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Emerging Technologies in Diabetes Care

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Diabetes mellitus is a chronic disease that affects 16 million Americans. It manifests in various ways and in different degrees, making the disease challenging to treat. Patients affected with diabetes undergo significant lifestyle changes involving diet, medication, injections and constant concern. Because of such adaptations, patients with diabetes are often in denial regarding their disease, often resulting in low compliance rates. Eventually, many diabetic patients develop serious, long-term complications, including lower limb amputation, renal failure, retinopathy, kidney disease and more. The quality of life of a diabetic patient is also challenged continuously and, therefore, great amounts of money and research are dedicated to the development of diabetes care technology that improves quality of life and outcomes. It is challenging to healthcare professionals to manage a disease with so many components and contributing factors. For this reason, this article profiles new and upcoming technologies in diabetes mellitus care. These innovations can increase patient monitoring ease, simplify therapy and improve outcomes. They include blood glucose monitors, lancets and lancing devices, insulin formulation developments, insulin delivery systems, novel dosage forms of insulin, and islet cell transplantation.

Blood Glucose Monitors

The goal of diabetes management is to attain normal or nearly normal blood glucose levels though exercise, diet, and drug therapy. Monitoring the effectiveness of these regimens is accomplished in part by frequent self-monitoring of blood glucose (SMBG). SMBG, or home blood glucose monitoring, has become a well-accepted tool in the management of diabetes mellitus.[1] Frequent blood glucose measurements help prevent hypoglycemic episodes, avoiding severe hyperglycemia (including ketoacidosis), and maintaining proper, long-term glycemic control.[2] Other benefits include reinforcing disease management by the patient, improving patient-healthcare practitioner relationship and possibly decreasing the use of other healthcare resources.[3-5] Advances in SMBG technology have improved both the accuracy and "user-friendliness" of these devices.

Since the first blood glucose meter was invented 30 years ago,[6] the number and quality of glucose meters has increased. Today, in the U.S. alone, nine companies sell about 30 meters. These more modern meters are considered to be relatively inexpensive, small, light and easy to use.

For over 35 years, urine-reactive strips were also used to test for abnormalities in glucose metabolism.[7] Currently, urine glucose testing is not recommended as the sole method for monitoring blood glucose.[8]

In the past decade, the desire to improve glycemic control has led to the use of blood-reactive strips to measure capillary blood glucose levels. Initially, these blood glucose strips were interpreted by colorimetry through visual readings and optionally by means of reflectance meters.[9] All current home glucose monitoring systems use either reflectance photometry (1st-generation systems) or an electrochemical process (2nd-generation systems).[10] Both technologies use an enzyme (glucose oxidase or hexokinase) that catalyzes the glucose reaction within the test strip.

First-Generation Monitors: 1st-generation blood glucose meters use a photometric measurement based on a dye-related reaction. This method is referred to as "enzyme-photometric," "reflectance photometry," or "light reflectance" method, wherein capillary blood glucose reacts with a chemical on the surface of the glucose meter's strip and creates a change in color.[11,12] The amount of color reflected from the strip is then measured photometrically or colorimetrically. The color-change is proportional to the amount of glucose in the blood; the darker the test strip, the higher the blood glucose content. First-generation meters include:

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• Glucometer Encore
• SureStep
• One Touch Basic
• Accu-Check Easy
• One Touch Profile
• Accu-Check Instant

These meters provided substantial benefits compared to urine glucose testing. Measurements became more accurate and devices became easier to use. However, some disadvantages compared to more advanced technologies include long processing time for measurement, requirement of large drop of blood, large size and limited memory features.[13,14]

The most recent first-generation glucose monitors (i.e., Accu-Check Active, Accu-Check Compact and LXN InCharge) offer several enhancements over previous models. (However the LXN InCharge is recalling all GlucoProtein Strips and ceasing operations.[15]) General advantages include: readings with significantly smaller blood sample (1-3.5 µL vs. 10-15 µL), readings in less time (5-20 seconds), additional GlucoProtein test (InCharge), data management capabilities, such as memory (up to 200 test results with time and date) and software to download and analyze the blood glucose results.

