Sugar, Spice, Too Much/Little of Everything is Not Nice:
An Immunological Discussion on the Global Diabetes Epidemic

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One of the greatest pleasures of living in the 21st century is having a variety of food options. From culture-specific cuisines and fast-food menus to beverages and desserts – all these we can often readily eat, and we usually pay little attention to how each food type affects our biochemistry. Now, imagine if we were required to keep track of our daily consumptions and restricted to eating the 'right' foods in 'correct' amounts to maintain a balanced diet. This entails avoiding a lot of foods that we eat for pleasure which may adversely affect our mental health (1). Thankfully, this is not the case since, if our bodies are healthy enough, many biochemical pathways work to re-establish homeostasis, a self-regulatory process that allows us to maintain internal stability and help us function properly despite not always eating healthy (8). However, such consumption limitations are the reality of those with type I diabetes (T1D).

Jasper, a 6-year-old boy, was diagnosed with T1D very early in his life (2). One night, he surprised his family as he screamed and convulsed on his bedroom floor. He experienced a hypoglycemic seizure that could have led to coma, brain swelling/injury, and death. Thankfully, his parents were able to inject him with glucagon to elevate his low blood sugar level, which could have been caused by them losing track of what he ate. Unfortunately, not all people with T1D were as lucky as Jasper. There was a case where a little girl died while in a coma due to hyperglycemia, another case where a boy died from severe dehydration at camp because the staff ignored him being diabetic, and many other tragic T1D stories that were primarily due to the difficulty of keeping blood sugar levels close to the normal/healthy range which is heavily influenced by their food consumptions (2, 3).

Currently, 15 per 100,000 people have T1D, and its prevalence is increasing worldwide (6). Additionally, there are already over 9 million people with the disease as of 2017 (5). Sadly, a cure is yet to be developed despite it being linked to lower life expectancy and was the 9th leading cause of death in 2019, along with other types of diabetes (4, 5). Thus, the missing cure is not necessarily due to a lack of motivation or funding, but instead a consequence of the complexity of type 1 diabetes' pathogenesis as an autoimmune disease.

What is Type I Diabetes?

One of our body cell's primary energy sources is glucose (9). It is a sugar that comes from many of the foods we eat, especially those rich in carbohydrates (like rice, desserts, sodas, and many more), which are broken down by our digestive system and absorbed by our bloodstream from the intestines for distribution to our various cells (10, 11). The main way that our cells acquire glucose from the blood is with the help of insulin. It is a hormone secreted by the β cells of the pancreatic islets that regulates glucose levels and promotes glucose storage in the liver, muscles, and adipose tissues (7, 12). As an analogy, we can liken insulin to a '*key'* that '*unlocks'* a cell's membrane so that glucose can get '*inside'* and be used as energy or be stored. Therefore, insulin is vital for our metabolism and overall health.

The most common symptom of T1D is unexplained weight loss and fatigue (13). This is because T1D is an autoimmune disease that is typically driven by a T cell-mediated destruction of the β cells resulting in insulin deficiency (7). Without insulin, we will not have the '*key'* that allows our cells to uptake glucose from the bloodstream. This entails that the cells will not be able to use glucose for energy resulting in fatigue, and that glucose cannot be stored resulting in excessive weight loss. Consequently, it will be difficult for our bodies to regulate blood glucose/sugar levels. In sum, without β cells to produce insulin, circulating glucose/sugar

levels will constantly be toxically elevated (hyperglycemia) for those who have eaten too much or alarmingly low (hypoglycemia) for those who eat too little. In both cases, blood vessels and nerves can be damaged, ultimately leading to death if untreated (20).

Who is Susceptible to T1D?

Despite decades of research, many of the factors associated with T1D development still have knowledge gaps. There are four major factors that are known to increase risk of T1D: genetics, environment, viral infections, and gut microbiome.

