Current Advancements in Anti-Diabetic Drugs

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ABSTRACT

Diabetes mellitus is among the top 10 life threatening diseases across the globe. It can further cause fatal diseases like cardiovascular complications, atherosclerosis, nephropathy etc. This disease affects millions of people each year in both rural as well as urban areas. Currently, many anti-diabetic drugs are available commercially, but there are many problems or side effects that are related to those drugs like hyperglycemia or hypoglycemia. With the help of advance technology, new formulations are being produced or modifications are being performed on the existing drugs for better efficacy. This review mainly focuses on the current advancements in the anti-diabetic drugs.

KEYWORDS

Diabetes, anti-diabetic, cardiovascular diseases, glucose levels, β-cells.

INTRODUCTION

Diabetes mellitus (commonly known as diabetes) is a chronic condition in which the concentration of glucose is higher than the normal levels in the blood and less glucose is present inside the cells. Glucose is the major source of energy to our body. The proper uptake of glucose by the cells is necessary for the body to remain in stable condition. Insulin is a hormone, secreted by β-cells of pancreas to maintain the blood glucose levels. In a healthy individual, this hormone is continuously secreted at low basal levels directly into the bloodstream. Blood insulin level in continuously up or down-regulated as per the blood glucose levels at a given instant. But in case of diabetes, body is unable to produce effective levels of insulin to regulate sugar levels. It can lead to condition like hyperglycemia (high blood glucose).

Between 1979 and 2000, the occurrence of diabetes has increased to 10 fold that is from 1.2 % to 12.1%. It was estimated that in 2011-12, about 61 million people between the age group of 19-78 years would get diagnosed with diabetes in India and it is anticipated that by 2030 this figure will increase to 101 million. The international diabetes federation has reported that in 2012, around 1 million people died in India due to this disease. According to WHO, if in a low-income family a diabetic patient is there then almost 25% of the family income get spent on diabetic medications only [4].

Diabetes can be classified into- Type-1, gestational diabetes and Type-2.

Type-1 Diabetes: Earlier it was called as insulin-dependent diabetes. It happens due to the destruction of pancreatic β- cells by our immune system [7]. The symptoms include excessive urine excretion, increased appetite, weight loss, loss of vision etc.

Gestational Diabetes: It occurs during pregnancy. In future, mother or child are a risk of suffering from type 2 diabetes.

Type-2 Diabetes: Earlier it was known as non-insulin dependent diabetes. It is estimated that approximately 90% of diabetic patients suffer from this type of diabetes [5]. It occurs due to excess body weight and less physical

activity. It shows similar symptoms of type 1 diabetes. It can be detected when our own body cells fails to respond to insulin. In other words, cells become resistant to insulin [3].

People suffering from diabetes are at high risk of having cardiovascular diseases, kidney failure, loss of vision and amputation of lower limb due to neural damage. It can't be cured but it can be managed by intake of healthy diet, reducing alcohol and tobacco consumption and by becoming more physically active [7].

