Pharmacologic Management of Hyperglycemia in Diabetes Mellitus: Implications for Physical Therapy
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Pharmacologic Management of Hyperglycemia in Diabetes Mellitus: Implications for Physical Therapy

Diabetes mellitus is a costly, chronic disease that affects millions of Americans each year. The classic triad of diabetes management includes diet, exercise, and pharmacological intervention. A variety of complications may result due to this chronic disease, and manipulation of the triad of treatment factors may be necessary in order to effectively treat the individual patient. Physical therapists are consulted in both the primary care of patients with diabetes and in the case of complications; therefore, an understanding of the various forms of the disease, the complications, and the treatment approaches is necessary for comprehensive patient management. The purposes of this article are to give an overview of the disease and its common complications and to discuss the various treatment approaches with emphasis on the pharmacological interventions and physical therapy concerns. [Betts EF, Betts JJ, Betts CJ. Pharmacologic management of hyperglycemia in diabetes mellitus: implications for physical therapy. Phys Ther. 1995;75:415-425]

Key Words: Diabetes mellitus, Insulin, Oral hypoglycemics, Pharmacology, Sulfonylureas.

Physical therapists practicing in acute care settings routinely treat patients who are diagnosed with diabetes mellitus (DM). What is not commonly appreciated is that the physical therapist in almost any practice setting may have occasion to treat a patient who has DM, because DM is known to affect more than 12 million persons in the United States. People with DM are at increased risk of developing chronic complications related to ophthalmic, renal, neurological, cerebrovascular, cardiovascular, and peripheral vascular disease. For example, persons with DM are more likely than their nondiabetic peers to have heart attacks, strokes, amputations, kidney failure, and blindness—medical conditions commonly exhibited in patients treated by physical therapy. The economic cost of DM in the United States is estimated to be $20.4 billion. This excludes the costs of surgical procedures, home health care, and services provided by licensed dietitians and physical therapists; thus, the health care dollars required are even higher.

The classic treatment approach to DM is the triad of diet, exercise, and drug therapy. Although we believe that it is important for the physical therapist to have a basic understanding of the rationale for the treatment regimens prescribed for patients with DM and the interactions of these three treatments in the management of these patients, it is beyond the scope of this article to discuss in detail the specific prescription for either diet or exercise. The intent of this article is to review the pharmacological management of DM in regard to control of blood glucose levels, with a focus on the use of insulin and oral hypoglycemic agents. An in-depth discussion of pharmacological agents commonly used to treat other metabolic abnormalities and complications accompanying DM will not be included. The effects of weight loss and the effects of both acute bouts of exercise and exercise training will be discussed as they relate to the pharmacological management of the patient with DM and their implications on physical therapy intervention.

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Overview of Diabetes Mellitus

Diabetes mellitus is a syndrome characterized by chronic hyperglycemia with resultant specific microvascular, macrovascular, and neuropathic complications. Abnormalities in the metabolism of carbohydrate, protein, and fat are features of the disease, and clinical signs related to the severity of the metabolic disturbance.

The World Health Organization has described diabetes under the clinical classes of DM and impaired glucose tolerance (IGT). The major classes of DM include insulin-dependent diabetes mellitus (IDDM), also known as type I DM, and non–insulin-dependent diabetes mellitus (NIDDM), also known as type II DM. The latter is subclassed as obese or nonobese. Malnutrition-related diabetes mellitus (MRDM), gestational diabetes mellitus (GDM), and other types of DM associated with specific conditions complete the classification of DM (Tab. 1). Persons with IDDM require insulin treatment for survival, whereas the person with NIDDM may or may not require insulin. The names IDDM and NIDDM are somewhat misleading, however, because insulin dependency is not always due to the same mechanism. Insulin-dependent diabetes mellitus, for example, is due to autoimmune beta (β) cell destruction. Non–insulin-dependent diabetes mellitus can progress to the state of requiring insulin treatment, but this progression is not necessarily related to β-cell destruction but rather to deficiency in insulin production or a condition of insulin resistance (a decreased biological response to insulin). Malnutrition-related diabetes mellitus is associated with nutritional deficiency and is seen in tropical developing countries. Gestational diabetes mellitus is DM that occurs for the first time during pregnancy. Impaired glucose tolerance describes hyperglycemia that occurs during an oral glucose tolerance test (OGGT), but below the level needed to diagnose diabetes. Individuals with IGT have an increased risk of developing diabetes and are subject to the macrovascular diseases common in diabetes. There are three subclasses of IGT: obese, nonobese, and associated conditions and syndromes.

