Diabetes Management and Future Trends

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LEARNING OBJECTIVES

1. Compare treatment options for type 1 versus type 2 diabetes mellitus
2. List and describe the advantages and disadvantages of the various classes of drugs used to treat diabetes mellitus
3. Identify future trends in diabetes mellitus research and treatment.

ABBREVIATIONS: NPH - Neutral protamine Hagedorn, ACE - Angiotensin-converting enzyme, ARBs - Angiotensin II receptor blockers, SGLT-2 - Sodium glucose cotransporter-2, DPP-4 - Dipeptidyl peptidase 4, GLP-1 - Glucagon-like peptide-1, CDC - Center for Disease Control and Prevention, DPCP - Diabetes Prevention and Control Program

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INTRODUCTION

Proper management of diabetes mellitus is crucial for the health and well-being of patients. Various options exist for the treatment of both type 1 and type 2 diabetes allowing tailored treatment toward each patient. Multiple classes of drugs developed to treat diabetes mellitus can be examined including sulfonylureas, biguanides, and alpha-glucosidase inhibitors. On the horizon for treatment and management of diabetes mellitus, new developments utilize concepts such as stem cell therapy, dietary management, metabolomics and education.

Diabetes Management

Treatment for type 1 diabetes mellitus may include multiple components. Blood sugar levels must be monitored throughout the day using a glucometer. Self-monitoring by the patient has become increasingly practical with the advent of small, portable glucometers and similar supplies.[1]

Treatment with insulin is required for those with type 1 diabetes mellitus to provide consistent blood glucose management and prevent diabetic ketoacidosis. Diabetic ketoacidosis, the buildup of harmful ketones in the body due to the utilization of fat for energy, is a serious threat for diabetic patients.[2] Multiple brands of insulin exist, each producing products that vary in intensity and length of action. Rapid-acting, long-acting and intermediate forms of insulin are available and may be administered via insulin pump, injection or an insulin pen.[3] Rapid-acting insulin treatments include insulin aspart, glulisine and lispro. Regular insulin is considered short-acting and insulin neutral protamine Hagedorn (NPH) is intermediate-acting. Insulin determir and glargine are both long-acting varieties of insulin.[4]

One or a combination of these insulin options are tailored for the patient based on the treatment plan developed by the physician.[4] A treatment plan for an individual with type 1 diabetes mellitus may also include several oral medications used for preventative measures. For example, blood pressure medications, such as angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs), are prescribed to patients with type 1 diabetes mellitus to maintain a blood pressure below 140/80 in efforts to maintain the health of the kidneys. Cholesterol-lowering medications,

including statins, are prescribed much earlier for patients with diabetes mellitus. Many individuals with diabetes mellitus also are on a low-dose aspirin regimen to reduce their risk of heart attack and stroke. It is imperative for patients with type 1 diabetes mellitus to maintain a healthy diet with moderate carbohydrate ingestion evenly distributed throughout the course of the day. Diabetes mellitus patients are discouraged from uncontrolled, rapid ingestion of large volumes of carbohydrates. Regular exercise and visits to the physician are important.[5]

Treatment for type 2 diabetes mellitus varies from that of type 1 diabetes mellitus. Similar to type 1 diabetes mellitus, patients with type 2 diabetes mellitus must be conscious about making responsible, low carbohydrate and low fat dietary choices and follow an exercise regimen. If diet and exercise alone do not suffice, oral or injected medications may be utilized.[6]

Various options exist in terms of medications for diabetes mellitus management. Sulfonylureas are used to treat type 2 diabetes mellitus that is mild to moderate in nature. Sulfonylureas are used along with diet and stimulate the β cells of the pancreas to release more insulin, leading to a reduction in blood glucose levels. Sulfonylureas are unique in that they can be used as the sole treatment or in combination with various hypoglycemic drugs such as metformin and thiazolidinediones.[7] Sulfonylureas have been in use for a many years, so many physicians are quite familiar with them.[8] In addition, sulfonylureas tend to work relatively quickly by taking a dose about 30 minutes before mealtimes.[9] In a few instances, sulfonylureas have been tied to cases of idiosyncratic drug-induced liver disease.[7] Weight gain, low blood sugar, skin rashes, upset stomach and increased irritability are possible side effects of these medications.[8,10]

Thiazolidinediones work to increase sensitivity to insulin by suppressing the release of glucose from the liver.[8,10] The use of thiazolidinediones allows for more efficient use of insulin in muscle and fat.[9] On average, thiazolidinediones do not produce hypoglycemia when the only diabetes medication being taken and may increase HDL cholesterol levels in patients. [8,9] The side effects that may occur include fluid retention that leads to swelling and an increased risk of congestive heart failure in individuals already at higher risk.[10] More serious risks include fractures and possible liver problems which need to be monitored by the physician.[8,9] There are advantages and disadvantages associated with the use of different types of thiazolidinediones. For example, Pioglitazone, a type of thiazolidinedione medication, also presents an increased risk for bladder cancer.[8]

