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# Innovative Treatments in Diabetes Type 1

**Bernadette Barbara Lenartowicz* and Emilian Snarski**

*Department of Hematology, Oncology and Internal Medicine, Medical University of Warsaw, Poland*

**Abstract**

Type 1 diabetes mellitus (T1DM) is a metabolic disease caused by autoimmune destruction of beta cells in the pancreas leading to insufficient production of insulin. The standard treatment of diabetes relies on multiple injections of insulin. One of the main drawbacks of this treatment is the inability to replicate timing and action on endogenous insulin secretion when beta cells are intact. Resulting hyper- and hypoglycemias cause long term and acute side effects of the disease. There are multiple approaches to overcome this problem: insulin pumps, oral insulin preparations, immunomodulatory treatments and transplantation of beta cells. This review summarizes recent advances in the treatment of diabetes.

**Keywords:** Diabetes type 1; Oral insulin intake; Immunomodulation; Beta cell replacement; Pancreas transplant; Islet cell transplant

## Introduction

Diabetes includes a group of heterogeneous disorders broadly defined by the inability to maintain normoglycemia. Diabetes mellitus, a metabolic disorder, occurs when glucose levels remain high due to insufficient insulin production or the body's inability to respond to the insulin that is produced. Hyperglycemia, which results from inadequate control of insulin injections or other hypoglycemic drugs, leads to microvascular, macrovascular, and neuropathic complications. The most common form of diabetes is type 2, caused by an inadequate insulin response. It generally develops later in life and in many cases if caught early can be managed through diet, physical exercise, and regular monitoring of blood glucose levels. On the other hand, diabetes type 1 is in 95% of the times an autoimmune reaction where beta-cells of the pancreas are destroyed and 5% of unlinked to autoimmunity [1]. There are also less common forms of diabetes caused by hormonal abnormalities, genetic mutations or metabolic imbalances.

According to The World Health Organization there are about 220 million people worldwide suffering from diabetes. The prevalence of the disease across Europe is approximately 7.8% [2]. Over 55 million people from the age of 20 to 79 years of age were living with diabetes in Europe in 2010 [2]. The highest rates of the disease are found in Central and Eastern Europe. In 2005, 1.1 million people died of diabetes related causes and it is estimated that deaths due to diabetes will double between 2005 and 2030 [3]. These numbers are compounding and show that innovative solutions to treating and managing diabetes are badly needed.

Sustaining glycemic control in many diabetic patients is one of the most important challenges for physicians. Recently published guidelines use a target hemoglobin A1c of 6.5% as being the goal for glycemic control [4]. Reaching this goal requires collaboration between doctor and patient so that the compliance to regiments proposed by the doctor such as drugs, diet and exercise can be achieved. The new options for diabetes treatment try to overcome the issues of noncompliance by providing more efficient and less demanding alternatives compared with standard insulin use. Below we address the principle treatment options for glucose control such as continuous subcutaneous insulin injections, islet and pancreas transplants, as well as some of the most innovative approaches currently applicable, for instance stem cell therapy.

## Alternative Routes for Insulin Intake

The subcutaneous insulin injection is the most readily available and used therapy for replacement of endogenous insulin secretion. This concept was further developed towards restoring the physiologic like action of insulin, by giving the insulin preparations that had action curves resembling endogenous insulin secretion or by continuous pump secretion. Pump therapy mimics natural secretion of insulin whereby insulin is given in a continuous infusion with additional boluses when the patient predicts higher insulin need. The continuous subcutaneous insulin injection (CSII-insulin pump therapy) was initially introduced a little over a quarter of a century ago [5]. It was developed due to a need for better regulation of glucose control therefore largely preventing hypoglycemic episodes in type 1. When used properly, CSII leads to an evident decrease in the glycosylated hemoglobin A1c level in comparison to treatments involving multiple injections. Aside from the clear advantage in maintaining proper glycemia as seen with lower glycosylated hemoglobin levels, better control of severe hypoglycemia can also be witnessed. Although in theory CSII resembles physiologic secretion of insulin even with proper patient usage, it is not as finely tuned. Furthermore, it also has been connected with some serious complications. Though varying in nature, some of those complications may be as serious as those found during standard insulin therapy such as ketoacidosis. This complication is frequently found at the introduction of pump therapy often due to doctors' inexperience of dosing or cannula dislodgement and leakage [6]. Additional problems experienced by patients using CSII are weight gain, discomfort, and it's expensive price. Such problems unquestionably limit the adherence to the insulin pump for many patients, ultimately influencing the development of diabetic complications.

