

# Insight into Newer Anti-diabetic Treatment

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### Introduction

Diabetes is a disease for great research. Before discovery of insulin by Benting and Best diabetes was like cancer of present days.

Diabetes mellitus is an entity of considerable morbidity comprising a spectrum of multisystem dysfunctions stemming from the combination of insulin resistance and inadequate insulin secretion. Management of diabetes, akin to a tightrope walk, requires a comprehensive understanding of various factors such as over-all clinical picture, adverse effect profile, the complex of inter-play of drugs, etc. More than two-thirds of people with type 2 diabetes will eventually require more than one oral agent, with or without insulin. There is a perpetually increasing newer range of antidiabetic drugs targeting novel aspects of diabetes which warrant adequate awareness by the treating clinicians

Multiple pathophysiological factors has been implicated in the etiology of diabetes mellitus. This knowledge have paved the ways of drug discovery.

**The ominous octate:** 1. Insulin: both it's deficiency and resistance is responsible for diabetes mellitus 2. Glucagon the antagonist of insulin remain unoffended to cause diabetes mellitus. 3. Glucose absorption threshold in the renal tubules is decreased which c causes increased reabsorption of glucose so increases blood glucose . 4. Lipid: increased fat/fatty acid increases glucose resistance to cause diabetes 5. Liver produces abundant glucose in situation of insulin deficiency 6. Decreased muscle utilization also affects glucose homeostasis. 7. Impairment of incretin effect imparts impairs insulin availability which causes hyperglycemia. 8. Neurotransmitter defect in brain in day by day is being recognized as an etiology of diabetes mellitus

Discovery of anti-diabetic agents has so far been occurred addressing these etiological factors.

1. Sulphonureas: Increases insulin secretion and also 2. decreases glucagon 3. SGLT 2 inhibitors increases

threshold of glucose absorption in renal tubules resulting in increased glucose excretion in urine causing reduction of blood glucose. 4. GLP-1 agonist: Improves pancreatic beta cell function, Inhibits glucagon secretion from alpha cell in the presence of higher plasma glucose. Lowered glucagon happen to decreases hepatic glucose production. These group of drugs also reduces hunger and energy intake in brain. 5. DPP4 inhibitor increases insulin availability in circulation, decrease glucagon secretion in circulation in glucose dependent manner. Blocks degradation of native GLP 1 and GPI resulting in increased half-lives of GPI and GLP-1.

2. **The Dirty Dozen of Diabetes (8+4):** addition of four well-known hormones were proposed to the list of players in diabetes etiology to bring the number to 12.

All four hormones have adequate biochemical, epidemiological, observational or clinical support to merit inclusion in the list of the Dirty Dozen of Diabetes.

### Catecholamines Including Dopamine (no.9).

The ninth player beyond the Ominous Octet is the catecholamine family. Dopamine, is the catecholamine with highest concentration in the brain, ". The dopamine modulator drug bromocriptine is used for the management of type 2 diabetes. Stress is linked with the onset of and with poor control in diabetes.

Judicial use of timed release bromocriptine helps in resetting the sustained hyperdopaminergic tone that is characteristic of many type 2 diabetes patients.

Vitamin D (no 10) acting as an immuno-modulatory hormone, it decreases pro-inflammatory cytokines, increases anti-inflammatory cytokines, reduces autoimmune insulinitis and protects against type 1 diabetes in children exposed to high doses of vitamin D *in utero* or in infancy. In adults, vitamin D is linked with both insulin secretion and insulin sensitivity, and there is a strong body of evidence, which justifies its inclusion in the Diabetes Dirty Dozen.

Low vitamin D levels are associated with a higher prevalence of metabolic syndrome, diabetes, obesity, hypertension, coronary artery disease and stroke.

Renin–Angiotensin System(11):Vitamin D deficiency and obesity are associated with stimulation of RAS activity. Randomized controlled trials reveal a lower incidence of new-onset diabetes in patients prescribed angiotensin -converting enzyme inhibitors and angiotensin receptor blockers. Because of this, and their nephro-protective and cardio-protective effects, these molecules have become drugs of first choice in hypertension associated with diabetes. The future holds promise for RAS-based intervention in diabetes care. RAS, therefore, should justifiably be included as part of the Dirty Dozen.