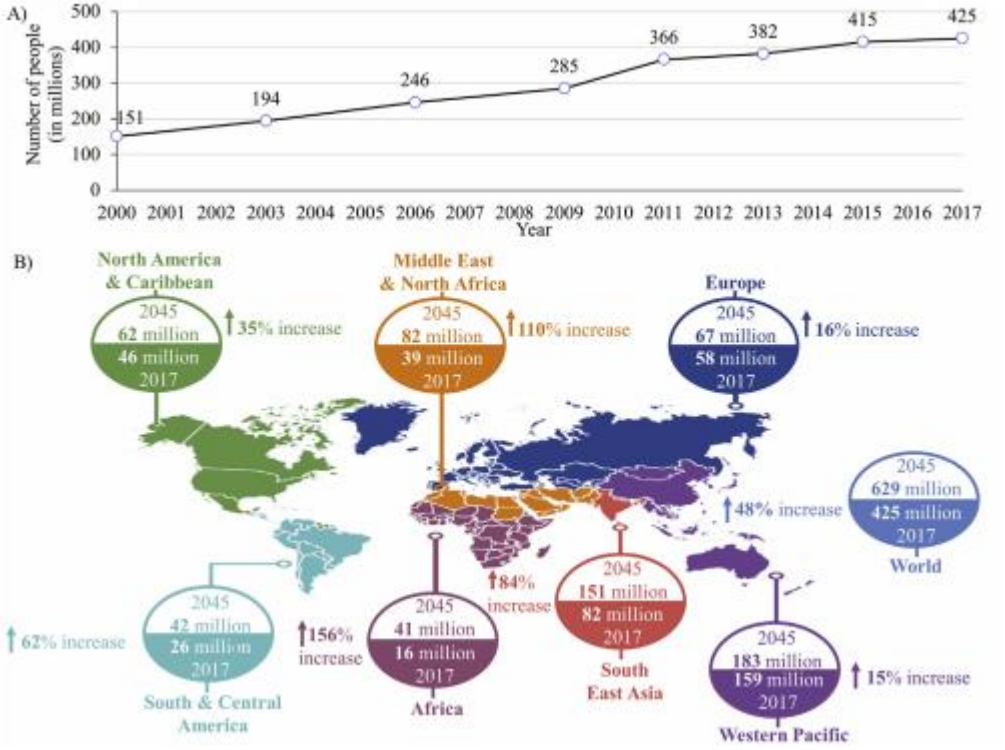

Figure 1- Worldwide population of diabetic patients. (A) Number of adults (19–78 years) suffering from diabetes in 2000-17, (B) Estimated rise in diabetic population (19–78 years) in 2045 in comparison to 2017 [7].

The most common anti-diabetic drugs used till now are- metformin, sulfonylureas, thiazolidinedione, α-glucosidase inhibitors, and glucagon like peptide-1 and dipeptidyl-peptidase 4 inhibitors. But these drugs also show various side effects like, weight gain, nausea, abdominal pain, diarrhea etc [3]. The research is still going on to discover novel, better and safer drugs or methods to treat this disease. The modifications are being done on the existing drugs also. Various factors like increase in bioavailability, extended release of drugs, fast-activity are under consideration to achieve better results. Each drug has a distinct mechanism of action which is not dependent on the functioning of β-cells. So there are chances that combination therapy which means using various anti-diabetic drugs or insulin could have better curing potential. Currently available drugs are less effective over time, so there is an immediate need for new advancements o occur in this field [2]. In this study, we have focused on the advancements on anti-diabetic drugs.

DISCUSSION

1. **Dipeptidyl peptidase-4(DPP-4) inhibitors:**
   These are anti-diabetic agents that are capable of maintaining blood glucose levels efficiently and show long-term effects. Their mechanism of action consists of inhibition of DPP-4 enzyme's functioning and therefore, increasing the half-life of glucagon-like peptide 1 (GLP-1). Commonly used DPP-4 inhibitor

are- omarigliptin, sitagliptin, saxagliptin and alogliptin [1]. Normal levels of hemoglobin (HbA1c) are observed, when patient is using DPP-4 inhibitor medications.

According to earlier studies it was found that majority of people taking anti-diabetic drugs are at high risk of suffering from cardiovascular disorders. So, it becomes essential to check the effects of DPP-4 inhibitors on such patients. Therefore, a systematic comparison was done between DPP-4 inhibitor users and non-DPP-4 inhibitor users. In this, 157,478 patients with diabetes were included out of which approximately 76,000 were assigned to the test group and around 81,000 were assigned as the control group. The data was collected between the years 2007-2017.

Table 1-Data collected from the study.

Type of study	Time period of patients' enrollment	Total no of patients assigned to DPP-4 inhibitors (n)	Total no of patients assigned to control group (n)
RCT	2012–2017	2092	2100
RCT	2008–2015	7332	7339
OS	2007–2011	1866	5179
RCT	2010–2011	8280	8212
OS	2009–2013	53,208	53,208
OS	2009–2011	547	2735
RCT	2009–2013	2701	2679

(Abbreviations: RCT-Randomized controlled trials, OS- Observational studies).

The final analysis showed that non-DPP-4 inhibitor users were having more cardiovascular outcomes than the DPP-4 inhibitor users. Majority cases of cardiovascular deaths or hospitalization due to cardiovascular complication were non-DPP-4 inhibitor users.