Patients with IDDM and NIDDM are most commonly seen in physical therapy because of the microvascular and macrovascular complications of the disease. They will, therefore, be discussed in greater detail.

### Table 1. Examples of Types of Diabetes Mellitus

<table>
<thead>
<tr>
<th>Type I (insulin dependent)</th>
<th>Type II (non–insulin dependent)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes due to pancreatic disease</td>
<td>Diabetes due to endocrine disease</td>
</tr>
<tr>
<td>● Chronic or recurrent pancreatitis</td>
<td>● Cushings's syndrome</td>
</tr>
<tr>
<td>Diabetes due to endocrine disease</td>
<td>● Hyperaldosteronism</td>
</tr>
<tr>
<td>Diabetes due to drugs and toxins</td>
<td>● Acronegaly</td>
</tr>
<tr>
<td>● Glucocorticoids and corticotropin</td>
<td>Diabetes due to abnormalities of insulin or its receptor</td>
</tr>
<tr>
<td>● Diuretics</td>
<td>● Insulinopenia</td>
</tr>
<tr>
<td>Diabetes due to abnormalities of insulin or its receptor</td>
<td>● Receptor defects</td>
</tr>
<tr>
<td>● Insulinopenia</td>
<td>Diabetes associated with genetic syndromes</td>
</tr>
<tr>
<td>Diabetes due to abnormalities of insulin or its receptor</td>
<td>● Myotonic dystrophy and other muscle disorders</td>
</tr>
<tr>
<td>● Cystic fibrosis</td>
<td></td>
</tr>
</tbody>
</table>
vascular condition of peripheral vascular disease.

Hyperglycemia of long duration is associated with structural and functional changes in capillary membranes, blood cells and platelets, nephrons, and neurons.27 Many of these changes are brought about by the accumulation of compounds (eg, sorbitol, diacylglycerol), the depletion of compounds (eg, myo-inositol), or the nonenzymatic linking of glucose and proteins or other macromolecules (eg, nucleic acids, receptors).27

Improved glycemic control has been reported to result in an improvement, or slowed progression, of the microvascular complications associated with DM.5 The Diabetes Control and Complications Trial (DCCT), a multicenter, randomized clinical trial with a total of 1,441 patients with IDDM, compared conventional therapy (one or two insulin injections per day) with intensive therapy (three or more daily insulin injections or use of an external insulin pump; see “Methods of Insulin Administration” section) on incidence of diabetic complications, specifically retinopathy. Previous studies53-55 have shown that intensive therapy caused worsening of retinopathy. In the DCCT trial, although early transient worsening did occur, patients who stayed on intensive therapy ultimately had a 74% reduction in the risk of subsequent progression as compared with patients with early worsening who received conventional therapy. Macrovascular complications, mainly hypertension, coronary heart disease, cerebrovascular disease, and peripheral vascular disease, are likely more associated with the pathogenic lipid abnormalities occurring with DM, although hyperglycemia, to an extent, is also a causative factor.

