Design of a Novel Extracellular Vesicle Therapy for Stabilizing Brain Microvessels in Diabetes
(Technical Paper)

An Autoethnographic Perspective on Type 1 Diabetes Burnout
(STS Paper)

A Thesis Prospectus
In STS 4500
Presented to
The Faculty of the
School of Engineering and Applied Science
University of Virginia
In Partial Fulfillment of the Requirements for the Degree
Bachelor of Science in Biomedical Engineering

By
Garrett Johannsen

November 1, 2021

Technical Team Members:
Stephen Muzyka
Connor McKechnie

On my honor as a University student, I have neither given nor received unauthorized aid on this assignment as defined by the Honor Guidelines for Thesis-Related Assignments.

ADVISORS

Bryn Seabrook, Department of Engineering and Society

Shayn Peirce-Cottler, Department of Biomedical Engineering

Introduction: Type 1 diabetes (T1D) is a persistent and complex medical problem that poses many unique challenges to more than 1.6 million patients in the United States (*Type 1 Diabetes Statistics*, n.d.). Of these challenges, two of the most pressing are the somewhat abstract emotional toll that blood glucose management takes on a diabetic, and the much more concrete physical repercussions that arise as a result of inconsistent personal care. Awareness should be raised of the diabetic experience and the resiliency that diabetes management requires because prevalence of diabetes is increasing (Wild et al., 2004). The STS Research Paper, "An Autoethnographic Perspective on Type 1 Diabetes," and the technical report, "Design of a Novel Extracellular Vesicle Therapy for Stabilizing Brain Microvessels in Diabetes," will provide the general audience necessary information to understand the emotional and physical complications of diabetes, respectively.

The STS Research Paper provides an analysis of diabetes burnout, a psychosocial condition in which diabetic individuals are overcome by depressive symptoms due to the time-consuming burden of continuous blood glucose management. There are no current treatments that offer adequate palliative care to those suffering from diabetes burnout, so potential solutions will be a focus. The technical project introduces diabetes complications, both macrovascular and microvascular, that are consequences of chronic hyperglycemia, and proposes a novel regenerative medicine therapy as a candidate to restore healthy vascular conditions. If successful, individuals suffering from microvascular complications of diabetes will be able to seek treatment that directly repairs these complications. Diabetes is a condition that exposes shortcomings of medical treatment in the United States, while accumulating a significant portion of direct healthcare expenditures each year (Williams et al., 2020). The following work raises awareness of the diabetic experience, intends to emphasize the extent to which the onus of management is placed on the individual, and explains the byproducts of poor blood glucose control.

Technical Report: The life of an individual affected by T1D is one of intense pressure, dictated by the necessity to be vigilant of every meal, outing and choice. A strict process of consistent testing and monitoring to accurately observe glucose levels and self-administration of insulin at correct amounts while anticipating how it will change occurs on a daily basis (Kalra et al., 2018; Penckofer et al., 2007; *The Psychological Impact of Diabetes*, 2019). Not only is there mental fatigue from monitoring and treatment, but the inability to keep glucose levels stable due to a myriad of factors such as socioeconomic status and access to healthcare can lead to both microvascular and macrovascular complications (Koufakis et al., 2021). The most common complications of diabetes are hypertension, nephropathy, neuropathy, and retinopathy. These terms are indicative of high blood pressure and the breakdown of the kidneys, nervous system, and retina, respectively. Left unchecked, these complications can lead to heart attack, stroke, chronic kidney disease, amputation, nerve damage to peripheral extremities, and blindness (CDC, 2019; *Diabetes Complications | ADA*, n.d.). Additionally, these complications drastically affect quality of life and make day to day living difficult—and if untreated, can result in death of the patient.

This design project is inspired by diabetic retinopathy, a microvascular complication that occurs in environments of high blood glucose concentration (hyperglycemia), resulting in hemorrhage of microvessels and often blindness (*Diabetic Retinopathy | National Eye Institute*, n.d.). Brain microvessels may be affected by the same cellular abnormalities because the retina is simply an extension of the brain (*Retina | Definition, Function, & Facts*, n.d.). Microvascular complications of the brain are a less published topic of research, but there is a correlative relationship between chronic hyperglycemia and increased risk of developing stroke and neurodegenerative disease (Bornstein et al., 2014).