Biguanides improve responsiveness to insulin and lower the amount of glucose released from the liver. Advantages to taking biguanides for diabetic patients may include weight loss and the possibility of a slight decrease in LDL cholesterol.[8] Loss of appetite, gas, bloating and stomach disturbances are possible side effects. Biguanides carry the risk of developing lactic acidosis in patients who have pre-existing impaired liver or kidney function.[10]

Meglitinides quickly promote the release of insulin when taken with a meal. This class of drugs must be taken with the patient's meal and can result in hypoglycemia if not taken properly.[10]

Alpha-glucosidase inhibitors work to decrease blood glucose levels by preventing the breakdown of starches and some sugar in the intestine. This results in a more gradual increase in blood glucose levels after eating. Based on their mechanism of actions, alpha-glucosidase inhibitors should be taken at the beginning of a meal.[9] Weight gain is not typically noted when taking this medication. Side effects are fairly mild and may include discomfort in the stomach, increased flatulence and diarrhea.[8]

Sodium glucose cotransporter-2 (SGLT-2) inhibitors block the reabsorption of glucose in the kidneys, resulting in surplus glucose being released in the urine. [8] These may help patients lose weight and lower blood pressure, but they carry the risk of urinary tract and yeast infections due to the increased levels of glucose in the urine.[8]

Dipeptidyl peptidase 4 (DPP-4) inhibitors work in two ways by restricting hepatic release of glucose and prompting insulin release.[8] Weight gain is not typical in patients who used DDP-4 inhibitors.[8] Use of DDP-4 also may result in reduced total cholesterol levels.[11] Sore throat, headache and upper respiratory tract infections are possible adverse effects of using DDP-4.[8]

Lastly, glucagon-like peptide receptor (GLP-1) agonists

may be useful for treatment of type 2 diabetes mellitus. GLP-1 agonists increase glucose-mediated production of insulin through the β cells of the pancreas. Carbohydrate absorption in the gastrointestinal system is decelerated through a decreased rate of "gastric emptying". Weight loss may result from the use of GLP-1 agonists as they may induce feelings of fullness and reduced hunger.[12] GLP-1 agonists carry low risks of hypoglycemia and may even lower systolic blood pressure.[12, 13] Possible adverse effects may be temporary nausea. Table 1 shows a summary of the advantages and disadvantages of the medications described.

Often, the first medication prescribed to those with type 2 diabetes mellitus is metformin or pioglitazone. Metformin and pioglitazone act on the liver to lower glucose production and increase tissue's responsiveness to insulin. Medications such as glipizide, glyburide, and glimepiride may be added to a therapy regimen (in addition to metformin) to stimulate the pancreas and increase insulin release.[6] The recently released drug, dapagliflozin, is used to aid in weight loss and blood sugar improvement. Already in use in Europe and approved in the United States by the Food and Drug Administration, this one-a-day pill helps reduce blood glucose levels through mechanisms different from insulin therapy.[14] The indication of dapagliflozin is for use in conjunction with modified diet and exercise regimens to improve glycemic control for type 2 diabetes mellitus.[15] A dapagliflozin and metformin hydrochloride extended-release medication was more recently released for the treatment of type 2 diabetes mellitus. Dapagliflozin works to inhibit SGLT2 while extended-release metformin hydrochloride is characterized as a biguanide. SGLT2 inhibiting medications are a unique class of drugs that utilize the kidneys to purge excess glucose present in patients.[16] Additionally, insulin therapy similar to that used in type 1 diabetes mellitus may be required, should the patient become completely insulin deficient.[17]

Treatment for gestational diabetes differs from the treatment for type 1 or type 2 diabetes mellitus. A combination of treatments are often required to maintain a healthy state for both the expecting mother and baby. As previously mentioned, the physician, and sometimes the mother, will monitor blood glucose levels. A diet low in fat and calories and high in fiber is suggested. Medication commonly is not utilized to treat gestational diabetes, however, insulin or oral medications may be prescribed. Breast-feeding is recommended to encourage healthy weight and prevention of type 2 diabetes mellitus in both mother and baby.[18]

Table 1. Advantages and Disadvantages of Various Classes of Type 2 Diabetes Mellitus Medications [7,8,9,10,11,12,13]

