Newer therapies in Type 2 diabetes

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Abstract: Type 2 diabetes is complex disease characterized by insulin resistance with absolute or relative insulin deficiency. Better understanding of role of incretins, glucagon & glucose excretion pathophysiology of is leading to availability of newer drugs in diabetes. Current status of diabetes treatment with respect to newer oral hypoglycemic agents & newer long acting insulin analogues is discussed.

Key words: Type 2 diabetes, Incretin effect, GLP1, DPP4 inhibitors, SGLT2 inhibitors, Amylin, Colesevelam&Bromocriptine

Article:

Diabetes mellitus (DM) refers to a group of common metabolic disorders that share the phenotype of hyperglycemia. Several distinct types of DM are caused by a complex interaction of genetics and environmental factors. Depending on the etiology of the DM, factors contributing to hyperglycemia include reduced insulin secretion, decreased glucose utilization, and increased glucose production.

Type 2 diabetes is traditionally treated with oral hypoglycemic agents (OHA) which increase insulin secretion called secretogogues. Metformin is 1st line drug for most of current guidelines (1). After metformin options available are sulphonylureas, alpha glycosidase inhibitors, GLP 1 inhibitors, DPP4inhibitors & insulin.

The main limitation of most commonly used drug therapies are hypoglycemia, fluid retention and weight gain. All these theoretically increase the risk of cardiac events in diabetic population. So newer therapies aim to overcome the above mentioned side effects.

Incretin based therapies:

- Gut-derived hormones, secreted from l- cells in ileum in response to nutrient ingestion, that potentiate insulin secretion from islet B cells in a glucose-dependent fashion, and lower glucagon secretion from islet A cells
- Two predominant incretins:
  - Glucagon-like peptide–1 (GLP-1)
  - Glucose-dependent insulinotropic peptide (GIP) (also known as gastric inhibitory peptide)
- Incretin effect is impaired in type 2 diabetes
  - Known as GLP-1 deficiency

The incretin effect: insulin secretion is greater in response to oral vs intravenous glucose, this effect is impaired in type 2 diabetes.
**Mechanism of action:** GLP-1 exerts its main effect by stimulating glucose-dependent insulin release from the pancreatic islets.

- Restores both first phase and second phase insulin response to glucose (2)
- Inhibits inappropriate post prandial glucagon secretion (3)
- Slows gastric emptying
- Decreases food intake
- Increases beta cell mass and maintain beta cell function
- Improves insulin sensitivity
- Enhances glucose disposal

**Half life:** GLP-1 exhibits a short half-life of one to two minutes due to n-terminal degradation by the enzyme dipeptidyl peptidase 4 (dpp-4).

Drugs available for therapeutic uses in class of GLP 1 agonists are

- Glucagon-like peptide–1 agonists (*incretin mimetics*)
  
  Exenatide, Liraglutide, Albiglutide, Taspoglutide, Lixisenitide

**Benefits:**

- Responds to increased physiologic levels of glucose
- Valuable option as add-on therapy in patients who fail to achieve glycemic goals with metformin and/or sulfonylurea
- Associated with weight loss
- Potential to promote β-cell proliferation and β cell preservation

**Limitations:**

- Dependent upon residual insulin secretion to exert antidiabetic effect not effective in type 1 diabetes
- Associated with side effects such as nausea, vomiting, and headache
- Increased risk of hypoglycemia when used with sulphonylurea
- Pancreatitis
- Associated with benign and malignant thyroid C-cell tumors (4)

**GLP1 agonists in conclusion are**

Useful add-on therapy for patients with type 2 diabetes who have:

- Suboptimal glycemic control with MET and/or SFU/TZD
- Inadequate glycemic control resulting from weight gain
- A need for weight loss
- Severe postprandial hyperglycemia

**Ongoing Clinical trials:**

- In a randomized open-label trial comparing exenatide with glimepiride in 1029 patients with type 2 diabetes taking metformin, treatment failure (defined as A1C >9 percent after the first three months of treatment, or >7 percent at two consecutive visits after the first six months) occurred less often in the exenatide group (3).

