The roles of microorganisms in the pathogenesis and prevalence of diabetes: a review

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Introduction

Diabetes is a chronic, progressive disease characterised by elevated levels of blood glucose. Three main forms of diabetes exist and these are classified based on the mechanisms of their pathogenesis and age class most often affected. Type 1 diabetes most often affects children and is caused by a lack of insulin due to the destruction of insulin-producing pancreatic beta cells. Type 2 diabetes often occurs in middle-aged and older people, and is caused by a combination of factors, including insulin resistance. Gestational diabetes occurs when a woman is approximately halfway through pregnancy. Women who have this form of diabetes are more likely to have larger babies than women who do not have gestational diabetes.[1-3]

Diabetes is now one of the most common non-communicable diseases globally. Complications from diabetes reduce life expectancy and caused enormous health costs globally. Diabetes is certainly one of the most challenging health problems in the 21st century.[4] Fortunately, many countries have committed to halting the rise in diabetes, reducing diabetes-related premature mortality, and improving access to essential diabetes medicines and basic technologies.[3] However, this can only be achieved through in-depth understanding of the causes and pathogenesis of the disease. Although genetic and environmental factors, and microbial infections have been implicated in the pathogenesis of diabetes, there are diverse opinions on their mechanisms. The aim of this structured review is to summaries mechanisms by which microorganisms may aid in the pathogenesis of diabetes.

Viral infection and diabetes

A virus cannot cause diabetes on its own, but people are sometimes diagnosed with type 1 diabetes during or after a viral infection, suggesting a link between the two. In addition, the onset of type 1 diabetes occurs more frequently during the winter when viral infections are more common. Viruses possibly associated with type 1 diabetes include Coxsackievirus B, cytomegalovirus, adenovirus, rubella, and mumps.[5] Viral infections may contribute to the development of type 1 diabetes through many mechanisms. Firstly, by mimicking the sequence homology of a self-peptide, a pathogen-derived peptide may trigger an immune response against self-tissue in the host organism (known as molecular mimicry). In this way, viral infections may provoke inflammation and destruction of host cells, causing release of autoantigens and activation of autoreactive T cells (bystander activation of T cells). Significant inflammation may induce stress in the endoplasmic reticulum (ER), resulting in protein denaturation and presentation of new autoantigens (known as antigen spreading). Secondly, human enteroviruses, including polioviruses, echoviruses, and rhinovirus, are associated with type 1 diabetes. Enteroviruses are generally transmitted through consumption of contaminated food and drink. The rarity of enteroviruses in most developed countries is correlated with an increase in the incidence of type 1 diabetes, supporting what is termed the 'Hygiene Hypothesis'. The hypothesis postulates that a cleaner lifestyle does not train the immune system against microorganisms and the system may respond inappropriately when exposed later.[6] Enterovirus infections can reach the pancreas where they are attacked by the immune system along with the cells that produce insulin. This is typically the situation with type 1 diabetes in infants, where the immune system destroys the body's own beta cells, leaving it unable to process glucose. However, it is also possible that there is something about the pancreas of a child who is prone to type 1 diabetes that makes the organ more vulnerable to enterovirus infection. It has not yet been shown that a viral infection occurs before the immune system begins to attack the pancreas, so it is still unknown which comes first: the viral infection or the immune response.[7]

Many studies have investigated the link between enteroviruses and the development of type 1 diabetes. In one study, 183 children with either type 1 diabetes or elevated glucose levels, and 366 children without autoantibodies or with moderate glucose levels were investigated. The study found that Coxsackievirus B1 was associated with an increased risk of developing type 1 diabetes, while two other viruses, Coxsackieviruses B3 and B6, were associated with a lower risk. This study

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suggests that developing a vaccine for Coxsackievirus B1 may prevent some cases of type 1 diabetes, but more research is needed to confirm that this virus causes type 1 diabetes.[8]

An experiment suggesting virus induction of type 2 diabetes is recorded on the web, although not as yet in a published journal.[9] This concerns a Dr Mike Snyder of Stanford University, USA, who used his laboratory to study sequentially his own development of type 2 diabetes. His blood glucose rapidly rose from normal following a documented infection with respiratory syncytial virus (RSV).

