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New insulin replacement technologies: Overcoming barriers to tight glycemic control

ABSTRACT

New insulin analogues act more quickly, allowing better postprandial glycemic control and making intensive control easier. New methods of delivering insulin, notably inhaled insulin, will soon provide alternatives to painful injections. Improved glucose sensors may eventually make an artificial pancreas possible.

KEY POINTS

Insulin lispro and insulin aspart have shorter times to peak action than does regular insulin, and therefore offer an advantage as preprandial agents.

The long-acting insulin suspension HOE901, when approved, should offer an advantage over other long-acting suspensions because it has a steadier and more predictable rate of absorption.

Highly motivated patients who cannot achieve good glycemic control by other means may benefit from using a continuous subcutaneous insulin pump.

Inhaled insulin systems are expected to gain approval from the Food and Drug Administration within 2 years. These should find wide use for preprandial insulin administration.

FOR PEOPLE WITH type 1 diabetes, tight glucose control does not come easily. Not only must they follow a strict diet, they must stick their fingers several times a day to monitor their blood glucose levels and give themselves multiple insulin injections on a complicated sliding scale. The risk of hypoglycemia is considerable. For this therapy to be safe and effective, patients and their health care teams must be highly motivated, committed, and sophisticated. Many people cannot keep up the effort over the long run.

People with type 1 diabetes, who depend on insulin treatment for their very survival, need better and more convenient alternatives to today's regimens, as do patients with type 2 diabetes who need insulin injections for reaching target HbA_{1c} levels.

This article reviews insulin regimens available today, and offers a glimpse of the exciting technological and pharmacological innovations expected in the near future.

BENEFIT OF TIGHT GLUCOSE CONTROL

Several major studies[1–4] in the last 10 years proved that people with diabetes can delay or prevent diabetes-specific complications such as retinopathy, nephropathy, and neuropathy by maintaining near-normal glucose levels. (Although diabetes hastens the development of atherosclerosis, which causes 80% of deaths in all forms of diabetes, atherosclerosis can be curtailed by aggressive lipid-lowering therapy[5] and strict blood pressure control.[6,7])

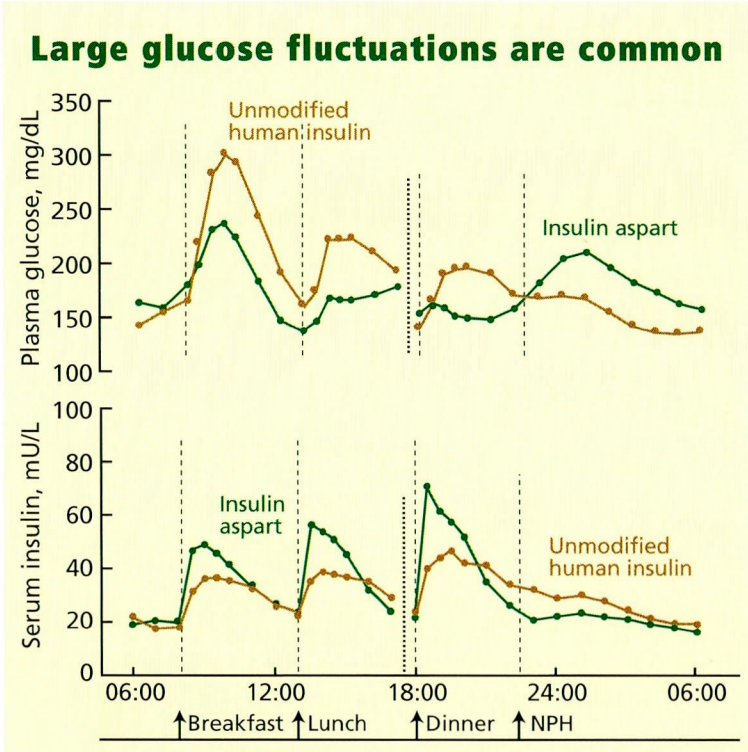


FIGURE 1. Mean serum insulin and plasma glucose levels in type 1 diabetic patients using insulin aspart (green) or unmodified human insulin (gold) before main meals. Sampling began at 1800 for each profile.

