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Drugs in Incretin Based Control of Type 2 Diabetes: Intervention for More Efficacy and Safety

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ABSTRACT: Diabetes mellitus (DM) is a global health disorder due to insulin resistance or insulin deficiency. T1DM is insulin dependant, while T2DM, which affects about 90% of all cases, known as non-insulin-dependent DM. Though impaired regulation of incretin hormones a fundamental defect in the pathogenesis of Type 2 diabetes, is not a primary event in the development of type 2 diabetes, but rather a consequence of the diabetic state. Glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are the two important incretin hormones secreted in small intestine in response to ingestion of food. Glucagon producing α-cells, participate in glucose counter-regulation to avoid dangerous hypoglycemia. Thus major intervention started at developing DPP-4 inhibitors for T2DM. DPP-4 resistant mimetics, GLP-1 receptor agonists (incretin mimetics) have been designed.Exenatide is the first analog of class incretin mimetics followed by liraglutide. Other smaller molecules of DPP-4 inhibitors available are vi., sitagliptin, saxagliptin, linagliptin, alogliptin and vildagliptin.Four more gliptins, namely teneligliptin, anagliptin, omarigliptin, and trelagliptin are also, found effective.

KEYWORDS: T2DM, incretin-effect, GLP-1 GIP, DPP-4 inhibitors

INTRODUCTION

According to WHO people living with diabetes rose from 200 million in 1990 to 830 million in 2022. The numbers are alarming in low- and middle-income countries than in high-income countries. Among the patients more than 50% are not medicated due to poor coverage.T2DM is a case of a insensitivity of the pancreatic β-cells to glucose stimulated insulin release and the impairment of skeletal muscle cells to insulin stimulated glucose entry,insulin resistance (IR).Now it is evident that impaired regulation of incretin hormones which reduce BG levels is another fundamental defect in the pathogenesis of Type 2 diabetes (1). It is likely that a reduced incretin effect impacts on postprandial glycaemic excursions leading to loss of glycaemic control.Oral glucose elicits a higher insulin response than intravenous glucose at identical plasma glucose (PG) profiles (isoglycemia) is known as incretin effect. Reduced incretin effect is not a primary event in the development of type 2 diabetes, but rather a consequence of the diabetic state (2,3). Incretin effect has been found to be reduced in individuals with type 1 diabetes (positive ICA) and normal fasting glucose levels (1,4). Incretin defect is clearly manifested in response to a mixed meal (5,6) by a reduced GLP-1, decreased insulinotropic potency of GLP-1 (7) and an almost complete loss of late-phase insulin secretion in response to GIP. Suppression of glucagon secretion is impaired during oral glucose tolerance tests (OGTTs) as opposed to isoglycemic intravenous glucose infusion in patients with type 2 diabetes (8).Two incretin hormones glucagon like peptide-1(GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) secreted in small intestine in response to ingestion of nutrients (9). In type 2 DM a substantially reduced or no incretin effect is found (1).The incretin effect is also mediated by glucose concentration, stimulating more insulin secretion in more extreme hyperglycemic states. Further presence of GIP and GLP-1 receptors on neuronal cells, suggest an additional indirect role in cell regulation (10). Glucagon producing α-cells, play a key role in glucose counter-regulation to avoid dangerous hypoglycemia. Now, incretin-based therapy has clearly emerged as one of the most sought out strategy in managing type 2 DM. DPP-4 inhibitors maintain active GLP-1 and GIP levels by blocking DPP-4 activity avoiding degradation by DPP-4. Present paper is a summary of the available DPP-4 inhibitors and incretin based therapy.

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INCRETIN HORMONES

The active incretins are glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) (11,12), but gastrin, secretin, and cholecystokinin may also have minor roles. GLP-1 and GIP enhance the effects of insulin, suppress glucagon release, and decrease hepatic gluconeogenesis to maintain BG levels in healthy subjects (13). Gastrointestinal tract produces these hormones, which trigger insulin secretion by acting on pancreatic β-cells after oral food ingestion (11,13). Both GLP-1 and GIP can stimulate β-cell growth (1).Glucose amplifies insulin secretion in a time dependent manner in addition to the normal stimulated insulin secretion. In a hyperglycemic state β-cells augment subsequent insulin secretory responses to glucose controlled by calcium levels (14,15).DPP-4 inhibitors maintain active GLP-1 and GIP levels by blocking DPP-4 activity which otherwise degraded by DPP-4 (16,17). Thus DPP-4 inhibitors are the key intervention for T2DM management.

