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The shifting paradigm of a “Cure” for Type 1 Diabetes. Is technology replacing Immune based therapies?

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Nearly fifty years after the autoimmune nature of type 1 diabetes was discovered, no therapy has been approved to alter the course of the disease at any stage. However, during that same period, technology has been delivering tools to help patients achieve better glycemic control and reduce the burden of the disease. With the imminent arrival of fully automated artificial pancreas systems that will continue to improve control and quality of life, it appears that we are on the verge of a major technological breakthrough that will significantly impact diabetes care. These devices have such a high degree of potential that they are, at times, mentioned as a virtual cure for the disease- a first for technology in this space. As such, these devices will undoubtedly alter the research landscape in a field that has predominantly been occupied by immunotherapies. This article reviews the history of type 1 diabetes and compares and contrasts the advancements that have come from the world of technology and immunology alike at this important crossroads in care that we are currently in.

We are at an interesting crossroads in type 1 diabetes research and clinical care. To understand the changing landscape, a brief historical perspective is warranted.

Type 1 diabetes was originally classified as an autoimmune disease in the early 1970s when islet cell antibodies were first discovered[1]. This discovery ushered in a great deal of interest in understanding the underlying mechanisms of the disease with an eye toward immunomodulatory therapy to hopefully prevent or reverse the disease. Roughly ten years

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later, the first studies with cyclosporine were reported with positive results suggesting that immunotherapy could halt or reverse the disease[2]. The cure, it was thought, was surely right around the corner. Meanwhile, technology had essentially no place in diabetes management. At that time, there were no home blood glucose meters, no insulin pens or pumps, no continuous glucose monitors, and certainly no artificial pancreas systems[3]. Technology did not exist in the eyes of patients and family members involved with T1D.

Now when we fast-forward to 2017, we can see how drastically this landscape has changed. Unfortunately, the harsh truth is that no therapy has been approved for use to alter the course of the disease at any stage, either due to lack of efficacy[4] or unacceptable side effects[5]. Numerous therapies have made their way to clinical trials with great hope from the scientific and patient community but all have led to disappointment. These have ranged from B-cell therapies, to attempts to modulate T regulatory and effector cells, to anti-apoptosis agents to combination therapies with various approaches[6]. Even in the early days of immunotherapy, optimism was sharply dampened by the realization, that autoimmunity would recur after cessation of cyclosporine therapy and that nephrotoxicity would preclude a widespread application of this intervention. Therefore, in the following decades, much time was spent in defining potential immune therapies that would be more ‘palatable’ for patients in terms of side effects – monoclonal antibodies against CD3 being the most notable advance[7]. However, over the years of testing in recently diagnosed patients, prevention of C-peptide decline has proven heterogeneous and often associated with reactivation of EBV when effective[8]. Thus, the efficacy to side effect balance remains a rather tenuous one, and the hope that the 1970s and 80s offered has not translated into a therapy nearly 50 years later.

Technology on the other hand, has slowly but surely been delivering tools that have made their way into clinical care. Home blood glucose monitors came into clinical use in the 1980s and replaced urine testing. These devices enabled patients to know almost immediately (and fairly accurately) what their blood glucose levels were and facilitated more accurate insulin delivery to tighten glucose control. These devices were originally extremely expensive, large, and took significant amounts of blood to deliver a result several minutes later. However, now they can easily fit into a pocket and deliver accurate results in roughly 5 seconds at a greatly reduced cost. Commercially available insulin pens and pumps soon followed that have continued to improve over the decades. These Insulin pumps allow precise delivery of insulin that can be changed throughout the day to match basal and prandial needs. Continuous glucose monitors (CGMs) then arrived in the late 1990s. These devices have also continued to improve to now accurate levels that can replace blood sugar monitoring (fingersticks) and provide patients continual, real-time information on their blood glucose levels. These devices can alert patients to dangerously high or low glucose levels which is especially important when they are sleeping and otherwise unaware. Furthermore, family members can “follow” their loved ones remotely, receive similar alarms, and know what their blood glucose levels are even if they are on the other side of the globe.