SOURCE: FROM HOME PD, LINDHOLM A, HYLLEBERG B, ROUND P, FOR THE UK INSULIN ASPART STUDY GROUP. IMPROVED GLYCEMIC CONTROL WITH INSULIN ASPART. DIABETES CARE 1998; 21:1904–1909.

PITFALLS OF INSULIN THERAPY

Ideally, insulin regimens should produce normoglycemia in the fasting state as well as postprandially. The old-fashioned "split-mixed" regimen (twice-daily doses of a mixture of an intermediate-acting insulin such as NPH or Lente plus short-acting regular insulin) did not do a good job of this, as it resulted in peaks and valleys of insulin action and a predictably poor match between physiological insulin requirements and insulin availability. However, as we shall see, pitfalls are also common with the newer, "tight" regimens (FIGURE 1).

The new approach is based on frequent glucose self-monitoring, and has two components: the basal component and the prandial component.

The basal insulin component consists of bedtime or twice-daily doses of intermediate-acting (NPH or Lente) or long-acting (Ultralente) insulin, with the goal of maintaining normoglycemia during the fasting state without causing hypoglycemia.

The prandial insulin component consists of doses of a short-acting insulin such as regular or lispro taken before meals, with the goal of minimizing hyperglycemia after meals.

Although each component of insulin therapy helps maintain tight glycemic control, each carries its own pitfalls due to natural variations in diet and activity level.

Pitfalls of the basal insulin component

Hypoglycemia occurs during periods of fasting if plasma insulin levels are inappropriately high, causing suppression of hepatic glucose production (glycogenolysis and gluconeogenesis). The action of human NPH insulin reaches a peak 4 to 10 hours after subcutaneous injection; therefore, hypoglycemia commonly occurs around 2 or 3 AM if NPH insulin is taken with dinner instead of at bedtime, and in the late morning or the afternoon if lunch is omitted, delayed, or small.

*Hyper*glycemia, on the other hand, can occur spontaneously in the morning due to a "dawn phenomenon" (circadian insulin resistance) or from waning of insulin activity, particularly if the evening dose of NPH insulin is taken with dinner instead of at bedtime. Conversely, fasting hyperglycemia and ketosis can occur as a rebound after nocturnal hypoglycemia ("Somogyi phenomenon"), which can go unnoticed unless the patient monitors his or her glucose level periodically overnight.

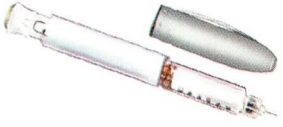
Pitfalls of the prandial insulin component

Regular insulin, injected subcutaneously, peaks too late (2–3 hours) and lasts too long (6–8 hours) to be an ideal prandial agent, and cannot prevent early postprandial hyperglycemia without risking subsequent hypoglycemia. To try to make the peak action coincide with the peak blood sugar level, patients are supposed to take their regular insulin 30 to 45 minutes before meals, but this is inconvenient and potentially dangerous, particularly if last-minute changes are made in the amount or timing of meals. For this reason, many patients do not follow this rule. New

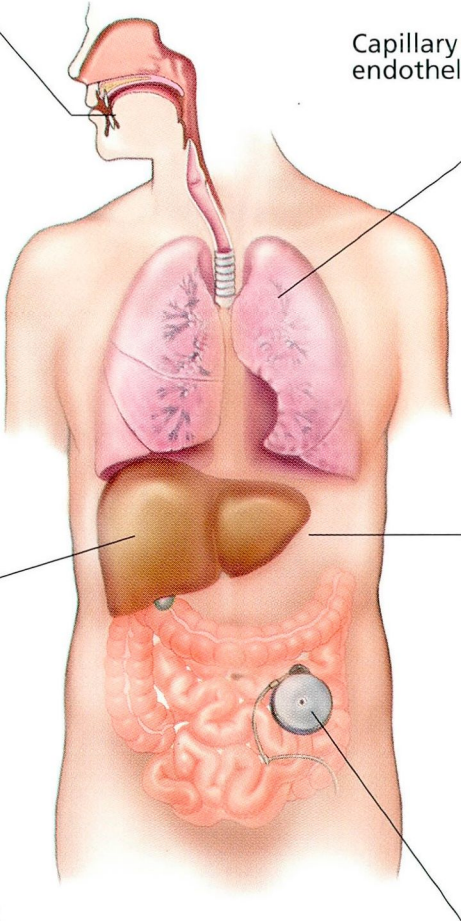
Alternate routes of insulin administration

