INDO AMERICAN JOURNAL OF PHARMACEUTICAL RESEARCH

AN OVERVIEW ON NEWER ANTIDIABETIC AGENTS

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ARTICLE INFO

Article history
Received 28/09/2019
Available online
30/09/2019

Keywords
Diabetes Mellitus,
Hyperglycemia,
Insulin.

ABSTRACT

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action. Different classes of diabetes mellitus type1, type2 ,gestational is summarized. It is predicted that the prevalence of DM in adults of which type2 is becoming prominent mostly in developing countries. The treatment strategies are listed and many new drugs are currently in development for treatment of diabetes including more products with new mechanisms .Drugs with application submitted for US food and Drug administration (FDA) approval and drugs currently in phase3 clinical trials are summarized.

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*Please cite this article in press as **Maliha Nishath** et al. An Overview on Newer Antidiabetic Agents. Indo American Journal of Pharmaceutical Research.2019:9(09).*

INTRODUCTION

DEFINITION

Diabetes mellitus is a group of metabolic diseases characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. Metabolic abnormalities in carbohydrates, lipids, and proteins result from the importance of insulin as an anabolic hormone. Low levels of insulin to achieve adequate response and/or insulin resistance of target tissues, mainly skeletal muscles, adipose tissue, and to a lesser extent, liver, at the level of insulin receptors, signal transduction system, and/or effector enzymes or genes are responsible for these metabolic ab-normalities. The severity of symptoms is due to the type and duration of diabetes. Some of the diabetes patients are asymptomatic especially those with type 2 diabetes during the early years of the disease, others with marked hyperglycemia and especially in children with absolute insulin deficiency may suffer from polyuria, polydipsia, polyphagia, weight loss, and blurred vision. Uncontrolled diabetes may lead to stupor, coma and if not treated death, due to ketoacidosis or rare from nonketotic hyperosmolar syndrome[1-3.]

Classification of Diabetes :

Type 1 diabetes encompasses diabetes that is a result of pancreatic beta cell destruction and is prone to ketoacidosis. This formincludes cases due to an autoimmune process and those for which the etiology of beta cell destruction is unknown.

Type 2 diabetes may range from predominant insulin resistance with relative insulin deficiency to a predominant secretory defect with insulin resistance.

Gestational diabetes mellitus refers to glucose intolerance with onset or first recognition during pregnancy.

Other specific types include a wide variety of relatively uncommon conditions, primarily specific genetically defined forms of diabetes or diabetes associated with other diseases or drug use [4.]

Includes latent autoimmune diabetes in adults (LADA); the term used to describe the small number of people with apparent type 2 diabetes who appear to have immune-mediated loss of pancreatic beta cells [5.]

Epidemiology :

It is estimated that 366 million people had DM in 2011; by 2030 this would have risen to 552 million[6.] The number of people with type 2 DM is increasing in every country with 80% of people with DM living in low- and middle-income countries. DM caused 4.6 million deaths in 2011[8.] It is estimated that 439 million people would have type 2 DM by the year 2030[7].The incidence of type 2 DM varies substantially from one geographical region to the other as a result of environmental and lifestyle risk factors[8.]Literature search has shown that there are few data available on the prevalence of type 2 DM in Africa as a whole. Studies examining data trends within Africa point to evidence of a dramatic increase in prevalence in both rural and urban setting, and affecting both gender equally[9.]The majority of the DM burden in Africa appears to be type 2 DM, with less than 10% of DM cases being type 1 DM[10-11.] Centre for Disease Control and Prevention (CDC) report estimates that DM affects about 25.8 million people in the US (7.8% of the population) in 2010 with 90% to 95% of them being type 2 DM[12.]It is predicted that the prevalence of DM in adults of which type 2 DM is becoming prominent will increase in the next two decades and much of the increase will occur in developing countries where the majority of patients are aged between 45 and 64 years[13].It is projected that the latter will equal or even exceed the former in developing nations, thus culminating in a double burden as a result of the current trend of transition from communicable to non-communicable diseases[14.]

TREATMENT STRATEGIES :

ORAL

INSULIN

ORAL[9] :

These are the OAD'S which have been in clinical research for good number of years and for which considerable research, clinical experience and safety data are available.

SULFONYL UREAS :

Glibenclimide
Glipizide
Gliclazide
Glimepiride

BIGUANIDES:

Metformin

THIAZOLIDINEDIONE:

Pioglitazone

ALPHA_GLUCOSIDASE INHIBITORS :

Agarose
Voglibose

MEGLITINIDE ANALOGES :
Repaglinide
Nateglinide

INSULIN :

Insulin is supplied conventionally through subcutaneous route. In the early days, impurities present in bovine insulin led to many immunological reactions. As a result of the advancements such as recombinant DNA technology, more purified forms of insulin is available today[10.]

INSULIN INHALERS

It is a non-invasive, well tolerated delivery systemwhich is effective for both type 1 and type 2 diabetes mellitus. The glycemic control by this method is comparable to subcutaneous route and it also enhances patient satisfaction, quality of life and acceptance for Intense Insulin Therapy in a diabetic patient11. The aerosolized insulin has a diameter of about 3µm which enhances the alveolar disposition and low oropharyngeal and large airway disposition. The onset of action following systemic absorption is about 20 minutes, which is rapid. The action lasts for about 6-8 hours, which is comparable to that in subcutaneous administration. Exuberant was the first inhaled insulin preparation available. It was delivered with an aerosol devise called exuberant inhaler. Nebulizers, metered dose inhalers and aqueous mist inhalers are being investigated. Inhalation is an excellent mode for delivering pre-meal time insulin. It can be used for delivering fast acting insulin only. It is less effective in smokers and those with pulmonary diseases. The incidence of hypoglycemia is also increased with this route.[11,12]