1. In terms of genetics, about 95% of T1D patients have at least one of HLA-DR3 or HLA-DR4 (14). Both are versions/alleles of our class II human leukocyte antigen (HLA) genes, which are the genes responsible for encoding class II molecules recognized by specific T cells. In the case of T1D patients, their HLA-DR genes encode for different class II molecules that leads to the activation of autoreactive T cells. Essentially, these T cells now recognize β cell antigens as non-self and induce an immune response against them (autoimmune attack), resulting to the loss of tolerance. HLA-DR3/-DR4 are most common in White/Caucasian ethnicities (around 40% in the US). However, only about 3-10% of individuals carrying such alleles develop T1D, which alludes to the potential major role of environmental factors (7). Mutations resulting in autoreactive antibodies can also trigger T1D development since the disease is usually associated with a pre-diabetic seroconversion period where autoantibodies to β cell antigens are created (16). Furthermore, T1D often coexist with other autoimmune diseases such as autoimmune thyroid disease. Thus, genes that contribute to the risk of other autoimmune disorders can influence our susceptibility to T1D. Nevertheless, the disease is heritable, which is why family history is one of the strongest risk indicators – we are more likely to develop T1D if our parents have it (18).

2. The exact environmental factors that increase the risk for T1D are still unclear as many combinations are possible. This includes diet, glucose overload, pollutants, and the physical and psychological stress induced by our environments (19). Some studies suggest that people in northern climates are more susceptible to T1D because they tend to stay indoors during winter, which increases viral infections that may trigger autoimmunity (15). All these environmental risk factors might cause the exhaustion of pancreatic β cells leading to its failure due to a secondary autoimmune infection. Recent studies discovered that exhausted β cells are likely the source of hybrid insulin peptides (HIPs) found in T1D patients, which are naturally occurring autoantigens that can initiate β-cell-specific autoimmunity in high-risk hosts – this idea emphasizes on the potential relevance of β cell stress on autoimmunity (19).

3. Viral infections from human enteroviruses (HEVs), including the poliovirus, have strong correlations with T1D because they are easily spread by poor hygiene/sanitation and primarily enter the gut. The main theory regarding how HEV infections lead to T1D posits that the viruses could have exposed β cells to the immune system in an 'unusual way' or changed some of its internal components resulting in autoimmunity (17, 20). This is still a working theory so the causality between viral infections and T1D susceptibility remains elusive.

4. Recent efforts in understanding potential causes of T1D have focused on the role of our gut microbiome, which encompasses all the bacteria/microorganisms living inside us that influence many aspects of our health, including how we process food and the functionality of our immune system. The composition of our microbiome is influenced by a variety of factors, such as our method of birth (natural/cesarian), childhood diets, and use of

antibiotics. Studies discovered that children with T1D have a different gut microbiome than those without it (20). This evidence suggests that the fewer types of gut bacteria present in T1D patients could be significant in the development of T1D (21).

Are there Treatments for T1D?

The 4 major risk factors for T1D are still undergoing extensive research. Thus, the causes of autoimmunity and T1D pathogenesis are incompletely understood, which is a significant factor why there is still no cure for the disease.

Before the 1920s, diabetes (both type 1 and 2) was a 'death sentence' for people with it. They either died from starvation due to the inadequate treatment of the disease by a low-calorie glucose-free diet or died from its complications (23). This all changed when a team of researchers at the University of Toronto were able to purify a pancreatic extract known as insulin. The success of their early insulin trials led to the rapid establishment of diabetic clinics and insulin injection manufacturers all over the world (24).

As mentioned, people with T1D have severe insulin deficiency because their insulin-producing pancreatic β cells are destroyed by autoreactive immune cells. Administering insulin via injecting controlled doses into a diabetic's bloodstream gives them the '*key*' that enables their cells to store glucose and use it for energy. As a result, T1D patients are now able to better maintain their blood glucose levels and live longer/healthier lives. However, as emphasized by Dr. Banting, one of the pioneers of the insulin discovery, "*insulin is not a cure for diabetes; it is a treatment*" (24). More often than not, diabetics require combinations of medications: they use various types of insulin to prevent/treat high blood sugar levels (hyperglycemia); they use glucagon injections to treat low blood sugar levels (hypoglycemia); they also use high blood

pressure medications to keep their kidneys healthy, and aspirin if they have increased susceptibility to cardiovascular events to protect their hearts (25, 26, 27). Additionally, they need to constantly monitor their blood sugar levels and carbohydrate intake, practice healthy eating, and engage in physical activities to keep blood sugar levels in the normal range, which is around 80-130 mg/dL before a meal and less than 180 mg/dL two hours after the start of a meal (27, 28).