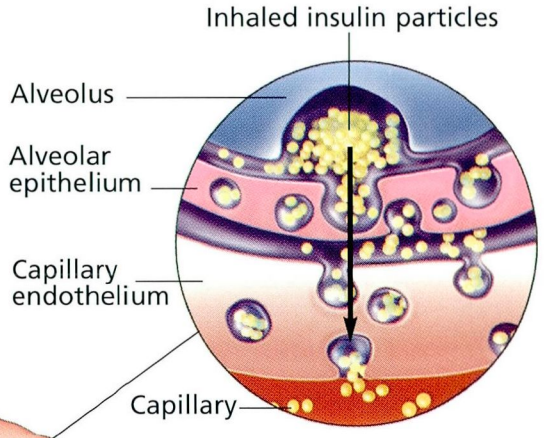
SEVERAL NEW THERAPIES for diabetes are either available or undergoing testing, and should make tight control of blood sugar easier.

SUBLINGUAL AND BUCCAL INSULIN PREPARATIONS are undergoing phase 2 and phase 3 clinical trials in Canada, and may soon begin clinical trials in the United States as well.

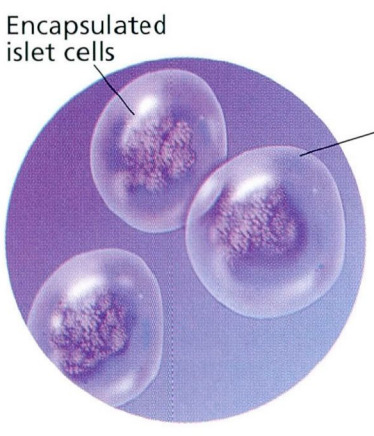


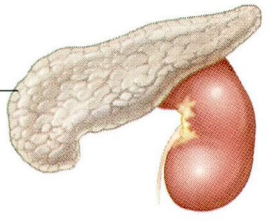
SMALLER, THINNER NEEDLES and **PEN-SHAPED MULTIPLE-DOSE SYRINGES** make injections less uncomfortable and more convenient. Several are available now.





INHALED INSULIN reaches the blood stream faster than parenteral insulin, an advantage for preprandial administration. Several systems are expected to receive FDA approval soon.





PANCREAS TRANSPLANTATION restores normoglycemia, but requires lifelong immunosuppression, so is usually done only when a patient also requires a kidney transplant.

TRANSPLANTED ISLET CELLS that are encapsulated in an artificial membrane might evade destruction by the immune system, eliminating the need for lifelong immunosuppression. Placed in the liver, peritoneum, or other organs, these have been surprisingly effective in animal studies.

INSULIN PUMPS, implanted or worn externally, release short-acting insulin at a steady rate. At present, the rate of infusion must be set manually in anticipation of need or in response to fingerstick glucose levels, but in the future a continuous glucose sensor may help "close the loop."

FIGURE 2

fast-acting insulin analogues (see below) are clearly advantageous in this regard (FIGURE 1).

NEW INSULIN ANALOGUES

Until recently, none of the insulin preparations available did a particularly good job of mimicking physiologic insulin secretory patterns, because of their pharmacokinetics when injected subcutaneously.[8] For example, as discussed before, regular insulin is not an ideal agent by the subcutaneous route because it takes too long to be absorbed (compared with the insulin response to food in healthy subjects, which is immediate.) The reason for the delay: insulin molecules tend to bond together in groups of six in the subcutaneous tissue, and these hexamers must then be slowly broken apart into dimers and monomers before the insulin can be absorbed into the circulation. Absorption is the rate-limiting step.

Insulin lispro

In 1996 the US Food and Drug Administration (FDA) approved insulin lispro, the first new insulin approved in 14 years. Insulin lispro [Lys(B28), Pro(B20)] is a fast-acting insulin analog marketed by Eli Lilly as "Humalog."[8,9] This preparation was engineered for faster absorption by exchanging the amino acids proline and lysine at positions 28 and 29 on the molecule's B chain, which decreases its electronegativity and allows the insulin hexamer to dissociate much faster. The resulting faster absorption makes it feasible to inject insulin lispro just before a meal, with lower postprandial glucose levels and less risk of hypoglycemia hours later.