Complications of Hyperglycemia

Chronic hyperglycemia (blood glucose >140 mg/dL), in both patients with IDDM and patients with NIDDM, is considered to be a significant factor in the development of microvascular complications (eg, retinopathy, nephropathy, neuropathy).32 The presence of chronic hyperglycemia likely plays a significant role in the macrovascular condition of peripheral vascular disease. Hyperglycemia of long duration is associated with structural and functional changes in capillary membranes, blood cells and platelets, nephrons, and neurons.27 Many of these changes are brought about by the accumulation of compounds (eg, sorbitol, diacylglycerol), the depletion of compounds (eg, myo-inositol), or the nonenzymatic linking of glucose and proteins or other macromolecules (eg, nucleic acids, receptors).27

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The Treatment of Diabetes Mellitus

Diabetes mellitus is traditionally treated using the triad of diet and weight management, exercise, and drugs. Patients with IDDM require insulin replacement, with diet and exercise completing the treatment plan, whereas patients with NIDDM are often managed by diet and exercise prior to any use of pharmacological agents. We will discuss pharmacological intervention in controlling blood glucose first, as it is the focus of this article, and we will then briefly discuss the role of diet and exercise in the management of the patient with diabetes.

Pharmacologic Management

Insulin-Dependent Diabetes Mellitus: Insulin Supplementation

Insulin, secreted by the β cells of the pancreas, is the principal hormone required for proper glucose use in normal metabolic processes. Banting and Best recognized insulin in 1921, and the intervening seven decades have witnessed many developments in insulin production, purification, and formulation.

Insulin is composed of two amino acid chains. Preparations are commonly extracted from either beef or pork pancreas, and have only a few amino acids different from human insulin. Antibodies to these species’ insulin, however, develop in some patients. Synthetic human insulin (eg, Humulin), derived from a recombinant deoxyribonucleic acid process in Escherichia coli, is now routinely used. Human insulin tends to have faster absorption and shorter duration of action compared with animal insulin,6 with fewer antibody problems. Methods for the development of analogues of insulin include identifying substances that have been found to have appropriate pharmacological properties (eg, human proinsulin) and adapting them for human use57 and the use of computational chemistry and computer modeling of the physicochemical and biological behavior of insulin.38,39

Types of Insulins and Insulin Regimens

Injectable insulins are divided into three categories according to promptness, duration, and intensity of action following subcutaneous injection: short acting, intermediate acting, or long acting (Tab. 2). The most commonly used injectable insulins are the short-acting regular insulin and the intermediate-acting NPH and Lente insulins. Combinations of the preparations are used to manage specific cases of diabetes. Insulin is commercially available in concentrations of 100 or 500 U/mL (designated U-100 and U-500). The desired reduction in blood glucose is dependent on the
Insulin is not given before lunch because insulin levels remain relatively high after the morning injections to counteract any midday glycemic changes.

The short-acting insulin injections are given 30 to 40 minutes before eating to optimize postprandial control. The intermediate-acting insulin carries over from breakfast to dinner. The disadvantage of this option is that insulin action does not last sufficiently throughout the night, thus episodes of nocturnal hyperglycemia may occur. A second option would be to schedule the evening intermediate-acting insulin injection for shortly before bedtime, at perhaps 10 PM. Other regimens have been developed that are classified as intensive insulin therapy and that attempt to simulate physiological insulin delivery and that consistency with reference to the site of insulin injection be encouraged. To avoid lipodystrophy (lipatrophy or lipo hypertrophy due to insulin injection at the same site), systematic rotation throughout the abdominal area could be encouraged. The results of the Stockholm Diabetes Intervention Study44 and the findings of the DCCT Research Group45 indicate that intensive therapy, designed to achieve blood glucose values as close to the normal range as possible, effectively delays the onset and slows the progression of microvascular complications. In the DCCT study, regular insulin was used to control the postprandial glucose excursion, and a slow infusion of regular insulin by a pump or injected intermediate- or long-acting insulin was used to balance fasting glucose utilization and production. Further investigation is ongoing, but modifications in insulin injection regimens are inevitable with growing information as to the effectiveness in decreasing risk of complications.

