Design of a novel *ex vivo* murine brain slice model for analysis of pericyte morphology in diabetes

(Technical Paper)

Life or Death: A Sociotechnical Analysis of the Factors that Influence the Cost of Insulin

(STS Paper)

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Prospectus

Introduction

Diabetes resulted in 79,000 deaths in the United States in 2020 and 1.5 million deaths worldwide in 2019 (*Explore Diabetes in the United States | 2020 Annual Report*, n.d.). By 2030, 417.3 million people 20 years or older are expected to suffer from diagnosed or undiagnosed diabetes, with a global financial cost of treatment at $2.1-2.5 billion (Association, 2018; *IDF Diabetes Atlas 9th Edition 2019*, n.d.; *The Cost of Diabetes | ADA*, n.d.). Diabetes is one of the most prevalent global diseases with large financial effects categorized by high healthcare prices and is a burden on individuals who suffer from it due to medical complications. Diabetes is categorized as a syndrome of impaired carbohydrate, fat and protein metabolism due to insulin sensitivity or inability to secrete insulin that can lead to fluctuations between hypoglycemic, low blood sugar, and hyperglycemic, high blood sugar, conditions within the body (Hall & Guyton, n.d.). The inability to control glucose levels has been known to compromise vascular integrity that can lead to large systemic problems such as retinopathy, retina failure, nephropathy, loss of kidney function, and neuropathy, nerve dysfunction, which all greatly decrease quality of life and can cause death (Corliss et al., 2020; *Diabetes Complications | ADA*, n.d.; *Diabetic Neuropathy | NIDDK*, n.d.; Lim, 2014).

Holistically, intensive insulin therapy has been successful in reducing the risk of developing systemic complications; however, the onus is often on the individual to maintain their glucose levels perfectly, which can be hindered by a myriad of factors (Donner & Sarkar, 2000). Therefore, there is a need for more accurate diabetic models and treatment options that specifically target microvascular complications beyond systemic insulin therapy. The need for novel diabetic models is a motivational component of the technical project, with the goal to design multiple models and an extracellular vesicle therapy to determine if a variety of dosage treatments can lead to improved microvascular interactions under diabetic conditions. The main focus on an alternate treatment to insulin is not only due to the systemic focus in the body of insulin treatment, but oriented around the cost of insulin treatment that hinders many individuals from accessing proper care (Belluz, 2019). The exorbitant cost of insulin and lifesaving drugs and technology to improve diabetes treatment and quality of life are often inaccessible. The STS project is focused on the cost disparity, which prompted a sociotechnical analysis of the factors that cause large pharmaceutical costs of insulin resulting in inaccessibility to diabetic treatments and the long-term effect on patient's well-being and overall health. Diabetes and the high cost of care are a wicked problem that have caused incredible harm to countless people and solutions must be found that limit the pain and suffering of those afflicted beyond the current technological fix in place. The Technical and STS projects plan to illuminate the problems associated with diabetes and treatment with insulin at high prices, while offering tangible solutions to improve the lives of individuals with diabetes in the future so no one has to suffer like this again.

Technical Topic

The life of an individual affected by diabetes 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 (high blood pressure), nephropathy neuropathy and retinopathy (CDC, 2019; *Diabetes Complications | ADA*, n.d.). Left unchecked, they can lead to heart attack, stroke, chronic kidney disease, amputation, nerve damage to peripheral extremities, and blindness. These complications drastically affect quality of life and make day to day living difficult—and if untreated, can result in death of the patient.

The design project is inspired by diabetic retinopathy, a microvascular complication that occurs in hyperglycemic environments, 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 (ECs), 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 ECs 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). The 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, our proposed solution is to design a novel *in vitro* extracellular vesicle (EV) therapy to stabilize brain microvessels in diabetes (CDC, 2020). 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 ECs and PCs to reduce detachment and return to expected interactions observed in normoglycemic environments. The research team hypothesizes that the use of EVs to target tissues in hyperglycemic environments will restore healthy PC/EC 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, while limiting overreliance on insulin as the sole therapeutic treatment. The final deliverable will be three defined diabetic experimental protocols for in vitro and ex vivo models. The expectation is that conclusive claims about the frequency in microvascular complications in diabetes and the viability of EVs as a therapeutic option to reduce complications will be drawn upon completion.