Lispro and aspart have a quick onset and a short duration of action

The superiority of lispro over regular insulin was demonstrated in a "real-life" double-blind cross-over experiment, in which participants with type 1 diabetes were given either lispro or regular insulin just before a carbohydrate-rich meal consisting of pizza, non-diet Coca-Cola, and a high-calorie Italian dessert called tiramisu. When the glucose levels were graphed over time for both insulins, the glucose area under the curve was 78% less for insulin lispro than for regular insulin,[10] indicating better glycemic control.

Insulin aspart

Insulin aspart [Asp(B9), Glu(B27), Asp(B10), Asp(B28)] is absorbed quickly because it retains its monomeric structure after subcutaneous injection. It is still under study by Novo Nordisk and has not been approved by the FDA, but could become available soon.

In a double-blind comparison with human regular insulin, insulin aspart achieved better control of postprandial glycemia and decreased significantly the frequency of hypoglycemia.[11]

Fast-acting insulins and HbA_{1c}

Even though using insulin lispro or insulin aspart leads to lower postprandial blood glucose levels than regular insulin, most studies have not shown that these newer agents lead to lower hemoglobin A_{1c} (HbA_{1c}) levels. The reason: they have a shorter duration of action and therefore allow glucose levels to rise higher several hours after the injection and also overnight. Hence, one must take care to provide sufficient *basal* insulin to prevent hyperglycemia and ketosis.[12] In practice, this means using an intermediate-acting or long-acting insulin at least twice daily.[12] This precaution will likely lead to lower HbA_{1c} levels, as has been the case in studies using insulin lispro by continuous subcutaneous infusion.[13]

HOE901

HOE901, a long-acting subcutaneous insulin formulation from Hoechst Marion Roussel, is undergoing phase 3 clinical trials and is likely to reach the market within the next year or two. It is produced by substituting the amino acid glycine for aspartic acid at position 21 of the A chain and adding two arginines to the carboxy-terminus of the B chain (B31, B32), which modifies the molecule's isoelectric point, increasing self-association and delaying absorption. HOE901 will be preferred over human Ultralente insulin[14] as an ideal agent for once-daily basal insulin administration because of HOE901's flat profile of action,[15] which contrasts with the unpredictable absorption peaks of Ultralente.[14]

In a small study,[15] normal volunteers received HOE901 while also receiving a glucose infusion by the glucose clamp method, and HOE901 was found to have an extended

plateau of action. In a 4-week randomized multinational European study of 333 type 1 diabetic patients,[16] treatment with HOE901 yielded lower fasting glucose and HbA_{1c} levels than treatment with NPH insulin. In addition, nocturnal hypoglycemia occurred less often with HOE901 than with single nightly doses of NPH.

MAKING MULTIPLE INJECTIONS EASIER

Intensive insulin regimens entail more injections than the older regimens. A few innovations have made these injections a little easier on the patient:

Thinner and shorter needles reduce discomfort.

Pen-shaped devices that conveniently fit in a shirt pocket preclude the need to carry vials and syringes. These have been popular for years in Europe, and to a lesser extent in the United States. The NovoPen (Novo Nordisk, Princeton NJ) and the BD Pen (Becton-Dickinson, Franklin Lakes, NJ) use replaceable cartridges containing 150 or 300 units of regular, lispro, NPH, or a 70%/30% mixture of NPH and regular insulin. Prefilled, disposable versions of both brands of insulin pens are now available; the entire device is discarded after its content is exhausted. None of the pens permit mixing of insulins: two injections are needed for taking NPH plus regular insulin, except in the fixed 70/30 ratio.

Air-powered injectors such as the Mediject (Minneapolis, MN) aerosolize and force insulin through the skin.[17] They do not use needles, and for this reason patients often inquire about them. Although they deliver precise doses that are quickly absorbed, they still cause discomfort at the injection site. Relatively bulky and heavy, they are seldom prescribed, except for children or adults with severe needle phobia.

