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Incretin – based therapy in diabetes mellitus: present scenario and expanding horizons

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The changing priorities in the fast paced world have disturbed the homeostasis between the people and their environment. Faulty food habits, physical inactivity, smoking, overuse of alcohol and stress of day to day life has resulted in an alarming rise in the prevalence of lifestyle related disorders. Type 2 diabetes mellitus (T2DM) is one of the most widespread disease in our culture today. Despite the availability of a number of drugs in the physician's armamentarium to treat this disease, there has been a long felt need for a therapeutic agent which would correct hyperglycemia, improve beta cell function, prevent microvascular/ macrovascular complications and correct pathophysiological disturbances responsible for type 2 diabetes mellitus.

Advancements in the field of molecular biology showed insights into the long recognized phenomenon of " Incretin effect " - whereby an equivalent dose of glucose provokes a greater insulin response when given orally than when administered intravenously [1, 2]. Incretins are naturally occurring glucoregulatory hormones released by the gut into the blood in response to nutrient ingestion. Two important incretin hormones identified to have major effects on carbohydrate metabolism are Glucose dependent insulinotropicpolypeptide (GIP) and glucagon-like peptide-1 (GLP-1). They have a short half life because of their rapid inactivation by dipeptidyl peptidase 4 (DPP-4) enzyme [3, 4]. The observation that exogenous administration of supra-physiological doses of GLP1 (and not GIP), showed similar effect as endogenous GLP1, led to the introduction of degradation resistant GLP-1 Receptor (GLP-1R) agonists (GLP-1 mimetics) on one hand and DPP-4 inhibitors which prolong the activity of endogenous incretin hormones GIP and GLP-1 by inhibiting their breakdown (incretin enhancers) on the other. GLP-1 acts by binding to its specific receptors (GLP1R) present not only in pancreatic beta cells, but also in many other tissues, mainly gastrointestinal tract, central nervous system, heart, lungs, and kidneys.

Initial preclinical studies with GLP-1 showed that it increases the insulin secretion in a glucose - dependent manner during hyperglycemia through direct activation of pancreatic beta cells and inhibits glucagon secretion in the same manner through direct activation of pancreatic alpha cells. However their capacity to secrete glucagon when blood sugar is low is preserved and the normal counter regulatory mechanisms are therefore not affected even at high GLP-1 concentrations [5]. GLP-1 in addition, by slowing gastric emptying contribute to promoting satiety which is mainly mediated through the activation of GLP-1 receptors expressed in hypothalamus and brain stem, where the nuclei for regulation of food intake and satiety are located, resulting in the weight loss. The above effects have been confirmed in human studies conducted by GLP-1 receptor (GLP-1 R) agonists administration. DPP-4 inhibitors have similar glycemic effects, though of a lesser

magnitude, but they do not affect gastric emptying and are essentially weight neutral [6]. The Incretin-based therapies due to their favorable effects on body weight, control of blood sugar with minimal risk of hypoglycemia and significant reduction of HbA1c have found an important place in the management of T2DM, especially in overweight and obese individuals. Surrogate parameters have also been reported to indicate an improvement in cardiovascular risk profile [7].

It was the outcome of preclinical studies in rodents models of T2DM [8] along with studies using cell lines and human islets cultured ex vivo [9, 10], highlighting incretins mediated proliferative and anti-apoptotic effects on beta cells, which generated considerable enthusiasm and anticipation that incretins-based therapies may be one step nearer to the ultimate goal of preservation and enhancement of beta cell mass and function in diabetes mellitus. Human studies on the effects of long term treatment with GLP1R agonists showed sustained preservation or enhancement of beta cell function [11] Although considerable evidence suggests that these agents exert multiple complementary actions that should directly or indirectly enhance beta cell health, it seems premature to definitely conclude that therapy with GLP-1R agonists is likely to be associated with sustained preservation or enhancement of beta cell function in subjects with T2DM [12].

The results of the above studies if corroborated by others can open exciting possibilities of use of GLP1R agonists in various other areas in the field of diabetes mellitus. A potential role of Incretin-based therapy of a longer duration in the prediabetic stage for prevention or delay to progression to overt diabetes has been perceived [13, 14]. It has been suggested that long term and large prevention trials be carried out to evaluate their possible application in clinical practice especially for the treatment of patients at the time of onset of type-1 diabetes or for the individuals with preclinical type-1 diabetes who still have a significant viable beta cell mass [15, 16].

Other major area of concern in diabetes is its vascular complications which have hither to defied any satisfactory solution. Macrovascular complications of diabetes include atherosclerosis, coronary artery disease', cerebrovascular disease, and peripheral vascular disease involving large vessel obstruction. The microvascular complications comprise of neuropathy, nephropathy, and retinopathy. They are major causes of morbidity and mortality in diabetes

The non-glycemic extra-pancreatic effectsof incretins is presently an area of active research mainly due to experimental evidence of their beneficial role in vascular complications of diabetes. A recent excellent review appearing in Journal of Diabetes research [17] deals with the current knowledge about the relationship between multiple adverse biological mechanisms in diabetes and putative incretin-based therapeutic interventions intended to prevent diabetic vascular complications. Citing the results from a number of animal studies, It was noted that due to their anti-inflammatory and anti-oxidative stress effects, GLP-1 and DPP-4 inhibitors elicit vasotropic effects in endothelial cells leading to various renal protective, cardio-protective, neuro-protective and anti-apoptotic effects in the retinal endothelial cells. Incretin-based therapies using incretin and DPP-4 inhibitors show promising potential for prevention of diabetic vascular complications due to their biological vaso-protective effects that surpass glycemic control. Since most favorable results appear to be realized in animal disease models, large scale clinical trials have been suggested to be performed to assess the effects of incretin-based treatments on diabetic vascular complications. Initial concerns about increased risk of pancreatitis, pancreatic cancer, heart failure and infections, associated with incretin-based therapies have largely been discounted in recent large scale studies [18, 19, 20, 21].

The horizons of incretin-based therapy are constantly expanding beyond their glycemic effects and are full of their clinical potential to prevent the progressive loss of beta cell function, mass and development of long term complications of diabetes. In the near future, a dynamic change within this field is anticipated, if the results of experimental studies are also proved in human studies as well.

In conclusion, it is felt that the incretin based therapy being a comparatively new addition to the existing therapeutic options in the management of type 2 diabetes mellitus has yet to find its due place beyond its present role as an add on therapy to metformin. The lingering safety concerns associated with long term therapy with incretins need to be further allayed convincingly. Full therapeutic exploitation of the unique potential of incretin based therapy in preservation of beta cell function and mass as well as prevention of diabetic vascular complications, which has been seen in animal studies, will have to wait pending its confirmation by robust human data.

Let us hope that best is yet to come which is likely to bring us nearer to achieving our cherished goal of finding a cure of diabetes. I would like to sum up with an optimistic note by quoting Cristopher Reeve “So many of our dreams at first seem impossible, then they seem improbable, and then when we summon the will, they soon become inevitable ‘’.

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