Oral insulin and paediatric diabetes; a mini-review

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ABSTRACT: Diabetes is progressive metabolic disorder and enhance level of glucose in extra cerebral fluids. It can be classified as Type1 and Type2 diabetes. Type 1 diabetes mellitus is auto immune disorder that can cause symptoms form childhood. For the treatments of type 1 diabetes insulin is only medicine effective. Oral insulin is one of the most exciting areas of development in the treatment of diabetes because of its potential benefit in patient convenience, rapid insulinization of the liver, adequate insulin delivery avoiding peripheral hyperinsulinaemia while potentially avoiding adverse effects of weight gain and hypoglycemia. Growing evidence that earlier initiation of intensive insulin therapy produces sustained tight glycaemic control resulting in a substantial delay in complications makes an effective oral insulin product even more vital for the management of patients with diabetes. In this article, we are mention type 1 diabetics and significant uses of oral insulin for the management of the disease.

Keywords: Diabetes Mellitus, Insulin, Pathophysiology
1. Introduction

Diabetes is a metabolic disorder in which it is enhance sugar contents in extra-cerebral fluid. Diabetes can be classified such as diabetes mellitus (DM) and diabetes insipidus. Diabetes mellitus is a chronic metabolic disease and glucose is a main source of energy for the cells, when glucose level increased in blood and it is controlled by insulin which is secreted by pancreas. The abnormal of glucose levels in blood for prolong periods due to insufficient insulin, defects in insulin secretion or both. Insulin is a hormones secreted by beta cells present in pancreas (Seema Abhijeet Kaveeshwar 2014). DM is mainly classified in three bases such as Type 1 Diabetes Mellitus (T1DM), Type 2 Diabetes Mellitus (T2DM), and Gestational Diabetes.

1.1 T1DM

T1DM is a condition in which your immune system totally destroy insulin secreting cell is called beta cells which present in your pancreas. T1DM is maximum diagnosis children’s and youngest. It is caused by different factors like genetic disorders, viruses, environment and lifestyle. T1DM also known as insulin dependent diabetes mellitus. T1DM has no permanent cure. The patient how suffered from T1DM they want to take insulin every day’s. T1DM is mainly caused by autoimmune system which helps to fight against foreign agents, here our immune system destroy insulin producing beta cells or pancreas (Zierath 2019).
1.2 Paediatric Diabetes:

Diabetes may be a condition during which the body cannot create enough hypoglycaemic agent, or cannot use hypoglycaemic agent unremarkably’. Sort one polygenic disorder is AN disease. The body’s system damages the cells within the exocrine gland that create hypoglycaemic agent (S 2013).

Hypoglycaemic agent may be an internal secretion. It helps sugar (glucose) within the blood get into cells of the body to be used as fuel. Once aldohexose can’t enter the cells, it builds up within the blood. This can be known as high glucose (hyperglycemia). High glucose will cause issues everywhere the body. It will injury blood vessels and nerves. It will hurt the eyes, kidneys, and heart. It may also cause symptoms like fatigue.

Type one diabetes may be a long-run (chronic) condition. It should begin at any age. Hypoglycaemic agent from the exocrine gland should get replaced with hypoglycaemic agent injections or AN hypoglycaemic agent pump (Asma Deeb 2018).

There square measure 2 sorts of sort one diabetes:

Immune-mediated polygenic disorder. This can be AN disease during which the body’s system damages the cells within the exocrine gland that create hypoglycaemic agent. This can be the foremost common reasonably sort one polygenic disorder (Ralph Ziegler 2018).

Idiopathic sort one. This refers to rare sorts of the malady with no well-known cause.
Challenges of paediatric Diabetes:

Childhood could be a time of growth and organ maturation. For polygenic disease, this relates to continual changes of internal secretion doses and assessment of however internal secretion is employed within the body. The goal of achieving traditional time of life is additionally necessary. Internal secretion resistance happens throughout time of life, with overall internal secretion response 25–30% lower in time of life kids than in prepubescent kids (Research 2016).

