Review Article

An overview of insulin therapy in pharmacotherapy of diabetes mellitus type I

Abdulkareem Alotaibi[1]*, Bashayer Al Sultan[2], Reem Buzeid[3], Mohammad Almutairi[4], Eman Alghamdi[3], Maram Aldhaeefi[5], Yaser Khogheer[6], Mohammad Albareqi[7]

[1]Department of Pharmacology and Pharmacotherapy, Medical and Health Science Center, University of Debrecen, Debrecen, Hungary
College of Medicine, [2]King Khalid University, Abha, [3]Imam Abdulrahman Bin Faisal University, Dammam, [4]Imam Muhammad ibn Saud Islamic University, Riyadh, Saudi Arabia
Department of Medicine, [5]King Khalid Hospital, Hail, [6]East Jeddah Hospital, Jeddah, [7]Primary Health Care, Aseer, Saudi Arabia

*Correspondence:
Dr. Abdulkareem Alotaibi,
E-mail: wow_0_@hotmail.com

ABSTRACT

Type 1 diabetes mellitus is a chronic disease, which characterizes itself with body's inability to produce insulin from pancreas. This condition can happen from different autoimmune processes, which subsequently leads into destruction of beta cells in pancreas, the cells responsible for production of insulin. This condition account for about 5-10% of all different forms of diabetes, which should be taken very seriously since its incidence seems to be increasing worldwide and it can result in different devastating short and long-term complications. Management and approaches in patients with type 1 DM is of major concern worldwide since in the lack of proper management these patients cannot survive. Therefore, it is very important to have a multidisciplinary health management team that can have full focus on every aspect of this condition from continuous glucose monitoring, meal planning, screening for different complications to insulin therapy, which is the mainstay in treatment of patients in this group. American Diabetes Association (ADA) suggests using patient's age in establishment of glycaemic goals, with targets for pre-prandial, bedtime and haemoglobin A1c levels. It is very important to educate patients on how to adjust the level of their insulin injection according to the amount of carbohydrate intake, premeal blood glucose, and anticipated activity. Insulin is and will remain the most important treatment approach in patients suffering from type 1 DM. According to recommendations of ADA, it is best when patients with type 1 DM are treated with multiple daily doses of insulin injections, such as three to four daily basal and prandial injections, or continuous subcutaneous insulin infusion devices should be used.

Keywords: Insulin, Insulin therapy, Pharmacotherapy, Diabetes mellitus type I

INTRODUCTION

Diabetes mellitus (DM) is a chronic metabolic disease characterized by the inability to maintain blood glucose concentrations within physiological limits. The review described in this thesis will focus on type 1 diabetes, a particular manifestation of diabetes mellitus. Type 1 diabetes is characterized by a loss of pancreatic beta-cell (B-cell) function and an absolute insulin deficiency.[1] Since insulin is the primary anabolic hormone that regulates blood glucose level, type 1 diabetics require a continuous supply of insulin for survival. Conventional therapy for type 1 diabetics involves insulin replacement through multiple daily injections (MDI) or a continuous subcutaneous insulin infusion (CSII) guided by daily

blood glucose measurements. This review will provide a brief overview about pathophysiology, etiology, epidemiology, clinical features, prognosis and diagnosis of type 1 DM (or insulin-dependent diabetes mellitus (IDDM) and will focus on the pharmacology of drugs used in treatment approach to patients with type 1 DM and more extensively will describe the role of insulin therapy in therapy of this condition.

PATHOPHYSIOLOGY OF IDDM

Type 1 DM is thought to have a complex pathophysiology from lymphatic infiltration to complete destruction of insulin secreting beta cells of the Langerhans islets in pancreas. Infiltration of beta cells with CD4+ and CD8+ will lead into autoimmune beta cell destruction, which eventually decrease the insulin production until the level of insulin in circulation is not adequate to keep up with normal blood glucose levels. After about 80% of the beta cells are non-functional and can't produce insulin, state of hyperglycaemia can develop and diabetes might be diagnosed.[2] Susceptibility to type 1 DM involves multiple genes. The concordance of type 1 DM in identical twins ranges between 40 and 60%, indicating that additional modifying factors are likely involved in determining whether diabetes develops. The major susceptibility gene for type 1 DM is located in the HLA region on chromosome 6. Polymorphisms in the HLA complex account for 40–50% of the genetic risk of developing type 1 DM. This region contains genes that encode the class II major histocompatibility complex (MHC) molecules, which present antigen to helper T cells and thus are involved in initiating the immune response.[3]