Second-Generation Monitors: Second-generation blood glucose monitors measure an electrical charge generated by the glucose-reagent reaction. This method is referred to as "enzyme-electrode" or "electrochemical process" method.[16,17] Second-generation meters can also be classified based on the electrochemical principle employed: amper-ometry, or colorimetry. Meters using amperometry biosensor technology require a relatively large sample size (4-10 µL), as only a small portion of the sample is utilized. Also, it may provide inaccurate results under certain conditions, such as variations in temperature or in hematocrit.[18] Meters whose glucose measurements are based on amperometry include:

•Glucometer Elite
• Accu-Check Complete
• Glucometer Dex F Precision Q.I.D.
• Accu-Check Advantage F ExacTech R.S.G.

In second-generation meters based on colorimetry measurement, all of the sample glucose is converted to an electrochemical charge and captured for measurement. Thus, as little as an 0.3 mL capillary sample became sufficient to assess a patient's blood glucose value. Furthermore, glucose measurement based on colorimetry technique is insensitive to temperature and hematocrit alterations.[19] The greatest value added to these monitors is the possibility of using alternative sites (e.g., arm or thigh) to obtain the capillary sample. At these sites, capillaries and nerve endings are less numerous; therefore, a more sensitive measurement technology was necessary to provide virtually painless blood glucose testing.

Although colorimetric meters are considered technologically improved versions of 1st-generation meters and amperometry-based 2nd-generation meters, two recent studies revealed a delay in the detection of fast elevation of blood glucose concentration at these sites compared to fingertip measures.[20,21] This lagging was not device specific and was likely the result of physiological differences in the measurement sites' blood flow. Representatives of colorimetric meters include:

•Amira AtLast
• One Touch Ultra
• FreeStyle
• SoftTact

Another milestone in blood glucose monitoring was set by GlucoWatch, developed by Cygnus Therapeutic Systems. The novelty of Cygnus's method is that it extracts and measures fluid from the skin (interstitial fluid), where nerve endings are not present. Thus, blood glucose measurement is virtually painless. Blood glucose readings (based on the enzyme electrode method) are provided every 20 minutes for up to 12 hours. Blood glucose values are displayed on the device, which is worn on the wrist like a watch. An alarm sound will signal the patient if there is a critically low or high reading. Disadvantages to this system include:

•The necessity of daily calibration with conventional blood glucose meters
• Long (3 hours) warm-up period
• High cost ($595 for the monitor and $4.40 for the strips)
Continuous measurement for 12 hours only

Despite these limitations, fluid extraction from the skin appears to be a revolutionary step toward non-invasive glucose monitoring. Several *in vitro* and *in vivo* experiments have shown good correlation between the glucose concentration of the blood and of the interstitial fluid.[22-24] Also, clinical trials have shown that the GlucoWatch system produces clinically acceptable results for 90% of its measurements.[25,26] Such accuracy is comparable to that of currently available blood glucose

monitors, although the ability to detect sudden changes in blood glucose concentration is yet to be assessed.[27]

Other companies are also in the product development phase to measure blood glucose from interstitial fluid (ISF) using several different methods (e.g. Integ and Therapeutic Chemical Product Innovation, Inc). Minimed, the manufacturer of insulin pumps, is in the process of developing a continuous blood glucose monitoring system (CBMS). In this system, a canula is inserted under the skin, which is attached to a sensor. A wire connects the sensor to the monitor, which records blood glucose values every 5 minutes for up to 72 hours. Thus far, the monitor has been used in the hospital setting. SpectRx, along with partner Abbott laboratories, is developing a continuous glucose monitor. The device uses a low-power laser beam to obtain the necessary ISF for glucose measurement. The sample is collected in a disposable biosensor worn on the top of the skin, lasting 1-3 days. The SpectRx device is worn on a belt and produces continuous glucose measurements every 5 minutes. Pilot studies show good correlations (r = 0.9) with conventional glucose monitors.[28]

Third-Generation SMBG Technologies: The next step in blood glucose monitoring is the development of noninvasive (3rd-generation) meters, in which the sample is obtained without direct interaction with body tissues. Access to noninvasive glucose monitors has been one of the main areas of interest for healthcare professionals, researchers, and patients with diabetes. These future meters will likely obtain the sample without invasive intervention, using various characteristics (e.g., spectral, optical, thermal, electromagnetic) and can be detected remotely. The most promising prototypes use radiation technologies. Radiation technologies use Near Infra-Red light (NIR) spectroscopy, Far Infra-Red (FIR) spectroscopy, radiowave impedance, and optical rotation of polarized light.