STS Topic

Diabetics face a life-or-death fight for survival rooted in the choice between living expenses and food on the table versus adequate amounts of insulin to prevent long term complications from diabetes. Insulin is a necessity for diabetic patients, as one of the oldest and common forms of treatment to maintain normoglycemic conditions and prevent long-term adverse health effects (Donner & Sarkar, 2000; Quianzon & Cheikh, 2012). However, the cost of insulin has tripled in the last decade, leading to out-of-pocket costs doubling for those afflicted in the US (Belluz, 2019; *Insulin's Out-Of-Pocket Cost Burden To Diabetic Patients Continues To Rise Despite Reduced Net Costs To PBMs*, n.d.; Meiri et al., 2020). If individuals are unable to pay the drastic increase in pricing for insulin, they are forced to ration it over longer periods of time or not treat themselves at all as they work to afford treatment (Sable-Smith, 2018). The failure to halt glucose fluctuations and remain below hyperglycemic levels can have disastrous effects on renal, heart and overall health which can lead to greater cost and damage later or accelerate the possibility of death. Therefore, individuals are putting themselves in danger as they try to afford life necessities and their insulin. The psychological effects of exceptional responsibility to administer insulin consistently while combatting the stress and pressure of trying to afford the insulin itself is an untold consequence that has extreme effects on the mental health of diabetic individuals (*The Psychological Impact of Diabetes*, 2019).

There is a complicated web of interactions that are intertwined to create a system in which diabetic patients face exorbitant treatment and testing costs necessary to survive, that have long-term negative effects on their quality of life. There are the individuals who suffer from diabetes, their doctors who treat them and offer therapeutic options, pharmaceutical companies, insurance companies, political leaders and government and global health organizations meshed in a tug-of-war of profit versus proper and adequate treatment (Beckfield & Bambra, 2016;

Insulin Prices Are Dramatically Higher in the United States Than in Other Countries | RAND, n.d.). The pharmaceutical company increase in insulin prices have been seen as the average yearly cost of insulin for consumers has risen from $2864 to $5705 per year or $250-$475 per month from 2012 to 2016 (*Spending on Individuals with Type 1 Diabetes and the Role of Rapidly Increasing Insulin Prices*, n.d.; Willner et al., 2020). One of the core reasons that insulin treatment is priced at sky-rocketing levels is that it is known as the most common treatment option, the ideal technological answer to treating diabetes (Rathore & Shereef, 2019). Insulin is an ingrained treatment that is known to be a necessity, allowing companies to set any price, knowing people will pay it to survive. The technology shapes societal norms, as the entire US system has accepted the high cost of insulin for survival instead of determining it a basic need and addressing the factors to limit high prices. Insulin is accepted as the perfect technological fix to treat diabetes, while the consequences that follow for diabetic individuals is vastly ignored. Furthermore, the overall search for a solution has been met with resistance. Drug companies claim that they need high prices to offset millions of dollars in research, while consumers state that they cannot afford insulin to survive. The inherent problem between pharmaceutical companies seeking money to pursue further invention against consumer needs and survival lends itself to be analyzed via a wicked problem framework, as no easy solution exists but one better than what exists now must be found.