### Methods of Insulin Administration

#### Subcutaneous injection. As mentioned earlier, insulin is routinely administered subcutaneously, with the sites of injection rotated, most commonly between the lower abdomen, upper outer arms, upper outer thighs, and buttocks. The rate of insulin absorption varies, however, depending on injection site. For instance, the rate of absorption is faster when insulin is injected into the abdomen than when injected into the arm or leg and thus it has recently been suggested that consistency with reference to the site of insulin injection be encouraged. To avoid lipodystrophy (lipatrophy or lipo hypertrophy due to insulin injection at the same site), systematic rotation throughout the abdominal area could be utilized, recognizing that even within the abdominal area, differences in insulin absorption exist.

<table>
<thead>
<tr>
<th>Insulin Preparation</th>
<th>Onset (h)</th>
<th>Peak (h)</th>
<th>Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Short acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insulin injection (regular)</td>
<td>0.5–1</td>
<td>6–8</td>
<td></td>
</tr>
<tr>
<td>Prompt insulin zinc suspension (Semilente)</td>
<td>1–1.5</td>
<td>5–10</td>
<td>12–16</td>
</tr>
<tr>
<td>Intermediate acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>isophane insulin suspension (NPH)</td>
<td>1–1.5</td>
<td>4–12</td>
<td>24</td>
</tr>
<tr>
<td>Insulin zinc suspension (Lente)</td>
<td>1–2.5</td>
<td>7–15</td>
<td>24</td>
</tr>
<tr>
<td>Long acting</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Protamine zinc insulin suspension (PZ)</td>
<td>4–8</td>
<td>14–24</td>
<td>36</td>
</tr>
<tr>
<td>Extended insulin zinc suspension (Ultralente)</td>
<td>4–8</td>
<td>10–30</td>
<td>&gt;36</td>
</tr>
</tbody>
</table>

Normal insulin secretion in the nondiabetic person consists of basal and meal-stimulated components. Insulin regimens for the person with diabetes attempt to mimic this naturally occurring phenomenon as closely as possible. Regimens of insulin injection include (1) combinations of short- and intermediate-acting insulins, (2) combinations of short- and long-acting insulins (Ultralente), and (3) premixed insulins (short-acting insulin combined with isophane insulin in various proportions). Conventional insulin therapy involves the administration of one or two injections of insulin (usually before breakfast and dinner), coupled with self-monitoring of blood glucose (SMBG) and adjustment in insulin dosage in response to the individual's glycemic pattern. Basal insulin requirement is supplied by the intermediate-acting insulins (Lente or isophane types), whereas mealtime insulin is usually short acting. For example, one option is to give twice-daily injections containing each of the two insulin formulations (short acting and intermediate acting) before breakfast and before the evening meal.
reduces the exposure of the liver to high insulin concentrations.48

**Insulin injection devices.** Low-dose (0.5-mL) syringes, syringe attachments that magnify the numbers, and ultra-fine needles have made insulin delivery easier, more accurate, and less painful. Fountain-pen-like devices are used for multiple insulin injections and consist of a conventional syringe inside a holder. Prefilled cartridges of short-acting or isophane insulin are available89 and are often preferred by patients.51 Disposable pens with premixed insulin regimens have been especially well received by children with diabetes.55 With the recommendations of the DCCT for tighter glycemic control using more intensive therapy, the availability of pen injectors that would allow adjustment of the proportions of different insulins would greatly contribute to the quality of life of individuals attempting to follow the more intensive treatment approach.57

Jet injectors deliver insulin transcutaneously by an air- jet mechanism rather than a needle. A fine stream of insulin penetrates the skin under high pressure. Insulin absorption has been found to be faster with jet injectors than with conventional needle delivery; however, this method is not used commonly due to its expense (>$1,000).48 The American Diabetes Association annually publishes a guide to the available insulin delivery devices to inform patients of newer techniques.57