TESTOSTERONE(NO 12):The fourth hormone, which should be added to the list of diabetes players to complete the Dirty Dozen, is testosterone. In diabetes, low levels of FSH may cause lower androgen synthesis through local cytokines and may lose its capacity to do so in diabetes. Studies have shown that low testosterone precedes the onset of diabetes, and androgen deprivation therapy exacerbates insulin resistance/worsens glycemia in prostate cancer patients. Hypogonadism in men with diabetes”condition affects much more than sexuality. Low testosterone levels should certainly be treated, aiming for high-normal values, but equally certainly should not be over-treated.

Treacherous thirteen -12+1 (iron included):we need to utilize every preventive and therapeutic strategy available to us in order to halt the diabetes pandemic. Each of the known pathogenetic mechanisms should be studied and assessed with an open mind for each individual patient in order to achieve the best possible outcomes.

How to decide drug treatment of diabetes:Tablet:Blood glucose:< 16 mmol/L.HbA1C :7-9%.To follow an algorithm: To start with Metformin pluslifestyle change. Address the comorbidities and never forget the patient preference. Insulin:High blood glucose with severe symptom.Secondary failure.HbA1C > 9.Renal failure.Hepatic failure.Diabetic emergency.Non diabetic emergency.Pregnancy.Acetonuria

Anti-hyperglycemic therapy in adults with T2DM how to **initiate**: at diagnosis Initiate lifestyle management and metformin(if no obvious contraindication)set A1c

target and initiate pharmacotherapy based on A1C. Initiate with monotherapy if A1c less than 9,dual therapy if A1c equal to or mor than 9.If A1C is equal to or greater than or equal to 10,blood glucose e their equal to or greater than 300mg/dl,or patient is markedly symptomatic consider combination injection therapy.

How to **select** a dual therapy:If patient has atherosclerovascular(ASCVD) disease viz Ischemic heart disease,TIA or Stroke add agent proven to reduce major cardiovascular events and/or cardiovascular morbidity.

How to **individualize**:SGLT 2 inhibitor specially empagliflozine and canagliflozin has proven evidence that they reduce cardiac and cerebral events.But they have limitataion in use in renal failure cases.Since 2008 FDA does not approve drugfor marketing until and unless they have proven evidence of cardiovascular safety. This drugs have proven safety. So if eGFR support this drugs should be used in (ASCVD) patients. Similar evidence based drug is Liraglutide,it has no eGFR limitation.Even if there is no ACSVD or eGVR limitation they have compelling indications in overweight patients.Liraglutadie has beneficial effect on blood glucose,overweight,systolic hypertension all renders ii most suitable for in patients with metabolic syndrome.When other things are not barrier patient preference and cost should be taken into consideration..Sulphonylureas still the drug of preference in these cases. Acarbose should not be used in renal failure,.DPP4 inhibitors (gliptins can cause, pancreatitis specially in presence of hyptryglyceridemia. Thyroid nodule should be excluded before their use’.SGLT-2 inhibitor cause genitourinary infection.

**Evolution of drug use** in diabetes treatment:Record shows a big evolution in discovery antidiabetic drugs.In 1996 Glimipride and Metiglinide came into the market. Rapid acting analog insulin aspart also came into the market in same year. It was 1999 when the Glitziness Rosiglitazone and Pioglitazone was introduced .Rosiglitazone was subsequently withdrawn from market due to it’s non favorable Cardiovascular profile. The long acting analog Glargine was introduced in tha same year.Biasp, the mixed insulin and combination metformin and glitazone came into the market in 2001 and 2002 respectively.Sitagliptin,vildagliptin,sexgliptin and linagliptin came over the years 2008-11.Liraglutide

was introduced in 2010. Subsequent years were for gliptins and glitides. SGLT 2 inhibitors canagliflozin came in 2013, Empagliflozin, dapagliflozin and other gliflozins in next year having proven their cardiovascular safety. Sotagliflozin (LX 4211), an oral SGLT1 and SGLT2 combined inhibitor for adult type-1 diabetes is in process of approval to be marketed.

**Drugs in pipeline:** GRP 119, GRP 90 like GLP1 agonist decrease gastric emptying, suppression of food intake thus glucose availability. They increase insulin availability and decrease glucagon. The first one in phase 1 trial while the second one in phase 3 trial. Extended action GLP-1 agonists- (HSA)-GLP-1 hybrid protein with half life of about a week and is found to display resistance to DPP IV. It has shown consistent efficacy in type 2 diabetics. Taspoglutide, another analogue, exerts insulinotropic action *in vitro* and *in vivo*, retains the glucoincretin property of human GLP-1, is fully resistant to DPP IV cleavage and has an extended *in vitro* plasma half-life. Upcoming GLP-1 agonists: Various companies are on the way to introduce GLP1 agonist with extended action profile (one week, one month).

