Published in final edited form as:

Nat Clin Pract Endocrinol Metab. 2008 December ; 4(12): 664–665. doi:10.1038/ncpendmet0971.

Insulin therapy versus cell-based therapy for type 1 diabetes mellitus—what lies ahead?

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The current or emerging therapeutic options for type 1 diabetes mellitus (T1DM) can be divided into three broad categories: insulin replacement by injection or infusion (insulin therapy); insulin replacement by transplanted cells (cell-based therapy); and modification or amelioration of the autoimmune process in individuals with new-onset T1DM or at high risk for the development of T1DM.^{1,2} Rapidly advancing research in all three areas is leading to new therapeutic options with considerable potential to ‘cure’ T1DM. In this Viewpoint, I will focus on the prospects for insulin therapy and cell-based therapy, and discuss how these two therapeutic approaches may compare in the future in terms of benefits, risks and challenges.

The efficacy and safety of any new therapy for T1DM must be judged against the outcomes achieved with standard or current therapy. In considering new therapies, several aspects about T1DM warrant emphasis. First, all current approaches are imperfect as patients still have hyperglycemia and/or hypoglycemia and long-term develop diabetes-related complications. Second, hypoglycemia resulting from a mismatch of insulin need and insulin delivery is the major limitation of current therapy. Third, although the duration and magnitude of hyperglycemia are important, they are not the only determinants of diabetes-related complications. Only a minority of individuals will develop diabetic nephropathy and not everyone with T1DM develops complications, regardless of the level of glucose control. Fourth, the risk of cardiovascular disease is increased in individuals with T1DM of long duration.^{3–5}

Furthermore, it should be noted that clinical outcomes for individuals with T1DM have improved considerably over the past few decades. For example, individuals who were diagnosed with T1DM in the late 1970’s have a lower mortality (20-year survival rate of 96.5% in one series) and less renal failure and neuropathy than individuals who developed the disease in earlier decades.^{3,5} Thanks to the widespread introduction of new therapies, such as statins, angiotensin-converting enzyme inhibitors, insulin analogs, insulin pumps, and improved glucose monitoring, the clinical outcomes for individuals with T1DM will continue to improve. My comments are not intended to minimize the morbidity and mortality associated with T1DM, nor the tremendous psychological and personal toll on the patient and his or her family. Rather, I wish to emphasize that any new therapeutic approach must demonstrate either superior efficacy with no increase in toxicity, or similar efficacy

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Competing interests

The author declared no competing interests.

and reduced toxicity when compared with current approaches over at least a 20-year timeline.

What is the future of insulin replacement by injection or infusion for T1DM? A large number of ancillary approaches—with many more on the way—are available to assist patients. These new approaches include ‘designer’ insulins with different absorption or physiologic profiles and programmable insulin pumps with multiple insulin delivery patterns and insulin-dosing algorithms that consider previous insulin doses and glucose values. Furthermore, blood glucose levels can now be measured in just a few microliters of blood in seconds and devices that monitor the interstitial glucose concentration on a nearly continuous basis are rapidly improving.^{6,7} Pharmacologic approaches that alter gastric motility or glucose absorption can also assist in the battle to match insulin delivery to physiologic need.

Despite this proliferation of devices and ancillary therapies, and the valiant efforts of our patients, insulin therapy for T1DM remains imperfect as patients still have both hyperglycemia and hypoglycemia. The major challenge for insulin therapy will continue to be the delivery of the correct amount of insulin at the appropriate time and for the required duration. Further technologic advances will improve insulin replacement, but the question is how closely insulin therapy can mimic the exquisite regulation of insulin secretion, resulting from a biologically based glucose-sensing mechanism tightly coupled to insulin exocytosis, like that in the beta cell. Furthermore, can insulin delivered into a peripheral, subcutaneous site (rather than the portal vein), without the delivery of other islet hormones, such as glucagon, based on interstitial rather than blood glucose determinations, normalize glucose homeostasis over decades and prevent all diabetes-related complications?

Will cell-based therapy overtake insulin therapy in this competition for the optimal therapeutic approach for T1DM? Important progress is being achieved by on-going efforts in clinical islet transplantation, but the insufficient source of human islets and the toxicity of currently used immunosuppressive agents limit the transplantation of normal human islets from organ donors to only a handful of patients.^{8,9} One possible solution to increase the number of islets or beta cells available for transplantation is the derivation of insulin-producing cells from stem cells. Kroon and colleagues¹⁰ devised a scheme to differentiate human embryonic stem cells into glucose-responsive, insulin-producing cells that reversed diabetes in mice. Knowledge gained from ongoing clinical trials of islet transplantation will be critical in the development of procedures and approaches to evaluate these new sources of insulin-producing cells.

The derivation of glucose-sensing and insulin-producing cells that function like normal beta cells is, nevertheless, only the first step in developing a cell-based therapy for T1DM. Equally essential is an intervention that will control or abrogate the beta cell-directed autoimmunity found in T1DM and protect the transplanted glucose-responsive, insulin-producing cells. Perhaps a new approach will come from research to control the autoimmunity in new-onset T1DM or from engineering the cells before transplantation to resist the autoimmune attack. In addition to these daunting problems, cell-mediated therapy must be safe and stable after transplantation. Little is known about the fate of insulin-producing cells derived from stem cells or about the stability of the phenotype after transplantation. As even a mild perturbation in an islet-enriched transcription factor, ion channel or enzyme can affect glucose-stimulated insulin secretion, it will be critical to determine how closely insulin-producing cells derived from stem cells mimic (and maintain) the insulin secretory pattern of normal beta cells.

What will therapy for T1DM look like in 10 or 20 years? Even if efforts to prevent T1DM are successful, large numbers of patients with T1DM or insulin-deficient type 2 diabetes mellitus will need a therapy that delivers insulin. With the continued integration of increasingly sophisticated insulin pumps and glucose monitoring devices, and a proven efficacy and known side effect profile, I feel that the short-term and medium-term competition favors insulin therapy. Nevertheless, it is not certain whether insulin therapy can completely restore glucose homeostasis with a desirable side effect profile and lifestyle profile over the life of an individual with T1DM. Cell-mediated therapy may, therefore, prove more advantageous in the medium-term and long-term competition, assuming that the substantial challenges of supply, safety, stability and immunity can be addressed. A central question for both therapeutic approaches is what defines treatment success: the restoration of normal glucose homeostasis, the avoidance of diabetes-related complications, or both? Like many races between competing approaches or technologies, continued research and work on both fronts, as well as in the areas of immune modulation and islet regeneration, are needed to develop the optimal therapeutic approach for T1DM.

Acknowledgments

Research in the author's laboratory is supported by grants from the Juvenile Diabetes Research Foundation International, the VA Research Service, the NIH (DK68764, DK66636, DK69603, DK63439, DK62641, DK068751), the Vanderbilt Mouse Metabolic Phenotyping Center (DK59637), and the Vanderbilt Diabetes Research and Training Center (DK20593), and by human islets provided by the Islet Cell Resource Centers.

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