**Insulin pumps.** External insulin pumps (CSII) are an option for patients requiring insulin. A needle is implanted in the subcutaneous tissue and connected to the pump via a catheter. Continuous subcutaneous insulin infusion delivers basal/bolus insulin doses with precision and provides a basal rate that does not fade after peak absorption. The patient considers, before each meal, exactly how much insulin is required and delivers just that amount. This method eliminates some of the problems associated with regular injection methods, such as depth of injection, and reduces the need for needle stick to every 2 to 3 days. Disadvantages are that this externalized system is susceptible to subcutaneous abscess development, pump failure, and dislodging of the needle. Reasons cited by patients for discontinuation of CSII include skin problems, inconvenience of the pump, and lack of metabolic improvement.58,59 Careful selection of potential users is important and includes evaluation of signs of acceptance of frequent (three to four times daily) SMBG, good understanding of diabetes, stable personality traits, reasonable expectations, and less than end-stage complication status. The converse of each trait increases the risk that CSII will prove unacceptable.60

Implantable insulin pumps were first used in humans in 1986 and are continuing to be studied.61,62 The pump is surgically implanted subcutaneously, usually on the left side of the abdomen. It is disk-shaped and weighs from 180 to 250 g. The catheter tip, which delivers the insulin, usually is placed in the peritoneal space. The pumps deliver a basal infusion of insulin with periodic, timed pulses, which allows some patient control. Since 1986, approximately 500 patients with IDDM have been implanted with pumps in 20 centers in the United States and Europe. Studies have shown the pumps to be safe and effective,63 with few incidences of hypoglycemia.64 The major disadvantage has been catheter obstruction in the peritoneum, usually due to fibrin plugs.65

**Other methods of insulin delivery.** Researchers continue to search for alternative routes and methods for insulin delivery, including the use of intranasal, rectal suppositories,66 rectal suppositories, and jelly capsules and via ocular route and pulmonary inhalation.72 Several attempts have been made to administer insulin orally, but the gastrointestinal tract readily breaks down the proteins, even when the proteins are encapsulated in small liposomes.73–75 Iontophoresis as a method of insulin drug delivery is also being investigated, but only in animal models.76

**Future Research**

**Glucose sensing.** A promising line of research with implantable insulin pumps is the development of a closed-loop system with continuous glucose monitoring that automatically translates changes in blood glucose concentration into appropriate changes in insulin delivery rate. The system would have an input (glucose-sensing) arm and an output (insulin-delivery) arm. Although the sensing device has been devised, implanting it in vivo is difficult.77,78 Research in this area is preliminary and has, to date, used animal models only.77,97

**Artificial pancreas and pancreatic transplantation.** Methods of transplanting live islet cells encapsulated within artificial membranes have been attempted in the last several years.80,81 As of 1989, 1,500 islet transfers have been performed throughout the world, restoring hormone function and normalizing glucose recovery from hypoglycemia.82 Immune rejection of the tissue has been the greatest cause of failure, but islet transfer remains an important line of research in the search for options to provide insulin delivery that more closely approximates physiological function. The reader is referred to the proceedings of the First International Congress on Pancreatic and Islet Transplantation83 for a complete review of research in this area.

**Non-Insulin-Dependent Diabetes Mellitus: Oral Hypoglycemics**

Patients with insulin resistance who are not successfully treated with diet are generally prescribed oral hypoglycemic drugs. These drugs help to promote a decrease in blood glucose, apparently by increasing the release of insulin from β cells in the pancreas or by increasing the sensitivity of peripheral tissues to insulin.84–86 and are, therefore, only effective in patients with some capacity for endogenous insulin production. Whether improved glucose tolerance results from enhanced early insulin release or greater total insulin secretion is unclear.47
The oral hypoglycemics belong to a group of chemical agents called sulfonylureas, which are sulfonamide derivatives. Sulfonylureas are divided into two groups: (1) first-generation oral agents such as acetohexamide, chlorpropamide (Diabinese), toiazamide (Tolazamide), and tolbutamide (Orinase) and (2) second-generation oral agents such as glibenclamide, glipizide (Glucotrol), glinazide, and glyburide (Micronase). The use of second-generation oral agents, which are more potent than first-generation oral agents, has been a recent advance in the management of patients with diabetes over the last decade. Evidence suggests that second-generation agents may also benefit patients with diabetes by favorably affecting lipids, by potentially slowing the progression of diabetic retinopathy, by reducing necessary insulin dosage, and by improving myocardial contractile function. Table 3 gives examples of some of the commonly prescribed sulfonylureas and their pharmacokinetics. In clinical practice, there is little difference between any of the agents, and the choice of sulfonylurea depends more on factors such as convenience and cost.

