

Insulin deficient type 2 diabetics: Urgent need for enhanced research in Pakistan

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Type 2 diabetes is classically associated with insulin resistance stemming from obesity along with relative pancreatic dysfunction to sustain this resistance.¹ In the recent past, Scandinavian researchers highlighted that a considerable proportion of type 2 diabetics are actually insulin deficient out of proportion to their insulin resistance.² These patients were younger, had low BMI, and more deranged glycemic control. Based on sophisticated tests measuring insulin secretion and resistance, high glycemia in this group was attributed more towards decreased insulin secretion instead of insulin resistance. This was described Cluster 2 or severe insulin deficiency diabetes (SIDD) in ANDIS data.² This data changed the perception about solitary attribute of insulin resistance in pathophysiology of type 2 diabetes, and the way we treat them on ameliorating insulin resistance predominantly.

South Asian population is facing a severe burden of diabetes. KMV Narayan, in Kelly West award lecture, highlighted the different nature of diabetes in India that relates more to poor insulin secretion. He urged for investigating beta cell dysfunction in South Asian population.³ Indians are shown to have lower insulin secretion and reduced beta cell reserves, irrespective of age, and insulin sensitivity.⁴ Their high visceral fat even at same BMI as that of Caucasians also puts them at high risk of developing diabetes at earlier age.⁵ The WellGen study from India established that insulin deficient group is predominant one (53%) in Indian diabetic patients.⁶ Xiong and co-researchers also identified same clusters and related insulin deficient cluster with retinopathy and diabetic foot.⁷ Severe insulin deficient type II diabetics are more prone to diabetic retinopathy and neuropathy while insulin resistance in diabetes is accompanied by renal events and fatty liver and rapidly progress towards insulin requirement after their diagnosis.^{8,9} A recent survey from Pakistan shows that in patients with pre-diabetes, impaired glucose tolerance is much more prevalent than fasting hyperglycemia.¹⁰ A sub-analysis from same group shows high prevalence of diabetes and pre-diabetes in normal and low BMI adults in Pakistani

population (14.92% and 9.79%, 10.14% and 8.99% respectively).¹¹ These patients' characteristics corresponds to SIDD subgroup of type-2 diabetes, and supports our suggestion that Pakistan is going to face a storm of insulin deficient diabetes in near future.

Recent ADA guidelines for treatment of type 2 diabetes focus on starting with GLP-1RA or SGLT-2 inhibitors. These guidelines, at the same time, give room for use of sulfonylurea drugs in resource constraint settings of developing countries.¹² Sulfonylureas are thought to burn out pancreas by forced insulin secretion, and this is especially true in patients with low beta cell reserve at start of treatment.¹³ This secondary failure of pancreas puts the patient with no choice but insulin in different regimens that may best suit his or her daily life and diet routine as well as affordability of the patient. Total pancreatic burnout also puts the patients at high glycemic variability that may need help of continuous glucose monitoring and artificial pancreas; all of it increases the cost enormously that is not in reach of every diabetic patient. Having many patients with pre-existing insulin deficiency at onset of diabetes and putting them on pancreas non-preserving drugs is going to play havoc in next coming years with health section dealing with diabetic population. SGLT-2 inhibitors and thiazolidinediones help the pancreas by decreasing the glycemic burden improving the insulin sensitivity respectively, but they don't seem to have pancreas preserving potential.¹⁴ VERIFY trial has established the supremacy of adding incretin pathway drugs (Vildagliptin used in this trial) at the start of treatment, in durability of glycemic control over 5 years without need of stepping up treatment, likely owing to preservation of insulin secretory potential of beta cells of pancreas.¹⁵ Similar preservation of pancreatic function was elegantly demonstrated with liraglutide, a daily GLP-1 receptor agonist drug.¹⁶ With preservation of pancreas, patients are more likely to avoid compulsory lifelong insulin administration, as well as they can enjoy some liberty in their diet because pancreas can take care of some dysglycemia.

Keeping in mind the prevailing insulin deficiency in newly diagnosed diabetics, those drugs that burden

the pancreas may be the worst choice in the face of already dying pancreas. Here comes the point of patient personalized medicine. Incretin pathway drugs seem promising in insulinopenic type 2 diabetes and it has been suggested as a step towards precision medicine.¹⁴ But before that, the cutoff values of C-peptide and insulin levels that identify insulinopenia with sufficient sensitivity and specificity have to be defined. These tests must be devised in easy to conduct method applicable in general practice. If these two tasks are achieved, type-2 diabetes in local population would be better treated with good long term glycemic control, enjoying some liberty of food in busy daily life routine, as well as prevention of complications. Pakistan needs extensive roll out of research on these untouched arenas in newly diagnosed diabetics and develop own guidelines to sustain our resource limited health system as well as long term health of our diabetic population.

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