory glycaemic control in spite of adequate pharmacotherapy are termed as having refractory diabetes³. These patients represent a challenge not only for the patient, but also for the treating physician. The diabetes care professional’s responsibility is to choose the best treatment regimen for that particular patient. This may involve a combination of oral anti-diabetes agents with insulin. The word “insulin” implies a humungous variety of drugs and delivery devices. Efficient diabetes management requires selection of the most suitable and appropriate insulin regime for a particular individual.

Mnemonics have a key role in helping health care professionals remember the best treatment practices in the easiest way. The DIET mnemonic (diet, depression, drugs, infection, indigenous, instrument, exercise, ethanol, endocrine, technique) to rule out the cause of persistent hyperglycemia, has been suggested earlier⁴. A person-friendly ‘diabetes therapy by the ear’ approach has been proposed to limit refractoriness of diabetes⁵. This communication

- Refractory diabetes is a global challenge.
- 5 D mnemonic based approaches help to overcome it.
- This can be achieved through reevaluation of
 - Diagnosis
 - Diseases causing poor control
 - Distress ie, psychological illness
 - Diet and life style
 - Drugs and regimen

improves upon earlier publications, and describes the 5 D approach to managing diabetes that cannot be controlled by ‘high’ doses of insulin.

Clinical Evaluation :

A meticulous clinical examination to key to determining the type of diabetes in an individual⁶. A lean patient with diabetes with poor muscle and fat mass is more likely to be insulinopenic and beta cell depleted, more likely to develop ketosis and would do better with intensive insulin therapy. In contrast, a patient of diabetes with normal to elevated body mass index for race/ethnicity, associated central obesity, acanthosis, skin tags and increased dorso-cervical pad of fat with associated history of polycystic ovary syndrome (females), non-alcoholic steatohepatitis are more likely to be insulin resistant and would do better with insulin sensitizers with/or without insulin in the management of diabetes. Looking for red flags signs in clinical history and examination for secondary diabetes eg history of pancreatitis, steroid use, Cushing’s phenotype, acromegaly, is important as well.

Diagnosis :

A review of the diagnosis is important in poorly controlled patients. Not all diabetes is type 2 diabetes⁷. The patient may have LADA (late onset autoimmune diabetes of adults) diabetes secondary to endocrinopathies (acromegaly, Cushing’s syndrome) or pancreatic disorders. Drug induced diabetes eg; due to corticosteroids or immuno-

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suppressants, is another differential diagnosis of diabetes. These types of diabetes need to be treated differently from type 2 diabetes.

Disease and Distress :

Persons with type 2 diabetes may have concomitant endocrine medical or surgical illness, which may contribute to poor control. Endocrine conditions such as hyperthyroidism, medical causes such as infections, inflammations and autoimmune disorders (eg; coeliac disease) and surgical illness including trauma may create 'refractoriness' to insulin. Psychological conditions, such as diabetes distress, and psychiatric illness like depression and schizophrenia, also lead to poor response to therapy^{8,9}.

Diet and Lifestyle :

It must be noted that insulin is not a substitute for lifestyle modification. Response to insulin will be inadequate if inappropriate diet quantity, composition and pattern, or suboptimal physical activity/exercise and stress / coping management are followed¹⁹.

Drugs and Delivery :

Often perceived refractoriness is due to inappropriate prescription or delivery of drug¹¹. One must review the choice of insulin regimes, preparation, delivery device, technique and timing, as well as choice of insulin dosage and frequency of administration. Often, unsuccessful use of a particular basal insulin may suggest refractoriness, though a switch to a long acting or ultra-long acting insulin preparation may work well. In patients requiring prandial control, pre-mix insulin, whether human, analogue or modern co-formulation, may overcome refractoriness, while avoiding complex regimes with greater number of injections and intrusion into lifestyle. Incorrect delivery device, needle length, injection technique and insulin site choice may lead to inadequate control as well. Use of long needle is associated with a greater risk of intramuscular injections. Administration of insulin into lipohypertrophic sites also leads to poorer, more variable insulin absorption¹².

Clinical Action :

We suggest a logical approach to evaluation and management of diabetes that is considered refractory to insu-

Table 1 — <i>The 5D approach to difficult patients with diabetes</i>	
D	Diagnosis to be reviewed <ul style="list-style-type: none"> • LADA • Pancreatic diabetes • Diabetes secondary to endocrinopathy <ol style="list-style-type: none"> i. Acromegaly ii. Cushing's syndrome • Drug included diabetes
D	Disease, comorbid, to be excluded <ul style="list-style-type: none"> • Medical <ol style="list-style-type: none"> i. Infection ii. Inflammation iii. Autoimmune • Endocrine <ol style="list-style-type: none"> i. Hyperthyroidism ii. Insulin resistance syndromes • Surgical <ol style="list-style-type: none"> i. Inflammation
D	Distress <ul style="list-style-type: none"> • Psychological, ie; diabetes distress • Psychiatric <ol style="list-style-type: none"> i. Depression ii. Schizophrenia iii. Substance abuse, eg, alcohol
D	Diet and lifestyle <ul style="list-style-type: none"> • Diet composition, quantity, pattern • Physical activity/exercise
D	Drug and drug regimen choice <ul style="list-style-type: none"> • Drug dosage • Drug preparation • Drug regimen • Delivery device • Insulin technique • Concomitant therapy

lin. This is based upon classical clinical methods. Take a history, perform anthropometric studies, physical examination (looking especially for markers of insulin resistance, viz. acanthosis, increased dorso-cervical pad of fat, skin tags, central obesity), and order rational investigations, to confirm the diagnosis of type 2 diabetes, and rule out comorbid bio psychosocial factors, which may cause insulin resistance. Maintain regular endovigilance and psychovigilance in persons with diabetes, to ensure a state of health that is conducive to treatment.

Assessment of concomitant non-injectable therapy is important. Modulation in dosage, preparation and timing of administration of metformin and other oral anti-diabetes agents may help manage hyperglycemia and optimize the insulin dose in managing diabetes.

Review the choice of insulin regimen, preparation, dosage, delivery device, and technique: ensure that insulin is administered correctly into healthy subcutaneous tissue. Ensure that optimal dosage has been achieved: while most guidelines suggest initiation with 0.1-0.2 U/kg/day of insulin, control usually requires a higher dose of 0.4-0.5 U/kg/day.

Consider changing preparations belonging to the same regimes, eg; switching from intermediate acting to long/ultra-long basal insulin if targets are not achieved. Review the choice of regimes: it is possible that a different regime (eg; basal bolus, premix, high mix, heteromix) may prove effective. Increasing the frequency of administration of insulin usually proves more effective than increasing the dose of insulin.

Summary :

The 5D rubric offers a simple and pragmatic approach to evaluation persons with diabetes who do not "respond" to insulin. The 5D challenge can be overcome by the Ds of determination and dialogue. Follow the hierarchy of evaluation: history taking, physical examination and investigations; keep the bio psychosocial model of health in mind; rule out significant medical, endocrine and surgical causes of poor control; review lifestyle; and the therapeutic regimes. Ensure effective dialogue with the patient; and reinforce his determination to defeat diabetes. These aspects of 'good clinical sense', if followed sincerely, will help convert most 'refractory' patients to responsive ones.

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