GLP-1 stimulates all steps of insulin biosynthesis to provide a continued supply of insulin.GLP-1(18)(Fehmann and Habener, 1992). In long-standing type 2 diabetes, GLP-1 secretion subsides altogether. GLP-1 is released from intestinal L-cells in response to enhance glucose-stimulated insulin secretion in humans after food ingestion(19). GLP-1 exists in two major molecular forms, as amide GLP-1(7-36) and GLP-1(7-37), collectively a bioactive GLP-1. GLP-1 binds a G protein-coupled receptor resulting in activation of insulin gene's cyclic-AMP (cAMP) response element (CRE) of the 5'-proximal control sequence (20) and stimulate transcription of the PDX-1 gene (21). Finally, it potentiates glucose-induced insulin gene transcription by activating NFAT (nuclear factor of activated T cells) (22). GLP-1 stimulate cell proliferation (23), and enhances the differentiation of new β-cells from progenitor cells in the pancreatic duct epithelium(24) and inhibits apoptosis of β-cells (25) to maintain a balance between apoptosis and proliferation.

GIP a 42 amino acid peptide hormone is secreted from specific endocrine cells of entire small intestinal mucosa called K cells in response to glucose, amino acids and lipids (26). GIP activates glucose-stimulated insulin secretion (27) through a specific GIP receptor (GIPR) (28). Late phase of the insulinotropic response is particularly impaired in type 2 diabetes (2). Hyperglycaemia and incretin actions in combination stimulate insulin secretion. GIP stimulates glucagon secretion in type 2 diabetes at lower plasma glucose concentrations, whereas the insulinotropic actions are more prominent during hyperglycaemia (29).

Both hormones contribute to insulin secretion from the beginning of a meal with progressive amplification with rise in plasma glucose concentrations. The pathogenesis of T2DM involves a dysfunction of both incretins. The reduced incretin effect is believed to contribute to impaired regulation of insulin and glucagon secretion in T2DM. However, insulin resistance is independent of decreased GLP-1 meal response (30,1) demonstrated that the elevated GIP concentrations elicited by oral glucose accounts for the augmented insulin release. According to Meier et al., (2003)(29) that the GIP effect was preserved in women who had a history of gestational diabetes and are therefore at high risk of developing type 2 diabetes.

THERAPEUTIC MEDIATION

In type 2 diabetes, the secretion of GLP-1 which suppresses glucagon secretion, delays gastric emptying and promotes satiety is dramatically reduced. Strategies to restore the incretin activity of GLP-1peptide were explored, because GLP-1 is rapidly degraded by the enzyme, Dipeptidyl peptidase-4 (DPP-4), DPP-4 resistant mimetics, GLP-1 receptor agonists (incretin mimetics) have been designed. Several randomized placebo-controlled studies with DPP-4 resistant GLP-1 confirmed their efficacy to improve glycemic control in type 2 diabetic patients. Incretin mimetics, exenatide and liraglutide with considerably longer half-lives have been developed to control hyperglycemia. Exenatide is a synthetic form of a natural peptide found in the saliva of Heloderma suspectum, first analogue of this class (31), followed by liraglutide. Other DPP-IV inhibitor class of small-molecules called gliptins are also demonstrated to be effective in antihyperglycemic state devoid of any major adverse events. Presently there are five DPP-4 inhibitors available vi., sitagliptin, saxagliptin, linagliptin, alogliptin and vildagliptin. Four more gliptins, namely teneligliptin, anagliptin, omarigliptin, and trelagliptin are also, found effective. Generally, the DPP-4 inhibitors are eliminated primarily via kidney (32) except linagliptin which is eliminated via the biliary pathway (16,33). Presently a combination of Metformin and DPP-4 inhibitor are being recommended to deliver synergistic action. DPP-4

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inhibitors enhance pancreatic islet function by activating endogenous GLP-1. Metformin known to improve IR and supposed to increase the levels of GLP- 1 and regulate its expression in pancreatic β-cells is found to efficacious combination for treating T2DM.The medication however, has few exceptions for recommendations. The therapy is not given to patients with either renal and pancreatic aberrations, gallstones,high levels of triglycerides. The medication is also, not to be given in cases of pregnancy and breastfeeding.

CONCLUSION

Type 2 Diabetes mellitus has become a major health disorder due to changed life style and poor diet practices. Focus should be on overall health without any risk factors while, treating T2DM. DPP-4 inhibitors are affective in glucose regulation by reducing blood glucose (fasting and postprandial) and HbA1c levels by augmenting the incretin system. Research sufficiently proved that DPP4 inhibitors are good as there are no known reports on weight gain, no dose escalation requirement and have a favorable anti-inflammatory and safety profiles. Also, they proved to be safe for elderly diabetic patients and kidney disease patients with diabetes.

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