We can imagine that living with T1D can be a challenging, expensive, and tedious for the diabetics and their families. One advancement that tries to reduce their workload is the insulin pump, which is a cellphone-size device outside their body where a tube connects an insulin reservoir to a catheter inserted under their skin (27). However, they still need to manually monitor their condition to ensure that the device is working properly.

A Glimmer of Hope in Stem Cells?

A promising advancement that may lead to curing the disease is the use of stem cells, which are cells that can potentially differentiate into other cell types. There are currently two competing methods in using stem cells (29):

First, the goal is to coax stem cells through various stages of development using signalling molecules/pathways involved in the natural development of pancreatic cells to create lab-grown cultures of β cells that can be transplanted to T1D patients. Although scientist now know how to transform human stem cells into pancreatic progenitor cells, the signaling mechanisms involved in the development of β cells from a pancreatic progenitor cell is still being studied.

Second, instead of trying to create β cells, pancreatic progenitor cells from stem cells can be sufficient to cure the disease. In this method, the lab-grown pancreatic progenitor cells will be transplanted to T1D patients. The hope is that the transplanted cells will then mature into β cells on their own. A concern for this theory is the variability and uncertainty that the progenitor cell may not mature as β cells. This suggests that implanting differentiated β cells can provide a more controlled treatment/cure for the disease.

In the end, these promising advancements offer millions of people affected by T1D a glimmer of hope for a potential cure in the near future. A future where they do not need to invest so much money for injections and other medications. A future where they do not have to constantly manage their physiologies or worry about eating too much or too little. A future where they can live normal and productive lives.

References

1. Cleveland Clinic. (2020). *Food Psychology: Understanding Eating Behavior & Habits*. https://my.clevelandclinic.org/health/articles/10681-the-psychology-of-eating
2. Edawards, C. (2015). *I think we saved our son's life last night.* Beyond Type 1. https://beyondtype1.org/i-think-we-saved-our-sons-life-last-night/
3. LeWine, H. E. (2015). *People with type 1 diabetes are living longer.* Harvard Health Publishing, Harvard Medical School. https://www.health.harvard.edu/blog/people-type-1-diabetes-living-longer-201501087611
4. Thompson, D. (2015). *Type 1 diabetes linked to lower life expectancy.* WebMD. https://www.webmd.com/diabetes/news/20150106/type-1-diabetes-linked-to-lower-life-expectancy-in-study
5. World Health Organization. (2021). *Diabetes.* United Nations. https://www.who.int/news-room/fact-sheets/detail/diabetes
6. Mobasseri, M., Shirmohammadi, M., Amiri, T., Vahed, N., Hosseini Fard, H., & Ghojazadeh, M. (2020). *Prevalence and incidence of type 1 diabetes in the world: a systematic review and meta-analysis.* Health Promotion Perspectives, *10*(2), 98–115. https://doi.org/10.34172/hpp.2020.18
7. Tetz, G., Brown, S. M., Hao, Y., & Tetz, V. (2019). *Type 1 diabetes: An association between autoimmunity, the dynamics of gut amyloid-producing E. coli and their phages*. Scientific Reports, *9*(1). https://doi.org/10.1038/s41598-019-46087-x
8. Billman, G. E. (2020). *Homeostasis: The underappreciated and far too often ignored central organizing principle of physiology*. Frontiers in Physiology, *11*. https://doi.org/10.3389/fphys.2020.00200