BUCCAL DELIVERY OF INSULIN

Mucosal membranes of the inner lining of cheeks can act as excellent sites for insulin delivery .The area is robust, rich in blood supply, has expansive smooth muscle and provides short cellular recovery following damage or injury[12,13]. Visibility and accessibility of buccal mucosa also makes it an ideal site for delivery. The insulin sprayed into buccal mucosa cannot enter deep lungs because of its size and hence it is safe for lungs[13.] Insulin which is administered through buccal route is called buccal insulin, when it reaches the systemic circulation.[1] The main disadvantage of this route is the lower bioavailability due to the relatively low passage of active agent across the mucosal epithelium. Bio adhesive polymers can be used as an alternative. They adhere to the biological substrate to provide continued contact of the agent with the site of delivery. The various bio adhesive formulations include gels, films, tablets, vesicles, nanoparticles and sponges. They are retained for longer time and hence show improved pharmacokinetic as well as absorption properties. Gels, transferosomes, pelleted nanoparticles, tablets, patches, films, sponges, sprays etc. are the currently available buccal delivery formulations.[12,13]

PULMONARY DELIVERY OF INSULIN

Insulin can be administered by pulmonary route using two techniques - aerosol inhalation and intratracheal instillation. Aerosol offers more uniform distribution with greater extent of penetration into peripheral or into alveolar region of the lungs.When delivered into the lungs, they are readily absorbed through the alveolar region directly into blood circulation. This can be achieved by liquid nebulizers, aerosol based metered dose inhalers and dry powder dispersion devices. Simplicity of self administration, large surface area of lungs that improves absorption, relatively high bioavailability and non-invasiveness are the advantages of this delivery system.[14]

ORAL DELIVERY OF INSULIN

An oral dosage form is the preferred form of delivery because of the ease of administration, patient compliance and economical issues. No oral preparations of insulin are available till date .The advantage of this route of insulin delivery is the capability of insulin to mimic normal physiological role. Thus it can become more efficacious in glucose homeostasis.[15]. The difficulties encountered in the oral delivery of insulin include degradation of the protein at lower pH of stomach and by different digestive enzymes in stomach and small intestine. This causes a decrease in bioavailability as low as ≤0.5%.[14,15] The variation in permeability across GIT for insulin and stability issues of the dosage form are the other major challenges for oral insulin delivery[16.] Several gastrointestinal patch systems are available today and they provide bio adhesion, unidirectional release and protection for the drug from pH variations and also from enzymes. This combination of functions improves bioavailability of large sized molecules[.2.] Protection of insulin from gastric environment has been achieved by coating the nanoparticles with pH sensitive polymers, which will dissolve in the mildly acidic environment of the intestine.[17,18] Complexation hydrogels significantly enhance oral absorption of insulin with notable hypoglycaemic effect.[19] Recombinant human insulin can be delivered by using niosomal formulations.[20-21]

TRANSDERMAL DELIVERY OF INSULIN

It is a needle free technique, which is convenient with good patient compliance and prolonged therapeutic application. It bypasses first pass metabolism and escapes degradation by gastric enzymes. Iontophoresis is a technique that improves the transdermal delivery of compounds through skin by application of a small amount of electrical current. Microdermabration is another method that improves the permeability of insulin through skin. It is achieved by mildly damaging or removing the outer layer of skin, stratum corneum.[22-23]

INSULIN DEVICES

Insulin infusion devices may be classified as open loop and closed-loop systems. Programmable open-loop micro pump insulin delivery device consists of a small, lightweight, portable insulin micro pump and plastic tubing which connects the pump to a needle inserted under the skin. Insulin release patterns in them can be preprogrammed and initiated by timer or by the diabetic patient himself. This device demands a very careful monitoring of blood glucose level. Also the patients using these devices were reported to show high incidence of ketoacidosis. Implantable versions of open loop insulin infusion devices were also introduced. Chemically controlled closed loop insulin delivery devices work by feedback mechanism. It is an effective alternative in the absence of an effective pancreas or β-cell transplantation. It mimics pancreatic activity. They are biocompatible and non-toxic. The bio hybrid artificial pancreas is another type of insulin diffusion device, which is under research. These contain β-cells enclosed within a semi permeable membrane, which is biocompatible. The semi permeable membrane is permeable to glucose and insulin. Special has to be given to exclude immune cells in order to prevent rejection by the body.[24-26]

INSULIN DELIVERY USING PEN DEVICES

It is a convenient and accurate method of insulin delivery. Its goal is to improve glyceamic control by making it less difficult to follow the current recommendations for intensive insulin regimens. Two types of pens are available; prefilled and reusable. Pens are available in various styles. Insulin pens have the potential to become a major asset for the improved compliance among all patients undergoing insulin therapy.

OTHER NOVEL METHODS IN INSULIN DELIVERY

Erythrocytes, which are the most abundant cells in the body, can be used as effective carriers of many different drugs including insulin. Biocompatibility, biodegradability, long circulation half life and the ability to get loaded with a variety of chemically and biologically active compounds make resealed erythrocytes excellent carriers of therapeutic agents [27]. Dendrimers are macromolecules with highly branched 3D structure[28.] They also are used for successful delivery of insulin.

NEWER ORAL ANTIDIABETIC AGENTS:

DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS:

The DPP-4 inhibitors are incre-tin enhancers. DPP-4 inhibitors are thought to work by slowing the inac-tivation of the incretin hormones glucagon-like peptide-1 (GLP-1) and glucosedependentinsulinotropic peptide. These agents are released by the gastrointestinal tract in response to food and are involved with the stimulation of glucose-dependent insulin secretion. By inhibiting their inactivation, these drugs prolong the effects of these incretin hormones. The DPP-4 inhibitors have been assessed as monotherapy and in conjunction with insulin, metformin, sulfonylureas, and thiazolidinedione's in patients with type 2 diabetes. Although the DPP-4 inhibitors have been shown to improve glycemic control, as with most other new agents used in the treatment of diabetes, data have not been published addressing the effects of the DPP-4 inhibitors on key outcome measures such as mortality, diabetes complications, or health related quality of life.[29]

Alogliptin

Alogliptin is a highly selective inhibitor of DPP-4, demonstrating > 10,000 times more selectivity for DPP-4 than for other related proteases. After oral administration of alogliptin in a range of doses from 25 to 800 mg.

