CURRENT DIABETES MEDICATIONS, SIDE EFFECTS AND FUTURE TREATMENTS

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ABSTRACT

Diabetes is a growing global health concern and is closely related to the epidemic of obesity. Diabetes mellitus can have various complications such as retinopathy, nephropathy and neuropathy as well as macrovascular complications, owing to hyperglycemia and individual components of the insulin resistance. Various environmental factors including obesity, poor lifestyle, imbalanced diet, physical inactivity and genetic factors contribute to the multiple pathophysiological disturbances. The treatment must not only be effective and safe, it must also enhance the quality of life. Several novel medications are under development, but the greatest need is to improve the insulin sensitivity that collapse the progressive pancreatic β-cell failure that is the characteristic of type II diabetes mellitus and prevent the reverse microvascular complications. Various medications available till today also have some adverse side effects which needs to be overcome to provide a better life for the patients. This review article discusses about available medications in market for both type I and type II diabetes mellitus and their side effects along with the future treatments.

INTRODUCTION

A recent study states that the global diabetes statistics of 2018 is 463 million people (9.3%), growing up to 578 million people (10.2%) by 2030 and 700 million people (10.9%) by 2045. [1] Diabetes is a long-term condition with great impact within the lives of individuals, friends, families and society worldwide. It become the top 10 cause of death in adults. With the exception of exenatide, insulin, liraglutide and pramlintide, all are delivered orally and often named as oral hypoglycemic agents or oral antihyperglycemic agents. [2] Various types of medications and their availability depends on the person’s type of diabetes, gender, age, as well as other factors. Three main types of diabetes are type I where people make very little or no insulin in their body which make it mandatory for them the to take insulin on regular basis to control blood sugar level. [3] Type II people’s pancreas do not make enough insulin or the insulin that is produced by the pancreas cannot be absorbed by the cells with results in higher glucose level. Gestational diabetes occurs to pregnant women. Some women need to take insulin to control their blood glucose level. Many classes of medications that are often delivered orally and in combination show great effectiveness. The therapeutic combination in type II treatment may include insulin, not necessarily because oral agents have failed completely, but in search of a desired combination of effects. The major benefit of type II insulin injection is that a well-educated individual can adjust the dose, or even take additional dosage, when blood glucose level is measured by the patient, usually with a simple meter. [4]

Type I Diabetes is an autoimmune disease in which pancreas is unable to produce with stabilizes the blood glucose. In order to maintain the glucose level in blood one has to take insulin externally to prevent severe complications. If enough insulin hormone not provided to the body, the sugar level increases which means hyperglycemia and if it gets below the average level then it is known as hypoglycemia. [5]

Managing glucose in type 1 diabetes: Insulin is the primary medications that is suggested for the patients having type I diabetes. After the manufacture of exogenous or synthetic insulin in humans, insulin and symlin are two...
insulin solutions that are approved by the Food and Drug Administration (FDA) as the standard care for type I diabetes patients. [6]

In 1922 insulin was first used in humans with complete effectiveness. Initially insulin was produced by separating it from the animal pancreas mainly from dogs, goats and pigs. By 1978 people started to produce synthetically in laboratories and it commercial as exogenous or synthetic insulin. [6-7]

Treatment of type I diabetes is all about the perfect dose and duration of insulin given to the patient in order to better manage the glucose stored in the bloodstream. Glucose is the main source of energy which helps us to maintain our vital processes working correctly. Insulin needs to be absorbed or utilized completely by the body for proper energy production for our day to day life and maintain blood glucose level. [8]

Understanding the type of insulin that can be regulated properly: All types of insulin have the same effect in helping the stabilization of the blood sugar. The original form of glucose needs to be administered through the blood vessel (injection) so that the body can consume it completely or inhaled into the lungs so that the body can make good use of it.

There are several different insulin forms that is eligible for use in today’s market, these relies on the insurance coverage, our lifestyle and the overall needs. [9]

<table>
<thead>
<tr>
<th>TERM</th>
<th>ACTION TIME</th>
<th>LASTING TIME</th>
<th>MEDICATIONS</th>
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| Rapid-acting injections   | 5 to 15 minutes | 2 to 4 hours | • Insulin Lispro (Humalog)  
• Insulin Aspart (NovoLog)  
• Insulin Glulisine (Apidra) |
| Short-acting injections   | 30 minutes to 1 hour | 3 to 8 hours | • Regular Insulin (Humulin R and Novolin R)  
• Insulin Isophane, also called NPH insulin (Humulin N and Novolin N) |
| Intermediate-acting injections | 1 to 4 hours | 1 to 4 hours | • Insulin Glargine (Toujeo)  
• Insulin Detemir (Levemir)  
• Insulin Degludec (Tresiba) |
| Long-acting injections    | 1 to 2 hours | 14 to 24 hours | • Insulin lispro protamine and insulin lispro (Humalog Mix50/50 and Humalog Mix75/25)  
• Insulin aspart protamine and insulin aspart (novolog Mix 50/50 and novolog Mix 70/30)  
• NPH insulin and regular insulin (Humulin 70/30 and Novolin 70/30) |
| Premixed injections (combination of above insulins) | 5 minutes and 1 hour | 10 to 24 hours | • Insulin lispro protamine and insulin lispro (Humalog Mix50/50 and Humalog Mix75/25)  
• Insulin aspart protamine and insulin aspart (novolog Mix 50/50 and novolog Mix 70/30)  
• NPH insulin and regular insulin (Humulin 70/30 and Novolin 70/30) |

Table 1: Different forms of insulin for type I diabetes [10]

Disadvantages:

Cost: The insulin pumps are costlier in comparison to the syringes, while the insurance companies with policies only covers the insulin pumps. There is always a challenge to obtain NHS permission to support the insulin pumps expenses. [11]
Steep Learning Curve: The patient takes couple of days to get used to adjusting the medication packs and controlling the basal insulin doses and practicing the prevention issues like bubbling. [12]

Complications: There is a high risk of ketoacidosis development if the pump fails to work properly, this problem may appear due to the following causes:

- The battery drains off
- Inactivation of insulin due to heat
- If the tubing is loose
- If the supply runs dry

Therefore, it become difficult for the pump users to regularly monitor the blood glucose level. [13]

Inconvenience: The insulin pump needs to be worn by the person all the time, even while sleeping, rough sports like swimming, etc. This may become a problem because the hook can be stuck anywhere. [14]

Skin Problems: The region where the cannula is inserted always grows a scar tissue on that place. [15] These scars are not easy to remove and also reduces the response of insulin on that spot that’s why the person has to keep on changing the place for insulin pumps.

Wastage: While refilling the pump tank sometime it has the possibility that some parts of insulin get wasted which adversely affect the dosage information. [16]

Type II Diabetes is the most common type of diabetes people are facing all around the globe. About 90 percent diabetic patient are suffering from type II only. This is also known as insulin resistance. In this the pancreas produces the insulin but the cells cannot absorb the glucose through the surface receptors therefore it cannot get inside the cell and accumulate on the cell surface. [17] The accumulated glucose increases the blood sugar level that leads to hyperglycemia. If the cell cannot absorb the glucose then it cannot metabolize it and unable to produce energy for our day to day work.

Type II diabetes is mainly found in older people but nowadays due to increased obesity and inadequate diet it started to show in babies and teens also. Type II diabetes treatment is the result of a balanced lifestyle, improved physical exercise and a maintained body weight. Oral medicines and insulins are used as to regulate the blood glucose rates in our body. [18-19]