**Glucokinase activators:** Glucokinase activator increase glucose utilization is in phase 2 trial. Glucokinase activators (GKAs) stimulate insulin biosynthesis and secretion and augment glucose metabolism and related processes in other glucokinase-expressing cells via GKA-mediated increase in the affinity of glucokinase for glucose and its maximal catalytic rate. GKAs mediate their antidiabetic effects via generalized enhancement of  $\beta$ -cell function and through fasting restricted changes in glucose turnover. Piragliatin, a GKA, has shown an acute glucose-lowering action in patients with mild type 2 diabetes. An experimental GKA molecule ZYGK1 showed promising efficacy in controlling both fasting and non-fasting blood glucose. The side effects although rare of GKAs are hypoglycemia, fatty liver, and hyperlipidemia.

**Dual PPAR (Peroxisome proliferator-activated receptor gamma) agonists:** Dual ppar  $\alpha/\gamma$  receptor agonist  $\downarrow$ hyperglycemia  $\downarrow$ dyslipidemia  $\downarrow$ atherosclerosis, but the side effect like fluid retention, bone fracture, bladder cancer are more. Inhibition of PPAR  $\alpha$ -agonists (Fibrates) lowers plasma triglycerides and VLDL particles and increases HDL cholesterol while PPAR

$\gamma$ -agonists (thiazolidinediones) influence free fatty acid flux and reduce insulin resistance and blood glucose levels. The PPAR  $\alpha/\gamma$  dual agonism addresses both insulin resistance and key aspects of the dyslipidemia that contribute to the high risk of cardiovascular disease (CVD) in diabetics.

Aleglitazar, a new balanced dual PPAR  $\alpha/\gamma$  agonist, reduces hyperglycemia and improves the levels of HbA1C, HDL-C, LDL, and triglycerides with minimal PPAR-related adverse effects. In *in vitro* models, aleglitazar strongly decreased the multiple aspects of the inflamed phenotype of human adipocyte/macrophage co-culture system compared to pioglitazone and fenofibrate suggesting its contribution to prevent progression of adipose dysfunction and insulin resistance, and increased cardiovascular risk. Although muraglitazar a similar molecule showed efficacy as an add-on therapy for poorly controlled diabetics, excess incidence of death, major adverse cardiovascular events (MI, stroke, TIA), and heart failure were noted with it and hence withdrawn.

**SGLT 1 & 2 inhibitor (oral type 1 DM)-Sotagliflozin,** dual SGLT-inhibitor currently is in Phase 3 studies. The FDA New Drug Application for Sotagliflozin is based on data from the inTandem clinical trial program which includes three Phase 3 clinical trials assessing the safety and efficacy of Sotagliflozin in approximately 3,000 adults with inadequately controlled type 1 diabetes. The safety and efficacy data have not yet been evaluated by any regulatory authority. The target FDA action date under the Prescription Drug User Fee Act (PDUFA) is anticipated to be March 22, 2019.

**Drugs in research:** (drugs to come into the market):

#### The target therapy

1. PTP 1B (Protein Tyrosine Phosphatase 1B) acts as a negative regulator for both insulin and leptin signaling. Inhibition of PTP 1B could address both Diabetes and Obesity. Traditional therapeutics cannot specifically target PTP 1B. Anti sense based oligonucleotides inhibit the expression and activity of PTP 1B gene without affecting other highly related Tyrosine Phosphatases. Protein tyrosin phosphatase inhibitor-new thiazolidinediones, dual ppar  $\alpha/\gamma$  antagonist, vanadyl thiamine hydrochloride complex and several other synthetic and natural antagonists
2. The cannabinoid receptor inhibitors-rimonabant is in market since 1994,

3. GSK3 (glycogen synthase kinase inhibitor has shown to increase the rate of beta cell replication by 2-3 fold. 4. Acetyl coA carboxylase 1&2 inhibitors(ND-630)-reduces hepatic steatosis,improves insulin sensitivity and modulates dyslipidemias. 5. Glucagon receptor antagonists. 6. The intranasal monthly GLP1 agonist for diabetes and neurodegenerative disorders 7. Fibroblast growth factor 21 (FGF21) is a novel metabolic regulator produced primarily by the liver that exerts potent antidiabetic and lipid-lowering effects in animal models of obesity and type 2 diabetes mellitus.. Experimental studies have shown marked improvements in diabetes compensation and dyslipidemia after FGF21 administration in diabetic mice and primates.