Mechanism of Action

Alogliptin is capable of decreasing the average A1C level in patients with type 2 diabetes when used alone or in combination with insulin, metformin, a sulfonylurea, or a thiazolidinedione.[30]

Adverse reactions reported have also included nasopharyngitis, headache, and upper respiratory tract infection.9 Alogliptin appears to have a neutral effect on weight and lipids[31-34]

Dutogliptin

Dutogliptin is also an oral DPP-4 inhibitor under evaluation for once daily dosing in patients with type 2 diabetes. To date, it has demonstrated activity in a short-term study when administered once daily in conjunction with metformin or metformin plus a thiazolidinedione; participants are now being recruited for a phase 3 study.

Linagliptin

Linagliptin is another oral DPP-4 inhibitor under evaluation for once daily dosing in patients with type 2 Diabetes. To date, it has demonstrated activity in a short-term study when administered once daily in patients with type 2 diabetes; recruitment is ongoing for a number of phase 3 studies assessing linagliptin as mono-therapy and in combination with pioglitazone, metformin, or metformin plus a sulfonylurea.

Saxagliptin

Saxagliptin is capable of decreasing the average A1C level in patients with type 2 diabetes when used alone or in combination with metformin, a sulfonylurea, or a thiazolidinedione. Treatment with saxagliptin alone has been weight neutral. Common adverse reactions reported in the clinical trials with saxagliptin include nasopharyngitis, headache, diarrhea, upper respiratory infections, influenza, and urinary tract infection.

Vildagliptin

Vildagliptin alone or in combination with metformin, a thiazolidinedione, or insulin is capable of decreasing fasting plasma glucose levels and improving A1C levels in patients with type 2 diabetes.

Adverse reactions reported in the clinical trials have generally been Simi-lar to those reported with placebo and have included cough, nasopharyngitis, headache, hypoglycemia, dizziness, dyspepsia, nausea, constipation, and diarrhea. Vildagliptin had no impact on patient weight in the majority of studies.

Glucagon-LIKE PEPTIDE 1 (GLP-1) ANALOGS

The GLP-1 analogs induce their activity through a glucose-dependent stimulation of insulin secretion, inhibition of glucagon secretion, slowing of gastric emptying, and reduction in appetite.

AVE0010/ZP-10

Limited clinical data are available for AVE0010.A1C was reduced 0.28% to 0.69% compared to placebo in a range of doses from 5 mμ once daily to 30 mμ twice daily administered subcutaneously. Efficacy was similar with once-daily and twice-daily regimens.Greater weight loss with AVE0010 than with placebo was observed at doses of 20 and 30 mμ once daily and 30 mμ twice daily. Nausea and vomiting were the most common adverse effects.Recruitment is ongoing for a number of phase 3 studies evaluating AVE0010 as monotherapy and in addition to basal insulin, metformin, a sulfonylurea, or pioglitazone in patients with type 2 diabetes, as well as a study comparing AVE0010 and exenatide in association with metformin in patients with type 2 diabetes.

Exenatide LAR

The slow-release or long-acting release (LAR) formulation of exenatide is in phase 3 development. It is intended for once-weekly subcutaneous admin-istration for the treatment of type 2 diabetes.

Liraglutide

Liraglutide is under evaluation for use in the treatment of patients with type 2 diabetes as an adjunct to diet and exercise, either as monotherapy or in combination with commonly used diabetes medications, including sulfonylureas and metformin. In clinical trials, Liraglutide has been associated with a reduction in A1C and fasting plasma glucose with either weight loss or no change in body weight. Significant reductions in A1C have been observed at doses of 0.1–2 mg administered sub-cutaneously once daily.

Adverse effects associated with Liraglutide therapy have included headache, dizziness, nausea, and vomiting.

LY2189265

Results of studies with LY2189265 have not been published. Recruitment is currently ongoing for a phase 2/3 study comparing LY2189265 with sitagliptin in patients with type 2 dia-betes on metformin.

Taspoglutide

Taspoglutide administered subcutaneously once weekly has been associated with reductions in fasting blood glucose, improvement in A1C, and weight loss when added to metformin therapy in patients with type 2 diabetes in short-term studies. Recruitment is ongoing for studies assessing taspo-glutide as initial monotherapy and in conjunction with metformin, met-formin plus pioglitazone, metformin plus a sulfonylurea, or metformin plus a thiazolidinedione. In several of these studies, Taspoglutide is being com-pared head-to-head with exenatide, insulin glargine, and sitagliptin.

PEROXISOME PROLIFERATOR–ACTIVATED RECEPTOR (PPAR) AGONISTS

The PPAR-γ agonists act as insulin sensitizers, reducing fasting glucose and A1C. The thiazolidinediones were the first class of PPAR-γ agonists to be approved for use diabetes.Balaglitazoneandrivoglitazoneare thiazolidinediones in phase 3 stud-ies in patients with type 2 diabetes.Thepartial PPAR-γ agonists, also known From Research to Practice/Pharmacological Management of Type 2 Diabetes as selective PPAR modulators, have been developed in an attempt to minimize the side effects of the full agonists while maintaining the thera-peutic effect.Insufficient data are available at this time to determine if the selective PPAR modulators will have fewer adverse effects.

Balaglitazone

Balaglitazone is a selective partial PPAR-γ agonist. It has been suggested that partial PPAR-γ agonists may have a favorable adverse effect profile relative to the full PPAR-γ agonists pioglitazone and rosiglitazone. However, results of clinical studies directly comparing these agents are not yetavailable. A phase 3 study assessing the efficacy and safety of balaglitazone compared to pioglitazone in patients with type 2 diabetes receiving stable insulin therapy is currently enrolling patients.