Table 3. Pharmacokinetics of Commonly Used Sulfonylureas

<table>
<thead>
<tr>
<th>Sulfonylureas</th>
<th>Equivalent Dosages (mg)</th>
<th>Doses per Day</th>
<th>Onset (h)</th>
<th>Duration (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>First generation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acetohexamide</td>
<td>500</td>
<td>1-2</td>
<td>1</td>
<td>12-24</td>
</tr>
<tr>
<td>Chlorpropamide</td>
<td>250</td>
<td>1</td>
<td>1</td>
<td>Up to 60</td>
</tr>
<tr>
<td>Tolbutamide</td>
<td>250</td>
<td>1</td>
<td>4-6</td>
<td>12-24</td>
</tr>
<tr>
<td>Tolazamidoe</td>
<td>1,000</td>
<td>2-3</td>
<td>1</td>
<td>6-12</td>
</tr>
<tr>
<td>Second generation</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Glipizide</td>
<td>10</td>
<td>1-2</td>
<td>1-1.5</td>
<td>10-16</td>
</tr>
<tr>
<td>Glyburide</td>
<td>5</td>
<td>1-2</td>
<td>2-4</td>
<td>24</td>
</tr>
<tr>
<td>Nonmicronized</td>
<td>1</td>
<td>1-2</td>
<td>1</td>
<td>24</td>
</tr>
<tr>
<td>Micronized</td>
<td>3</td>
<td>1</td>
<td>1</td>
<td>24</td>
</tr>
</tbody>
</table>

Biguanides

Biguanides are a class of drugs that are not currently used in the United States. Clinical trials, however, are currently being conducted in the United States, so we will briefly discuss this class of drugs. The majority of the information on the use of these drugs for individuals with NIDDM is found in the European literature. Biguanides appear to act by enhancing peripheral glucose uptake, and they may also reduce gluconeogenesis in the liver, thereby lowering hepatic glucose output. Biguanides are the therapeutic choice for patients who are morbidly obese, because these agents usually do not induce weight gain.

Metformin is the most commonly used biguanide. It decreases fasting blood glucose by suppression of hepatic glucose production and is mediated by suppression of free fatty acid and lipid oxidation. Metformin does not normally cause hypoglycemia and has no effect on insulin activation of skeletal muscle glycogen synthase, the rate-limiting enzyme controlling muscle glucose storage. Because metformin is not metabolized and is eliminated through the kidneys, it is not generally prescribed in patients with renal impairment.

Insulin

Patients with NIDDM who fail to achieve their target blood glucose control using a combination of diet and oral agents will be treated with insulin alone. Insulin administration has numerous effects in patients with NIDDM, including reducing fasting and postprandial hyperglycemia, reducing gluconeogenesis and hepatic glucose production, inducing antiatherogenic changes in serum lipids and lipoprotein profile, and reducing glycosylation of proteins and lipoproteins. Adverse effects include increasing body weight, primarily fat mass, and hyperinsulinemia. Traditionally, there are three indications for insulin therapy: (1) Insulin need is temporarily increased, (2) there is no endogenous insulin secretion, and (3) hyperglycemia does not respond to other forms of therapy. A dose of insulin in the evening (evening insulin therapy) is usually given. Long-term improvements have been found with treatment using insulin alone in patients with NIDDM, despite weight gain and hyperinsulinemia.

Combinations of Sulfonylureas and Insulin

Some patients with NIDDM who have difficulty controlling daytime glycemia by the evening insulin dose alone are, as noted, treated with a combination of sulfonylureas by day and insulin in the evening. Several researchers have investigated the use of combination therapy in patients with type II diabetes. Most of these researchers reported improvement in glycemic control, and some reported a fall in insulin dosage after the addition of sulfonylurea drugs. Few negative results have been reported.