NIR spectroscopy was the first noninvasive glucose monitoring technology reviewed by the FDA in 1996. The site of this type of measurement is usually the finger, but can be any accessible extremity. Devices of this nature are fast, convenient and easy-to-use by patients.[29] However, they suffer from low sensitivity, and therefore are not particularly accurate in the physiologic glucose range.[30] Another problem with these devices is their poor selectivity; the absorption of NIR by other body substances.[31] Measurements may also be affected by variables at the measurement site (e.g., skin location, skin and tissue structure, and skin contamination by foreign substances).[32] For these reasons, frequent recalibration is necessary, resulting in FDA's denial of market approval.[33] To overcome the technological difficulties, companies are developing larger, more sensitive monitoring devices. Diasensor by Biocontrol, DreamBeam by Futrex and GlucoNIR by CME Telemetrix are marketed to the clinical, hospital, and nursing home settings, where larger size is less problematic.

In summary, there are many promising 3rd-generation devices to measure blood glucose non-invasively, although they do not yet target home glucose monitoring. Home blood glucose measurement technologies instead have been focusing on providing continuous blood glucose testing, to give patients and healthcare providers the ability to closely monitor blood glucose fluctuations and alter therapy according to the readings. Close glycemic control is expected to improve patients' quality of life and decrease long-term diabetes-related complications.

Lancets and Lancing Devices

Traditionally, lancets have been used to obtain the capillary blood sample used for blood glucose measurement. Using a typical lancet, the operator has to aim accurately and impart sufficient force and speed to penetrate to the "correct" depth for effective skin puncture. Such a freehand technique is difficult to control and may result in infection.[34] Puncture pain can also be excessive.[35] Skin puncture causes acute pain (sometimes followed by residual soreness) due to the release of chemicals that react with free nerve endings (nociceptors). The amount of pain varies with the depth of tissue punctured and the site of the measurement.[36]

Skin puncture is usually performed at the fingertip for two reasons: 1) availability of capillary blood vessels and 2) convenience in sample collection for measurement. Alternative site measurement (i.e., from the thigh, forearm, abdomen, etc.) provides a virtually painless alternative that became possible by more sensitive blood glucose monitors. Lancing devices can vary, but those that produce large blood volumes generally tend to be more painful.[37] The lancet must penetrate at least 0.6-1.3 mm to expose sufficient blood samples.[38] Individual variations in epidermis, blood circulations, etc., require an adjustable penetration depth of the lancing devices. Advances in lancing technology were targeted to get sufficient volume of blood sample with the least amount of pain. This can be achieved by varying the diameter and degree of concavity at the end of the lancet, and adjusting the length the lancet extends from the end of the lancing device during puncture.

Lancet Characteristics: The geometrical characteristics of the lancets determines the amount of blood yielded and the amount of pain associated with the process. The most prevalent lancet is made by grinding facets (typically three) into the tip of a metal rod of a specified diameter. Based on the lancets' compatibility to lancing devices, they can be categorized into three groups:

• Type A lancets fit most devices, although not every combination may be recommended by the manufacturer

• Type B lancets are longer and fit a more limited range of devices

• Type C lancets are designed to use with specific devices only

Manufacturers often recommend specific lancets to use with their device. However, pharmacists should understand what combinations are compatible to specific lancing devices when considering 1) lancet availability and 2) lancet diameter. In general, narrow lancets tend to decrease pain and blood volume. Manufacturers quote lancet diameters in swg (standard wire gauge), where large numbers indicate smaller diameters. **TABLE 1** provides information on the diameters and compatible devices to some of the most popular lancets.

Lancing Device Characteristics: All of the commercially available lancing devices can yield sufficient blood sample, since required sample volumes have fallen considerably in recent years. On the other hand, more attention has been placed on reducing the expected blood volume, since that is associated with reduced pain. Non-finger (alternative) puncture sites became popular because they produce less than 3 µL of blood. **TABLE 2** summarizes characteristics important in selecting a lancing device. These include:

• **Safety:** Is it possible to reuse the lancet? Although it may sound convenient and cheap (reduced cost per puncture), the lancet may become blunted and less effective

• **Operating steps:** Most lancing devices are pen-shaped, which facilitates good aiming of the sampling site. The less operating steps they require, the better; and

• **Cost:** Cost per puncture is represented by the endcap and the lancet. Endcaps are usually supplied with the device and lancets are priced competitively ($0.01-0.03).