2. **Sodium glucose co-transporters(SGLT) inhibitors:**

It is a new strategic treatment of diabetes. The first known SLGT inhibitor was Phlorizin (1835), a β-glucoside which occurs naturally. Phlorizin was extracted from the bark of apple tree. Theses anti-diabetic agents does not stimulate the insulin secretion. Their mechanism of action is not dependent on the functioning of β- cells of islets of Langerhans. They decrease the blood glucose levels by promoting the removal of glucose from our body through urine excretion. These drug basically inhibits the reabsorption of glucose from renal tubules. These drug basically inhibits the reabsorption of glucose from renal tubules This reduction in glucose levels improves the sensitivity of liver to insulin. The hepatic glucose production gets suppressed and improvement is observed in the patient's state. They also helps in reducing the calories and thereby causes weight loss. They can be classified as- SLGT1 and SLGT2 [3].

Table 2- Comparison between SLGT1 and SLGT2

	SGLT1	SGLT2
Site	Mainly intestine, other sites include brain, skeletal and heart muscle, liver, lungs, kidneys	Kidney
Gene encoding	SLC5A1	SLC5A2
Substrate	Glucose or galactose	Glucose
Affinity for glucose	High	Low
Capacity for glucose transport	Low	High
Main function	Dietary glucose absorption	Renal glucose reabsorption
Renal location	Late proximal straight tubule (S3)	Early proximal convoluted tubule (S1 and S2)
Percentage of renal glucose reabsorption	10%	90%
Mutation of encoding gene	Glucose/galactose malabsorption, leading to fatal diarrhoea*	Familial renal glucosuria, a benign condition
Inhibitors of transporter	Selective SGLT1 inhibitors: KGA2727 (Kessei Pharmaceutical Co. Ltd) GSK1614235/ KGA3235 (Kissei Pharmaceuticals Co. Ltd, GlaxoSmithKline plc)	Dapagliflozin, canagliflozin, empagliflozin etc. advanced in clinical trials

*The gastro-intestinal infections were not reported during clinical trials. (Abbreviation: SLC- Solute carrier family) [3].

According to various studies it is observed that SLGT2 inhibitors show therapeutic effect only in those diabetic patients which have normal renal functioning. So, it is advised to monitor renal functioning before starting the course of this medication. Otherwise, adverse consequences would occur.

Commercially, many SLGT 2 inhibitors are available with better properties like resistance to intestinal degradation, increased oral bioavailability [3].

Table 3- Examples of SLGT2 inhibitors.

Drug candidate	Manufacturing company
Canagliflozin	Johnson & Johnson
Empagliflozin (BI 10773)	Boehringer Ingelheim
Ipragliflozin (ASP 1941)	Astella Pharma. Inc.
LX 4211*	Lexicon Pharmaceuticals
Luseogliflozin (TS071)	Taisho Pharmaceuticals Co. Ltd
Tofogliflozin (CSG452)	Chugai Pharmaceuticals
Ertugliflozin (PF 04971729)	Pfizer
EGT1474	Theracos Inc.
ISIS 388626	Isis Pharmaceuticals

*It is a dual SLGT1 and SLGT2 inhibitor [3].

3. **NaoXinTong (NXT) Capsules:**
   It is originated in China which is used to treat cardio-vascular or cerebro-vascular diseases. But clinical studies shows that it has anti-diabetic properties also. It's mechanism of action is not clear. It is observed that long-term course of statins (another anti-diabetic drug) can cause conditions like diabetic nephropathy. Diabetic nephropathy is a disease in which the kidney of diabetic patient gets damaged. In such cases NXT capsules can be used to inhibit or suppress the disease.
   NXT capsule is a powdery mixture of eleven herbs having medicinal properties. Those herbs are- Astragali Radix (Huangqi), Paeoniae Radix Rubra (Chishao), Salviae miltiorrhizae Radix et Rhizoma (Danshen), Persicae Semen (Taoren), Angelicae Sinensis Radix (Danggui), Achyranthis bidentatae Radix (Niuxi), Chuanxiong Rhizoma (Chuanxiong), Spatholobi Stem (Jixueteng), Cinnamomi Ranulus (Guizhi), Carthami Flos (Honghua) and Mori Ramulus (Sangzhi). Along with the herbs it also contains two types of

resin based medicines [Olibanum (Ruxiang) and Myrrha (Moyao)] and three types of animal based medicines [Scorpio (Quanxie), Pheretima (Dilong) and Hirudo (Shuizhi)].