Additional problems with adherence to the treatment are in part

***Corresponding author:** Bernadette Barbara Lenartowicz, Department of Hematology, Oncology and Internal Medicine, Medical University of Warsaw, Independent Public Central Clinical Hospital, ul. Anacha 1a, 02-097 Warsaw, Poland, Tel: (22) 599-28-18; Fax: (22) 599-28-18; E-mail: integral_cycles@hotmail.com

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caused by the life long need for multiple daily injections in patients using self injecting insulin. Many of these patients may be embarrassed, uncomfortable and will tend to omit injections in certain atmospheres. Based on an internet study involving 502 self proclaimed diabetics in the U.S, 50% admitted missing injections and 20% regularly missed injections [7]. The solution to this problem is the development of alternative routes for insulin administration that exclude or minimize the need for injections. One method of administration that has been directly compared to subcutaneous injection is continuous intraperitoneal insulin infusion (CIPII) and has proven to reduce the number of hypoglycemic episodes as well as not cause weight gain while improving quality of life [8].

Inhalation is a route of drug administration that is used with success for various drugs, and all together avoids injections. This route was explored with an inhaled preparation of insulin. One major advantage of the oral route is that the insulin delivery almost identically replicates the naturally physiological hepatic route, which allows for continued hepatic engagement in glucose metabolism [9]. However, despite the success of achieving adequate insulin absorption without injections, other serious drawbacks appeared. Apparatus needed for administration was quite large; making it almost impossible to use discreetly, such as is the case with most of the inhaled anti-asthmatic drugs. Additionally, an unexpected side effect was found, namely, the large amount of insulin that had to be inhaled significantly increased the risk of lung cancer among patients using the treatment [10]. This led to the withdrawal of the inhaled insulin from the market. Another approach that can be explored to omit injections is the application of insulin to the oral mucosal tissue. An aerosolized spray of tasteless mist is administered to the buccal mucosa. In this way insulin is absorbed into the bloodstream using a proprietary delivery system including a surfactant, solubilizer, micelle creating agent, and an emulsifying agent [11]. Administration looks similar to the asthmatic inhalator, making it more convenient for patients. The insulin used in spray form is a formulation of recombinant human insulin. Though having a faster onset, it has a shorter duration of action than regular insulin given subcutaneously [11]. It quickly enters the blood stream and is absorbed in the direct proportion to the amount that is delivered. Studies with regular insulin showed good tolerance among patients [12]. It may indeed become the solution for a large percentage of diabetics that omit insulin injections due to mere inconvenience.