Recent Technologies in Lancing: Researchers have been working on lancing technologies in order to achieve painless blood glucose monitoring. Two of the most recent lancing technologies, Microlet Vaculance by Bayer and Lasette Plus by Cell Robotics, target patient comfort in drawing the blood sample.

Microlet Vaculance allows patients to take samples from other areas of the body, where nerve endings are sparse (e.g., underside of the forearm, base of the palm, outer thigh, or the abdomen). The Vaculance develops a vacuum to help suck blood out from the above areas, where capillary blood vessels are also fewer. For many people, using these alternate sites to draw a capillary sample is less painful than the conventional fingertip method.

Lasette Plus uses a laser beam as opposed to the steel lancet to obtain the capillary blood sample. Two types are available: one for professional and one for personal use. A recent study indicates similar results when using the Lasette Plus or a conventional lancet in the measurement of blood glucose. (However, the delayed detection of fast changes in blood glucose concentrations that has been associated with other alternate-site measurements has not been evaluated with Lasett Plus.) Other advantages include: 1) reduced residual soreness associated with the use of lancets; 2) alternative for "needle-phobic" patients; and 3) reduced chance of contamination. Cost is the major obstacle--more than $1,000 for the device and $15 for the film cartridge, which lasts for 120 tests. However, since January 1, 2002, the elderly can obtain both Lassett Plus and the film cartridge free of charge through Medicare.

Table 1: Lancet Characteristics

Lancet	Manufacturer/ Distributor	Diameter (mm/swg)	Compatible Device
	TYPE A		
Cleanlet Fine (Cleanlet 28)	Gainor Medical (MediServe)	0.36 / 28	Auto Lancet Autolet Mini
Cleanlet 25	Gainor Medical (MediServe)	0.50 / 25	Glucoject Plus Lancer
FinePoint	LifeScan	0.50 / 25	Microlet
One Touch	LifeScan	0.66 / 23	Microlet Vaculance
Monolet	Sherwood Medical	0.80 / 21	Monojector Penlet Plus Soft Touch
	TYPE B		
Cleanlet 25XL	Gainor Medical (MediServe)	0.50 / 25	Autolet Lite CliniSafe
Monolet Extra	Sherwood Medical	0.80 / 21	Glucolet
	TYPE B		
Softclix II	Roche Diagnostics	0.40 / 28	Softclix Softclix II
Softclix Pro	Roche Diagnostics	0.80 / 21	Softclix Pro

Table 2: Lancing Device Characteristics

System	Soft Touch	Penlet Plus	Softclix	Glucolet	Microlet Vaculance	Lasette
Manufacturer or Distributor	Roche	Lifescan	Roche	Bayer	Bayer	Cell Robotics
Cost of Device	$20	$24	$35	$15	$22	$1,400
PERFORMANCE						
Depth Settings	2 (endcaps)	7 (integral)	11 (integral)	2 (endcaps)	4 (integral)	16 (power settings)
Shallow	beige	yes	yes	light grey	yes	N/A
Intermediate	blue	yes	yes		yes	
Deep		yes	yes	dark grey	yes	
Recommended Lancet	Soft Touch Autoclix	FinePoint	Softclix II	Ames	Mikrolet Baylent Glucolanz	N/A
Alternative Lancet	various (Type A)	various (Type A)	none	various (Type B)	various (Type A)	N/A
SAFETY						
Automatic lancet retraction	yes	yes	yes	yes	yes	N/A
Lancet ejection mechanism	no	yes	yes	no	no	N/A
Prevention of lancet reuse	no	no	no	no	no	N/A
NUMBER OF OPERATING STEPS						
	8	8	9	9	13	6

Insulin

Formulation Developments: Regular insulin has been used in diabetic patients before meals to mimic the normal physiologic pattern of insulin secretion during and after a meal. However, mealtime injections may be more challenging since blood glucose concentrations can increase more rapidly than the onset of regular insulin. The delay in onset of regular insulin could result in postprandial hyperglycemia and late hypoglycemia. The ideal insulin for mealtime use has a prompt onset and short duration of action. Lispro (Humalog) was introduced in 1996 and the newest insulin aspart (NovoLog) was approved in 2000. Both insulin aspart and lispro have similar pharmacokinetic profiles (see **TABLE 3**). They have a faster rate of absorption and a shorter duration of action compared to regular insulin.[40] Insulin lispro is administered within 15 minutes before a meal and insulin aspart is administered within 5-10 minutes before a meal.[41] Although they have similar mechanisms of action, they are not automatically substitutable by pharmacists because they are different compounds.