CONTINUOUS SUBCUTANEOUS INSULIN INFUSION PUMPS

In some patients who try hard to achieve ideal control but cannot meet their goal with multiple daily injections, a continuous subcutaneous insulin infusion pump can make a tremendous difference in improving control,[18] while reducing the risk of hypoglycemia.[19] However, patients must be carefully selected: they must be strongly motivated and willing to accept responsibility in their daily care.

Continuous subcutaneous infusion of short-acting insulin is more predictable in its effects on blood glucose levels than are regimens that include modified insulins such as NPH and Ultralente, because the latter have variable absorption. Large day-to-day fluctuations in the rate of absorption of the slower-acting insulins contribute to the unpredictability of glucose control and the "brittleness" of diabetes. Depot insulin absorption varies according to the site of injection, exercise, temperature, and unknown factors.

Continuous subcutaneous infusion, in contrast, is highly predictable because it uses only rapid-acting insulin delivered at a precise rate, programmed according to need. Adjusting the basal rate overnight, for example, can guarantee that the proper amount of insulin will be delivered during sleep, a source of concern with all other regimens. In addition, pump use provides the flexibility to delay or skip meals without undue risk of hypoglycemia, because the basal rate of insulin infusion is set to maintain safe glucose levels in the fasting state. Insulin boluses commensurate with the amount and composition of food are taken separately at mealtimes.

For some, an insulin pump can make a tremendous difference

Buffered regular insulin (Velosulin, Novo Nordisk) is preferred over standard regular insulin for use in insulin pumps, because it is less prone to aggregate or obstruct the catheter. Insulin lispro (discussed above) is also appropriate and improves postprandial glucose levels while also decreasing the chance of subsequent hypoglycemia.[9,20]

Although intentional or inadvertent interruption of insulin delivery can cause ketoacidosis within hours, later-generation pumps have alarms that signal problems with obstructed or broken infusion lines. Improvements in catheters and subcutaneous needles have enhanced comfort and convenience. Clamping of the catheter now allows short-term removal of the pump, such as during vigorous activity or bathing. Sof-set (Sylmar, CA) is a soft Teflon cannula that stays under the skin after a needle used for its insertion is withdrawn, reducing local pain.

Today's pumps are small, accurate, reliable, and easy to use. The Minimed 507 (Minimed Technologies, Sylmar, CA) is the size of a pager and uses a short 3-mL syringe. The H-Tron (Disetronic, Minneapolis, MN) is waterproof and only slightly larger, and uses a refillable insulin cartridge.

Still, these devices have disadvantages. They are quite expensive, and patients without insurance rarely can afford them. (One model of pump costs $4,995, and monthly costs for pump supplies average $225.) Further, as external devices, they get in the way. The patient has to take care of the infusion site to prevent skin infection. Finally, the patient still has to perform frequent fingersticks for self-glucose testing and adjust the insulin dose accordingly.

ALTERNATIVE ROUTES OF INSULIN ADMINISTRATION

Until now, the oral, transdermal, and nasal routes have been inefficient in delivering insulin into the circulation in humans. Systems in which insulin is inhaled deep into the lungs hold the greatest promise for clinical application in the near future. I predict that soon many diabetic patients will choose to take a single daily injection of a long-acting insulin such as HOE901 to satisfy their basal insulin requirements, and use inhaled fast-acting insulin before meals, with results that could very well match those achievable now only with multiple daily injections or continuous subcutaneous infusion.

Few patients without insurance can afford an insulin pump

Oral insulin

In tests in diabetic rodents, insulin-loaded polymeric microspheres escaped proteolytic digestion in the stomach and were absorbed intestinally.[18,21] Chitosan-coated liposomal microparticles that release insulin slowly[22] could in theory supply basal insulin via the gastrointestinal tract. Much research is needed on the safety, bioavailability, and pharmacodynamic properties of enteral insulin before human application can be considered.

Transdermal insulin

Limited transdermal absorption of insulin has been achieved by means of ionophoresis and ultrasound,[18] but this is very inefficient.

Nasal insulin

Nasal administration of insulin for up to 3 months has been studied in type 1 diabetes,[23] but bioavailability was poor and rhinitis affected absorption. Surfactants have been used to enhance insulin absorption, but these tend to irritate the nasal mucosa.