Rivoglitazone

Rivoglitazone is a potent PPAR-γagonist currently under evaluation in a phase 3 study comparing it to Placebo and pioglitazone in patients with type 2 diabetes not adequately controlled with diet and exercise or with no thiazolidinedione antihy-perglycemic monotherapy. In an earlier open-label comparative 6-week study, rivoglitazone 2-mg and 5-mg doses once daily were associated with greater reductions in fasting plasma glucose than pioglitazone 30 mg; how-ever, these rivoglitazone doses were also associated with a greater incidence of peripheral edema and weight gain.

SELECTIVE SODIUM GLUCOSE COTRANSPORTER 2 INHIBITORS

The selective sodium glucose cotrans-porter 2 inhibitors are a new class of agents. The sodium glucose cotrans-porter type 2 (SGLT2) located in the plasma membrane of cells lining the proximal tubule mediates the majority of renal glucose reabsorption from the tubular fluid. Blood glucose is continu-ously filtered by the renal glomeruli and then reabsorbed in the renal proximal tubules by SGLT2, and to a lesser extent SGLT1, preventing the loss of glucose in the urine. Competitive inhibitors of SGLT2 provoke renal excretion of glucose; potentially low-ering elevated blood glucose levels in patients with diabetes. These agents are expected to improve plasma glu-cose levels and decrease body weight in patients with type 2 diabetes without causing hypoglycemia.

Dapagliflozin

Dapagliflozin is in the early portion of phase 3 development for use as a monotherapy agent or in combination with other oral hypoglycemic agents. The drug has been well tol-erated in early clinical studies with the most common adverse reactions being urinary tract infection, dizzi-ness, headache, fatigue, back pain, and nasopharyngitis. is in the early portion of phase 3 development for use as a monotherapy agent or in combination with other oral hypoglycemic agents. The drug has been well tol-erated in early clinical studies with the most common adverse reactions being urinary tract infection, dizzi-ness, headache, fatigue, back pain, and nasopharyngitis.

Dapagliflozin is currently under evaluation in a number of phase 3 stud-ies assessing the agent as monotherapy in patients with type 2 diabetes not adequately controlled with diet and exercise, as well as studies assessing Dapagliflozin in conjunction with metformin, a sulfonylurea, a thiazo-lidinedione, or insulin.

GLINIDES

The glinides, including Nateglinide, repaglinide, and mitiglinide, are agents that enhance mealtime insulin secretion and reduce postprandial hyperglycemia. Nateglinide and rep-aglinide have been available in the United States since 2000 and 1997, respectively.

Mitiglinide

Mitiglinide has been available in Japan since 2004 and is currently in phase 3 studies in the United States. It has been reported to have a more β-cell–selective effect on the adensine triphosphate-dependent potassium channels than Nateglinide and repaglinide and to have no active metabolites or cyto-chrome P450 drug interactions. Several recently published stud-ies conducted in Japan have assessed premeal mitiglinide combined with once-daily insulinglargineandtwicedailypremixedinsulin.[46]

INSULINS

Rapid acting insulin

These insulin analogs have a more rapid onset of ac-tion (15-30 min) and shorter activity duration (4 to 5 h).Their peak action ranges from 30-90 min post injec-tion. By a single or two amino acid alterations in the insulin molecule, the ability to associate into hexamersis reduced such that they are readilyabsorbed, however, these modifications do not change the biologicalproperties of these analogs. Examples of rapid actinginsulin include Lispro and Aspart. In Insulin Lispro(LysB28, ProB29), the positions of proline at positionB28 and lysine at position B29 in the B chain have been reversed.In insulin Aspart, the proline at position 28 has been replaced by aspartic acid.75 These rapid acting analogs can be used at mealtime to achieveoptimum level of insulin for utilization of glucose released after eating.[47]

Short acting insulin

Short acting insulin analogs have an onset of action ofaround 0.5-1 h, peak action of 2-4 h and activity duration of 6-8 h. Examples of these preparations includeActrapid, Humulin, Hypurin and Neutral. These insulin analogs should be injected into the body 20-30 minbefore meal so as to get optimum insulin activity forcarbohydrate metabolism.

Intermediate acting insulin

Intermediate acting insulin analogs have an onset ofaction around 1-2 h, peak action of 6-10 h and activ-ity duration of 10-16 h. Examples of intermediateacting insulin include NPH (Neutral ProtamineHagedorn) and LENTE (from the Latin "lentus,"meaning slow, or sluggish) insulin. The absorptionrate of NPH insulin is reduced by the addition ofprotamine to the insulin preparation. In insulinLENTE, the same is achieved by the addition of zincto the insulin preparation.

Long acting insulin

These insulin analogs have an onset of action around 2 h, peak action (sometimes no peak action) of 6 h 76andactivity duration of up to 36 h. One way to prolong insulin activity is designing analogs with more positivelycharged amino acids so as to raise the isoelectric pointof insulin to near neutral pH.77 This helps in reducingthe solubility of insulin at neutral pH after injection into the body and the absorption into the blood streamwill be delayed. Some of the long acting insulin preparations also have protamine or zinc added to them toincrease absorption time. Insulin detemir, also calleddesB30 insulin, is an example of long acting insulin. Ininsulin detemir, the threonine at position B30 in the Bchain is removed and a 14-C fatty acid i.e. myristic acid is attached to the lysine at position B29 in the Bchain. Attachment of myristic acid helps in insulinhexamer formation and increases the binding of insulinto plasma albumin which delays the free insulin releaseand which prolongs the activity of insulin.[48-49]

NEWER INSULIN ANALOGUE

A variety of insulin formulations are currently in development includ-ing inhaled formulations, intranasal formulations, oral formulations, and injectable analogs.

Inhaled Technosphere Insulin

Inhaled Technosphere insulin is inhaled insulin in development for administration using a palm-sized handheld breath-activated inhaler. The Technosphere particles are composed of human regular insulin loaded into a diketopiperazine molecule. The par-ticles dissolve rapidly at physiological pH, providing for rapid insulin absorp-tion from the lungs. Technosphere insulin is absorbed within 15 minutes, has an onset of action of ~ 25–30 min-utes, and has duration of action of ~ 2–3 hours.