Cognitive changes have an effect on care as children's ability to know, verbalize thoughts, and learn new info evolves. Symptom could be a major concern in polygenic disease, notably because it relates to potential adverse effects on the brain. Target aldoehexose levels is also higher in to the developing brain of young kids. That's why strategies to forestall symptom events are crucial; such events have a widespread psychological impact on the family's ability to stay glucose levels in target.

Risk factors of paediatric Diabetes patients:

The major risk factors of paediatric diabetes patients like heart and blood vessel disease, nerve damage when sugar level increase in blood that injure the nerves, it cause pain and burning sensation, kidney damage, eye damage, osteoporosis, etc (Research 2018)

Compared to men, women have higher risk in death upto 40% who suffered in T1DM. And most of the T1DM patients suffered by urinary tract infection, it decrease the urinary bladder sensation.
1.3 **T2DM:**

It’s most common disease compare to T1DM, in worldwide 3% of people affected by Type 2 diabetes. It is developed by the abnormal metabolism like insufficient insulin products, pancreatic beta cells failure, insulin resistance is known as heterogeneous group of metabolic disorders. When glucose levels increased in blood it affects the nerve. The damage occur in automatic nervous system that reduce life expectancy (Medicine 2013). T2DM also affect kids and teen mainly who suffered from childhood obesity.

Once who suffered T2DM is a lifetime disease mainly middle-age or olden-age peoples are affected more due to there obesity, food habits etc (Diabetes 2018). There is no permanent treatment but it can be control by physical exercise, diabetes diet, weight loss, insulin therapy, etc.

**History of oral insulin:**

In history many of them tried to prepare oral insulin with no success, in 1922 joslin the first scientists prepared oral insulin and failed (Sanjay Kalra 2010). Currently they design few insulin molecules for oral administration. And some of them in clinical trials, it will come soon for clinical use.

2. **Causes and Symptoms**

T1DM is caused by autoimmune system which destroyed the insulin making beta cells of the pancreas. Your immune system detect that Beta cells as a foreign agents which enter inside the
body so immune system act against beta cells and it’s totally destroyed. The basic symptoms of the T1DM extreme thirsty, dry mouth, vomiting, increasing hunger, weight losses, blurry vision, frequently urination, stomach upset, fatigue, frequently infections (A.Ramachandran 2014). And during sever manifestation rapid breathing, belly pain or abdominal pain, loss of consciousness also seen.

3. Pathophysiology

T1DM is autoimmune disorder and it is characterized by destroy of insulin producing beta cells of the islet of Langerhans in the pancreas. As beta cells insulin decreased due to 80 to 90% of the beta cells destroyed by T-cells and diabetes developed (Palicka 2002). When beta cells synthesis insulin the autoimmune system release the antibiotics and beta cells detected as antigen so CD4+ T cell damage and destruction of beta cells of the islet of Langerhans. Pathophysiology of T1DM are showed in Fig.1
Genetic factors:

T1DM is generally present in people without a family ancestry. Just 10–15% of the patients have a first-or second-degree relative with the disease. Nonetheless, the lifetime risk for creating T1DM is altogether expanded in family members of patients, as about 6% of kids, 5% of kin and half of monozygotic twins present the infection contrasted with 0.4% commonness of everyone. In excess of 50 T1DM hereditary danger loci have been distinguished by genome-wide affiliation contemplates and meta-examinations. The primary qualities inclining to T1DM are inside the significant histocompatibility complex (MHC) locale, frequently called HLA (human
leucocyte antigen) and situated on chromosome 6. HLA complex polymorphic alleles are answerable for 40–half of the hereditary danger of T1DM improvement (Shao Chin Lee 2007). The insulin quality (Ins-VNTR, IDDM 2) polymorphisms on chromosome 11 and the cytotoxic T lymphocyte-related antigen-4 quality (CTLA-4) on chromosome 2 follow, as these are answerable for 15% of the hereditary inclination. Numerous other diverse hereditary loci have been found to contribute in a lesser degree to the hereditary defenselessness for T1DM alone or in blend with other immune system disease.

