Mini Review

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Antidiabetic Drugs: Implications for Type 2 Diabetes

Abstract

This article provides an overview of the development of insulins, oral agents, and noninsulin injectable agents used in the management of hyperglycemia in patients with diabetes. It also briefly reviews the pharmacological impact and salient side effects of these medications. The management of diabetes has changed dramatically during the past several thousand years. The option preferred by "experts" of the pharaoh of Egypt 3,500 years ago was a mixture of "water from the bird pond," elderberry, fibers from the asit plant, milk, beer, cucumber flower, and green dates.1 Although our therapeutic options today are significantly more effective, they will likely be considered arcane by our successors 100 years from now if the current trajectory in treatment development continues. Clearly, however, the current pharmacological armamentarium used to manage diabetes has resulted in a dramatic reduction in morbidity and mortality. This article provides a brief overview of the development history and effectiveness of various agents used in the pharmacological management of diabetes.

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Introduction

Before the 1920s, there were no effective pharmacological agents for the management of diabetes. Because of this, type 1 diabetes was a fatal malady. This changed dramatically with Frederick Banting's work [1].

Dr. Banting served as a surgeon in World War I. Captain Banting initially spent some time in hospitals in England, but later was sent to the front as a battalion medical officer, where he was wounded by shrapnel. He received a Military Cross for his courage in action. After returning from the war, Dr. Banting opened an office outside of Toronto, Canada [2]. After seeing only one patient in the first month of his practice (a patient seeking a prescription for ethanol), Banting embarked upon a career in academics. One of his first teaching assignments involved carbohydrate metabolism. This led to his interest in diabetes and his erroneous assumption that one needed to surgically ligate the pancreatic duct and then wait 6–8 weeks before extracting anything that might be useful from the endocrine portion of the gland. Over time, and without the ligation step, he was able to extract a substance from canine pancreas glands that had an impact on hyperglycemia in other diabetic animals. Banting and his student, Charles Best, continued working on various extraction processes. Patient a sterile abscess developed at the site of one of the injections, but the patient's blood glucose dropped. After that injection, the push to perfect the extraction process and commercialize insulin was on. Banting's team entered into an agreement with Eli Lilly and Company, and, by July 1922, the first bottles of Lilly's Iletin (insulin) arrived in Banting's office. Insulin was commercially available in the United States by 1923 [3].

The next major advancement in insulin was its crystallization in 1926.3 the technique of insulin crystallization led to improved soluble (regular) insulin purity and also opened the door to insulin formulation modifications with different time-action profiles. There was a great need for extended-action insulin. With the availability of only rapid-acting insulin, patients required multiple daily injections and had to be awakened at night for injections. Children not awaked for nighttime injections were at risk for a significant reduction in growth, or diabetic

dwarfism syndrome [4]. Children with diabetic dwarfism syndrome, which was also known as Mauriac's syndrome, suffered from stunted growth, hepatomegaly, and delayed puberty. In 1936, the first commercially available, extended-action insulin, PZI (protamine zinc insulin), was released. This formulation was composed of an amorphous combination of protamine, zinc, and insulin. PZI continues to be used today in the management of cats with diabetes [5].

Clinical Diagnosis of Type 2 Diabetes

Diabetes may be identified in low-risk individuals who have spontaneous glucose testing during routine primary clinical care, in individuals examined for diabetes risk assessment, and in frankly symptomatic patients. Early diagnosis of T2DM can be accomplished through blood tests that measure PG levels. FPG is the most common test to detect diabetes: a level of ≥126 mg/dL or 7.0 mmol/L confirmed by repeating the test on another clinic visit effectively diagnoses the disease. This test requires fasting for at least the previous 8 h and generates enhanced reliability when blood is drawn in the morning [6]. Another criterion is the 2 h PG of ≥200 mg/dL or 11.1 mmol/L in a patient presenting with the traditional symptoms of diabetes such as polyuria, polydipsia, and/or unexplained weight loss. A positive 2-h OGTT will show a PG level of ≥200 mg/dL or 11.1 mmol/L after a glucose load containing 75 g of glucose solution in water. Two-hour PG OGTT is not commonly used in the clinic because, although it is more sensitive than FPG test, it is less convenient and more expensive for patients. Additionally, this test holds less relevance in routine follow-ups after confirmed diagnosis of diabetes is obtained. In the past, the glycated hemoglobin (HbA1C) test was used mainly to monitor the adequacy of glycemic management and has strong predictive value for diabetes complications. HbA1C is a chronic marker of hyperglycemia and reflects patient's blood glucose level over a period of 3–4 months, coinciding with the lifespan of the red blood cells (RBCs). However, in 2009 after its standardization, the International Expert Committee recommended it to be used in diagnosing T2DM but not in T1DM and gestational diabetes. HbA1C level is reported in percentages, and a normal level is below 5.7%. The main advantage of the HbA1C test over other blood glucose tests is the convenience it offers to patients; it does not require fasting and can be done at any time of the day. However, this test is more expensive and may not be readily available in certain locations, which may limit its usefulness [7]. HbA1C may be inaccurate in conditions such as anemia, hemolysis, and other hemoglobinopathies like sickle cell disease and hemoglobin (Hb) variants like HbC, HbE, and HbD, as well as elevated fetal hemoglobin. Thus, HbA1C assay in people of South Asian, Mediterranean, or African origin merit taking these issues into account. In conditions associated with increased RBC breakdown, such as in the advanced trimesters of pregnancy, recent hemorrhage, intravascular hemolysis or transfusion or erythropoietin treatment, only blood glucose estimation should be used to diagnose diabetes. There are limited data supporting the use of A1C in diagnosing T2DM in children and adolescents. Although A1C is not routinely suggested for diagnosis of diabetes in children with cystic fibrosis or symptoms that portend development of acute onset of T1DM, the ADA recommends HbA1C for diagnosis of T2DM in children and adolescents [8].