## Beta Cell Replacement Therapy

Another approach to diabetes control is directed towards replacement of replenished beta cell population. This goal can be achieved either by transplantation of the whole pancreas or just the insulin producing cells. The first pancreas transplantations were performed in 1966 [13]. This method is still used and is being further developed in the treatment of patients with type 1 diabetes. It relies on the ability of insulin secretion by healthy islet cells that are present in the transplanted pancreas. As with any transplantation, the biggest obstacle is finding a compatible match and maintaining immunosuppression so that limited rejection occurs. Current indications for pancreas transplantations in diabetes type 1 patients show serious complications, outweighing the risk of surgery and immunosuppression [14]. Thus, the procedure is only performed in a highly selected patient population. According to the International Pancreas Transplant registry, 87% percent of non-US pancreas grafts are functioning after one-year post transplantation [13] Simultaneous kidney transplantation is more commonly performed, as kidney failure is a factor where the implications of immunosuppression may not be of such consequence compared to purely pancreas transplants [15]. At the moment, 75% of pancreas transplants are simultaneously conducted alongside kidney transplants (SKP) transplants [16]. When successful, the quality of life of patients with pancreas transplants is much improved compared to the state prior to transplantation. Roughly about 75% of patients receiving pancreas transplants are able to maintain normal glucose levels free of any exogenous insulin therapies one-year post operation. This leads to a normalization of glycosylated hemoglobin levels and shows benefits in reduction of secondary complications in diabetes. The effect is maintained as long as the allograft is intact and functioning. It is difficult to pinpoint a time frame of function for successful pancreatic transplants as many are still functioning well after 16 years from transplantation. Normalization of glycemia and glycosylated hemoglobin levels lead to improvements in the patients' quality of life, kidney structure, and motor-sensory and nerve function .

A more simplified approach involves transplantation of islet tissue alone rather than the whole pancreas. Initially, efforts concentrated on injection of islet cells that replenished the destroyed cells and provided patients with insulin secretion. Unquestionably one of the biggest obstacles for islet transplantations at the beginning was the use of steroid therapy for prevention of rejection. Steroids were not tolerated well by patients; moreover, they were toxic for beta cells and quickly caused destruction of newly injected islets. Islet transplantation was further developed in 1999 in Edmonton, Canada where the original protocol of placing the islets derived cells into the liver to help fight diabetes type 1 was described [17]. The Edmonton Protocol is based on specific glucocorticoid-free immunosuppression and isolating cadaveric donor cells using a specific enzyme mixture. Isolated islets are derived from at least one to possibly three different donors [18]. Islet cells are delivered to the portal vein by fluoroscopic guidance through a percutaneous transhepatic approach [18]. The issue at hand remains that due to transplantation, the patient has to be on immunosuppressants to prevent rejection of the transplanted islet cells. Today further research concentrates on alternative sources for cells for transplantation, such as differentiation of islet cells from the pluripotent stem cell lines of the patients themselves [19]. This method, if successful, could potentially allow differentiation of beta cells from the patients' own cellular lines. Additionally, if the method to control the autoimmune reaction is developed it could alleviate the need for immunosuppressants completely.

The transplantation of beta cells can be further expanded with the use of xenografts. Encapsulated porcine pancreatic cell products abolish the need for a donor-a major obstacle in pancreas or pancreas island transplantation [20]. The encapsulation serves the cells as a protective barrier preventing their destruction by the autoimmune cell clones [21]. The results indicate that the transplanted intraperitoneal xenogeneic islets efficiently secrete insulin and can avert long-term consequences of diabetes type 1 that conventional insulin therapies cannot . One of the main concerns of this therapy is xenotic infections, more particularly that of pigs endogenous retroviruses (PERVS) [22]. However, with proper isolation, genetic manipulation, and control, the animals can remain pathogen free [22]. To date, worldwide, there are 200 patients that have porcine islet transplantations of which none experienced xenotic infections [23]. This treatment, however, leaves patients on small doses of insulin, giving it an arguable advantage over islet transplants as it eliminates the use of immunosuppression thanks to the encapsulation of the porcine islets, hence preventing rejection.