9. *Nemours KidsHealth. (n.d.). Definition: glucose (for teens)*. Kidshealth.org. https://kidshealth.org/en/teens/glucose.html#:~:text=Glucose%20is%20the%20main%20type,glucose%20levels%20in%20the%20blood.
10. Medicine Plus. (n.d.). *Carbohydrates*. National Library of Medicine. https://medlineplus.gov/carbohydrates.html
11. Watson, S. (2016). *What is glucose.* WebMD. https://www.webmd.com/diabetes/glucose-diabetes
12. Rahman, M. S., Hossain, K. S., Das, S., Kundu, S., Adegoke, E. O., Rahman, Md. A., Hannan, Md. A., Uddin, M. J., & Pang, M.-G. (2021*). Role of insulin in gealth and disease: An update*. International Journal of Molecular Sciences, *22*(12), 6403. https://doi.org/10.3390/ijms22126403
13. Diabetes Education Online. (2022). *What are the symptoms diabetes.* University of California, San Francisco. https://dtc.ucsf.edu/types-of-diabetes/type1/understanding-type-1-diabetes/basic-facts/what-are-the-symptoms-of-diabetes/
14. Steck, A. K., & Rewers, M. J. (2011). *Genetics of type 1 diabetes*. Clinical Chemistry, *57*(2), 176–185. https://doi.org/10.1373/clinchem.2010.148221
15. Smith-Marsh, D. E. (2009). *Type 1 diabetes risk factors*. Endocrineweb. https://www.endocrineweb.com/conditions/type-1-diabetes/type-1-diabetes-risk-factors
16. Vehik, K., Haller, M. J., Beam, C. A., Schatz, D. A., Wherrett, D. K., Sosenko, J. M., & Krischer, J. P. (2011). *Islet autoantibody seroconversion in the DPT-1 study*. Diabetes Care, *34*(2), 358–362. https://doi.org/10.2337/dc10-1494
17. Filippi, C. M., & von Herrath, M. G. (2008). *Viral trigger for type 1 diabetes*. Diabetes, *57*(11), 2863–2871. https://doi.org/10.2337/db07-1023

18. Kuo, C.-F., Chou, I-Jun., Grainge, M., Luo, S.-F., See, L.-C., Yu, K.-H., Zhang, W., Doherty, M., & Valdes, A. (2018). *Familial aggregation and heritability of type 1 diabetes mellitus and coaggregation of chronic diseases in affected families*. Clinical Epidemiology, *Volume 10*, 1447–1455. https://doi.org/10.2147/clep.s172207
19. Rewers, M., & Ludvigsson, J. (2016). *Environmental risk factors for type 1 diabetes*. The Lancet, *387*(10035), 2340–2348. https://doi.org/10.1016/s0140-6736(16)30507-4
20. Diabetes UK. (2019). *Research spotlight: What causes type 1 diabetes*. https://www.diabetes.org.uk/research/research-round-up/research-spotlight/research-spotlight-what-causes-type-1-diabetes#:~:text=Hygiene%2C%20pollutants%2C%20vaccines%2C%20maternal,involved%20in%20Type%201%20diabetes
21. Zheng, P., Li, Z., & Zhou, Z. (2018). *Gut microbiome in type 1 diabetes: A comprehensive review*. Diabetes/Metabolism Research and Reviews, *34*(7), e3043. https://doi.org/10.1002/dmrr.3043
22. Drew, L. (2021). *How stem cells could fix type 1 diabetes*. Nature, *595*(7867), S64–S66. https://doi.org/10.1038/d41586-021-01842-x
23. Parks Canada. (2017). *Discovery of Insulin National Historic Event*. Pc.gc.ca. https://www.pc.gc.ca/en/culture/clmhc-hsmbc/res/information-backgrounder/decouverte-insuline-insulin-discovery
24. Insulin 100. (2021). *Insulin 100: University of Toronto*. https://insulin100.utoronto.ca/
25. Mayo Clinic. (n.d.). *Glucagon (injection route) aescription and brand names.* https://www.mayoclinic.org/drugs-supplements/glucagon-injection-route/description/drg-20064089#:~:text=Glucagon%20injection%20is%20an%20emergency,form%20of%20sugar%20by%20mouth.
26. Centers for Disease Control and Prevention (CDC). (2021). *Types of insulin*. https://www.cdc.gov/diabetes/basics/type-1-types-of-insulin.html

27. Mayo Clinic. (2021). *Type 1 diabetes: Diagnosis and treatment*. https://www.mayoclinic.org/diseases-conditions/type-1-diabetes/diagnosis-treatment/drc-20353017

28. Centers for Disease Control and Prevention (CDC). (2021). *Manage blood sugar*. https://www.cdc.gov/diabetes/managing/manage-blood-sugar.html#:~:text=A%20blood%20sugar%20target%20is,Less%20than%20180%20mg%2FdL.

29. Drew, L. (2021). *How stem cells could fix type 1 diabetes*. Nature, *595*(7867), S64–S66. https://doi.org/10.1038/d41586-021-01842-x