Recently, 16 new compounds have been discovered in formulation of NXT capsules. Those 16 compounds are further classified into 6 types-

- Phenolic acids (gallic acid, chlorogenic acid, ferulic acid, 3, 5-dicafeoylqunic acid, 1, 5-dicafeoylqunic acid, rosmarinic acid, lithospermic acid and salvianolic acid B).
- Flavonoids (kaempferol-3-o-rutinoside, caycosin and formononetin).
- Lactones (ligustilide and butyllidephthalide).
- Monoterpenoids (paeoniforin).
- Phenanthraquinones (cryptotanshinone).
- Furans (5-hydroxymethylfurfural).

To check the impact of NXT capsules on blood glucose levels, lipid profiles and diabetic nephropathy db/db mice is used an animal model. The db/db mice was injected orally with NXT for fourteen weeks. The study shows that NXT improves glucose metabolism by activating insulin signaling pathway. It also improves glomerular functions and hence, inhibits diabetic nephropathy disease [6].

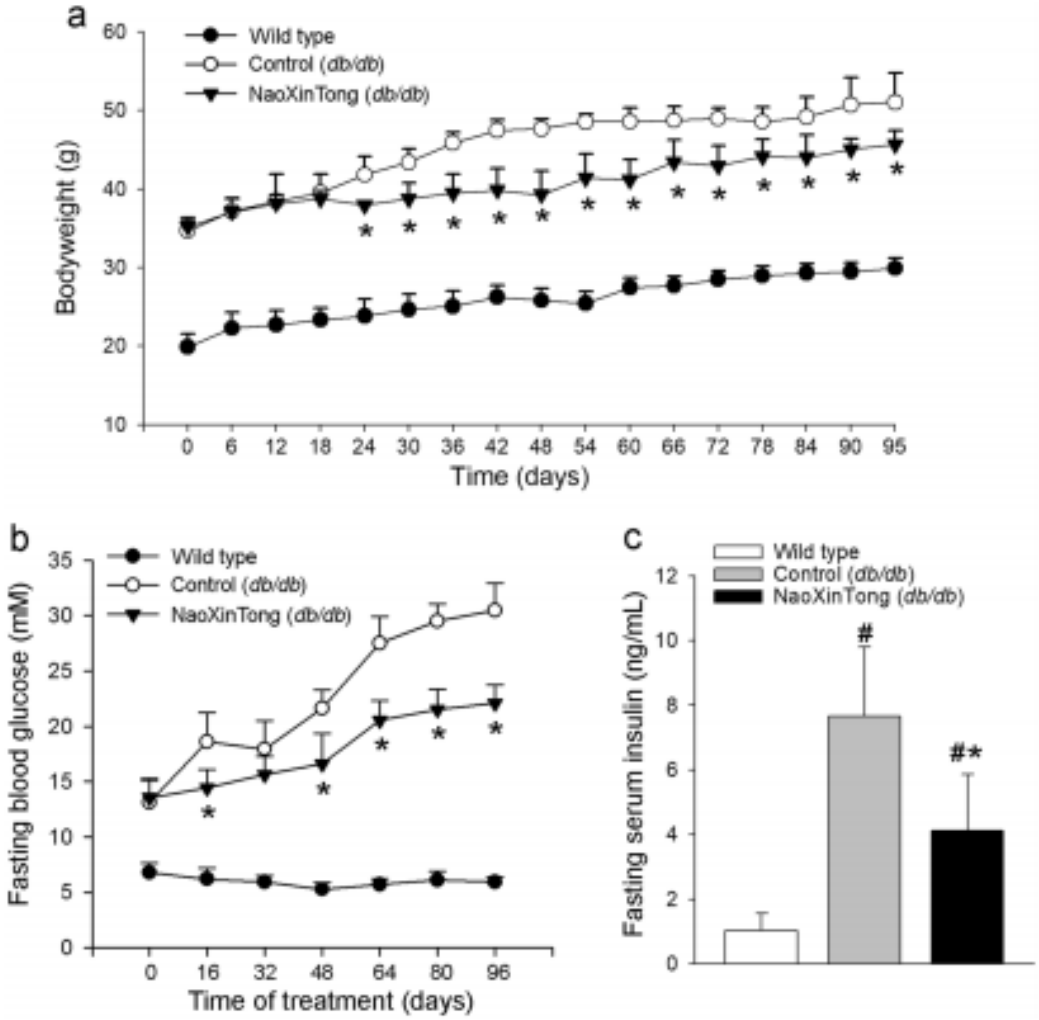

Figure 2- NXT prevents hyperglycemic condition induced due to diabetes in db/db mice. Male db/db mice (~6-week old) in two groups (10/group) received the mentioned treatment continuously for fourteen weeks: Control group, mice were fed normal chow; In NaoXinTong (NXT) group, mice were fed normal chow which also contains

NXT (620 mpk). Wild type mice fed normal chow were used as the normal control. During the course of treatment, some factors like (a) mouse bodyweight and (b) fasting blood glucose levels were measured, at the particular time. At the end of study, (c) fasting blood insulin levels were also obtained. * p <0.05 vs db/db control group; #p <0.05 vs wild type group (n=10) [6].

4. Nano-medicines:

Nano-formulations is a promising solution for the treatment of diabetes. The need of nano-medicine arises due to the problems related to solubility and permeability of available anti-diabetic drugs. Sulfonylurea shows less bioavailability. Metformin has high solubility but low permeability which causes slow or incomplete absorption of the drug. In case of thiazolidinedione, poor bioavailability is seen therefore less therapeutic effects are observed. In some cases, drug is administered through subcutaneous which may cause itching or irritation at the site of injection. To overcome the mentioned issues, nano-medicines come into play.

According to several studies it has been reported that when sulfonylureas are delivered by nano-formulations, higher bioavailability and improved are under curve (AUC) is obtained. Sustained release nano-formulations of metformin have been prepared to overcome the permeability problems.

When nano-structured lipid carriers of pioglitazone is integrated inside the transdermal patch, then the reduction is observed in blood glucose levels which lasts for up to 24 hours. On the other hand, the effect of other medications lasts for only 6 hours [7].

Table 4- Few examples of nano-formulations [7].