### Monoclonal antibodies

To induce immune tolerance via monoclonal antibodies has been tried as a way to prevent and effectively treat diabetes. Otelixizumab, an anti-CD3 monoclonal antibody, is known to stimulate C-peptide levels and reduce insulin requirement in type 1 diabetes. Similarly studies with teplizumab are also reassuring. Other monoclonal antibodies such as anti-CD20, anti-CTGF, anti-IL-1 $\beta$ , have shown promising results and are yet to be approved.

### Dopamine-2 receptor agonist

Timed bromocriptine (centrally-acting dopamine D2 receptor agonist) is believed to act on circadian neuronal activities within the hypothalamus to reset abnormally elevated hypothalamic drive for increased plasma glucose, triglyceride, and free fatty acid levels in fasting and postprandial states in insulin-resistant patients.

Chromium (Cr) may reduce myocellular lipids and enhance insulin sensitivity in subjects with type 2 diabetes mellitus independent of its effects on weight or hepatic glucose production.[41] Clinical response to Cr is more likely in insulin-resistant type 2 diabetics with elevated fasting glucose and A1C levels

Proxyfan, a central histamine H3 receptor ligand, is shown to significantly improve glucose excursion by increasing plasma insulin levels via a glucose-independent mechanism

### Obesity and Type 2 Diabetes

Glycogen synthase kinase-3 (GSK-3) has important roles in the regulation of glycogen synthesis, protein synthesis, gene transcription, and cell differentiation in

various cell types .Increased GSK3 has been reported in type II diabetics and obese animal models.

Inhibitors of GSK3 have been demonstrated to have anti-diabetic effects in test tubes and animal model.Overexpression and overactivity of GSK-3 in the muscle of rodent models of obesityand type 2 diabetic humans are associated with an impaired ability of insulin to activate glucose disposal and glycogen synthase.

Increased hypothalamic GSK3 $\beta$  signaling contributes to deleterious effects of leptindeficiency and exacerbates high-fat diet-induced weight gain and glucose intolerance. Since obesity is pandemic and diabetes is endemic in present world.an agent addressing both the metabolic disorder is worthy research.

Newer targets:1. uncOCN: undercarboxylated form of Osteocalcin (uncOCN) : seems to have positive effects on the metabolic syndrome, including improvement of insulin resistance,  $\beta$ -cell function and dyslipidemia.2.INDY Gene ('I'm not dead yet'):Its deletion mimics aspects of dietary restriction and protects again adiposity and insulin resistance in mice3.VEGF-B Blocker. 4. 2H10ABHD6-  $\alpha/\gamma$  hydrolase domain-6: breaks down monoacylglycerol and thus negatively controls insulin release. Inhibition may help in treating diabetes.5.FFAR3:  $\beta$  cell short-chain fatty acid receptors.Newer drugs:Glargine U-300: Three-fold more concentrated formulation of GlargineReduced volume (1/3) and reduced surface area (1/2) of subcutaneous depotSlower and more constant rate of absorption Gla-300 provided sustained glycemic control with a lower risk of hypoglycemia compared with Gla-100

### DAPD: A Knowledgebase for Diabetes Associated Proteins.

Recent advancements in genomics and proteomics provide a solid foundation for understanding the pathogenesis of diabetes. Proteomics of diabetes associated pathways help to identify the most potent target for the management of diabetes. .. Thus, a web source "Diabetes Associated Proteins Database (DAPD)" has been developed to link the diabetes associated genes, pathways and proteins using PHP, MySQL. The current version of DAPD has been built with proteins associated with different types of diabetes. In addition, DAPD has been linked to external sources

to gain the access to more participatory proteins and their pathway network. DAPD will reduce the time and it is expected to pave the way for the discovery of novel anti-diabetic leads using computational drug designing for diabetes management.