To investigate the source of these microvascular complications, one must understand the specific cellular interactions of the brain microvasculature. Two crucial components of the microvasculature are capillary endothelial cells (CEC), thin cells that constitute the structure of capillaries and allow nutrient-filled blood to flow throughout the brain, and pericytes (PC), outer-lying cells that attach to external walls of CECs and play a role of structural support and communication to surrounding cells. In hyperglycemic environments of diabetic patients, abnormal interactions have been observed in PCs (Corliss et al., 2020). This project is primarily focused on a phenomenon called pericyte decoupling, in which pericytes will detach from the surrounding microvessels and either adsorb onto a different blood vessel or initiate cell death. Pericyte decoupling and dropout compromise the integrity of affected capillaries which can result in vessel necrosis, a term defining functional loss and effective death of a blood vessel. Due to the high level of vascularization in the brain and difficulty in direct access, a treatment that offers local relief to the specific affected sites in the brain is needed.

In addressing the vast medical problem of microvascular complications of diabetes, a disease that affects more than 30 million Americans (CDC, 2020), our proposed solution is to design a novel *in vitro* extracellular vesicle (EV) therapy to stabilize brain microvessels in diabetes. EVs are lipid-based particles produced by most cells in the body that contain proteins and RNA that show promise as a regenerative medicine candidate (van Niel et al., 2018). After isolation from the urine, plasma, or cell cultures, these vesicles contain highly specific contents that can be used as a signaling method upon delivery to CECs and PCs to reduce detachment and return to expected interactions observed in normoglycemic environments. The research team, composed of Garrett Johannsen, Stephen Muzyka, and Connor McKechnie, hypothesizes that the use of EVs to target tissues in hyperglycemic environments will restore healthy PC/CEC interactions. If successful, the downstream implementation of this therapy could serve as a direct treatment for microvascular complications of the brain, and a successful EV protocol could initiate similar therapies for related complications of diabetes. An EV treatment would improve quality of life for diabetic patients and reduce the high medical expenditures each year due to diabetes. The technical report will serve as a final deliverable of this project and describe its outcomes in further detail.

STS Topic: The general public is aware of diabetes, the fact that it is a chronic condition affected by food consumption, and that there are different diabetes disease types, but this is where public understanding of diabetes ends. The human experience of living with T1D needs to be disseminated to the public and contextualized in a way that nondiabetics can understand. Communicating the struggles associated with living with T1D, defining diabetes burnout as the emotional and physical labor of diabetes management that lead to psychological damage and subsequent physical complications, and proposing palliative care to those suffering from diabetes burnout, are all main foci of this research.

Type 1 diabetes mellitus, also commonly referred to as insulin-dependent diabetes or juvenile diabetes, is a chronic autoimmune disease in which beta cells of the pancreas are attacked by autoreactive immune cells of the body (Ozougwu, 2013). This immune response is significant because beta cells secrete insulin, the molecule that allows for transport of glucose out of the bloodstream to maintain glucose homeostasis. The autoimmune response that triggers beta cell death is not fully understood; we only know that T1D patients must have a level of genetic predisposition to this event, and that environmental factors are likely involved as well

(Pugliese, 2016). At diagnosis, previously healthy individuals are given a heavy burden of responsibility that coincides with having to consciously make decisions on insulin dosage, meal timing, and being aware of the macronutrients of every single meal they will eat for the rest of their lives. Technology and manufactured insulin help diabetics do consciously what their body would otherwise do subconsciously, but it is not a perfect system. This load of extra responsibility weighs heavily on T1D patients and can result in temporary neglect of blood glucose control, classifying the condition of diabetes burnout (Abdoli et al., 2019). There is a lack of research on diabetes burnout, despite it being a well-known condition that many diabetics suffer from (Abdoli et al., 2020). Thus, I will investigate potential solutions that can be palliative to those struggling with T1D burnout, while offering my own experiences of living with T1D and framing those experiences to help other patients.