Oral Insulin Spray

An oral insulin spray in development by Generex Biotechnology is in phase 3 studies in the United States but has already been approved in Ecuador and India. The insulin is absorbed buc-cally following administration with a proprietary RapidMist device that resembles the metered-dose inhal-ers used in the treatment of asthma. The formulation is tasteless and odorless.

Rapid-Acting Insulin for Injection (VIAject)

VIAject is a novel ultra-fast insulin formulation composed of human solu-ble insulin and ingredients designed to increase the rate of absorption (EDTA and citric acid). These ingredients pull the zinc ions away from human insu-lin hexamers and mask charges on the surface of the insulin molecule, causing the insulin hexamers to dis-sociate and preventing re-association to the hexameric state with subcuta-neous administration. VIAject has exhibited a quicker onset of action than insulin lispro and human soluble insulin (time to early half-maximal activity 33 minutes with VIAject vs. 85minutes with insulin lispro and 66 minutes with human soluble insu-lin; $P < 0.05$).When administered immediately before a meal, VIAject was associated with improved post-prandial blood glucose control, reduced hyperglycemia in the first 3 hours after a meal, and reduced hypo-glycemia through 8 hours compared to regular human insulin.115Phase 3 studies comparing insulin VIAject and regular human insulin in patients with type 1 and type 2 diabetes have recently been completed.

Other AGENTS

A wide variety of other agents are also in development for the treatment of type 1 or type 2 diabetes.

Bromocriptine

Bromocriptine is a dopamine D2 receptor agonist that is approved for the treatment of dysfunctions asso-ciated with hyperprolactinemia, acromegaly, and Parkinson's disease and has been in development for the treatment of type 2 diabetes for several years. A new drug application for a quick-release formulation was granted approvable status by the FDA in 2006. However, at least one additional safety study was necessary before the drug could be approved.

Otelixizumab

Otelixizumab is a humanized anti-CD3 monoclonal antibody currently being evaluated in clinical studies in patients with new-onset type 1 diabetes. Otelixizumab binds to the CD3/TCR complex and blocks full T-cell acti-vation, proliferation, and cytokine release. It has been hypothesized that otelixizumab's downregulation of T effector cells via binding of the T-cell receptors will result in inhibition of the autoimmune attack on β-cells in the pancreatic islets and establishment of longlasting operational tolerance by the generation and expansion of regu-latory T-cells, which prevent further autoimmune destruction.89A phase 3 study is currently under-way assessing whether an 8-day series of otelixizumab infusions will lead to greater improvement in insulin secre-tion than placebo in adults 18–35 years of age with new-onset type 1 diabetes.

Recombinant Human Glutamic Acid Decarboxylase-65 (rhGAD65)

RhGAD65 is a vaccine that induces immunotolerization and may thereby slow or prevent autoimmune destruction of pancreatic islet cells.Antibodies against GAD are present at the time of diagnosis in 80–90% of patients with type 1 diabetes.In patients with adult-onset autoimmune diabetes and the presence of antibodies against GAD, administration of rhGAD65 has been associated with reduced A1C and increased fasting and stimulated C-peptide levels for 2 years.Two phase 3 studies were recently initiated to assess whether rhGAD65 formulated in alum preserves the body's own insulin-producing capacity in patients recently diagnosed with type 1 diabetes. One study will enroll subjects 10–20 years of age; the other will enroll subjects 8–45 years of age. Results will not be available for several years.

Succinobucol

Succinobucol is an oral antioxidant lipid peroxidation inhibitor and vascu-lar cell adhesion molecule antagonist that are in phase 3 development for the treatment of atherosclerosis and type 2 diabetes. It is a monosuccinate ester of probucol, a previously approved lipid-lowering agent.

Teplizumab

Teplizumab is a humanized anti-CD3 monoclonal antibody. Like otelixi-zumab, teplizumab is hypothesized to minimize cytokine release and pre-vent the progressive destruction of β-cells.136A phase 3 study is currently evaluat-ing the effects of 14 days of intravenous teplizumab in patients 8–35 years of age with new-onset type 1 diabetes, followed by retreatment at 6 months. The primary study endpoint is a suc-cessful clinical response as assessed by subjects' total daily insulin usage and A1C at 1 year.[50]

ROLE OF PHARMACIST IN COUNSELLING DIABETES MELLITUS:

The pharmacist can educate the patients about the proper use of medication, screening for drug interactions, explain monitoring devices, and make recommendations for ancillary products and services.The pharmacist can monitor the patient's blood glucose levels and keep a track of it. During their contact, the patients can ask the pharmacist any questions they did not ask the physicians and can get further information regarding diabetes. The pharmacist can also counsel the patients regarding insulin administration regularly so that the onset of complications can be postponed by having tight glycemic control. Another important role of pharmacist is always being available to answer the questions of the patients. Overall, it is the pharmacist's role to help a diabetic patient in the best possible way to cope with their disease.[21]

Essential components of diabetic counseling

Since diabetes is a chronic complication affecting the diabetic patient at various levels, the counseling should focus on the nature of the disease, lifestyle modifications, medications, and acute and chronic complications.

I. Counseling regarding the disease: The diabetic patients should be explained that the disease is lifelong, progressive and needs necessary modifications in the lifestyle pattern. They should also stress upon the importance of pharmacotherapy, especially the need for strict compliance with the prescribed medication. The patients should be also explained that the disease may affect the quality of life if not well controlled.

II. Counseling regarding lifestyle modifications: While counseling regarding the life style modifications, the pharmacist should focus on the key areas including diet, exercise, smoking and alcohol intake.

A. Diet: Dietary control is the mainstay of treatment in type 2 diabetes and an integral part in type 1 diabetes. Among the dietary counseling, importance should be given for the dietary content including carbohydrate, fat and fiber intake.