ETIOLOGY OF IDDM

The main causative reasons behind DM are still unknown however number of different theories has been described. Genetic susceptibility is thought to be one the main risk factors in relatives of those with type 1 DM, for example the lifetime risk of a person developing type 1 DM seems to higher among patients with positive family history (0.4% with no family history, 1-4% in offspring of diabetic mother, 3-8% of affected father, 3-6% among non-twin siblings and 30% in monozygotic twins).[4] It is thought that in genetically susceptible individuals, having one or more environmental factors can be a booster in triggering an immunologic attack, which further more can lead into destruction of insulin producing beta cells. Environmental risk factors include viral infections, particularly enteroviruses, immunizations, diet, especially exposure to cow's milk at an early age, higher socioeconomic status, obesity, vitamin D deficiency, and perinatal factors such as maternal age, history of preeclampsia, and neonatal jaundice.[5]

EPIDEMIOLOGY OF IDDM

The occurrence of type 1 DM depends on number of factors, which subsequently makes the study of

epidemiology of DM very difficult. These factors are geographical location of patients, their gender and age as well as family history and their race. Interestingly the incidence of type 1 DM in Europe and China seems to be to some extent in direct relationship with geographical latitude, in a way that the more we move towards north of these regions we see more occurrence of this medical condition, however these relationship between location from equator cannot be apply to all countries.[6] The highest prevalence of type 1 DM has been reported in Scandinavia, which reaches of almost 20 percent of all population and it seems to be at its lowest in Japan, however it should be bear in mind that the rate of type 1 DM is increasing by 2 to 5 percent per year in following countries; Europe, the Middle East and Australia.[7]

COMPLICATIONS AND PROGNOSIS OF IDDM

The most common encountered complications of type I DM are hypoglycaemia from management errors, microvascular complications such as nephropathy and neuropathy, and macrovascular disease and neuropathic complications. These complications can consequently lead into increasing chance of cardiovascular and cerebrovascular as well as gangrene of lower limbs and chronic renal disease, which can subsequently worsen patients' conditions and cause even death. According to ADA standard of care, in order to reduce morbidity and mortality of type 1 DM, it is very important to educate patients and care givers about the benefits of close glycaemic control and cessation of risk factors such as alcohol consumption and drug usage as one study suggest that women tend to fare worse in both cohorts and that alcohol and drug use account for more than one third of deaths.[8]

DIAGNOSIS OF IDDM

Diabetes mellitus is diagnosed based upon one of the following four signs of abnormal glucose metabolism: Fasting plasma glucose ≥126 mg/dl (7mmol/l) on more than one occasion, random venous plasma glucose ≥200 mg/dl (11.1 mmol/l) in a patient with classic symptoms of hyperglycaemia, plasma glucose ≥200 mg/dl (11.1mmol/l) measured two hours after a glucose load of 1.75 g/kg (maximum dose of 75 g) in an oral glucose tolerance test (OGTT) and glycated haemoglobin (A1C) ≥6.5 percent.[9] After confirming the presence of DM, type 1 DM is to be differentiated from type 2 through antibodies such as circulating, islet-specific, pancreatic autoantibodies against glutamic acid decarboxylase (GAD65), insulin, and/or zinc transporter 8 (ZnT8), which suggest type I DM, and high fasting insulin and C-peptide levels suggest Type 2 DM.[10]

PHARMACOTHERAPY OF TYPE 1 DIABETES

People with type 1 DM need the lifelong supply of different forms of insulin therapy. Because of chronicity of this condition, it should be treated lifelong by a team

of physicians, nurses, dietitians, and different subspecialists to overcome the devastating possible complications of this condition.