To analyze this topic, two STS themes—wicked problems and social construction of technology—will be used. Framing diabetes burnout as a wicked problem enables the researcher to frame burnout as a complex issue with many parts. The pathology of and complications associated with diabetes (*Pathophysiology of Diabetes - an Overview | ScienceDirect Topics*, n.d.), the role that health professionals have played thus far (Arent, 2002), the lack of adequate treatment for this condition (*How to Beat Diabetes Burnout*, n.d.), the exorbitant cost of medication to manage blood glucose levels (Clarice, 2019), and the many different reasons individuals face psychological turmoil (*The Psychological Impact of Diabetes*, 2019) all must be adequately outlined to propose a solution. German design theorist Horst Rittel and American urban designer Melvin M. Webber introduced the framework of the wicked problem in 1973, defining it as a problem, usually social or cultural, that is challenging or impossible to solve either because not enough is understood about the problem, the number of stakeholders involved, the number of varying opinions, the economic burden, or the impact of these problems with other problems (Rittel & Webber, 1973). Since wicked problems are generally difficult to define and open to interpretation, the topic of diabetes burnout can be used as a model under this framework. With so many stakeholders involved, framing the problem as a "wicked problem" will help acclimate the reader to all of the involved actors and streamline the process of analysis. However, the theme of wicked problems has been critiqued in the past for its ineffectiveness in proposing solutions for the problem at hand (Turnbull & Hoppe, 2019). Therefore, the theme of social construction of technology (SCOT) will be used to further explore the relationship between society and technology and their role in burnout, as well as identifying potential solutions for diabetics who experience burnout.

A valuable piece of defining diabetes burnout and gauging the diabetic perspective is gathering input on what specific difficulties diabetics face while managing blood glucose (BG) levels. Modern BG management is assisted by many different devices, such as insulin pumps and continuous glucose monitors (CGMs). The STS theme of SCOT will be used to answer several questions about the patient-device interactions that will be crucial to develop solutions for diabetes burnout. What role does this technology play in BG management, and how does this compare to BG management before its inception? Are diabetics more or less likely to experience diabetes burnout with this technology? Is the technology easy to interpret and understand? How do physicians use data from CGMs, and does analysis of this data help prevent episodes of burnout? All of these questions will be investigated to propose solutions to individuals who struggle with diabetes management. The theme of SCOT was originally introduced by British sociologist Trevor Pinch and Dutch philosopher Wiebe Bijker in a publication called "The Social Construction of Facts and Artifacts: Or How the Sociology of Science and the Sociology of

Technology Might Benefit Each Other" (Pinch & Bijker, 1984). SCOT contains four components that will further categorize different actors involved in burnout: interpretive flexibility, relevant social group, closure and stabilization, and wider context. Interpretive flexibility is valuable for the same reason that the theme of wicked problems is valuable—burnout is a complex issue with many moving parts. Therefore, the relevant stakeholders and definition of diabetes burnout is open to interpretation. The relevant social group is rather straightforward in this case. Closure and stabilization is a component in which different interpretations of the issue are resolved so that members of a social group (diabetic patients suffering from burnout) share a common consensus of the definition of burnout. The wider context will investigate how diabetic patients have influenced the construction of current technology and how this technology can be optimized for the patient.

Research Question and Methods

Research Question: What are societal, physical, and emotional consequences of diabetes burnout, and what are potential solutions for those who struggle with this condition?

Methods: Two methodologies will be used to answer this research question: wicked problem framing and autoethnography. Wicked problem framing is a technique used to understand complex and dynamic problems, and in the context of diabetes burnout, to gather and assemble evidence in ways that reveal indirect, non-obvious connections between symptoms and root causes of burnout. Background information will be used to collect personal testimonies of diabetic patients (Abdoli et al., 2019, 2020, 2021), define diabetes pathology (Pugliese, 2016) and diabetes burnout as a psychosocial, psychological condition resulting in physical and emotional consequences (Abdoli et al., 2020; *The Psychological Impact of Type 1 Diabetes*, 2021). Further research will be dedicated to investigating current treatments (Abdoli et al., 2021;

How to Beat Diabetes Burnout, n.d.) and their inability to adequately address the root causes that result in subsequent physical and emotional trauma. Wicked problem framing will organize and re-interpret this information such that an amenable fix is conceivable. Autoethnography is a technique allowing myself as the author to reflect upon and document personal experience as a diabetic; interrogating cognitive, performative, or inter-actor relationships between myself and the key stakeholders involved in diabetes burnout. The STS paper will serve as a critical examination of my own experiences in hopes to solidify potential solutions for others and provide valuable insight for nondiabetics.