Sublingual insulin

Generex Biotechnology Corp (Toronto, Ontario) recently received regulatory approval from Canada's Health Protection Branch to conduct late phase 2 and phase 3 clinical trials of Oralin, an oral insulin preparation for buccal and sublingual mucosal absorption. The trials are designed to determine Oralin's bioavailability and efficacy in type 1 and type 2 diabetes. Trials will be conducted at the Banting and Best Diabetes Center, University of Toronto. An IND (investigational new drug) application is also under review by the US Food and Drug Administration.

Inhaled insulin systems

Recent technological advances now make it possible to deliver insulin deep into the lungs, from where it is rapidly absorbed into the bloodstream. The richly vascularized surface of the alveolar epithelium measures 100 m^2 (the size of a singles tennis court) and is highly permeable, making inhalation an attractive alternative to injections for delivering a variety of drugs and hormones. In contrast, the thick-layered mucosa of the upper airways and the bronchial tree is relatively impermeable to peptide drugs. Several manufacturers are testing different types of inhalers.

Inhale Therapeutics (San Carlos, CA) in collaboration with Pfizer Inc (New York) makes an inhaler that delivers a fine-powdered formulation of human regular insulin deep into the lungs. These tiny dry particles—less than 5 microns in diameter—dissolve in the alveoli, releasing insulin which then enters the circulation by "transcytosis" through the alveolar epithelium and the capillary endothelium (FIGURE 2). In contrast to aqueous aerosols, in which only 1% to 2% of the particle composition is drug and the rest is

water, dry powder aerosol particles contain up to 95% drug in a chemically stable form called an "amorphous glass state."

Powdered insulin comes in blister packs for exact dosing, and can be kept at room temperature for up to 2 years. When insulin is needed, the patient inserts a blister pack into the flashlight-sized device and activates its pneumatic mechanism to pop the pack open, creating a visible suspended cloud of the powder in its clear chamber, from where it is inhaled in a deep breath through a mouthpiece. The Inhale device is easy to use and requires no special training or coordination ability, resulting in excellent reproducibility of the insulin dose absorbed.[24] This is a purely mechanical instrument with no electric power and no electronic circuitry.

In clinical studies of patients with type 1 or type 2 diabetes,[24–27] inhaled insulin taken before meals compared favorably with injections in terms of efficacy, safety, and patient satisfaction. In view of the frequent reluctance of type 2 diabetic patients to accept insulin injections when their oral medications fail,[28] it is encouraging to note that adding inhaled insulin to the oral regimen helps restore excellent glycemic control.[27] Phase 3 trials of the Inhale/Pfizer system are scheduled to start soon in 1,000 patients in various protocols at multiple centers, which should clear the way for FDA approval within 2 years.

Aradigm Corp (Hayward, CA) has developed a hand-held inhalation device that contains microprocessors to produce a consistent dose, regardless of the patient's breathing ability. Aradigm's proprietary method creates a unit-dose aerosol from liquid, commercially available insulin formulations of different strengths. The liquid is inserted into the device, and the aerosol is generated and delivered directly to the patient, circumventing any problems associated with converting proteins into powders, including aggregation and stability. The device produces particles of 2 to 3 microns in diameter to target the alveoli for systemic drug delivery.

In a pharmacokinetic study,[29] 11 normal subjects received either regular insulin U100 subcutaneously or either U250 or U500 insulin by inhalation. Both inhaled preparations resulted in much faster insulin absorption (7 and 16 minutes, respectively) than did subcutaneous injection of human regular insulin (55 minutes).

PURSUING A 'CURE' FOR DIABETES

Pancreas transplantation

Intensive insulin treatment improves but does not normalize blood glucose levels and is labor-intensive, difficult to implement for most patients, and limited by increased frequency of hypoglycemia. Pancreas transplantation is the only treatment of type 1 diabetes that restores insulin secretion and consistently establishes long-term euglycemia.[30–33]

Nearly 12,000 pancreas transplantations were performed between 1977 and 1998 worldwide, with more than 1,200 in 1997 alone.[33] Patient survival ranged from 92% to 95% at 1 and 3 years. From 1994 through 1997, overall pancreatic graft success ranged from 82% at 1 year to 72% at 3 years. For diabetic patients with chronic renal insufficiency, the best results are obtained by performing simultaneous kidney-pancreas transplantation as compared with pancreas-only or pancreas-after-kidney transplantations.[33]

Renal biopsies in kidney-pancreas recipients show reduced rates of mesangial expansion and less glomerular basement thickening than in those with kidney transplants alone, evidence of a beneficial effect of normoglycemia over imperfect diabetic control.[31] In addition, quality of life improves as a result of unrestricted diet, freedom from injections, and absence of serious hypoglycemia. While several indices of nerve function also improve, no clear effect is seen in established retinopathy.