In another study conducted across tertiary care medical centres in the USA, researchers linked hepatitis C virus (HCV) to the development of insulin resistance (IR) and type 2 diabetes.[10] The study was conducted by the National Health and Nutrition Examination Survey (NHANES) between 1988 and 2008. A total of 39,506 individuals from three NHANES cycles (1988–1994, 1999–2004, and 2005–2008) with complete demographic and relevant clinical data took part in the survey. During the first NHANES cycle (1988–1994), IR and diabetes were independently associated with hepatitis C; however, in the later study cycles (1999–2008), these associations were no longer significant. In contrast, other important known risk factors for diabetes and IR (male gender, non-Caucasian race, age, and obesity) remained significant over all three NHANES cycles. This shows that in the later cycles, the association between HCV infection may have been diluted by the rapid rise of other risk factors for diabetes, specifically, obesity.[10]

Bacterial infections

A study by microbiologists at the College of Medicine, University of Iowa, USA, suggests that bacteria may be a cause of type 2 diabetes.[11] It was found that prolonged exposure to a toxin produced by *Staphylococcus aureus* caused rabbits to develop symptoms of type 2 diabetes, including insulin resistance, glucose intolerance, and inflammation. Type 2 diabetes was reproduced in the rabbits simply through chronic exposure to the toxins produced by all strains of staphylococcal bacteria. The findings suggest that therapies aimed at eliminating such bacteria or neutralising the superantigens might have a potential for preventing or treating type 2 diabetes. Obesity is a known risk factor for type 2 diabetes, but obesity also alters a person's microbiome, some of which may affect health. As people gain weight, they are increasingly likely to be colonised by staphylococcal bacteria and have large numbers of these bacteria living on the surface of their skin. People who are colonised by these bacteria are being chronically exposed to the superantigens the bacteria are producing.[11]

A similar study has shown that *Helicobacter pylori* infection may be associated with elevated levels of glycolated haemoglobin (HbA1c). This association was stronger in obese individuals with a higher body mass index (BMI), suggesting the bacteria may play a role in the development of diabetes in adults. There have been conflicting reports about the association between *H pylori* infection and type 2 diabetes, which has necessitated more studies to understand the relationship. Among such studies is one from the NHANES studies;[12] *H pylori* was consistently positively related to HbA1c level in adults. In addition, this association was stronger in individuals with a high BMI compared with those with a lower BMI.

Recently, several studies have linked a group of bacteria found in the gut with the development of type 2 diabetes. Specifically, two main phyla of microbes in the gut, namely Bacteroidetes and Firmicutes have been suspected to aid the pathogenesis of diabetes. Bacteroidetes are thought to be important for protein and carbohydrate digestion in the gut, while the Firmicutes are involved in dietary fat processing.[13] Each individual has a unique gut microbiome based on a number of factors such as genetic background, diet, antibiotic exposure, and age. The *Christensenellaceae* family is associated with a lean and healthy lifestyle and is very strongly inherited in families. Some gut bacteria may protect against external bacteria and boost the immune system. They also help regulate intestinal hormone secretion and synthesise vitamin K and several B-vitamins, including folate and vitamin B_{12}. They may also increase energy harvest from the diet and alter fatty acid metabolism and composition in adipose tissue and the liver. Other mechanisms may include modulation of gut peptide YY and glucagon-like peptide (GLP)-1 secretion, activation of the lipopolysaccharide toll-like receptor-4 axis, and modulation of intestinal barrier integrity by GLP-2.[14]

Several animal models of obesity have linked an altered microbiota composition to the development of obesity, insulin resistance, and diabetes in the host. The first definite evidence for the role of the gut microbiota in the regulation of host energy homeostasis and adiposity came from researchers at Washington University, USA. They noticed that germ-free mice (i.e. raised in the absence of microorganisms) had 40% less total body fat than conventionally raised mice. After 2 weeks of conventionalisation (i.e. colonisation of their gut with a caecum-derived distal microbial community) there was a 57% increase in total body fat. It also produced a 2.3-fold increase in hepatic triglycerides and a dramatic increase in IR.[15] In another study by the same authors, germ-free and conventionalised mice were fed a high-fat, high-carbohydrate Western diet for 8 weeks. At the end of the study period, germ-free mice gained significantly less fat and weight compared with conventionalised mice and were protected against a Western diet-induced glucose intolerance and insulin resistance.[16]

In one of the largest longitudinal studies of the microbiome to date, researchers identified a connection between changes in gut microbiota and the onset of type 1 diabetes. The study monitored changes in the gut microbiome of 33 infants who were genetically predisposed to type 1 diabetes from birth to 3 years old. They found that the onset of diabetes for those who developed

the disease was preceded by a 25% drop in microbial diversity a year earlier. There was also a decrease in the number of species known to promote health along with an increase in potentially harmful bacteria known to promote inflammation.[17] This is a typical example of how the depletion of beneficial gut bacteria may lead to the onset of diabetes.