Result

All insulin preparations available before 1983 were derived from animal sources (primarily beef and pork). This changed in 1983, when the first recombinant medication, human insulin, was approved. One of the primary problems at the time of the release of human insulin was the pharmacokinetic/pharmacodynamic profiles of the available insulins. The search for"flat" basal insulin and rapid-acting insulin that more closely approximated physiological insulin secretory patterns accelerated after the release of human insulin [9]. In 1996, the first rapid-acting human insulin analog, lispro, was approved. This was followed in the past 15 years with a succession of additional insulin analogs, including the rapid-acting insulins aspart and glulisine and the long-acting basal analogs glargine and detemir. The U.S. Food and Drug Administration (FDA) declined to approve degludec, an ultra-long-acting insulin (duration of 42 hours), in 2013. However this compound is available in Europe and will probably be resubmitted for approval in the United States [10].

Conclusion

Type 2 diabetes mellitus is one of the leading causes of renal failure, ASCVD, non-traumatic lower limb amputation, blindness, and death worldwide. It is a serious chronic medical condition that requires a multidisciplinary team approach, consisting of healthcare professionals, dietitians, patient educators, patients, and their families. Lifestyle intervention designed to manage body weight and treat obesity, as well as patient education, are essential for all patients with diabetes. Treatment options may be individualized and medication(s) chosen based on a patient's risk factors, current HbA1C level, medication efficacy, and ease of use, patient's financial situation/insurance/costs, and risk of side effects such as hypoglycemia and weight gain. Effectiveness of therapy must be evaluated as frequent as possible using diagnostic blood tests (HbA1C), as well as monitoring for development of diabetic complications (e.g., retinopathy, nephropathy, and neuropathy). Furthermore, aggressive efforts from physicians and motivating patients for compliance are the two important aspects of the prevention and management of diabetes. Sociocultural issues should be carefully considered. For example, during religious fasting (e.g., during the holy month of Ramadan), the use of pharmacologic agents that induce hypoglycemia should be used with care and insulin doses (for example, premix formulations) should be appropriately titrated and the patient should be educated for blood glucose monitoring and breaking of fast as needed. With infectious diseases (such as AIDS and tuberculosis). Evidence from landmark T2DM prevention trials indicates that lifestyle modification is more effective, cheaper, and safer than medication and provides sustained benefits. Lifestyle modification may be promising approach to T2DM prevention in developing countries. This will be useful for many ethnic groups in the U.S. as well, such as South Asian, Latino, Pima Indians, and African-American populations, which may face socioeconomic challenges similar to what is seen in developing countries. Cost-contained strategies to identify at-risk individuals, followed by the implementation of group-based, inexpensive lifestyle interventions ("comfortably uncomfortable" life, as lived by people in blue zones), seem to be the best options for resource-constrained settings. T2DM pathophysiology is increasingly understood as a mix of insulin resistance and secretory defects of β-cells.

Several options for pharmacologic therapy of lowering blood glucose are currently available, which have revolutionized long-term management of DM. Several antidiabetic drugs may have important CV complications, which the provider team should always be aware. The polypharmacy issues, management of diabetes, as well as hypertension, hyperlipidemia, and use of aspirin should be carefully explained to patients to ensure adherence to therapy to prevent significant CV morbidity and mortality. Careful attention should be paid to development of insulinopenic states by clinical assessment of C peptide and lack of control of HbA1C with multiple medications, and complete lack of secreted insulin conditions should be treated by initiation of appropriate insulin regimens. Every clinical encounter should also be utilized to explain the benefit of weight loss and motivated for such. Even though not yet conclusive, clinical trial and data support consideration of bariatric surgery as a possible strategy to monitor blood glucose levels and body weight, especially in morbid obesity. Balanced hypocaloric diets that cause weight loss must be adopted and regular interactions with dietitian is a useful approach. Aerobic training and resistance training can control increasing lean mass in middle-aged and overweight/obese individuals. Behavioral strategies for weight loss should be encouraged in primary care settings and appropriate maintenance of body weight prior to conception may help after development of gestational diabetes. Weight loss may be particularly challenging for incapacitated patients and subjects with disabilities, so comprehensive approaches should be undertaken. Newer molecular studies have demonstrated the transcriptional link between inflammatory pathways and increased adipose tissue storage, contributing to insulin resistance. Drug repurposing of the anti-inflammatory agent for aphthous stomatitis, amlexanox, is currently undergoing trials as newer agents for management of diabetes.

Acknowledgement

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Conflict of Interest

None

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