2016 saw a momentous landmark in diabetes history. Late last year, the first baby step to an “artificial pancreas” system was approved for commercial use, the 670g hybrid closed loop system. This device connects the readings from a continuous glucose monitor to insulin

pump to modulate insulin delivery based on ambient glucose value and predicted levels over time. Essentially it is able to fine-tune basal insulin delivery based on glucose levels which is particularly valuable overnight as it can tighten control and reduce hypoglycemia. However, the device falls short of being a fully automated insulin delivery system as individuals still have to determine insulin dosing with meals. While it undoubtedly has flaws, it represents a significant step forward and the first venture of such a device into clinical care. Results from the uncontrolled pivotal trial showed improvement in A1c values in an already well controlled group (7.4 down to 6.9%), reduction in hypoglycemia (values less than 70mg/dl 44% lower), and no episodes of severe hypoglycemia [9].

Looking into the very near future, multiple commercial and research enterprises have targeted the next few years to release a fully automated insulin delivery artificial pancreas system. These “closed loop” devices promise to tighten glucose control, reduce hypoglycemia, and generally reduce the burden of disease that patient’s feel. As an example, one company named BetaBionics is working on a device (the iLet) that requires a patient only to enter their weight when initiating on the system. It then essentially learns from their habits and can begin to modulate insulin and/or glucagon delivery with little to no interaction from the patient[10]. It is likely that by the year 2020, there will be several such devices for patients to choose from.

After looking through the rearview mirror of diabetes treatment, the crossroads we are at becomes a bit clearer. Technology has always been viewed as a nice clinical tool to help patient dose insulin, but it only recently has started to venture into the “cure” category. This category has, up until now, been solely occupied by classic scientific research focused mainly on immunotherapies. With the arrival of this new partner comes many questions. Of particular concern to some is how technology will affect the research landscape for ongoing immune based efforts.

To answer this question, we must ask, what motivates a society or a group of individuals to pursue a cure? The answer is rather simple and is directly related to how intrusive or bothersome that disease is to the individual and their family. Currently type 1 requires 24/7 care with dangerous repercussions of high and low blood glucose levels. As a result, multiple groups are desperately working to fund a cure for type 1 diabetes, primarily via immune based therapies. Contrast this, for example, to Hashimoto’s thyroiditis. This is an extremely common autoimmune disease that results in destruction of the thyroid gland. In many ways, it is a pathophysiology that is very similar to that of type 1 diabetes. However, the treatment is a simple, once a day pill. As a result, there are no efforts to cure Hashimoto’s, no work on thyroid stem cells, no artificial thyroid systems in development that we are aware of. The treatment has negated a need to further explore the disease. Is it possible this could happen in T1D?

Perhaps we need to first revisit another seemingly simple question. Namely, what is it that bothers patients living with type 1 diabetes? What is it about the disease that patients and family dislike the most, and can those problems be mitigated or solved by technology? Research has shown that patients living with T1D are most bothered by the sense of powerlessness that comes with the unpredictable nature of this disease[11]. The feeling that

no matter how hard they work, the disease will ultimately get the better of them and long-term complications will occur. Close behind feeling powerless comes distress around eating; the fears of not being in control of their diet. Finally, concerns regarding hypoglycemia are also common with patients being fearful that they may not be as aware of their hypoglycemic episodes as they should be and could experience a fatal event while driving or sleeping. These stressors can manifest themselves in many ways from frank depression, to worsening diabetes control, to unproductivity at work. Many patients state that ‘if they could only get a few days of vacation from this disease’ it would mean the world to them.

So can technology and the artificial pancreas systems solve these problems? At face value, it would seem that these systems should at least put a significant dent in these stressors. AP research suggests that, in the short-term at least, essentially all patients on these devices can achieve guideline recommended glycemic goals[10]. Hopefully this would help eliminate some of the powerlessness that patients currently experience and the constant feeling that they should “do better”. Similarly, the devices will likely require little to no input surrounding meals (carbohydrate counting) which would hopefully allay some of the fears around eating. Finally, these systems also provide significantly less hypoglycemia, and nearly eliminate severe/life threatening hypoglycemia. So it would seem that the major concerns that drive patients, and by extension us as a scientific community, to demand a cure could be solved by technology.