Applicability of the DCCT Findings to NIDDM

Although the DCCT study focused primarily on the prevention of microvascular complications in patients with IDDM, it is likely that the glycemic hypothesis applies to NIDDM as well. Trends in the DCCT study suggest that intensive therapy may have a favorable effect on incidence of macrovascular events, which is a major consideration in the NIDDM population. Recent research supports the view that...
chronic hyperglycemia is involved in the pathogenesis of atherosclerosis and thrombosis in DM.\textsuperscript{110-112} A negative finding of the DCCT study, however, was that the risk of becoming overweight in the subjects undergoing intensive therapy was 33\% greater than in the conventional therapy group.\textsuperscript{113} This finding could possibly contraindicate intensive therapy in the NIDDM population, as weight loss is often an essential goal of the patient with NIDDM. The NIDDM Primary Prevention Study, which is scheduled to begin soon, is likely to provide well-controlled data that address the issue of more aggressive therapy in the NIDDM population.\textsuperscript{114}

**Exercise as a Treatment for Hyperglycemia**

**Response in the Nondiabetic State**

Exercise has an effect of increasing glucose uptake of insulin-sensitive tissues by two mechanisms: (1) increasing blood flow and thus enhancing glucose and insulin delivery to muscle and (2) stimulation of glucose transport by muscle contraction. Exercise and insulin have additive effects on muscular glucose transport, perhaps by separate transport mechanisms—one insulin-dependent and the other contraction-dependent.\textsuperscript{115,116}

In a nondiabetic person, insulin levels fall during acute exercise and hepatic glucose production rises to meet demands of the exercising muscle. If exercise lasts several hours, hepatic glucose production can no longer keep pace with utilization and hyperglycemia ensues. Exercise training causes enhanced whole-body sensitivity to insulin, suggested by low fasting plasma insulin levels and reduced insulin responses to a glucose challenge in the presence of normal glucose tolerance.\textsuperscript{117}

**Response in the Diabetic State: Exercise in the Patient With IDDM**

Exercise has been suggested for the treatment of IDDM because of its effect on glucose uptake. Allen et al\textsuperscript{118} first demonstrated that exercise lowers blood glucose concentration of patients with diabetes and transiently improves glucose tolerance. After insulin was introduced, a single exercise bout was shown to potentiate the hypoglycemic effect of injected insulin, and exercise training was shown to decrease insulin requirements.\textsuperscript{119} A single exercise bout, however, may also result in a further rise in blood glucose and the development of ketosis in patients with IDDM who have poor metabolic control.\textsuperscript{120} These outcomes may be due to the fact that in this diabetic state muscle glucose utilization does not increase normally during exercise; levels of counter-insulin hormones are inappropriately high; and plasma glucose, free fatty acids, and ketone bodies increase. That is, there are great intraindividual and interindividual variations in hypoglycemic effects; thus, exercise may not be indicated for improving glycemic control in all patients with IDDM.\textsuperscript{121-125}

**Effects of Exercise on Insulin Requirement: Exercise Training**

Improved whole-body insulin sensitivity occurs in patients with IDDM who undergo exercise training.\textsuperscript{117} This improved sensitivity may result in a decreased insulin requirement. Patients who regularly exercise will therefore need to adjust insulin dosage accordingly. This dosage adjustment should be done in consultation with the patient's physician, who is better able to recommend specific changes.

**Exercise in the Patient With NIDDM**

Exercise has been prescribed for patients with NIDDM to improve glycemic control, reduce certain cardiovascular risk factors, and increase psychological well being.\textsuperscript{124} Because obesity, hyperlipidemia, and hypertension are commonly associated with type II diabetes, treatment is frequently aimed at reversing all of these abnormalities by weight reduction via a combination of caloric restriction and increased energy expenditure through regular physical exercise. Physical training increases sensitivity to insulin,\textsuperscript{125} although the mechanism is not well understood. In addition, physical training in patients with NIDDM has been shown to produce changes in insulin resistance, such as an increase in the number of skeletal muscle glucose transporters,\textsuperscript{126} which may reduce the need for hypoglycemic agents.