EFFECTS OF INSULIN ON HUMAN BODY

Insulin is a peptide hormone, which contains an A and a B chain that come together with a pair of disulphide bridges. Blood glucose concentration is known to be the major factor that regulates insulin secretion. The pattern of insulin secretion (Figure 1) seems to start with an initial burst of insulin, which is followed by sustained secretion. Mechanism of insulin secretion starts with glucose as the main stimulant for insulin secretion, binds to the Glut 2 receptor on the beta cells in islets of Langerhans in pancreas. Inside these beta cells, glucose will be further oxidized to ATP, which closes K^+ channels in the cellular membrane and would lead into a depolarization of the beta cells. This depolarization process will lead into opening of Ca^{2+} channels that enhances the level of intracellular Ca^{2+} that consequently leads into secretion of insulin.[11] Main focus of insulin actions is on the muscles, adipose tissues and liver. Insulin decreases blood glucose concentration via increasing glucose uptake into the target cells by instantly introducing glucose transporters into cell membranes and as glucose gets into the cells, the blood glucose level decreases. Insulin also promotes formation of glycogen from glucose in liver and muscle tissues and participates in inhibition of glycogenolysis. Insulin also decreases gluconeogenesis via enhancement of production of 2.6-bisphosphate, which leads to increase activity of phosphofructokinase that deviates the process from glucose production. Furthermore, insulin decreases blood fatty acid and ketoacids concentrations via stimulation fat deposition and inhibition of lipolysis in adipose tissue. It also decreases blood amino acid concentration by stimulating its cellular uptake into the cells, increasing protein synthesis, and inhibits protein degradation.[12]

INSULIN THERAPY

Insulin replacement therapy is necessary for the survival of patients with type 1 diabetes. Insulin preparations have evolved since the discovery of insulin by Banting and Best in 1921. Currently, human insulin is mass-produced using recombinant DNA technology, which has reduced the severity and frequency of immune responses (compared to prior insulin preparations obtained from animals). Through amino acid manipulation or the addition of a buffering solution, insulin preparations with various characteristics (onset time and duration) have been developed for use in subcutaneous insulin injection therapies. Establishment of target level of glycaemic control, is one of the most important factors in approach to DM patients, because the complications of DM are related to glycaemic control, and it should also be noted that in order to achieve 'tight' glycaemic control, a diabetic's therapeutic regimen must also focus on proper diet and exercise.[13]

There are many types of insulin used to treat diabetes that are classified according to how rapid they start to work, when they reach their "peak" level of action and how long their effects last.[14,15] The types of insulin include rapid-acting insulin, which starts working within a few minutes and lasts for a couple of hours, regular- or short-acting insulin, which takes about 30 minutes to work and lasts for 3 to 6 hours, intermediate-acting insulin, which takes 2 to 4 hours to work and its effects can last for up to 18 hours, and long-acting insulin, which takes 6 to 10 hours to reach the bloodstream, but it, can keep working for an entire day.[16,17]
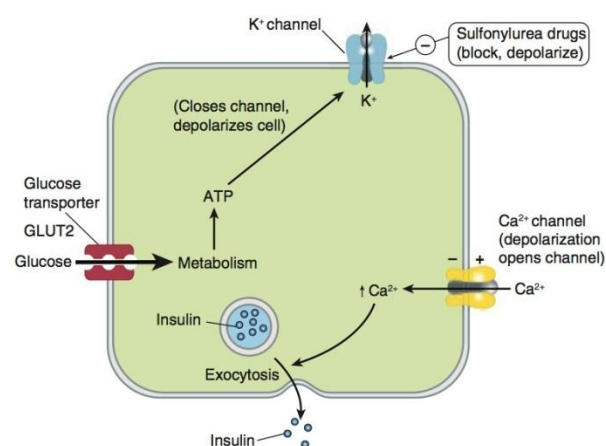

Figure 1: Process of insulin release after stimulation by Glucose and sulfonylurea drugs.[23]

Complications of insulin therapy

The major side effects of insulin include hypoglycaemia, hypertrophy, and skin injection site reaction. Hypoglycaemia presents with extreme hunger, fatigue, irritability, cold sweats, trembling hands, intense anxiety and a general sense of confusion. Despite its danger, it can be prevented by patient education and following simple rules.[18] Diabetic ketoacidosis (DKA) is another insulin complication, which often results from non-intake of insulin. DKA is characterized by severe elevation of blood glucose levels that results in excessive urination and subsequently severe dehydration and electrolytes disturbance. Lack of insulin also results in dysfunction of fat and protein metabolism and storage leading to the release of ketones into the blood which shifts the blood PH to the acidic side leading to ketoacidosis (DKA). The main precipitating factors for DKA include infections, stress, or trauma, as they increase the body requirements for insulin. Patients with DKA present with nausea, vomiting, and abdominal pain and, if not promptly and appropriately treated, will develop shock, coma, and even death.[19] Urgent treatment of diabetic ketoacidosis involves the intravenous administration of fluid, electrolytes, and insulin, usually in a hospital intensive care unit. Dehydration can be very severe, and it is not unusual to need to replace 6-7 litres of fluid when a