1. Carbohydrates: The blood glucose level is closely affected by the carbohydrate intake. Daily intake should be kept fairly constant and the amount given should be appropriate to the level of physical activity. Most young people will require 180 g of carbohydrate per day, whereas 100 g may suffice for an elderly patient. If fiber rich food such as whole meal bread, jacket potatoes, etc. are eaten, then the carbohydrate content of the diet make up to 50% to 55% of the calories. People with diabetes should limit their sugar intake, but total exclusion of sugar from the diet is impractical and unnecessary.
2. Fat: Since there is an increased risk of death from coronary artery disease in diabetics, it is wise to restrict saturated fats and to substitute them with unsaturated fats. Furthermore, obesity is a major problem in diabetes, and fats contain more than twice the energy content per unit weight than either carbohydrate or proteins. More severe restrictions may be indicated for individuals with hypercholesterolemia.
3. Fiber: Dietary fiber has two useful properties. Firstly it is physically bulky and increases satiety. Secondly, fiber delays the digestion and absorption of complex carbohydrates, thereby minimizing hyperglycemia. For an average person with NIDDM, 15gm of soluble fiber (from fruits, pulses and vegetables) is likely to produce a 10% improvement in fasting blood glucose, glycated hemoglobin and low- density lipoprotein cholesterol.[21]

B. Exercise and physical activity: Exercise can help to promote weight loss and maintain ideal body weight when combined with restricted caloric intake. In type 1 diabetes, care must be taken to have adequate metabolic control prior to exercise and to monitor blood glucose before and after exercise. Exercise is not recommended if the patient has poorly controlled labile blood glucose level or is at increased risk of diabetic complications.

C. Alcohol intake: Even if the blood glucose of the patient is well controlled, modest amount of alcohol will significantly alter blood glucose levels. In general, the same guidelines of alcohol use applicable to the general public apply to patients with diabetes.[21]

D. Smoking: People with diabetes, especially those over age 40 years, who smoke and have high blood pressure and cholesterol, are at a higher risk for cardiovascular problems. When the large blood vessels (arteries) are blocked, heart attack and stroke often result. This hardening or blockage may also occur in the small arteries that supply blood to the legs and feet. Smoking can also lead to serious complications like infections, ulcers, gangrene, and even amputations.

III. Counseling regarding medications: Though lifestyle modifications play an important role in diabetes management, it is well established by land mark studies that the chronic complications can be prevented by strict glycemic control. Hence, the pharmacist has an immense role in counseling diabetic patients regarding the drugs. Counseling should be emphasized for oral anti diabetic agents as well as for insulin.

1. Oral hypoglycemic agents (OHAs): If the patient is diagnosed with Type 2 diabetes, he/ she is more likely to be prescribed OHAs. Some of the commonly prescribed oral hypoglycemic agents and the important counseling points are discussed below.

Some general principles to be followed for patients on OHAs:

The patient should be cautioned not to skip meals at any time and to follow regular eating patterns to prevent hypoglycemia. OHAs are comparatively safe drugs. However some patients may develop loss of appetite, nausea and vomiting, abdominal pain, cramps, malaise, diarrhea or weight loss.

1. Insulin: All patients with type 1 diabetes require insulin. Some patients with type 2 diabetes who initially respond to dietary modification and/ or oral anti diabetic medications eventually require insulin therapy. There are a wide variety of insulin preparations available now. These may differ in source, onset of action, time to peak effect, and duration of action. The clinician will prescribe the type of insulin which suits an individual best.

CONCLUSION

Diabetes mellitus is the outbreak of the century and without effective diagnostic procedures at an early stage, diabetes will rise unstoppably. This review focuses on diabetes and newer classes of drugs which are available. As the prevalence of diabetes is increasing at an alarming rate, more approaches are to be focused towards the early diagnosis and prevention of the disease. There is a need for the development of newer classes of drugs to show more precise action of drug at molecular level on the human body.

ABBREVIATION:

FDA : Food and Drug administration
DM : Diabetes mellitus
LADA : Latent autoimmune diabetes in adults
CDC : Centre for disease control and prevention
DPP_4 : Dipeptidyl peptidase 4
GLP : Glucagon like peptide
LAR : Long acting release
PPAR : Peroxisomes proliferatoractivated receptor
SGLT2 : Sodium glucose co-transporter type2
EDTA : Ethylene diamine tetraacetic acid
RHGAD65: Recombinent human glutamic acid decarboxylase 65