4. Treatment

T1DM does not have permanent treatment and cure. Once the person suffered by T1DM they want to take insulin daily to maintain blood glucose levels. There are few types of insulin therapy such as long acting insulin, short acting insulin, rapid acting insulin, premixed insulin and intermediate-acting insulin. Patients with T1DM required 0.5 to 1.0 unit insulin per kg each day depend on disease severity (Rendell 2000). The common insulin administration route is subcutaneous route which injected in the fatty layer of skin or most recommended in stomach. Compare to other injection insulin injection have short needle. T1DM patients need two to four injections each day. And they can minimize the insulin intake by dietary or lifestyle.

4.1. Insulin

Insulin is a hormone which helps to maintain or manage the blood glucose level. It is produced by beta cells which present in the pancreas. Insulin is a anabolic hormone to regulated the metabolism of the carbohydrates, fats and proteins (Yu-Hsin Lin 2007). When blood glucose
level increased then beta cells secret insulin and released in blood vessels and glucose level is
maintained. Insulin is made up of 2 chain polypeptides and it’s consists of 51 amino Acids and
its molecular weight is 6000. Chain-A has 21 amino acids and Chain-B has 30 amino acids. The
two chains are connected by the disulfide bonds. Structure of insulin are showed in Fig. 2.

![Structure of insulin](image)

**Fig.2 Structure of insulin**

**4.2. Type and Classification of Insulin:**

There are 5’ types of present in markets.

1. Rapid acting insulin
2. Long acting insulin
3. Short acting insulin
4. Mixed insulin
5. Intermediate insulin
4.2.1. **Rapid acting insulin**

Rapid acting insulin is very quick in action 5 to 15 minutes it’s normally used before or after the meals to minimize the blood glucose level. Its overall action period is about 3 to 5 hours.

Rapid acting insulin mainly prescribed to T1DM patients.

E.g- Novalog, Humalog

4.2.2. **Long acting insulin**

Long acting insulin are take more time 1 to 2 hours to work and its overall action period is too high when compared to other types of insulin. Its action time is 24 hours, one injection is sufficient per day. It’s recommend for T1DM patients with Rapid acting insulin.

E.g- Levemir

4.2.3. **Short acting insulin**

Short acting insulin are take action with 30 to 60 minutes. It’s overall action period is 5 to 8 hours, two injections per day it cover day and night something it is called as regular acting insulin.

E.g- Novalin, velosulin

4.2.4. **Intermediate acting insulin**

Insulin starts working within 1 to 2 hours and it is reach higher level in blood at 4 to 12 hours. It is also stand for 12 to 18 hours. It is recommend for T2DM and less for T1DM patients.

E.g- NPH
4.2.5. premixed insulin

Mixed insulin means two types of insulin were mixed commonly Rapid acting insulin and short acting insulin are used. Generally takes before a meals 2 to 3 injections per day.

15 to 30 minutes before meals it can take.

E.g- Humulin 70/30, Novalog 70/30.

6. Pharmacological managements Insulin is used many disease related to diabetes, high potassium levels in blood, ketoacidosis, hyperglycaemia. Glucose were utilisation by intracellular- phosphorylation to form glucose-6-PO4 increased synthesization of glucokinase and also glucogen synthese. Inhibits gluconeogenesis from proteins and glycerol by decreasing production of phosphoenol pyruvate carboxykinase. Inhibits lipolysis in adipose tissues and favours triglyceride synthesis in diabetes- increased FFA and glycerol- ketone bodies. Amino acids entry and their synthesis of proteins- also inhibits proteins breakdown in muscles and other cells (Donner T 2019)

7. Challenge associated with insulin for oral delivery

The oral route of administration is considered as the most adapted for chronic conditions like diabetes. Oral insulin administration well reduce the side effects and easy way of administration. The major challenge are poor bioavailability, insulin are quick degradation in stomach, poor absorption of drugs, dose dumping and etc.