  GLP-1 analogs are effective in improving glycemic control, as illustrated by the findings of a meta-analysis of 17 randomized trials comparing GLP-1 analogs (exenatide, liraglutide, albiglutide,
tasppoglutide&lixisenatide) with placebo or an active comparator (insulin glargine, DPP-4 inhibitor, thiazolidinedione, sulfonylurea) in patients with type 2 diabetes and suboptimal control on one or two oral agents (metformin and/or sulfonylurea) The duration of the individual trials ranged from 8 to 30 weeks. In comparison to placebo, all GLP-1 analogs reduced glycated hemoglobin (A1C) by approximately 1 percentage point (treatment difference 0.47 to 1.56 percent).

In comparison to thiazolidinediones, DPP-4 inhibitors, and insulin glargine, liraglutide was superior in reducing A1C. Similarly, exenatide once weekly (2 mg) reduced A1C more than thiazolidinediones, & DPP-4 inhibitors.

DPP-4 INHIBITORS:

DPP-4 inhibitors are not considered as initial therapy for the majority of patients with type 2 diabetes in current guidelines

Dipeptidyl peptidase 4 (DPP-4) is a ubiquitous enzyme expressed on the surface of most cell types that deactivates a variety of other bioactive peptides, including glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1).

DPP-4 inhibitors have advantage over GLP 1 analogues as they are oral drugs. Drugs available in market are Sitagliptin, Saxagliptin, LinagliptinVildagliptinand Alogliptin

SITAGLIPTIN:Sitagliptin is the first DPP4 inhibitors available for use.

The usual dose of sitagliptin is 100 mg once daily,

50 mg for moderate to severe renal insufficiency (glomerular filtration rate [GFR] 30 to 50 mL/min) 25 mg for severe renal insufficiency (<30 mL/min).

Main advantage of DPP-4 inhibitors is they are oral. They have unique mechanism of action as they responds to increased levels of physiologic glucose regulated by physiologic glucose levels. Hypoglycemia risk is almost negligible. They also improve differentiation, proliferation, and survival of β-cells.

Limitations:

- Unlike GLP-1 and exenatide, DPP-IV inhibitors do not increase satiety and are not associated with weight loss.
- Limited efficacy and long term safety data.
- DPP-IV inhibitors can impact the normal development and function of the immune system.

DPP4 inhibitors are future for type 2 diabetes therapy. But more data are needed regarding efficacy and safety in combination with other antidiabetic medications. Their long term efficacy & safety is also question mark Their efficacy and safety in pregnancy pediatric and elderly patients are still not clear.

Clinical trials: Addition of sitagliptin compared with glipizide provided similar HbA(1c)-lowering efficacy over 52 weeks in patients on ongoing metformin therapy. Sitagliptin was generally well tolerated, with a lower risk of hypoglycemia relative to glipizide and with weight loss compared with weight gain with glipizide (5,6)

Sodium glucose cotransporter 2 (SGLT2) inhibitors:

Currently SGLT2 inhibitors are used as a third-line agent. They have been approved recently by US FDA
In patients with inadequate glycemic control on two oral agents (e.g., metformin and sulfonylurea) or if for some reason combination metformin and insulin is not a therapeutic option.

**Mechanism of action:**

The sodium-glucose co-transporter 2 (SGLT2) is expressed in the proximal tubule and mediates reabsorption of approximately 90 percent of the filtered glucose load.

SGLT2 inhibitors promote the renal excretion of glucose and thereby modestly lower elevated blood glucose levels in patients with type 2 diabetes. The glucose-lowering effect is independent of insulin (beta cell function and insulin sensitivity). Dapagliflozin and canagliflozin are available for therapy. Remogliflozin, empagliflozin and ipragliflozin are still in phase 3 trials.

**Canagliflozin:**

Canagliflozin is taken orally before the first meal of the day (7). The initial dose is 100 mg once daily, and it can be increased to 300 mg daily to achieve glycemic goals. eGFR 45 to 59 mL/min - dose should not exceed 100 mg daily.

These drugs are contraindicated in patients with eGFR<45 mL/min or severe hepatic impairment. No dose adjustment is needed in patients with mild or moderate hepatic impairment.