German design theorist Host Rittel and American urban designer Melvin M. Webber introduced the framework of the wicked problem in 1973. A wicked problem is defined as a social or cultural problem that is impossible or incredibly difficult to solve due to the problem not being fully understood, the number of stakeholders involved or varying opinions on the topic, the economic or political burden and the way the problem influences other problems (*Dilemmas* *in a General Theory of Planning | SpringerLink*, n.d.). The extreme price of insulin can be representative of a wicked problem within the for-profit healthcare system of the US as there are countless stakeholders involved, various opinions on the topic and no clear solution between the interests of pharmaceutical companies and the diabetic patients desire to survive (Seager et al., 2012). This problem is something individuals face every day, and it results in death and untold pain and suffering. Insulin appeared as the perfect technological fix, which could help diabetics address medical needs and maintain glucose levels. Yet, the current prices and frequency of insulin treatment has had negative effects on the lives of diabetics. Therefore, the problem of adequately addressing diabetic medical needs without accessibility to treatment causing harm is needed, displaying fundamentally that the current pricing of insulin is a wicked problem that needs further analysis. A greater understanding of the problem can lend a voice to those who suffer from it and push towards solutions that benefit those affected by the high cost. Treatment beyond insulin must exist, or if insulin is ideal, the current distribution and sale in the US healthcare system is ineffective at benefiting the most people. Therefore, the next solution must take into account these failures and adequately consider consequences to offer the best possible solution that helps diabetic patients after further analysis of the wicked problem.

Research Question and Methods

In what ways are the current prices of diabetic treatment and testing options determined by pharmaceutical companies due to a for-profit healthcare system harming diabetic individuals by decreasing quality of life and what solutions exist to remedy this in an equitable way?

The primary ways to address the overarching question are through three methodological approaches. The three primary methods that best apply are documentary research methods, wicked problem framing and discourse analysis with brief intertwinement of policy analysis and network analysis for foundational support. Network analysis will display the way in which the patient using insulin is connected to the larger drug companies and how the roles of the government and their health agencies, doctors and society itself impact insulin prices and these effects on diabetic individuals. Documentary and discourse analysis will provide robust scientific grounding for how diabetes is treated, what has led to the sky-rocketing insulin prices seen today, individual experiences and societal perception of the problem. There is an abundance of resources and opinions due to the sheer prevalence of diabetes leading to diabetic research and media analysis resulting in ample evidence of the effects of high insulin prices. The key words focused upon to accurately gather results were "diabetic insulin pricing," "insulin cost out of pocket," "inability to afford insulin," "diabetes novel treatments," "diabetic healthcare failures" and "US Healthcare shortcomings". Furthermore, evidentiary support of novel technology and insulin as a technological fix to address diabetes, and the impact on pricing with unintended consequences will be focused on. The shortcomings of insulin as a technological fix with unintended consequences will allow for wicked problem framing to be methodologically applied to discuss not only the technological fix of insulin delivery and diabetic testing technology but how they avoid the overarching flaws built into a healthcare system in which drug companies have free reign over pricing options and how past amendments have failed and now harm individuals. A competent and robust analysis will be created as current failures are identified and future opportunities of success discussed to optimize a solution that most equitably helps diabetics and addresses the problem of extreme insulin pricing. By using these methods, a valuable analysis of the intricacies impacting the high price of insulin will occur in which the final deliverable will be the discussion of optimal and equitable solutions that benefit diabetic individuals and improve their quality of life to remedy the wicked problem.

Conclusion

The harm that diabetes causes an individual significantly decreases quality of life as they suffer from complications due to fluctuating blood sugar levels. The exorbitant cost of insulin only exacerbates the likelihood of these complications as individuals try to handle constraints of socioeconomic access and lack of healthcare by rationing their insulin to increase time between purchases. There is an over reliance on insulin as the primary technological fix to combat diabetes, which forces individuals to have to use it as the main therapeutic option to address macrovascular complications and pay whatever price is asked. This is motivation for the technological project which focuses on the design of an alternative therapy using extracellular vesicles to treat microvascular effects of diabetes. If successful, this can be used in tandem or possibly separately from insulin, allowing microscale complications to be addressed and limit the impact of the high cost of insulin, providing both a medical and social based solution. There is no guarantee the technical project can lead to complete resolution of exorbitant insulin prices. The STS project focuses on the causes of these high prices and their effects on diabetic individuals and possible resolutions that can lead to relief. If both projects are successful, then the biological based effects of diabetes can be addressed as well as the social aspect of improved quality of life for afflicted individuals. One small step forward in progress can open the door to a better life for those who have diabetes and move solutions forward to one day hopefully eradicating it or allowing those who have diabetes to live the best life possible without additional societal hinderances.

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