Table 3: Pharmacokinetics of Available Insulins

Insulin	Onset	Peak	Duration
Rapid acting			
• Lispro (Humalog)	5-15 min	1 hr	3-5 hr
• Aspart (Novolog)	5-15 min	1 hr	3-5 hr
Short acting			
• Regular	0.5-1 hr	2-4 hr	6-10 hr
Intermediate acting			
• NPH	1-3 hr	6-14 hr	24+ hr
• Lente	1-3 hr	6-14 hr	24+ hr
Long acting			
• Ultralente	6 hr	18-24 hr	36+ hr
• Glargine	1-2 hr	Peakless	24+ hr

Intermediate and long-acting basal insulins such as NPH, Lente and Ultralente have been available for some time, but have limitations to their use. Some disadvantages are variable absorption, unwanted peaks in hypoglycemic action and an inadequate duration of action. This may result in nocturnal hypoglycemia and fasting hyperglycemia in the morning. These insulins require multiple daily doses and can limit the flexibility of meal schedules. The ideal basal insulin is slowly absorbed, has consistent bioavailability, provides constant plasma concentration without a peak, and has a long duration of action that permits once-daily administration.

Insulin glargine (Lantus) is a long-acting analog that has a prolonged plateau of action. Therefore, it is suitable for once-daily dosing. It has a smooth, 24-hour duration with no noticeable peak. Also, it results in less variability in absorption characteristics and has dose-to-dose absorption consistency. Using glargine in combination with lispro has been recommended to better emulate normal insulin production in healthy patients, in whom insulin is continuously secreted between meals and throughout the night to control glucose production from the liver.[35] Pharmacists should counsel

patients that although Lantus is clear, it should not be confused with regular insulin. Healthcare providers and patients should be aware that Lantus and Lente sound similar and are sometimes confused by practioners.

Insulin Delivery Systems: Traditionally, patients with diabetes who use insulin have to manipulate small insulin syringes and use acute vision to be able to draw up insulin accurately. Unfortunately, many of these patients have peripheral neuropathy and retinopathy. Overall, this process has proven time-consuming, cumbersome, inconvenient, painful, and risky due to potential dosage errors. Therefore, patients will potentially greatly benefit from new insulin delivery systems. Insulin pens have been used more frequently outside the U.S. In some countries, 70%-90% of all insulins are delivered by pen and only ~2% in the U.S. The insulin pen combines the insulin container and the syringe as a single unit and allows patients to dial the amount of insulin they want to inject. Its compact size allows discreet insulin administration while maintaining extremely accurate insulin delivery. Advantages of the pen include:

• Convenience in insulin delivery and therefore higher compliance rates
• Consistently accurate dosing
• Less pain due to larger-gauge needles
• Simpler for specific populations to use (children, adolescents, elderly, and women with gestational diabetes)
• Improved social acceptability
• More flexibility because of disposable and reusable options

There are two types of pens available: prefilled and reusable. Some disadvantages include longer injection time and higher cost of therapy. Some patients may also require two different types of insulins in ratios different from those commercially available.

The InnoLet system from Novo Nordisk (approved by the FDA in December 2001) is a prefilled insulin device that features a large dial that looks similar to a kitchen timer. It enables patients to dial and click-in the insulin dose. The large grip helps make the device easy and comfortable to hold. This provides stability during injection for better control over injection depth and decreased tremor at the needle tip. Like the insulin pens currently available, InnoLet provides an alternative to the traditional syringe-and-vial insulin delivery system. InnoLet uses replaceable insulin cartridges and needles. Its biggest advantage may be the decrease in potential errors in dosing with insulin. Patients with vision or dexterity problems may find the InnoLet the most appealing.[36]

Insulins available with the InnoLet are Novolin 70/30, Novolin R, NovoLog and Novolin N. A disadvantage is the large size of the device. Some patients without the manual dexterity problem may find it too bulky to carry. Novo Nordisk also launched Innovo, a state-of-the-art insulin doser that has a built-in memory that records the number of units of your last insulin dose and how much time has elapsed since you took it. The large digital display includes a 6-second countdown feature that tells you when the entire dose has been delivered and when the needle may be withdrawn. Innovo is specifically designed for compact carry-along convenience.[44]

Next, Minimed has come out with a continuous subcutaneous insulin infusion pump. This is an implantable insulin pump that is small in size and simple to operate. Its features include:

• A quick release to detach the pump from the wearer
• A low volume alert
• An optional vibrate mode
• Programming capabilities at three basal rates
• A child-block feature to restrict reprogramming

Additionally, the frequency of severe hypoglycemia is generally lower with use of insulin pumps.[45] Disadvantages are that they require rigorous self-monitoring and there is a risk of infection at the injection site.