Drug	Drug Delivery System	Dose and Route of Administration(*only for in vivo studies*)	Remarks
Nanoparticles (NPs)			
Metformin	Chitosan and gum arabic NPs (146.5 ± 8.7 nm)	40 mg/kg (~9.2 mg/kg metformin), for 21 days, orally	Significant reduction in fasting BGL as compared to pure metformin (150 mg/kg, orally)
	Alginate NPs (60–150 nm)	1.5 g/kg (~46.8 mg/kg metformin), orally	Significant reduction in BGL as compared to pure metformin (150 mg/kg, i.p.)
	Chitosan-PLGA NPs (506.7 ± 13.6 nm)	–	Burst release (~20%) within 30 min, 98% release within 144 h
	Eudragit®RSPO and Eudragit/PLGA NPs (268.8–288 nm)	–	Initial burst release (74–80%) followed by sustained release (92%–100%) in 12 h and 24 h for Eudragit®RSPO NPs and Eudragit/PLGA NPs respectively
	Chitosan based mesoporous MCM-41 (5.8 nm) and MCM-41 (5.93 nm) – aminopropylsilane NPs	–	Sustained release till 15 days, no cellular toxicity
Pioglitazone	Polaxomer 188 and Eudragit L 100 NPs (138.8 nm)	–	97.5% drug released within 60 min with 10 folds increase in drug solubility than of pure drug
Glipizide	PLGA NPs and Eudragit RS 100 NPs (~200 nm)	800 μg/kg, orally (single dose)	Sustained release till 24 h, excellent biocompatibility in cells
	PLGA NPs (522 ± 5.2 nm)	–	8.7% drug release in 1 h, with slow release up to 19% within 12 h, followed by sustained release (91%) till 72 h
	Polycaprolactone NPs (209.6 nm)	800 μg/kg, t.i.d for 7 days	Decrease in BGL not more than 25% (in 1 h) thus lowering the chances of hypoglycemia, levels maintained for 7 days
	Alginate and chitosan NPs (253.7 ± 10.4 nm)	–	~50% drug release within 5 h, followed by a sustained release till ~24 h (~80%), MRT of 12.34 ± 1.34 h
Glimepiride	Lipoid S 100, PEG 600 and PVPK 30 nanocrystals (200–400 nm)	5 mg/kg of capsule (~2 mg of glimepiride), i.g.	*Dose ~2 mg of glimepiride* / $AUC_{(0-36h)}$ (μg min/mL) / MRT (min) / $t_{1/2}$ (min) / C_{max} (μg/mL)
			Marketed preparation, i.g. / 421.49 ± 97.93 / 698 ± 28.92 / 61.74 ± 23.59 / 0.55 ± 0.104
			Microcrystals loaded capsules, i.g. / 405.49 ± 66.91 / 671.49 ± 80.36 / 31.24 ± 15.3 / 0.48 ± 0.041
			Nanocrystals / 769.93 ± 115.53 / 896.55 ± 88.06 / 106.21 ± 15.3 / 0.65 ± 0.032
	Eudragit RLPO nanosuspension (~525 nm)	2.5 mg/kg/day, orally (7 days)	Higher $AUC_{(0-24h)}$ of 6460.80 ng h/mL, compared to AUC of glimepiride suspension (2.5 mg/kg/day, orally) of 3172.3 ng h/mL, lesser side effects
