Managing diabetes patients in India: Is the future more bitter or less sweet?

Diabesity defined as obesity and type 2 diabetes is likely to be the greatest epidemic in human history.[1] If the total number of diabetics in the world is to be collected in one country, it would be the third biggest country in the world.[1] In recent years, the prevalence of diabetes, as well as prediabetes, has significantly increased in India. A recent Indian Council of Medical Research sponsored study suggests the widespread seriousness of this condition across rural and urban areas with some areas showing prevalence as high as 13%.[2] The association of diabetes and future micro and macrovascular disease especially kidney failure and heart disease and impact on health-care increases the gravity of the situation as well as economic aspect of India.

There is now sufficient evidence of an "Asian phenotype" in diabetes.[3] The Asian diabetes patient is characterized by onset at a younger age, higher risk even at lower body mass index, higher abdominal adiposity, higher cardiovascular disease in South Asia, and stroke in East Asia.[3] These typical characteristics must influence the choice of treatments that are available and selected for our patients.[4]

While diet and lifestyle changes are cornerstone in the management of type 2 diabetes, most if not all patients eventually require pharmacological interventions to manage blood sugar as well as the complications. It is needless to state that while control of blood glucose (either fasting/postprandial or glycosylated hemoglobin) is a pivotal aspect of diabetes treatment, it should not be the only aspect that influences the selection of treatment options. On the one hand, the American Diabetes Association/European Association of Study in Diabetes guidelines suggest an "individualized approach" focusing on aligning a patient's needs and status to a variety of options,[5] the American Association of Clinical Endocrinology guidelines are more specific providing options in preferential order and could be more direct in terms of recommendations.[6] These guidelines suggest that newer agents such as glucagon-like peptide-1 agonists (GLP-1), sodium glucose linked transporter 2 inhibitors (SGLT2), and dipeptidyl peptidase 4 inhibitors (DPP4) (in that order) be preferred over other older options owing to their glycemic as well as extra-glycemic benefits.

Further, the last 2–3 years have provided revolutionary evidence that new agents such as SGLT2 inhibitors reduce cardiovascular events either in secondary prevention setting (EMPA-REG study);[7] or in primary and secondary prevention (CANVAS)[8] both in clinical trials as well as real-world settings (CVD-Real).[9] Similarly, the newer GLP-1 agonists have also shown a favorable effect on cardiovascular disease (LEADER, SUSTAIN-6, and EXSCEL)[10,11] To take this forward, many of these agents have benefits beyond diabetes. GLP-1 agonists have now been approved in obesity (even in the absence of diabetes).[12] Two SGLT2 inhibitors dapagliflozin and empagliflozin are being evaluated in prevention and treatment of heart failure and chronic kidney disease (again in presence as well as the absence of diabetes).[13,14] Results of these studies are being awaited with great interest and curiosity.

This needs to be weighed against the fact that several commonly used agents such as the sulfonylureas do not have such evidence in dedicated randomized clinical trial settings. While these agents are potent glucose lowering agents, the risk of hypoglycemia, effects on weight, and probable effects on the cardiovascular system should not be underestimated.[15] If the objective of treating a patient is to reduce the risk of cardiovascular/renal disease, these factors assume relevant significance. Hence, the selection of treatment options would depend on the long-term sustainability of glycemic control, safety, especially in terms of hypoglycemia and effects on weight as both of these can influence cardiovascular health, effects on heart and kidney – two vital organs which are often "victims" of uncontrolled diabetes. In addition, long-term cost-effectiveness (rather than only short-term costs) and effects on "Quality of life" including mode of administration should influence this decision. A patient-centric approach rather than a "laboratory report-centric approach" warrants further consolidation in clinical practice.

An article in the current issue looks at the quality of life (QOL), treatment satisfaction, and tolerability of antidiabetic drugs. Chaturvedi *et al.* administered QOL questionnaires to 200 patients in a tertiary care

hospital.[16] Majority of patients were on oral hypoglycemic agents either single or in combination while about 17% were on insulin. While glycemic parameters improved in all groups of patients, key QOL parameters such as physical endurance, general health, treatment satisfaction were higher in patients taking either one or two medications compared to those taking more or taking insulin. The study observed that periodic QOL assessment and treatment satisfaction is recommended in diabetes and using lesser medicines may provide better treatment satisfaction and QOL. This clearly points out that use of multiple oral medications and injectable treatment can have an adverse impact on QOL. If not controlled, impact on QOL may lead to challenges in compliance to treatment and eventual control of diabetes in the long term. This, of course, raises the question of initiating the most appropriate treatment and the timing. Newer agents have lower risks of hypoglycemia – one of the most troublesome adverse events and hence their inclusion in the study would have provided more practical understanding. Nevertheless, the study provides us an opportunity to do large-scale real-world studies in patients taking older as well as newer antidiabetic medications.

As we debate on the generalizability of these results, the following approaches may help us in taking appropriate decisions.

First, local evidence generation. There is a need to develop good real-world evidence studies to address-specific issues in India including association of complications and overall disease control, effectiveness of therapeutic options, role of herbal medicines (which are often consumed by patients) This would include use of simple technology to collect simple data, training of primary care physicians and allied health professionals, creating networks and forums where this data could be generated and shared. A recent study (Discover) has provided us valuable evidence of the state of diabetes management in India and the emerging world,[17] we must develop a long-term robust platform for data collection in the real world.

Second, the concept of disease management has to be entrenched in our system. Diabetes is a multisystem disease. This is a strong need for the primary caregiver to be in tandem with specialists in diabetes, cardiology, renal disease, eye disease, and surgeons to manage the patient holistically. Just as we have tumor boards in oncology, we should have diabetes boards for type 2 diabetes. The role of nurse educators should not be undervalued. Our group showed that high-quality diabetes nurse educator support leads to more independence and adherence to even injectable therapies even in real world when compared to clinical trial settings.[18]

Third, we need to consider "personalized medicine" in diabetes. Addressing the phenotypic characteristics to specific groups of medications may be more appropriate. For example, SGLT2 inhibitors could address clinical issues in Asian phenotype diabetes to a great extent, GLP-1 agonists could be treatments of choice in obese diabetics and DPP4 inhibitors may be a good add-on choice in younger, working professionals. For this, we must again generate local evidence with these newer agents in real-world Indian settings in term of clinical effectiveness, long-term safety and cost-effectiveness. The evidence would help us in identifying and addressing barriers in the selection of appropriate treatments that would otherwise impede their potential benefits in our population.

To conclude, prevention of diabetes in the first place and cardiovascular disease should be our main objective. An integral approach of generating robust local real-world evidence, capability building and empowering of medical and allied health professionals, patients, and caregivers and developing long-term robust disease management approaches are likely to propel us to attain victory over this devastating disease.

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