REFERENCES

1. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2014; 37 Suppl 1: S81-S90 [PMID: 24357215 DOI: 10.2337/dc14-S081]
2. Craig ME, Hattersley A, Donoghue KC. Definition, epidemiology and classification of diabetes in children and adolescents. Pediatr Diabetes 2009; 10 Suppl 12: 3-12 [PMID: 19754613 DOI: 10.1111/j.1399-5448.2009.00568.x]
3. Galtier F. Definition, epidemiology, risk factors. Diabetes Metab 2010; 36: 628-651 [PMID: 21163426 DOI: 10.1016/j.diabet.2010.11.014]
4. American Diabetes Association. Diagnosis and classification of diabetes mellitus. Diabetes Care 2012; 35(suppl 1):S64e71.
5. Turner R, Stratton I, Horton V, et al. UKPDS 25: autoantibodies to islet-cellcytoplasm and glutamic acid decarboxylase for prediction of insulin requirement in type 2 diabetes. UK Prospective Diabetes Study Group. Lancet 1997;350:1288e93.
6. Global burden of diabetes. International Diabetes federation. Diabetic atlas fifth edition 2011, Brussels. Available at http://www.idf.org/diabetesatlas. (Accessed 18th December 2011).
7. Chamnan P, Simmons RK, Forouhi NG, Luben R. Khaw Ky, Wareham NJ et al. Incidence of type 2 diabetes using proposed HbA1c diagnostic criteria in the EPIC-Norflok cohort: Implication for preventive strategies. Available at http://care.diabetesjournal.org. (Accessed 19th December 2011).
8. Zimmet P, Alberti KG, Shaw J. Global and societal implications of the diabetes epidemic. Nature 2001 Dec;414(6865):782-787.
9. Mbanya JC. The burden of type 2 diabetes mellitus in the African diaspora. Available at www.medscape.com/view article/560718_2.
10. Department of Health and Human Services. Centres for Disease Control and Prevention, 2011. National diabetes fact sheet: national estimates and general information on diabetes and prediabetes in the United States, 20 projections for 2030. Diabetes Care 2004;127(5):1047-111. Available at http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. (Accessed December, 20th 2011).
11. .Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: estimate for the year 2000 and 053 .
12. Yach D, Hawkes C, Gould CL, Hofman KJ. The global burden of chronic diseases: overcoming impediments to prevention and control. JAMA 2004Jun;291(21):2616-2622.
13. Seino Y,Yabe Glucose dependent insulinotropic polypeptide and glucagon like peptife-1: Incretin actions beyond the pancreas.Journal of Diabetes Investigation 2015 Mar;4(2):108-130. DOI:10.1111/Jdi.12065
14. Moore B,Edie ES,Abram JH.On the treatment of Diabetes mellitus by acid extract of Duodenal Mucous Membrane.Biochem J 1906;1: 28-38
15. VikasAgarwal, Mansoor.A.Khan- Current Statusof the Oral Delivery of Insulin- Pharm Tech-2001:76-98
16. P Guntur, Rajiv Dhand- Inhaled Insulin:extending the horizones of inhalation therapy-Respiratory care-2007;52(7):911-922.
17. Various emergingtechnologies in insulin delivery system- Int. JPharm Sci Rev and Res;2010 ;2(1):14-16

18. ChauhanNitesh, ChauhanSanjeev, HandaVandana, AroraAlka, Singh Vijendar-RecentAdvances in Insulin Delivery Systems: An Update-World Appl. Sci.J-2010; 11(12):1552-1556
19. Gerald Bernstein-Delivery of Insulin To the BuccalMucosa Utilizing the Rapid Mist system-Expertopin.Drug deliv.2008;5(9):1047-1055
20. ChoudharyAmruta, PatelBinal, R. Mahalakshmi, Devmurari Viral, N.P.Jivan-Pulmonary delivery as a route for insulin,Int.J.Pharmtech Res- 2009;1(4):1190-1197
21. T.Cefalu- Optimizing GlycemicControl:The Search for Feasible Non-InvasiveInsulin Delivery Systems-Canadian J. Diabetes-2003;27(1):42-51
22. M.Morishita,T.Goto,K.Takayama,N.A.Peppas- Oralinsulin delivery system based on complexationpolymer hydrogels,J.Drug del.Sci.Tech-2006;16(1):19-24
23. Ali Nasir, Harikumar SL, KaurAmanpreet-Niosomes: An Excellent Tool For Drug Delivery-IJRPC-2012;2(2):479-487
24. C. Zion, Henry.H.Tsang, Jackie Y. Ying-Glucose sensitive nanoparticles for controlledinsulin delivery-http://hdl.handle.net/1721.1/3783
25. Valerie Ravaine, Christophe Ancla, BogdanCatargi- Chemically controlled closed-loopinsulin delivery, J. Contrl. relea, 2008;132:2-11
26. H.Clemens- Programmable Open loopmicropump insulin delivery system, Diab.Care,1980;3(2):359-361
27. Shah- novel Drug DeliveryCarrier:Resealed Erythrocytes-Intl. J.Phar. andBioSci,2011;2(1):394-406
28. Onkar Singh, SaahilArora, RSRMurthy- Dendrimer a novel scaffolding for drug delivery- Intl. J.Phar.Sci.Rev.and Res,2011;7(2):211-220.
29. Terri L.Levin ,pharm_D and Danial E.Baker,Pharm-D,FASHP,FASCP,New Drugs in development for the treatment of Diabetes.
30. B, Bandeira-Echtler E, Bergerhoff K, Lerch CL: Dipeptidyl peptidase-4 (DPP-4) inhibitors for type 2 diabetesmellitus. Cochrane Database Syst Rev2008;2:CD006739
31. Mekki Q, Fleck P, Wilson C, DeFronzo R: Efficacy and safety of alogliptin monotherinpatientswith type 2 diabetes inadequately controlled with diet and exercise [abstract]. Diabetologia 51 (Supp1):S344, 2008
32. Fleck P, Mekki Q, Kipnes M, Wilson C, Pratley R: Efficacy and safety of aloglip-tin and glyburide c2mbination therapy in patients with type 2 diabetes [abstract]. Diabetologia 51 (Suppl. 1):S37, 2008
33. Rendell M, Rosenstock J, Gross J, Fleck P, Wilson C, Mekki Q: Addition of alogliptin to insulin therapy reduces HbA1c without increasing weight gain or hypoglycemiain patients with type 2 diabetes [abstract]. Diabetologia 51 (Suppl. 1):S37–S38, 2008
34. Pratley R, Reusch J, Fleck P, Wilson C, Mekki Q: Alogliptin added to pioglitazone therapy improves glycaemic control in patients with type 2 diabetes without increas-ing weight gain or hypoglycaemic [abstract]. Diabetologia 51 (Suppl. 1):S343, 2008
35. Ellis G, Fleck P, Wilson C, Mekki Q, Nauck M: Alogliptin added to metformin therapy in patients with 2 diabetes reduces HbA1c without changing weight or increasing gastrointestinal symptoms or hypoglycae-mia [abstract]. Diabetologia 51 (Suppl. 1):S343–S344, 2008
36. Garcia-Soria G, Gonzalez-Galvez G, Argoud GM, Gerstman M, Littlejohn TW, Schwartz SL, O'Farrell AM, Li X, Cherrington JM, Bennett C, Guler HP: The dipeptidyl peptidase-4 inhibitor PHX1149 improves blood glucose control in patients with type 2 diabetes mellitus. Diab Obes Metab 10:293–300, 2008
37. Phenomix: Safety and efficacy study of dutogliptin/PHX1149T to treat type 2 diabetes mellitus [online]. Available from http://clinicaltrials.gov/show/NCT00690638 (NLM Identifier: NCT00690638). Accessed 3 December 2008
38. Forst T, Uhlig-Laske B, Ring A, Ritzhaupt A, Graefe-Mody U, Dugi KA: The novel, potent, and selective DPP-IV inhibitor BI 1356 significantly lower HbA1c after only 4 weeks of treatment in patients with type 2 diabetes [abstract]. Diabetes 56 (Suppl. 1):A157–158, 2007
39. Boehringer Ingelheim Pharmaceuticals: Efficacy and safety of BI 1356 versus placebo in type 2 diabetic patients with insufficient glycemic control [article online]. Available. from. http://clinicaltrials.gov/show/NCT00621140 (NLM Identifier: NCT00621140). Accessed 3 December 2008
40. Beranger Ingelheim Pharmaceuticals: Efficacy vs. placebo as initial combination therapy with pioglitazone [article online]. Available from: http://clinicaltrials.gov/show/NCT00641043 (NLM Identifier: NCT00641043). Accessed 3 December 2008
    a. Boehringer Ingelheim Pharmaceuticals: A randomized, db, placebo-controlled study of BI 1356 for 18 weeks followed by a 34 week double-blind extension period (placebo patients switched to glimepiride) in type 2 diabetic patients for whom treatment with metformin is inappropriate [article online]. Available from http://clinicaltrials.gov/show/NCT00740051 (NLM Identifier: NCT00740051). Accessed 3 December 2008
    b. Boehringer Ingelheim Pharmaceuticals: Safety and efficacy of BI 1356 as monother-apy or in combination in type 2 DM [article online]. Available from http://clinicaltrials.gov/show/NCT00736099 (NLM Identifier: NCT00736099). Accessed 3 December 2008
    c. Boehringer Ingelheim Pharmaceuticals: BI 1356 in combination with metformin and sulphonylurea in type 2 diabetes [article online]. Availablefromhttp://clinicaltrials.gov/show/NCT00602472 (NLM Identifier: NCT00602472). Accessed 3 December 2008
    d. Boehringer Ingelheim Pharmaceuticals: Efficacy and safety of BI 1356 vs. placebo added to metformin background therapy in patients with type 2 diabetes [article online]. Available from http://clinicaltrials.gov/show/NCT00601250 (NLM Identifier: NCT00601250). Accessed 3 December 2008
    e. Boehringer Ingelheim Pharmaceuticals: Efficacy and safety of BI 1356 in combina-tion with metformin in patients with type 2 diabetes [article online]. Available from ://.gov/show/NCT00622284 (NLM Identifier: NCT00622284). Accessed 3 December 2008