#### **Available injections:**

**Insulins:**Rapid acting: Glulisine, Aspart, Lispro.Short acting: Regular Insulin.Intermediate acting: NPH.Long acting (basal): Glargine,, Detemer.Ultra-long acting (true basal)-degludeg

**GLP-1 analogues:** Exenatine, Lixisenatide, Liraglutide..Best option is early insulin overcoming the inertia of doctor and physicians. We now have evidence for action of insulin beyond glycemic control. These actions beyond glycemic control are 1. Improves beta-cell function(reduces glucotoxicity & Lipotoxicity) 2. Reverses insulin resistance 3.Beneficial effects on lipids and 4. Improves Quality of Life

**Insulin evolution:**Since discovery of insulin by Best and his teacher Banting treatment of diabetes mellitus has undergone a revolutionary change.Thomson the first diabetic victim treated with insulin has given the diabetic patients the light of insulin blessing.since 1922 manufacturer has brought into the market different brands of insulin.Initially it was crude(animal) bovine and porcine insulin.In 1977 the breakthrough came with mass production of insulin using recombinant technology ,the human insulin.1990 was the year of introduction of analog insulin.All the effort of discovering insulin with profile of human physiology.The tremendous improvement was in insulin delivery system

**Eras in the history of therapeutic insulin-100 years of lessons:**Insulin has proved to be a difficult molecule to isolate, to purify, and to understand.The major consequence is that we still give it subcutaneously, as 90 years ago, and we still have no small molecule analogues.Technologically, the major advances have been in manufacturing technology, allowing the production of rapid-acting and long-acting insulin analogues delivered by easy to use pen-injectors.

**Potential advantages of even faster-acting insulin analogues:**Earlier onset and peak of biologic activity.

Lower post-prandial glucose. Shorter duration of action. Less late prandial hypoglycaemia. Less biologic variability. Fewer glycaemic fluctuations. The action profiles of modern insulins, while an improvement on human insulin, do not accurately mimic the physiological release of endogenous insulin. Therefore, the aim of future insulins is to more closely mimic the endogenous response. We need ultra fast insulin to cover postprandial peak of blood glucose.Our aim is true basal to have twenty four hours flat profile,premix should have prandial peak only.

**Insulin delivery system:**The refill pen is the cheapest at present. Monitoring also have been changed.The continuous glucose monitoring (CGM) gives the exact ideas of fluctuation.Continuous subcutaneous insulin infusion(CSII)-the open and closed loop pump makes the delivery comfortable and ease to use costly system.The exubra and afrezza are inhalation insulin. Starts to work immediately after inhalation, peaks in about 12mins, and wanes off by 3 hrs. Oral Insulin Delivery Systems undergoing lot of clinical Trials.

**Smart insulin :** Smart insulins is something beyond CGM,CSII. It is defined as a pharmaceutical preparation which contains a 1. Inbuilt sensor mechanism to assess ambient hyperglycaemia, and 2. Ensures release of insulin based upon this information. **The patch** contain glucose responsive vesicles (GRV)-containing Micro Needle MN-array patch (smart insulin patch) for in vivo insulin delivery triggered by a hyperglycemic state to release combines the nanotechnology of tiny pyramid-shaped microneedles with pancreatic cells that detect glucose levels. The needles in the patch—each 800 micrometers long and thinner than a human hair—penetrate only the top layer of skin, making it painless. The duration of action of these nano-networks is 10 days in type 1 mice, and has been noted to last up to 14 days in some animal subjects.It works only when glucose is higher,donot release in normoglycemic state no risk for hypoglycemia. Scientists worldwide are working on administering smart insulin in different forms, such as capsules and patches. But the research is in its infancy - in many cases, human testing of smart insulin is not scheduled for several years.

**Bionic Pancreas** (not closed loop insulin pump only) is dual-chambered. It has

- Two separate pumps for delivering both insulin and glucagon,
- A continuous glucose monitor (CGM)
- A control algorithm built into an iPhone app.

The **bionic pancreas** system includes a continuous glucose monitor and a smart phone app that wirelessly connects with insulin and glucagon pumps

The bi hormonal “bionic pancreas” continues to perform well in clinical trials and could reach the US market by 2022.

### **Conclusion**

There is rapid and accelerated progress in the antidiabetics drug-development front that runs parallel to our ever evolving comprehension of the pathophysiology of diabetes. Clinicians need to be abreast of this plethora of newer antidiabetic drugs coming up, their efficacy, adverse effect profile and stand in diabetes management that empowers them to better manage diabetes.

<http://www.easdvirtualmeeting.org/resources/isis-ptp-1brx-a-novel-ntp-1b-antisense-inhibitorimproves-hba1c-and-body-weight-in-patients-with-type-2-diabetes-on-metforminsulphonylurea-3>.