Conclusion: The technical component of this project covers the microvascular complications of diabetes and proposes a novel therapy for direct treatment, whereas the STS portion investigates the psychological and psychosocial implications of T1D.

The successful design of a novel extracellular therapy will have many benefits for the field of biomedical engineering. Three immediate contributions to the field are the creation of a reproducible protocol for coculturing PCs and CECs *in vitro*, analyzing microvascular interactions of murine brain slices *ex vivo*, and incorporating extracellular vesicles to both models. The downstream success of this technical project hinges on creating protocols that are concise, clear, and reproducible, so that the project team can collect meaningful data. If these protocols are published, scientists will be able to continue to progress the field in advancing treatment options for diabetic patients. A direct treatment for microvascular complications grows more important as the prevalence of diabetes increases.

By exploring the condition of diabetes burnout, connections will be made between the lived experience of a patient with T1D and the role that society plays in the status of their burnout; that is, society may perpetuate feelings of diabetes burnout by placing too much weight and responsibility on the patient, or it may be helpful to struggling individuals by offering a sense of community. This project will educate a general audience about personal and specific emotional and psychological reactions to living with T1D, analyze current treatments or the lack thereof for burnout, and propose potential solutions as a deliverable for such analyses. The outcomes of this project will hopefully aid struggling individuals in improving diabetes management, thereby improving quality of life for such patients, and reducing direct healthcare expenditures due to medical intervention as a result of diabetic complications.

References

Abdoli, S., Hessler, D., Vora, A., Smither, B., & Stuckey, H. (2020). Descriptions of diabetes burnout from individuals with Type 1 diabetes: An analysis of YouTube videos. *Diabetic Medicine*, *37*(8), 1344–1351. https://doi.org/10.1111/dme.14047

Abdoli, S., Jones, D. H., Vora, A., & Stuckey, H. (2019). Improving Diabetes Care: Should We Reconceptualize Diabetes Burnout? *The Diabetes Educator*, *45*(2), 214–224. https://doi.org/10.1177/0145721719829066

Abdoli, S., Miller-Bains, K., Fanti, P., Silveira, M. S. V. M., & Hessler, D. (2021). Development and validation of a scale to measure diabetes burnout. *Journal of Clinical & Translational Endocrinology*, *23*, 100251. https://doi.org/10.1016/j.jcte.2021.100251

Arent, S. (2002). The Role of Diabetes Health Care Professionals in Diabetes Discrimination Issues at Work and School. *Diabetes Spectrum*, *15*(4), 217–221. https://doi.org/10.2337/diaspect.15.4.217

Bornstein, N. M., Brainin, M., Guekht, A., Skoog, I., & Korczyn, A. D. (2014). Diabetes and the brain: Issues and unmet needs. *Neurological Sciences: Official Journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology*, *35*(7), 995–1001. https://doi.org/10.1007/s10072-014-1797-2

CDC. (2019, October 21). *Put the Brakes on Diabetes Complications*. Centers for Disease Control and Prevention. https://www.cdc.gov/diabetes/library/features/prevent-complications.html

CDC. (2020, February 11). *National Diabetes Statistics Report, 2020*. Centers for Disease Control and Prevention. https://www.cdc.gov/diabetes/library/features/diabetes-stat-report.html

Clarice. (2019, September 13). The high costs of diabetes medications. *Baylor College of Medicine Blog Network*. https://blogs.bcm.edu/2019/09/13/the-high-costs-of-diabetes-medications/

Corliss, B. A., Ray, H. C., Doty, R. W., Mathews, C., Sheybani, N., Fitzgerald, K., Prince, R., Kelly-Goss, M. R., Murfee, W. L., Chappell, J., Owens, G. K., Yates, P. A., & Peirce, S. M. (2020). Pericyte Bridges in Homeostasis and Hyperglycemia. *Diabetes*, *69*(7), 1503–1517. https://doi.org/10.2337/db19-0471

Diabetes Complications | ADA. (n.d.). Retrieved October 31, 2021, from https://www.diabetes.org/diabetes/complications

Diabetic Retinopathy | National Eye Institute. (n.d.). Retrieved October 31, 2021, from https://www.nei.nih.gov/learn-about-eye-health/eye-conditions-and-diseases/diabetic-retinopathy