**Clinical trials:**

Dapagliflozin significantly reduced HbA1c, fasting plasma glucose, body mass index, systolic, and diastolic blood pressure, and serum uric acid. Dapagliflozin treatment increased the risk of urinary and genital tract infection and it mildly increased the risk of hypoglycemia when co-administered with insulin (8).

**11-betaHydroxysteroid Dehydrogenase Type 1 Inhibitor (INCB13739): still in phase 3 trials**

- 11beta HSD1 is an 11beta-reductase that catalyzes the intracellular conversion of inactive cortisone into active cortisol.
- 11beta-HSD1 is expressed in specific tissues, most notably in liver, adipose, vasculature, brain, and macrophages where it increases intracellular cortisol levels but does not participate in adrenal cortisol biosynthesis from cholesterol.
- 11beta-HSD1 activity is elevated in adipose tissue of obese rodents and humans.

INCB13739 is an oral and selective 11beta-HSD1 inhibitor being developed to treat type 2 diabetes. **Clinical trials:**

INCB13739 added to ongoing metformin therapy was efficacious and well tolerated in patients with type 2 diabetes who had inadequate glycemic control with metformin alone. 11beta-HSD1 inhibition offers a new potential approach to control glucose and cardiovascular risk factors in type 2 diabetes (9).

**Newer insulins:**

**Degludec insulin:**

Insulin degludec is almost identical to human insulin, except for deletion of the last amino acid from the B-chain and the addition of a glutamyl link from LysB29 to a hexadecanedioic fatty acid. This feature allows
it to form soluble multihexamers at the injection site, from which monomers slowly separate and are absorbed.

This property confers a long duration of action (>40 hours) and reduces variability in plasma concentration with once daily.

These properties make this insulin to use preferably as it achieves target of glycemic control with lower risk of hypoglycemia

- Long and predictable action profile
- Lower variability of action throughout the day
- Retains biological profile, safety efficacy of human insulin
- Can form soluble coformulation with rapid acting insulin aspart.

NICE guidelines recommend use of long-acting insulin analogue when:

- Nocturnal hypoglycemia is a problem on NPH (isophane) insulin
- Morning hyperglycemia on NPH (isophane) insulin results in difficult daytime blood glucose control

**Clinical trials:**

1) Phase 3, randomized open label, treat to target non inferiority trial conducted by Heller et al concluded Insulin degludec might be a useful basal insulin for patients with type 1 diabetes because it provides effective glycemic control while lowering the risk of nocturnal hypoglycaemia (10)

2) Randomized control trial conducted bt Bode et al concluded Long-term basal therapy using insulin degludec in Type 1 diabetes required lower doses and was associated with a 25% lower risk for nocturnal hypoglycemia than insulin glargine (11, 12)

**Novel agents:**

**Amylinomimetics.** Amylin is a neuroendocrine hormone that is cosecreted with insulin by pancreatic beta cells. As would be expected, amylin deficiencies are evident in patients with T1DM or T2DM, in parallel with the insulin deficiencies. Amylin and insulin have complementary actions in regulating plasma glucose. Amylin binds to brain nuclei. It promotes satiety and reduces appetite, and through vagal efferents it mediates a decrease in the rate of gastric emptying. It also regulates suppression of glucagon
secretion in a glucose-dependent fashion, thus regulating the rate of glucose appearance from the gastrointestinal tract and the liver(13)

**Colesevelam.** is a second-generation bile acid sequestrant. It was observed to mediate modest reductions in glucose during the clinical development program. An expanded program in patients with T2DM resulted in approval for marketing of this drug as an adjunct for the treatment of diabetes. It provides an HbA1c reduction of about 0.5% in addition to approximately 15% improvement in LDL(14).

**Bromocriptine.** A quick-release formulation of bromocriptine administered within 2 hours of rising in the morning has been developed and is approved by regulatory authorities in the United States, although it is not yet marketed for the treatment of T2DM(15)

To conclude the present-day management of T2DM is significantly more effective and easier for patients than the situation that prevailed. A better understanding of the barriers to effective diabetes management and how to overcome them would be of great benefit has been achieved with availability many new drugs in pipeline

REFERENCES:


