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 type1 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 is 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]**

TERM	ACTION TIME	LASTING TIME	MEDICATIONS
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)
Intermediate-acting injections	1 to 4 hours	1 to 4 hours	• Insulin Isophane, also called NPH insulin (Humulin N and Novolin N)
Long-acting injections	1 to 2 hours	14 to 24 hours	• Insulin Glargine (Toujeo) • Insulin Detemir (Levemir) • Insulin Degludec (Tresiba)
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]**

DRUG	APPLICATION	COMPOSITION INCLUDED
Sulfonylureas	• Improve the secretion of insulin into the blood by the pancreas	• Glimepiride (amaryl) • Glipizide (glucotrol) • Glyburide (diabeta, micronase, glynase)
Meglitinides	• Enhance insulin secretion • Also improve the effectiveness of the body in releasing insulin during meals	• Nateglinide (starlix) • Repaglinide (prandin)

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 • Lowers 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 II 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 growt	• 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]** The

diabetes industry is expected to reach a dramatically high €86 Billion by 2025 including both type I and type II. **[33]**

REFERENCES

1. Pouya Saeedi, Inga Petersohn, Paraskevi Salpea, Dominic Bright, Rhys Williams, on behalf opf the IDF Diabetes Atlas Committee: Global and regional diabetes prevalence estimates for 2018 and projectiopns for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edition:Volume 157, 107843, Janurary, 1, 2018
2. International Diabetes Federation. IDF Diabetes Atlas, 4th ed. Brussels, Belgium: International Diabetes Federation; 2009.
3. Aaboe K, Knop FK, Vilsboll T, et al. Twelve weeks treatment with the DPP-4 inhibitor, sitagliptin, prevents degradation of peptide YY and improves glucose and non-glucose induced insulin secretion in patients with type II diabetes mellitus. Diabetes Obes Metab. 2010 Apr;12(4):323–33
4. Apovian CM, Bergenstal RM, Cuddihy RM, et al. Effects of exenatide combined with lifestyle modification in patients with type II diabetes. Am J Med. 2010 May;123(5):468 e9–17
5. Abdelgadir M, Elbagir M, Eltom M, Berne C. The influence of glucose self-monitoring on glycaemic control in patients with diabetes mellitus in Sudan. Diabetes Research and Clinical Practice. 2006;74(1):90–94
6. Brunetti P, Muggeo M, Cattin L, Arcangeli A, Pozzilli P, Provenzano V, et al. Incidence of severe nocturnal hypoglycemia in patients with type I diabetes treated with insulin lispro or regular human insulin in addition to basal insulin glargine. Nutrition, Metabolism, and Cardiovascular Diseases. 2010;20(7):519–526
7. Beck RW, Lawrence JM, Laffel L, Wysocki T, Xing D, Huang ES, et al. Quality-of-life measures in children and adults with type I diabetes: Juvenile Diabetes Research Foundation Continuous Glucose Monitoring randomized trial. Diabetes Care. 2010;33(10):2175–2177
8. Battelino T, Conget I, Olsen B, Schutz-Fuhrmann I, Hommel E, Hoogma R, et al. The use and efficacy of continuous glucose monitoring in type I diabetes treated with insulin pump therapy: a randomised controlled trial. Diabetologia. 2012;55(12):3155–3162.
9. Eeg-Olofsson K, Cederholm J, Nilsson PM, Zethelius B, Svensson AM, Gudbjornsdottir S, et al. Glycemic control and cardiovascular disease in 7,454 patients with type I diabetes: an observational study from the Swedish National Diabetes Register (NDR). Diabetes Care. 2010;33(7):1640–1646.
10. Amy Hess-Fischl MS, RD, LDN, BC-ADM, CDE and Daphne E. Smith-Marsh PharmD, CDE | Reviewed by W. Patrick Zeller MD: Type I Diabetes Treatments: Learn about the different types of insulin for type I diabetes and newer therapies to help you better manage your glucose better.
11. Bode BW. Use of rapid-acting insulin analogues in the treatment of patients with type I and type II diabetes mellitus: Insulin pump therapy versus multiple daily injections. Clin Ther. 2007;29(Suppl 4):S135–S144
12. National Institute for Health and Clinical Excellence. Technology Appraisal Guidance Number 151: Continuous Subcutaneous Insulin Infusion for the Treatment of Diabetes Mellitus. London: National Institute for Health and Clinical Excellence; 2008.
13. American Diabetes Association. Standards of medical care in diabetes—2009. Diabetes Care. 2009;32(Suppl 1):S13–S61
14. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. N Engl J Med. 1993;329:977–986.
15. Pickup JC. Renard E. Long-acting insulin analogs versus insulin pump therapy for the treatment of type I and type II diabetes. Diabetes Care. 2008;31(Suppl 2):S140–S145.
16. Bode BW. Use of rapid-acting insulin analogues in the treatment of patients with type I and type II diabetes mellitus: Insulin pump therapy versus multiple daily injections. Clin Ther. 2007;29(Suppl 4):S135–S144
17. Gupta AK, Smith SR, Greenway FL, et al. Pioglitazone treatment in type II diabetes mellitus when combined with portion control diet modifies the metabolic syndrome. Diabetes Obes Metab. 2009 Apr;11(4):330–7. 2009.
18. Bakris GL, Ruilope LM, McMorn SO, et al. Rosiglitazone reduces microalbuminuria and blood pressure independently of glycemia in type II diabetes patients with microalbuminuria. J Hypertens. 2006 Oct;24(10):2047–55. 2006
19. Malone JK, Bai S, Campaigne BN, et al. Twice-daily pre-mixed insulin rather than basal insulin therapy alone results in better overall glycaemic control in patients with Type II diabetes. Diabet Med. 2005 Apr;22(4):374–81. 2005.
20. Arun Chaudhury, Chitharanjan Duvoor, Vijaya Sena Reddy Dendi, Shashank Kraleti, Aditya Chada, Rahul Ravilla, Asween Marco, Nawal Singh Shekhawat, Maria Theresa Montales, Kevin Kuriakose, Appalanaidu Sasapu, Alexandria Beebe,

Naveen Patil, Chaitanya K. Musham, Govinda Prasad Lohani and Wasique Mirza: Clinical Review of Antidiabetic Drugs: Implications for Type II Diabetes Mellitus Management: 24 January 2017

21. Internal Clinical Guidelines Team. Type II Diabetes in Adults: Management. London: National Institute for Health and Care Excellence; (2015).
22. Inzucchi SE1, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycaemia in type II diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia. 2012;55:1577–1596
23. Perez-Monteverde A, Seck T, Xu L, et al. Efficacy and safety of sitagliptin and the fixed-dose combination of sitagliptin and metformin vs. pioglitazone in drug-naive patients with type II diabetes. Int J Clin Pract. 2011 Sep;65(9):930–8
24. Pavo I, Jermendy G, Varkonyi TT, et al. Effect of pioglitazone compared with metformin on glycemic control and indicators of insulin sensitivity in recently diagnosed patients with type II diabetes. J Clin Endocrinol Metab. 2003 Apr;88(4):1637–45. 2003
25. Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, et al. Management of hyperglycemia in type II diabetes, 2015: a patient-centered approach: update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care (2015) 38(1):140–9.10.2337/dc14-2441
26. Inzucchi SE, Lipska KJ, Mayo H, Bailey CJ, McGuire DK. Metformin in patients with type II diabetes and kidney disease: a systematic review. JAMA (2014) 312(24):2668–75.10.1001/jama.2014.15298
27. Wing RR, Bolin P, Brancati FL, Bray GA, Clark JM, Coday M, Crow RS, Curtis JM, Egan CM, Espeland MA, et al. Cardiovascular effects of intensive lifestyle intervention in type II diabetes. N Engl J Med. 2013;369:145–154
28. . Nathan DM, Buse JB, Davidson MB, Ferrannini E, Holman RR, Sherwin R, Zinman B. Medical management of hyperglycemia in type II diabetes: a consensus algorithm for the initiation and adjustment of therapy: a consensus statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care. 2009;32:193–203
29. Escalante-Pulido M, Escalante-Herrera A, Milke-Najar ME, Alpizar-Salazar M. Effects of weight loss on insulin secretion and in vivo insulin sensitivity in obese diabetic and non-diabetic subjects. Diabetes Nutr Metab. 2003;16:277–283
30. Andrews RC, Cooper AR, Montgomery AA, Norcross AJ, Peters TJ, Sharp DJ, Jackson N, Fitzsimons K, Bright J, Coulman K, et al. Diet or diet plus physical activity versus usual care in patients with newly diagnosed type II diabetes: the Early ACTID randomised controlled trial. Lancet. 2011;378:129–139.
31. Cappuccio FP, Cooper D, D'Elia L, Strazzullo P, Miller MA. Sleep duration predicts cardiovascular outcomes: a systematic review and meta-analysis of prospective studies. Eur Heart J. 2011;32:1484–1492.
32. Sha S, Devineni D, Ghosh A, Polidori D, Hompesch M, Arnolds S, Morrow L, Spitzer H, Demarest K, Rothenberg P. Pharmacodynamic effects of canagliflozin, a sodium glucose co-transporter 2 inhibitor, from a randomized study in patients with type II diabetes. PLoS One. 2014;9:e105638
33. Bolinder J, Ljunggren Ö, Johansson L, Wilding J, Langkilde AM, Sjöström CD, Sugg J, Parikh S. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type II diabetes mellitus inadequately controlled on metformin. Diabetes Obes Metab. 2014;16:159–169.