7.1 Bioavailability

Most of the proteins and peptides has less than 1% bioavailability because gastrointestinal tract present protein digestive enzymes like pepsin. Due to proteolytic in GTI has less absorption. The oral administration of the insulin most acceptable in chronic therapy. Compare to subcutaneous
route, oral route is not as effective (Bruno 2007). There different parts of smaller intestine, proteins and peptides are not absorb uniform. The small intestinal cellular morphology are change from region to region. There are some methods to preventing or protect from enzymatic degradation by the help of anti proteolytic agents. Use different penetrating enhance and promote the absorption of insulin in the gastrointestinal track.

7.2 Chemical modification

Chemical structure modification of proteins and peptides for enhance bioavailability and increased its stability, this another way to prevent the enzymatic degradation (Wong 2009).

7.3 Peptides inhibitors

It is helps to increase ‘the oral absorption of therapeutic proteins and peptides by minimizing proteolytic breakdown in the GIT.

7.4 Stability of dosage form

Action of proteins and peptides depends upon the 3D molecular structure. During measurements structure advancement, proteins may be dependent upon physical what's more, substance corruption. Physical debasement includes change of the local structure to a higher request structure while substance corruption including bond cleavage brings about the arrangement of a new item (Stephen T. Buckley 2016). Proteins must be described for change in adaptation, size, shape, surface properties, and bioactivity upon detailing preparing. Changes in compliance, size, shape can be seen by utilization of spectrophotometric strategies, X-beam diffraction, differential examining calorimetry, light dissipating, electrophoresis, and gel filtration.
8. Oral insulin formulation

There are more approaches in Oral insulin formulation like Oral insulin pills, emulsion, microcapsules, oral spray, tablets and etc.

8.1. Tablets

Thiolated chitosan is an orally administration insulin have been developed and improved. 2-Iminothiolane has covalently linked with chitosan. Chitosan-TBA insulin tablet formulation Chitosan-TBA 5mg, insulin 2.75 mg, glutathione 0.75 mg, and two inhibits in which 0.75mg (BBI and Elastatinal) were compared by tablet punching machine. This tablet are made by controlled release method it’s time is 8 hours (Eric Zijlstra 2014).

8.2 Microemulsions

It was developed by Cho & Flynn. It is water-in-oil emulsion preparation aqueous phase is insulin and oil phase I’s lacithin, non-esterified fatty acids and cholesterols in critical proportions (Harsha kamath 2017).

8.3 Hydrogels

Hydrogels are made by natural and synthetic hydrophilic polymers. This polymers are insoluble in stomach due to physical and chemical cross-linking agents. In small intestine pH values were increased and insulin were released in hydrogel.
8.4 Nano capsule

Nano capsules are help to prevent the entire release of insulin, it’s particles size is 10 to 1000 nm. Various synthetic polymers were used to improve physicochemical properties and helps to increase insulin bioavailability (Bruno Sarmento 2007).

There is muco-adhesive polymer whish is help to prevent enzymatic degradation of insulin in GIT. Insulin will be encapsulate in nanoparticles by chitosan, alginate this are muco-adhesive polymer.

8.5 Liposomes

Liposomes are increase stability by encapsulate proteins and peptides. It’s improve the stability of oral drugs delivery systems in GIT. Liposomes are one or multi lipid bilayer made by phospholipid. 20 nm to 10 micrometer size range. It is bilayers are similar to cells members so it’s have good permeability.

Compare subcutaneous route, oral route have less bioavailability this is one of the biggest drawback of oral insulin formulation (Mayyas Al-Remawi 2017). Scientists and researchers approached different techniques to prepare oral insulin because it’s easy to administration and less side effects. Another reason is there why proteins are poor absorption in GIT because proteins molecular weight is high 5800 Daltons.

9. Conclusion

Oral insulin is very Nobel and new challenge for the worldwide that can simplify the use of insulin. In present study we unlighted some of new approached and formulation studies
conducted in recently. We mentioned T1DM, type, symptoms, pharmacological managements, and new formulations of oral insulin and challenge associated with oral insulin for the treatments of diabetes.

10. Reference