f. Chen R, Pfutzner A, Jadzinsky M, Paz-Pacheco E, Xu Z, Allen E: Initial combination therapy with saxagliptin and metformin improves glycaemic control compared with either monotherapy alone in drug-naïve patients with type 2 diabetes [abstract]. Diabetologia 51 (Suppl. 1):S38, 2008

g. Ravichandran S, Chacra AR, Tan GH, Apanovitch A, Chen R: Saxagliptin added to a sulfonylurea is safe and more effective than up-titrating a sulfonylurea in patients with type 2 diabetes [abstract]. HiDiabetologia 51 (Suppl. 1):S342, 200

41. 26Allen E, Hollander P, Li J, Chen R: Saxagliptin added to a thiazolidinedione improves glycaemic control in patients with inadequately controlled type 2 dia-betes [abstract]. Diabetologia 51 (Suppl. 1):S342–S343, 2008.
42. Rosenstock J, Sankoh S, List JF: Glucose-lowering activity of the dipeptidyl peptidase-4 inhibitor saxagliptin in drug-naive patients with type 2 diabetes. Diabetes Obes Metab10:376–386, 2008
43. Scherbaum WA, Schweizer A, Mari A, Nilsson PM, Lalanne G, Jauffret S, Foley JE: Efficacy and tolerability of vildagliptin in drug-naïve patients with type 2 diabetes and mild hyperglycemia. Diabetes Obes Metab10:675–682, 2008
44. Scherbaum WA, Schweizer A, Mari A, Nilsson PM, Lalanne G, Wang Y, Dunning BE, Foley JE:Evidence that vildagliptin attenuates deterioration of glycaemic control during 2-year treatment of patients with type 2 diabetes and mild hyperglycemia. Diabetes Obes Metab 10:1114–1124, 2008
45. Novartis: Safety and tolerability of vilda-gliptin versus sitagliptin in patients with type 2 diabetes and severe renal insufficiency [arti-cle online]. Available fromhttp://clinicaltrials.gov/show/NCT00616811 (NLM Identifier: NCT00616811). Accessed 15 December 2008
46. TerriL.Levien ,Pharm-D, Danial E.Baker,Pharm-D,FASHP ,FASCP ,New Drugs in development for the treatment of Diabetes.
47. Howey DC, Bowsher RR, Brunelle RL, Woodworth JR.Lys (B28), Pro (B29). human insulin: a rapidly absorbedanalogue of human insulin. Diabetes 1994; 43(3):396-402.
48. Mudaliar SR, Lindberg FA, Joyce M, et al. Insulin aspart(B28 asp-insulin): a fast-acting analog of human insulin:absorption kinetics and action profile compared with regu-lar human insulin in healthy nondiabetic subjects. Diabe-tes care 1999; 22(9): 1501-1506.
49. Rosskamp RH, Park G. Long-acting insulin analogs. Dia-betes Care 1999; 22 Suppl 2: B109-B113.
50. Whit Ingham JL, Havelund S, Jonassens I. Crystal struc-ture of a prolonged-acting insulin with albumin-bindingproperties. Biochemistry 1997; 36(10): 2826-2831.