## Immunosuppressive/Immunomodulatory Treatment

The concept of diabetes type 1 being an autoimmune disorder was developed over 30 years ago with a major component of it being that insulin is not produced and the c-peptide level is low as a result. Since then, various attempts have been made to alter the malfunction of the immune system in patients with diabetes type 1. There are plenty of new immunosuppressive treatments in the clinical trials right now including anti CD3 antibodies, anti-IL1 antibodies, rituximab, ATG, GAD vaccine and others. Most of them show some response, such as the reduction of insulin need and improved glycemic control; however the effects are usually transient and based a positive c-peptide level. To date, the highest response measured as cessation of insulin therapy after the treatment is observed in patients undergoing immunoablation with hematopoietic stem cell transplantation [24-26]. Immunoablation is based on applying high doses of immunosuppressive therapy that enable destruction of the immune system with autoimmune clones. The hematopoietic stem cells that are transplanted after the treatment are the source for renewal of the immune system. Another important approach is inducing pluripotent stem (iPS) cells to develop into beta cells similarly to human embryonic stem cells having the ability to become fully developed beta cells [27] Changes, which take place during the treatment lead to the halt of autoimmune reaction and lead to the remission of diabetes in the majority of cases. So far, data published by two group's states initial remission rates of over 95% [24,25]. In follow up, some of the patients revert to insulin, usually in smaller doses when compared to prior treatment. In observation, though, it seems that 30% of patients were able to remain in the sustained remission for over 50 months. This method is still in the very early phase of clinical use and the potential usefulness in clinical practice has yet to be shown. It does, though, provide some credibility for immunosuppressive treatments in diabetes, in that intervention that abolishes immune reaction might lead to lasting remission of diabetes.

Another pathologic interventionist approach in diabetes is the modulation of the response to autoantigens by vaccination. Unlike conventional anti-infection vaccines where the response to pathologic proteins of pathogens is desired, the vaccine against autoimmune diseases should lead to a state of tolerance against auto-antigens. The introduced antigens should lead to over-stimulation of peptide specific regulatory T cells and cause suppression of auto-aggressive T cells [28]. In theory, this should slow down or arrest the immune system from attacking insulin-secreting cells. One of the most common auto-antigens in diabetes patients is glutamic acid decarboxylase (GAD). Over 90 percent of patients have auto-antibodies against GAD. Given as a vaccine, GAD showed very promising results in murine models [28].

In humans, the recombinant human glutamic acid decarboxylase (rhGAD65) is used as a vaccine. It has undergone phase II clinical trials and shown to maintain beta function in 320 newly diagnosed children [29] Deposits of rhGAD65 are processed by antigen presenting cells (APCs) and peptide fragments of rhGAD65 are presented to the T-cells [29]. The constant presentation of rhGAD65 determinants result in the development of a subset of GAD65-specific regulatory T-cells, which in turn down regulate antigen specific killer T-cells that would attack insulin secreting beta cells [29]. The subcutaneous administration of rhGAD65 is safe, ultimately helping to preserve beta cell function in children and adolescents with type 1 diabetes that have GAD autoantibodies.

## Conclusion

Diabetes remains a major health burden in today's world. The methods discussed earlier address crucial problems concerning diabetes type 1-most notably, better and easier insulin application, prevention of the disease by modulation of autoimmune reaction that leads to diabetes, and the replenishment of beta cell population. There exist plenty of recent advances that give hope for better life quality of already affected patients and the possibility of preventing the disease in the future. First, oral insulin would cease the need for insulin injections and would improve compliance. However, it still needs extensive research before being fully available. Secondly, there is continual progress in the field of beta replacement therapy, particularly islet replacement. After one year, remissions are observed in approximately 70% of patients while 10-20 % will remain in remission over 5 years (though at the cost of immunosuppressive treatment). Thirdly, advances within the field of immunosuppression-by use of daclizumab or etanercept for example, might denote higher rates of insulin independency over time and decrease loss of utility of the grafts. There is also progress in the field of immune intervention in diabetes. The immunoablation with autologous stem cell transplantation have proven to be very effective in inducing short-term remissions in over 95% of patients undergoing the procedure. Of these patients, around 30% remain insulin free after 5 years. Despite this, the exact mechanism and workings of immunoablation works is still unknown and the long-term effects will need to be assessed in the future. The substantial rise in the percentage of patients in recent years that become and remain insulin free over a 5-year period adds hope towards creating even more effective treatments and ultimately curing those with diabetes.

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