Glibenclamide	HPMC K15M and lactose NPs (168.6 nm)	5 mg/kg, orally	*Dose ~5 mg/kg drug, orally* / $AUC_{(0-\infty)}$ (ng h/mL) / $t_{1/2}$ (h) / C_{max} (ng/mL)
			Pure drug (in water) / 71680.24 ± 63.6 / 5.73 ± 0.42 / 9428.42 ± 897.8
			NPs / 172383.64 ± 237.2 / 9.57 ± 0.23 / 24451.14 ± 2170.5
	HPMC NPs (220 nm)	–	Higher drug dissolution of NPs (85%), when compared with pure drug (35%) and commercial preparation (56%) in 5 min; 88% dissolution by NPs and commercial preparation in 45 min, compared with 55% by pure drug
Repaglinide	PLGA and methoxypolyethylene glycol biodegradable NPs (310.2 ± 12.4 nm)	100 μg/kg (t.i.d. incorporated in a single dose) for 7 days, orally	Lower BGL, when compared with pure drug (100 μg/kg, t.i.d. for 7 days), orally, sustained release for 7 days
	Soluplus® (SLPS) and Kolliphor™ E-TPGS nanocrystals, (304 ± 6 nm for 1% w/v SLPS (TD-A) and 331 ± 34 nm for SLPS and 0.5% w/v of TPGS (each) (TD-B))	2 mg/kg, orally	*Equivalent dose of 2 mg/kg drug, orally* / $AUC_{(0-\infty)}$, fasted state μg h/L / $AUC_{(0-\infty)}$, fed state μg h/L
			Pure drug (in distilled water) / 25.76 ± 4.17 / 18.57 ± 6.13
			TD-A / 257.75 ± 7.32 / 241.63 ± 13.51
			TD-B / 384.07 ± 9.54 / 355.88 ± 10.69
	Ethyl cellulose and Poly vinyl alcohol	–	15% drug released in 15 h, with complete drug release in 5 days, hemocompatibility

CONCLUSION

On the basis of the advancements in anti-diabetic drugs (mentioned above), it can be concluded that these drugs provide better therapeutic effects than the conventional medications. DPP-4 inhibitors does not increase the risk of cardiovascular diseases, therefore safer to use in case of heart related problems. SLGT inhibitors helps in reducing glucose-toxicity and in improving lipid profile and blood pressure. It also reduces the chances of occurrence of various side effects like weight gain. NXT capsules decreases the malfunctioning of renal tubules and thereby reducing the risk of diabetic nephropathy. Use of nanotechnology in diabetic medications is o0ne of the most revolutionary change in the history. Nano-particulate drug based delivery systems were used to enhance the bioavailability of the drug. Along with the intake of these medications, healthy lifestyle is equally important. The anti-diabetic drugs are very beneficial to the patients in managing the diabetes. It is expected that in coming more advanced medicines would be available in the market with be better efficacy.

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