Novel Dosage Forms of Insulin: Insulin dosage forms have not changed in decades; therefore, patients must still inject insulin subcutaneously. The new inhaled form of insulin would dramatically increase compliance rates since many patients have an aversion to self-injections. The insulin is stored as a powder in blister packs inside the inhaler. When the inhaler is pumped, air is forced into the chamber and breaks open the blister pack. This, in turn, forces the drug deep into the lung. Despite previous conceptions, this form of insulin has proven to have consistent and reproducible results.[46] The major disadvantage with the inhaler is that it is inefficient, delivering only about 30% of the drug into the blood stream, resulting in higher medication costs.[47]

Generex is continuing to work on their product, RapidMist, a form of inhaled insulin absorbed through the oral mucosa. It is currently undergoing Phase III trials and is being evaluated for safety and efficacy in replacing insulin injections. Inhale Therapeutic Systems Inc. has licensed its inhaled product to Pfizer and Aventis and is currently in late Phase III clinical trials. The inhaled insulin, called Exubera, is expected to be equivalent in effectiveness to injected insulin. However, it may have a tendency to cause a slight but significant decline in breathing ability. The unfavorable lung function

trend will cause Pfizer to delay its U.S. marketing application for one year.[48] Also, Lilly and Dura are collaborating to produce the Spiros Pulmonary Delivery System. Similarly, this drug is formulated as a powder for inhalation. The powder formulation is delivered through the inhaler, a hand-held, battery-powered, multi-dose system designed to deliver consistent doses of medicine to the lung independent of the patient's inspiratory effort. Upon reaching the lung, the insulin enters the bloodstream. It is not anticipated to replace insulin injections entirely because it comes as rapid-acting only (similar in kinetics to lispro).[49]

New Class of Agents Coming Soon

Current pharmacological treatment options of type 2 diabetes consist of five classes: sulfonylureas, biguanides, thiazolidinediones, a-glucosidase inhibitors, meglitinides and insulin. With type 1 diabetes, the clinician's only FDA-approved option is insulin. Newer drug classes are currently being tested that could offer several options for both type 1 and type 2 patients. Pramlintide (Symlin), a new injectable, is currently being tested and may have a place in therapy for type 1 and type 2 diabetics. Pramlintide is a synthetic analog of the human hormone amylin, which is produced along with insulin in normal beta cells, but is deficient in diabetes. It suppresses the secretion of glucagon, an anti-insulin hormone, in response to food. It also slows stomach emptying, which helps lower postprandial glucose levels. Pramlintide would be used in combination with insulin. Because it affects the appetite center, it can contribute to weight loss. This aspect is a big advantage for patients with diabetes since most medications cause weight gain.[50] The next novel pharmacological agent is Glucagon-like insulinotropic polypeptide (GLIP), which also targets the suppression of postprandial hyperglycemia. GLIP increases insulin production in response to a meal. Like amylin, GLIP must be administered subcutaneously also. Also in clinical trials is AC2993 or synthetic extendin-4, which is a peptide that stimulates secretion of insulin when blood glucose is elevated. This peptide has been shown to reduce both postprandial and fasting blood glucose levels. Clinical trials are investigating monotherapy and combination therapy with sulfonylureas and metformin.[51]

Pancreatic Transplantation

People with type 1 diabetes mellitus do not have functional pancreatic islet beta-cells, and therefore, are not able to produce insulin. This absolute lack of insulin production mandates that these patients receive exogenous sources of insulin. Theoretically, the ultimate solution would be to replace the dysfunctional pancreas or pancreatic islet cells. This idea is not a novel one. Surprisingly, pancreatic islet transplantation was first performed a century ago in a rodent.[52] Because of high rates of noncompliance and complications secondary to diabetes, transplantation appears to be a very attractive alternative to traditional treatment. Despite this, there have not been significant improvements in this procedure until very recently.