person presents in diabetic ketoacidosis. Antibiotics are given for infections. With treatment, abnormal blood sugar levels, ketone production, acidosis, and dehydration can be reversed rapidly, and patients can recover remarkably well. Similar to DKA, hyperosmolar hyperglycaemic nonketotic syndrome (HHNS) causes profound dehydration and can be life-threatening. It is an extremely serious complication that can lead to diabetic coma and even death in type II diabetes. Hyperosmolar hyperglycaemic syndrome is much less common than DKA and tends to happen in older, obese patients with type II diabetes.[20]

GUIDELINES OF PHARMACOLOGICAL THERAPY OF TYPE 1 DIABETES ACCORDING TO 2016 STANDARD OF CARE, AMERICAN DIABETES ASSOCIATION

Insulin is the mainstay treatment for patients with type 1 DM. According to recommendations of ADA, it is best when patients with type 1 DM are treated with multiple daily doses of insulin injections, such as three to four daily basal and prandial injections, or continuous subcutaneous insulin infusion devices should be used.[21] A systematic review and meta-analysis exploring the effects of multiple-dose insulin versus pump therapy concluded that there are minimal differences between the two forms of intensive insulin therapy in A1C (combined mean between-group difference favouring insulin pump therapy 20.30% [95% CI 20.58 to 20.02]) and severe hypo-glycemia rates in children and adults.[22]

Recommended therapy according to ADA for type 1 DM include:[21]

1. Multiple-dose insulin injections (three to four injections per day of basal and prandial insulin) or CSII therapy.
2. Match prandial insulin to carbohydrate intake, premeal blood glucose, and anticipated physical activity.
3. For most patients (especially those at elevated risk of hypoglycemia), use insulin analogs.
4. For patients with frequent nocturnal hypoglycemia, recurrent severe hypoglycemia, and/or hypoglycemia unawareness, a sensor-augmented low glucose threshold suspend pump may be considered.

Common insulin regimens include the following:

- Split or mixed NPH with rapid-acting (eg, lispro, aspart, or glulisine) or regular insulin before breakfast and supper
- Split or mixed variant NPH with rapid-acting or regular insulin before breakfast, rapid-acting or regular insulin before supper, and NPH before bedtime (the idea is to reduce fasting hypoglycemia by giving the NPH later in the evening)

- Multiple daily injections (MDI) A long-acting insulin (e.g., glargine or detemir) once a day in the morning or evening (or twice a day in about 20% of patients) and a rapid-acting insulin before meals or snacks (with the dose adjusted according to the carbohydrate intake and the blood glucose level).

Continuous subcutaneous insulin infusion (CSII) Rapid-acting insulin infused continuously 24 hours a day through an insulin pump at 1 or more basal rates, with additional boluses given before each meal and correction doses administered if blood glucose levels exceed target levels.

CONCLUSION

Type 1 diabetes mellitus is the result of insulin deficiency caused by destruction of the pancreatic beta cells. Type 1 DM is one of the most common chronic diseases of childhood. It accounts for approximately two-thirds of all cases of diabetes in patients younger than 19 years of age. The incidence and prevalence of Type 1 DM is increasing worldwide, it is very important to raise awareness through social media, governmental program, and social programs, which are designed to decrease the risk factors of this metabolic condition. The diagnosis of diabetes is based upon measurement of blood glucose level, autoantibodies, insulin level, and C-peptides. Diabetes mellitus is a lifelong condition that can be controlled with lifestyle adjustments and medical treatments. Keeping blood sugar levels under control can prevent or minimize complications. Insulin treatment is one component of a diabetes treatment plan for people with type 1 diabetes. There are many types of insulin used to treat diabetes classified according to the onset and duration of action into rapid-acting insulin, regular- or short-acting insulin, intermediate-acting insulin, and long-acting insulin. According to recommendations of ADA, it is best when patients with type 1 DM are treated with multiple daily doses of insulin injections, such as three to four daily basal and prandial injections, or continuous subcutaneous insulin infusion devices should be used. Along with pharmacotherapy it is similarly important to educate patients on how to adjust the level of their insulin injection according to the amount of carbohydrate intake, premeal blood glucose, and anticipated activity.

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