FDA approval for inhaled insulin is expected within 2 years

On the down side: This is a major operation that demands considerable technical expertise and carries significant costs and risks both from the surgical procedure itself and from the need for permanent immunosuppression.[31] Another problem is that pancreas transplantation leads to significant peripheral hyperinsulinemia (two to three times normal), because the venous outflow of the graft bypasses the liver and drains directly into the systemic circulation. In theory, this could be atherogenic. New techniques that drain the insulin into the portal vein are being explored.[31]

Guidelines from the American Diabetes Association propose that pancreas transplantation be considered whenever patients with type 1 diabetes receive a kidney transplant for end-stage renal failure.[32] In the absence of renal failure, pancreas transplantation should only be used in rare cases of extreme metabolic instability (eg, recurrent life-threatening hypoglycemia) or intractable psychological problems that render other treatments ineffective.[32]

Islet cell transplantation

Autotransplantation of islet cell tissue prevents diabetes in nondiabetic subjects who undergo pancreatectomy for chronic pancreatitis.[31,34] Infused through the portal vein, the islet cells seed the patient's own liver and remain viable in the long run, affording insulin independence for 1 year or more in 74% of patients who receive more than 300,000 islet cells.[34]

In contrast, allotransplantation of cadaveric islet cells with the intention of curing type 1 diabetes has been a difficult challenge. Less than 10% of recipients of these transplants have maintained insulin-independence at 1 year. Worldwide, 305 adult islet allografts were performed in type 1 diabetic patients between 1974 and 1996; 33 patients became insulin-independent soon after the procedure, and 1 has been insulin-independent for 5 years.[35] While this record certainly establishes proof-of-concept, and some patients have excellent results,[36] most patients eventually require insulin injections.

Nearly 12,000 pancreas transplants have been performed

An obvious possible reason for allograft failure in patients with type 1 diabetes is the presence of autoimmunity. Whether the intrahepatic placement of the islet cells makes them more vulnerable to immune (or nonimmune) damage is unclear. Because an enormous need exists for a simple, risk-free procedure to correct hyperglycemia early in the course of diabetes, more research is needed to resolve the mystery of early and late islet graft failure seen in type 1 diabetes.[35] Improved immunomodulation will be key, since all currently available drugs such as cyclosporin and FK506 are themselves toxic to the islet cells and to renal function, and glucocorticoids can cause insulin resistance.

Islet cell encapsulation is a potential way to protect islet cell transplants from immune attack. Various biohybrid devices involving encapsulation, hollow fibers, or sacs containing unmodified islet cells or engineered cell lines have been used with surprising success in animal studies.[37–40] These devices can be placed freely in the peritoneum or liver, inside a large blood vessel, as an arteriovenous shunt, or subcutaneously. Xenotransplants (ie, grafts from a different species) survived in the absence of immunosuppression in nonhuman primates if they were isolated inside selective permeable membranes that permit diffusion of glucose and insulin while shielding the graft from humoral and cellular immune attack.[38] Researchers hope that one day a biohybrid xenotransplant device (using for example pig islet cells) will solve the problems of human donors and allografting.

PURSUING THE ARTIFICIAL PANCREAS

We now have insulin pumps that can be implanted subcutaneously and drain into the peritoneal cavity, mimicking the action of the pancreas.[9,41–44] But these pumps cannot truly be considered an artificial pancreas, as they still lack one important capacity: glucose-sensing. Therefore, patients using insulin pumps still have to test their glucose levels and decide about adjustments in their dosage.

Even so, implantable insulin pumps maintain long-term glucose control as well as external pumps do, but with lower rates of severe hypoglycemia and possibly less weight gain.[41,44] The DCCT trial[45] showed that intensive treatment of type 1 diabetes by the subcutaneous route can cause excessive weight gain, with changes in lipid levels and blood pressure similar to those seen in the insulin resistance syndrome, which could aggravate the coronary risk profile. For this and other reasons, the implantable insulin pump appears advantageous.