Bariatric surgery improves glucose tolerance and insulin sensitivity. In one study, gastric bypass was carried out in a mouse model of type 2 diabetes.[18] The improved metabolism observed occurred in conjunction with changes in gut microorganisms and not just weight loss, suggesting that gut microbiota play a role in the diabetes remission. This implies that duodenum–jejunum gastric bypass (DJB) surgery may be applied to cure diabetes of both genetic and environmental origin. Such surgery can cause gut microbiota alterations, which may be the key reason for diabetes remission after bariatric surgery. Data obtained from the study indicate that suppressed inflammation is also a result, not the cause, of diabetes reversal in these genetically modified mice.[18]

Conclusions

Many studies agree that microorganisms may aid in the onset and remission of diabetes. Harmful bacteria and viruses may cause inflammation and destruction of pancreatic beta cells, leading to insulin resistance and diabetes. Beneficial bacteria, especially gut bacteria, may protect against harmful microbes, support the immune system, induce hormonal secretion, and cause remission of diabetes. Therefore, it is possible that some diabetic conditions may be treated with elimination of microbes, and some may be treated by increasing gut bacterial diversity.

References

1. Yahaya T, Obaroh IO, Oladele EO. The roles of environmental pollutants in the pathogenesis and prevalence of diabetes: a review. *J Appl Sci Env Mgmt* 2017; 21: 5–8.
2. Disabled World. Diabetes: types, symptoms and treatment [Cited 3 May 2015]. Available from www.disabled-world.com/health/diabetes
3. World Health Organization (WHO). Global report on diabetes [Cited 5 Oct 2016]. Available from: www.who.int/diabetes/global-report/en
4. Richard SS, Jonathan Z, Paul M. The global burden: diabetes and impaired glucose tolerance. IDF Diabetes Atlas, 2010 4th edition, 1–105. Available from http://www.diabetesatlas.org/
5. National Institute of Diabetes and Digestive and Kidney Disease (NIDDK). Causes of Diabetes [Cited 2 Sept 2014)]. Available from www.niddk.nih.gov/health-information/diabetes/causes
6. Ghazarian L, Diana J, Simoni Y, et al. Prevention or acceleration of type 1 diabetes by viruses. *Cell Mol Life Sci* 2013; 70: 239–55.
7. Lin HC, Wang CH, Tsai FJ, et al. Enterovirus infection is associated with an increased risk of childhood type 1 diabetes in Taiwan: a nationwide population-based cohort study. *Diabetologia* 2015; 58: 79–86.
8. Olli HL, Hanna H, Outi O, et al. Coxsackievirus B1 associated with induction of β-cell autoimmunity that portends type 1 diabetes. *Diabetes* 2014; 63: 446–55.
9. Barry S. Virus-induced type 2 diabetes [Cited 12 Aug 2013]. Available from ww2.kqed.org/science/2013/08/12/virus-induced-type-2-diabetes
10. Stepanova MB, Lam Y, Younossi MK, et al. Association of hepatitis C with insulin resistance and type 2 diabetes in US general population. *J Viral Hepat* 2012; 19: 341–45.
11. Brown J. Bacteria may cause type 2 diabetes [Cited 1 Dec 2015]. Available from www.eurekalert.org/pub_releases/2015-06/uoih-bmc060115.php
12. Chen Y, Blaser MJ. Association between gastric *Helicobacter pylori* colonisation and glycated haemoglobin levels. *J Infect Dis* 2012; 205: 1195–1202.
13. Hatipoglu B. Exploring the link between gut microbes and diabetes [Cited 5 June 2015]. Available from http://health.us-news.com/health-news/patient- advice/articles/2015/06/08/exploring-the-link-between-gut-microbes-and-diabetes
14. Shrestha UK. Role of altered gut microbiota in the development of obesity, insulin resistance and type 2 diabetes mellitus. *Nepal J Med Sci* 2013; 2: 1–2.
15. Bäckhed F, Ding H, Wang T, et al. The gut microbiota as an environmental factor that regulates fat storage. *Proc Natl Acad Sci* 2004; 101: 15718-15723.
16. Bäckhed F, Manchester JK, Semenkovich, et al. Mechanisms underlying the resistance to diet-induced obesity in germ-free mice. *Proc Natl Acad Sci* 2007; 104: 979–84.
17. Kostic AD, Dirk G, Heli S, et al. The dynamics of the human infant gut microbiome in development and in progression towards type 1 diabetes. *Cell, Host Microb* 2015; 17: 260–73.
18. Jiang S, Wang Q, Huang Z, et al. Gastric bypass surgery reverses diabetic phenotypes in bdnf-deficient mice. *Am J Path* 2016; 186: 2117–28.