Examples of technology replacing medical therapies abound in medicine. In the cardiology world, pacemaker therapy, for example, is standard of care for patients with heart block. Implantation is relatively straight forward and the devices are not particularly intrusive for patients. Certainly, we can imagine, at one point, a fully implantable insulin delivery system that could automate insulin delivery without much, or any patient interaction. Patients could be implanted with such a device at diagnosis, and perhaps periodically come back in for replacement and that would be that. Such a therapy is definitely within our grasp.

The question then, is will patients use the technology? Certainly, anything man built is prone to failure, but at what point does the burden of technology become worth it? In 2017, we have not quite reached this threshold. While current pumps and sensors are huge advances, the overwhelming majority of patients are still *not* using them. In fact, only about 30% of patients in the United States use pumps, and only roughly 15% use CGM systems (T1Dexchange.org). The reasons for this are many fold from insurance, to access, to patient and provider inertia, but even in premier diabetes clinics, rates of adoption are still incredibly low. Many patients currently feel that wearing these devices is more intrusive and burdensome than the disease itself and opt not to use them. Even in patients that begin using a CGM device, roughly a third have discontinued use a year later. However, as these devices continue to provide more and more benefit, not only to the patient, but to the healthcare system in terms of reducing complications, costs, and so on, the needle will continue to move, and more and more will adopt these therapies. The feeling that we are on the edge of a major technological breakthrough in T1D management is palpable. This critical tipping point where wearing the devices is greater than their burden is happening now, virtually as we speak.

So where does this put us in exploring immune based therapies? Ultimately what every patient with type 1 diabetes wants is a true “walk away” cure. No buttons, infusion lines, alarms, or maintenance, just a therapy that restores their life to what it was before diabetes or prevents the disease altogether. There is no argument that this is now and should always remain the goal. Therapies such as islet/pancreas transplants have the potential for such a cure, but also have significant drawbacks. Yet, we have to wonder if the window for innovation and opportunity is potentially shrinking with recent technological advances. When all patients with T1D (adults and children) can wear a device that lets them sleep at night with ZERO concern for hypoglycemia, regulates their blood sugar so long-term microvascular complications are a thing of the past, and lets them live a long and healthy life, we have to wonder what will happen to funding for different therapies. Could T1D become like Hashimoto’s thyroiditis? It’s hard to imagine, but it’s possible.

If technology does not dramatically alter the research landscape, it will unquestionably alter what we perceive as acceptable risks for T1D therapies. 20 years ago, a therapy that preserved C-peptide function but increased rates of malignancies or infections would likely have been acceptable. However, when artificial pancreas systems become widely available, this risk not only becomes unacceptable, it is unnecessary. Ideally, AP systems will act as a bridge to a cure by improving patients’ lives while we all wait for a biological cure that will make all the technology unnecessary. In this way, we like to think of technology not as at odds with “science” but pushing us in the research community to develop therapies that are efficacious *and* safe. The bar has certainly been raised.

For the path forward, perhaps the best way to look at future developments is through the eyes of the patient. If you had type 1 diabetes, what would you want? Again, the answer is relatively straightforward. You would want a therapy that gave you the biggest benefit with the lowest burden to you. In the future, artificial pancreas systems will certainly improve the quality of life for patients and will hopefully augment our other research ventures. Many potential therapies would likely improve if glycemic control can be improved. In this way patients could wear these devices as part of a protocol to improve stem cell replacement strategies, or reduce beta cell stress while immunotherapies are administered. These approaches should work in tandem, but one thing remains certain. Technology has already begun to redefine type 1 diabetes research, and the field will potentially be unrecognizable in 5 years when these devices becomes standard of care. The scientific community should be aware of this, prepared for this, and ready to work with it to improve patients’ lives.

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