How to Beat Diabetes Burnout. (n.d.). EndocrineWeb. Retrieved October 31, 2021, from https://www.endocrineweb.com/conditions/type-1-diabetes/how-beat-diabetes-burnout

Kalra, S., Jena, B. N., & Yeravdekar, R. (2018). Emotional and Psychological Needs of People with Diabetes. *Indian Journal of Endocrinology and Metabolism*, *22*(5), 696–704. https://doi.org/10.4103/ijem.IJEM_579_17

Koufakis, T., Garas, A., Zebekakis, P., & Kotsa, K. (2021). Non-insulin agents for the management of gestational diabetes: Lack of evidence versus lack of action. *Expert Opinion on Pharmacotherapy*, *0*(0), 1–3. https://doi.org/10.1080/14656566.2021.1942842

Ozougwu, O. (2013). The pathogenesis and pathophysiology of type 1 and type 2 diabetes mellitus. *Journal of Physiology and Pathophysiology*, *4*(4), 46–57. https://doi.org/10.5897/JPAP2013.0001

Pathophysiology of Diabetes—An overview | ScienceDirect Topics. (n.d.). Retrieved October 31, 2021, from https://www.sciencedirect.com/topics/medicine-and-dentistry/pathophysiology-of-diabetes

Penckofer, S., Ferrans, C. E., Velsor-Friedrich, B., & Savoy, S. (2007). The Psychological Impact of Living With Diabetes. *The Diabetes Educator*, *33*(4), 680–690. https://doi.org/10.1177/0145721707304079

Pinch, T. J., & Bijker, W. E. (1984). The Social Construction of Facts and Artefacts: Or How the Sociology of Science and the Sociology of Technology might Benefit Each Other. *Social Studies of Science*, *14*(3), 399–441. https://doi.org/10.1177/030631284014003004

Pugliese, A. (2016). Insulitis in the pathogenesis of type 1 diabetes. *Pediatric Diabetes*, *17*(S22), 31–36. https://doi.org/10.1111/pedi.12388

Retina | Definition, Function, & Facts. (n.d.). Encyclopedia Britannica. Retrieved October 31, 2021, from https://www.britannica.com/science/retina

Rittel, H. W. J., & Webber, M. M. (1973). Dilemmas in a General Theory of Planning. *Policy Sciences*, *4*(2), 155–169.

The psychological impact of diabetes. (2019, June 4). Diabetes Research & Wellness Foundation. https://www.drwf.org.uk/news-and-events/news/psychological-impact-diabetes

The psychological impact of Type 1 diabetes: Burnout, etc. (2021, April 8). Dbl-Diabetes. https://www.dbl-diabetes.com/the-psychological-impact-of-type-1-diabetes-burnout-distress-depression-exhaustion-etc/diabetes-basics/psychology/the-psychological-impact-of-type-1-diabetes-burnout-distress-depression-exhaustion-etc

Turnbull, N., & Hoppe, R. (2019). Problematizing ‘wickedness’: A critique of the wicked problems concept, from philosophy to practice. *Policy and Society*, *38*(2), 315–337. https://doi.org/10.1080/14494035.2018.1488796

Type 1 Diabetes Statistics. (n.d.). Beyond Type 1. Retrieved October 31, 2021, from https://beyondtype1.org/type-1-diabetes-statistics/

van Niel, G., D’Angelo, G., & Raposo, G. (2018). Shedding light on the cell biology of extracellular vesicles. *Nature Reviews Molecular Cell Biology*, *19*(4), 213–228. https://doi.org/10.1038/nrm.2017.125

Wild, S., Roglic, G., Green, A., Sicree, R., & King, H. (2004). Global Prevalence of Diabetes: Estimates for the year 2000 and projections for 2030. *Diabetes Care*, *27*(5), 1047–1053. https://doi.org/10.2337/diacare.27.5.1047

Williams, R., Karuranga, S., Malanda, B., Saeedi, P., Basit, A., Besançon, S., Bommer, C., Esteghamati, A., Ogurtsova, K., Zhang, P., & Colagiuri, S. (2020). Global and regional estimates and projections of diabetes-related health expenditure: Results from the International Diabetes Federation Diabetes Atlas, 9th edition. *Diabetes Research and Clinical Practice*, *162*, 108072. https://doi.org/10.1016/j.diabres.2020.108072