Types of Transplantations: *Pancreatic organ transplantation:*[53] This procedure has been performed in over 15,000 patients worldwide. It requires lifelong immunosuppressive therapy. Although the technology has improved dramatically, it is still not widely performed in patients, with the exception of combined pancreas and kidney transplantation.

Allo-islet transplantation:[54] Pancreatic islet cells (also known as the islets of Langerhans) are composed of alpha, beta, gamma and PP-cells (**TABLE 4**). Islet transplantation was attempted as early as 1894, but has not been perfected until more recently. In 2000, Shapiro *et al.* experienced a significantly higher success rate compared to previous attempts.[55] Other researchers, including the Edmonton group, report a 12-month success rate in seven patients receiving islet cell transplantation. These seven patients achieved total independence from exogenous insulin use as well as normal fasting glucose levels and normal HbA1c levels in the first year. However, the post 1-year reports on these patients reveal five have impaired glucose tolerance and three have post-transplant diabetes.[56]

Transplantation of encapsulated pancreatic cells:[57] Encapsulation creates an artificial membrane around the cell, which protects it from the host immune system. Therefore, immunosuppressive therapy may not be required. Various methods of encapsulation are being studied (e.g., intravascular macrocapsules, extravascular macrocapsules and extravascular microcapsules). This procedure is not currently an option, because it has not been studied widely in humans.

Implantation of genetically engineered B-cells or embryonic stem cells:[58] This procedure is a possible means of successful transplantation in the future. One of the problematic issues surrounding islet transplantation is a lack of supply. Currently, two pancreases are required to produce enough islet cells for successful islet transplantation in one patient.[59] Genetically engineered islet cells would potentially solve this supply problem. Another benefit is that the engineered islets could be produced from the patient's own body, bypassing the need for immunosuppressive medications. Very recently, *Health Scout News* and the *American Diabetes Association (ADA)* published a report stating that the third and final gene that regulates insulin production has been identified and cloned.[60] This will enable scientists to produce insulin from stem cells or other non-insulin-producing cells.

Table 4: Cells of the Pancreas

Activity

	Hormone that is released		Effect on serum glucose
Alpha	Glucagon	Glycogenolysis (breaks down glycogen into glucose)	Increases
Beta	Insulin	Uptake of glucose into peripheral tissues	Decreases
Gamma	Somatostatin	Decreases release of glucagon and insulin	None
PP	Polypeptide	Unknown	Unknown

Current Status: The *American Diabetes Association (ADA)* acknowledges that transplantation may be beneficial in some patients with type 1 diabetes by improving quality of life (i.e. eliminate SMBG, insulin administration, etc.) and decreasing the risk of short-term complications. However, they recommend this procedure only in patients with a minimum of a 20-year history of diabetes.[61] One must consider the risk of surgery as well as the need for lifelong immunosuppression necessary to prevent rejection of the transplanted pancreatic graft. The use of immunosuppressive agents and steroids in diabetic patients may exacerbate insulin resistance, which increases the workload of the transplanted islet cells. There is also a risk of reoccurrence due to the primary disease process.

The *ADA* position on pancreatic transplantation includes:[62]

• Pancreatic transplantation should be considered in patients who are also receiving kidney transplantation because this may improve kidney survival. These patients should not have a high surgical risk for a dual transplant procedure.

• For patients not undergoing kidney transplantation, patients should have: a) a history of frequent, acute and severe metabolic complications requiring medical attention b) severe clinical and emotional problems in relation to insulin therapy and c) consistent failure of insulin-based management.

• Pancreatic islet cell transplantation holds advantages over whole-gland transplantation, but is still experimental.

The technology of pancreatic transplantation is progressing rapidly and in novel ways. However, it is not a current option for the vast majority of patients with diabetes. The next couple of years should prove to be fruitful because of a joint research project among ten clinical centers internationally.[63]

Conclusion

New technologies in diabetes management have great potential to increase patient compliance, quality of life and provide optimal health outcomes. It is crucial for pharmacists to stay informed of such developments because they serve as key players in the medical management of diabetes. Pharmacists are often a patient's first contact when they have questions regarding their diabetes treatment regimen. Pharmacists and patients can be comforted with the idea that although there is no current cure available for diabetes, new research and technology is making care easier and more effective. An enormous amount of research is being conducted in the field of diabetes and therefore, the technology is constantly changing. Interested pharmacists should use articles such as this one, in combination with resources such as the American Diabetes Association and local diabetes chapters, to stay abreast of all changes.

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