Regrettably, the development of implantable insulin pumps has been delayed by trouble maintaining patency of the infusion line,[45] due to foreign body reaction elicited in the peritoneum, and insulin precipitation. These problems have been addressed[42] with the addition of a side port that permits rinsing of the clogged infusion line without surgery, and

with a better formulation of the special insulin used, HOE21PH (Hoechst AG, Frankfurt, Germany).

Two brands of implantable insulin pumps exist. The Infusaid Model 1000 pump (Norwood, MA) is a freon-driven device that has been used in more than 150 study patients in the United States and Italy. The MiniMed model MIP 2001 implantable pump (Sylmar, CA) has been used in more than 600 patients with type 1 diabetes in France and the United States. Both are enclosed in a round titanium case and controlled by short-distance radio-wave handheld programmers.[9] Batteries last approximately 3 years. The insulin reservoir is refilled percutaneously every 1 to 3 months. The pumps are implanted under local or general anesthesia in the subcutaneous tissue of the lower abdomen, and the catheter is inserted into the peritoneum or (rarely) the portal vein. The cost is approximately three times higher than with an external pump.

Needed: A reliable, implantable glucose sensor

A wearable or implantable artificial pancreas that frees patients from doing self-glucose testing and deciding insulin doses could become a reality within a few years. To achieve this goal, such a device must continuously measure glucose, follow an algorithm for selecting insulin dose according to need, and pump insulin reliably.[46] As discussed previously, reliable pumps already exist, and computer programming is not a problem. The missing ingredient for "closing the loop" is a reliable glucose sensor.[46,47]

Optical glucose sensors shine a beam of near-infrared light through a blood vessel or a fingertip and use light absorption to estimate glucose concentration. Unfortunately, other substances compete for similar wavelengths and can obscure the weak glucose signal.[46] In spite of media hype and the use of mathematical models to attempt to filter out interfering signals, optical glucose sensors have yet to produce reliable glucose readings. Their noninvasive nature and their potential for instant readings (in contrast to the approximately 12-minute delay inherent in dermal glucose measures) make them highly attractive.

Enzymatic glucose sensors in the form of intravenous implants and needle-like probes inserted under the skin, consist of an immobilized enzyme and an interface to an electrochemical transducer. Biocompatibility is an issue—after only a few days, proteins fixate on the sensor surface, limiting the oxygen available for the glucose oxidase reaction, especially in the low oxygen environment of the skin. As a result, the sensor signal begins to fade. To extend the life of the glucose sensor, researchers recently used a highly biocompatible membrane that extends accuracy to 7 days.[47]

Clinical experience with a tiny electroenzymatic glucose sensor inserted subcutaneously that connects to a small pager-like device, the continuous glucose monitoring system (CGMS, Minimed Technologies), showed a good correlation with fingerstick readings ($r = 0.85$) and potential as a Holter-type glucose tracking device that could be used as a hypoglycemia alert.[48] Each sensor lasted an average of 70 hours. This monitor was unanimously recommended to the FDA by an expert advisory panel in February 1999 and is expected to gain FDA approval by the summer of 1999.

Using a similar enzymatic needle-type microdialysis skin glucosensor, a German group[49] studied 7 type 1 diabetic patients believed to be in good control (HbA_{1c} 6.9 ± 0.8%) for a period of 48 hours. To their surprise, continuous monitoring revealed that these subjects experienced extremely wide glucose excursions, including 1.4 episodes of hypoglycemia per patient per day, with one third of these occurring during the night. Seven episodes of the dawn phenomenon were observed—0.5 episodes per patient per day. The investigators concluded that even patients with "good HbA_{1c}" could benefit from continuous glucose monitoring, and that current methodologies underestimate the need for changes in therapy.

Even patients with "good HbA_{1c}" could benefit from continuous glucose monitoring

An exciting new technique offers painless, bloodless glucose monitoring based on dermal glucose extraction through intact skin with the use of a watch-like device, and was shown to be accurate compared to blood testing ($r > 0.9$) for periods of up to 8 hours.[50]

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