**Diet as a Treatment**

Generally, the goals of appropriate diet treatment of DM are (1) to provide optimum nutrition, (2) to attain or maintain ideal body weight, and (3) to maintain plasma glucose as near the normal physiologic range as possible. The role of diet in the treatment of IDDM is first to minimize the short-term fluctuations in blood glucose, particularly hypoglycemia, and second to reduce the risks of long-term complications. The nutritional requirements of patients with diabetes are considered to be no different from those of nondiabetic people, and
dietary recommendations are fairly similar. In the treatment of patients with NIDDM, dietary restriction is recommended to achieve weight loss and reduce the risk factors for macrovascular diseases, particularly ischemic heart disease, the main causes of death in NIDDM. Weight loss lowers blood pressure and improves blood lipid concentrations, especially triglycerides and very low density lipoprotein cholesterol. These lipid-lowering actions are of value, as they are not achieved by oral hypoglycemic medications. Each kilogram of weight lost during the first year of treatment is associated, on average, with 3 to 4 months of prolonged survival. In addition, weight loss improves insulin resistance and hyperglycemia and, therefore, results in a decreased reliance on hypoglycemic agents for achieving a normal blood glucose concentration. Because hyperglycemia improves more rapidly than weight loss, it has been hypothesized that caloric restriction alone may have an important regulatory effect on the metabolism of obese patients with NIDDM. Dietary regimens are described in the literature, and the reader is referred to specific recommendations for patients with IDDM and NIDDM.

Clinical Implications

Interventions That Cause Insulin to Be Absorbed Too Rapidly

Heat. The application of heat causes local vasodilation with hyperemia. In physical therapy practice, this application can take the form of hot packs, paraffin, water therapy, infrared radiation, or ultrasound. Studies have shown that heat (eg, hot bath, whirlpool, sauna, use of a sun bed) accelerates the absorption of subcutaneous injections of insulin, presumably by increasing skin blood flow. In order to reduce the subsequent risk of hypoglycemia, it is advisable for the physical therapist to refrain from applying local heat to the site of recent insulin injection.

A rise in ambient temperature will also cause an increase in insulin absorption from subcutaneous injection sites. The insulin disappearance rate when insulin is injected into the arm may be as much as 50% to 60% greater with an increase in ambient temperature of 15°C.

Cold. Vasoconstriction and decreased skin blood flow would, logically, be expected to slow or delay insulin absorption from the injection site. Therefore, topical application of cold (ice) to the area would likely have such an effect, although we are unaware of any specific studies demonstrating this effect.

Exercise. The effect of exercise on subcutaneous insulin absorption is well documented in the literature. When insulin is injected into an extremity and that limb is exercised, acceleration in insulin absorption can occur. Exercise such as bicycling immediately after insulin injection in the leg or arm exercise after injection in the arm should be avoided.

Massage. There have been few studies evaluating the effect of massage on tissue absorption of insulin. More research must be done in this area before specific recommendations can be given.

Summary

As has been pointed out, the physical therapist is often involved in the treatment of patients with IDDM or NIDDM, whether directly related to the disease management or to its complications. We propose that to better serve these patients, the therapist should be aware of the following: the patient’s type of DM and the severity of the DM, the complications of the disease, the typical pharmacological regimens for the management of hyperglycemia, the effects of topical administration of vasoactive modalities on insulin absorption, the effects of a single exercise bout on insulin absorption and glucose uptake, and the effects of exercise training on improving insulin resistance.

References


Pharmacologic Management of Hyperglycemia in Diabetes Mellitus: Implications for Physical Therapy
Elaine Filusch Betts, Jeffery J Betts and Candice J Betts