<table>
<thead>
<tr>
<th>DRUG</th>
<th>APPLICATION</th>
<th>COMPOSITION INCLUDED</th>
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<tbody>
<tr>
<td>Sulfonylureas</td>
<td>• Improve the secretion of insulin into the blood by the pancreas</td>
<td>• Glimepiride (amaryl)</td>
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<td></td>
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<td>• Glipizide (glucotrol)</td>
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<td></td>
<td>• Glyburide (diabeta, micronase, glynase)</td>
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<tr>
<td>Meglitinides</td>
<td>• Enhance insulin secretion</td>
<td>• Nateglinide (starlix)</td>
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<td>• Also improve the effectiveness of the body in releasing insulin during meals</td>
<td>• Repaglinide (prandin)</td>
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<tr>
<td>Medications</td>
<td>Description</td>
<td>Examples</td>
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| Biguanides                        | • Increase the effect of insulin  
                                   • Decrease the amount of glucose the liver releases into the blood  
                                   • Also increase the uptake of blood glucose into the cells | Metformin is the only licensed biguanide in the United States, in the form of  
                                  • Glucophage  
                                  • Glucophage xr  
                                  • Glumetza  
                                  • Riomet  
                                  • Fortamet |
| Thiazolidinediones                 | • Reduce the resistance of tissues to the effects of insulin  
                                   • Have been associated with serious side effects, so they need monitoring for potential safety issues | Ioglitazone (Actos)  
                                  Rosiglitazone (Avandia) |
| Alpha-glucosidase inhibitors      | • Cause carbohydrates to be digested and absorbed more slowly  
                                   • Lower glucose levels in the blood after meals | Acarbose (Precose)  
                                  Miglitol (Glyset) |
| Dipeptidyl peptidase inhibitors   | Slow the rate of the stomach contents emptying further along the gut, and so slow down glucose absorption | Alogliptin (Nesina)  
                                  Linagliptin (Tradjenta)  
                                  Sitagliptin (Januvia)  
                                  Saxagliptin (Onglyza) |
| Sodium-glucose co-transporter 2 inhibitors | • Cause the body to expel more glucose into the urine from the bloodstream  
                                   • Might also lead to a modest amount of weight loss, which can be a benefit for type 2 diabetes | Canagliflozin (Invokana)  
                                  Dapagliflozin (Farxiga)  
                                  Empagliflozin (Jardiance)  
                                  Ertugliflozin (Steglatro) |
| Incretin mimetics                 | • Mimic the hormone incretin, which stimulates insulin release after meals | Exenatide (Byetta, Bydureon)  
                                  Liraglutide (Victoza)  
                                  Dulaglutide (Trulicity)  
                                  Lixisenatide (Adlyxin)  
                                  Semaglutide (Ozempic) |
| Glucagon-like peptide-1 receptor agonist (GLP-1 receptor agonists) | • Similar to the natural hormone called incretin  
                                   • Increase B-cell growth | Albiglutide (Tanzeum)  
                                  Dulaglutide (Trulicity)  
                                  Exenatide (Byetta)  
                                  Exenatide extended-release (Bydureon)  
                                  Liraglutide (Victoza)  
                                  Semaglutide (Ozempic) |
| Meglitinides                       | • Help your body release insulin  
                                   • In some cases, they may lower blood sugar too much | Nateglinide (Starlix)  
                                  Repaglinide (Prandin)  
                                  Repaglinide-Metformin (Prandimet) |
Sodium-glucose transporter (SGLT) 2 inhibitors

- work by preventing the kidneys from holding on to glucose
- body gets rid of the glucose through urine

- dapagliflozin (Farxiga)
- dapagliflozin-metformin (Xigduo XR)
- canagliflozin (Invokana)
- canagliflozin-metformin (Invokamet)
- empagliflozin (Jardiance)
- empagliflozin-linagliptin (Glyxambi)
- empagliflozin-metformin (Synjardy)
- ertugliflozin (Steglatro)

Table 2: Glimpse of Type II Diabetes Mellitus drugs [20]

Potential side effects of some common type II antidiabetic drugs:

- Sulfonylureas: lowers blood sugar level, skin rash, stomach pain, weight gain.
- Biguanides/Metformin: Metal taste, sickness with alcohol, kidney complications, stomach ache [21]
- Alpha-glucosidase inhibitors: bloating and diarrhea, gas
- Thiazolidinediones: increase risk of live disease, weight gain, anemia [22]
- Meglitinides: Low blood sugar, weight gain [23]
- Dipeptidyl peptidase inhibitors: upper respiratory tract infection, nasopharyngitis, and headache with sitagliptin, urinary tract infection [24]
- Sodium-glucose co-transporter 2 inhibitors: Genital yeast infections in men and women, Urinary tract infections, Increased urination, Kidney problems, Urinary discomfort
- Incretin mimetics: Diarrhea, nausea, vomiting, headache, dizziness, increased sweating, indigestion, constipation [25]
- Glucagon-like peptide-1 receptor agonist: Nausea, vomiting, headache, weakness, abdominal pain. [26]

THE FUTURE OF DIABETES TREATMENT AND MEDICATIONS

Advancement in diabetic management: Introducing new therapies: Doctors are looking to use a different class of medications named as SGLT2 inhibitors including insulin. Within these studies there is one named DEPICT that gave placebo or dapagliflozin to patients. Patients became to have better AICs and time in range (TIR), lost more weight in comparison to those not on this treatment. [27-29] Another sequence of seven randomized placebo-controlled studies, including empagliflozin as an adjunctive to insulin, or EASE trials of a sodium glucose co-transporter 2, SGLT2 receptor, Jardiance. [30] These medications block the reabsorption of some glucose in the kidneys so the excess glucose is ejected through the urine. This way of medication also proved to lose weight much easier. For those who are not ready to take insulin by syringes, an oral insulin capsule is under development. People can also look for ORA-Lyn, an insulin spray that is applied in the cheek. [30-31]

An unbalanced structure of microbiota has been observed in diabetes patients. Researchers at the University of Amsterdam have recently demonstrated the transplant of a balanced person’s microbiota to the gut of one with diabetes, which may result in short term increase resistance in obese patients with type II diabetes. [32]
diabetes industry is expected to reach a dramatically high €86 Billion by 2025 including both type I and type II. [33]

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