Drug Class	Advantages	Disadvantages
Sulfonylureas	-Long history of use -Can be used alone or in combination with other medications - Quick action	- Weight gain - Low blood sugar - Skin rashes - Upset stomach - Irritability - Low risk of idiosyncratic drug-induced liver disease
Thiazolidinediones	- Infrequent side effects - May increase HDL cholesterol	- Fluid retention - Swelling - Increases risk of congestive heart failure in those already at risk - Fractures - Possible liver problems
Biguanides	- Weight loss - May decrease LDL cholesterol	- Loss of appetite - Bloating - Stomach disturbances - Risk of lactic acidosis in patients with already compromised liver and kidney function
Meglitinides	- Works quickly	- Risk of hypoglycemia
Alpha-glucosidase Inhibitors	- Weight gain uncommon	- Mild stomach discomfort - Increased flatulence - Diarrhea
SGLT-2 Inhibitors	- Weight loss - May lower blood pressure	- Urinary tract infections - Yeast infections
DPP-4 Inhibitors	- Weight gain is rare - Hypoglycemia is uncommon - May reduce total cholesterol levels	- Sore throat - Upper respiratory tract infections - Headache
GLP-1 Agonists	- Weight loss - Feel "full" more easily - Low risk of hypoglycemia - Can lower systolic blood pressure	- Nausea

FUTURE TRENDS

New developments in the treatment of type 1 diabetes mellitus include research in the use of stem cell therapy. Recent discoveries indicate that in type 1 diabetes

mellitus not only are insulin producing β cells destroyed, but the blood vessels are also heavily affected. These blood vessels are crucial in the cells' insulin production. To counteract this blood vessel destruction, combining adult stem cells with a new drug is the focus of intense research. New research suggests the use of a drug created from stem cells of the bone marrow helped replenish the cells of the blood vessels and increase β cell production.[19] In order to address the autoimmune destruction of β cells in type 1 diabetes mellitus patients, the concept of introducing the produced β cells in "immunoprotective capsules" is being researched. Additionally, the ability of multipotent stem cells used for β cell production to potentially proliferate into cancerous masses has yet to be fully addressed.[20]

Potential dietary modifications for the prevention and treatment of diabetes mellitus is the focus of a significant portion of current research. Researchers are studying the beneficial effects of increasing the amino acid arginine in the diets of diabetics. Arginine, an amino acid commonly found in nuts, salmon and eggs, has been shown to aid in the metabolism of glucose in mice. Dietary arginine stimulates a peptide called glucagon-like peptide-1 (GLP-1).[21] GLP-1 is produced by endocrine cells in the gut after nutrient ingestion. GLP-1 stimulates the secretion of insulin, decreases food intake, increases β cell proliferation and decreases apoptosis among the β cells.[22] Interestingly, these GLP-1-stimulating effects are not noticed when arginine supplements, as opposed to dietary arginine, are ingested. Research focuses on uncovering the potential benefits of increased dietary nut consumption particularly for type 2 diabetes mellitus.[21]

Research on diabetes mellitus in the field of metabolomics is a rapidly growing trend. Metabolomics is defined as a "systematic study of the unique chemical fingerprints that specific cellular processes leave behind."[23] Metabolomics is being used not only to predict the incidence of diabetes mellitus but also to gain insights into the pathology of the disease itself. Many metabolites affecting the occurrence of diabetes and insulin resistance have been identified. Additionally, strides toward the identification of new diabetes biomarkers have been made through metabolomics research. With an ever-expanding knowledge base, advancements are being made in both treatment decisions and in the monitoring of disease progression.[24] An often overlooked, yet increasingly implemented trend in diabetes mellitus prevention is the utilization of education. Education is occurring at all levels, from educating children about healthy eating and staying active to raising awareness in adults about the prevalence of diabetes mellitus and the need to maintain a healthy lifestyle. For example, limiting time watching television, eating less fast food, and incorporating more physical activity into the daily routine are all healthy steps that children can take to help prevent type 2 diabetes.[25] The Center for Disease Control and Prevention (CDC) mentions three large educational undertakings in the United States that are producing successful outcomes. The Minnesota Diabetes Prevention and Control Program (DPCP) focuses on raising awareness about prediabetes and the increasing prevalence of type 2 diabetes mellitus. Through their efforts, the DPCP has increased detection of prediabetes in Minnesota and partnered with other local programs to promote healthy weight loss in residents. The Kansas Diabetes Prevention and Control Program helped to launch the Kansas Quality of Care Project in 2004, which is associated with 38 hospitals and 68 clinics in the state. The project has worked to increase the percentage of patients receiving recommended preventative services such as eye and foot exams. Furthermore, the CDC created the Native Diabetes Wellness Program to provide educational information to American Indian and Alaska Native peoples. Tribal programs are working to implement healthy changes in the communities as well as promote the use of storytelling to disperse the information available.[26]

The management of type 1 and type 2 diabetes mellitus is complex and uniquely based on the individual patient. The management of blood glucose can be achieved through multiple means, both behavioral-based and medicinal in nature. A glance at the trends in diabetes mellitus research, treatment and education demonstrates the expanding understanding of the disease state of diabetes mellitus and the advances being made in management.

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