Etiology of Type 1 Diabetes

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Type 1 diabetes, or Insulin Dependent Diabetes Mellitus (IDDM), is a disease characterized by "auto-destruction" of the pancreatic beta cells that produce insulin. Overtime, your body silently destroys these cells creating an insulin deficiency. IDDM appears to stem from an inherited defect in the immune system, triggered by some environmental stimuli. The exact cause of the disease is still unknown; however, scientists have isolated a few factors that may be related to development of the disease. The purpose of this review is to provide insight on where research is headed and what we already know about the progression of IDDM.

Genetics

Recent mapping of the human genome has opened many areas to explore in the field of diabetes research. Animal models and large population studies have led to some possible genetic links. The major histocompatibility complex (MHC) on chromosome 6 is a regulator of immune response because it recognizes "self" and "not-self" things in the body. If something is seen as foreign, the MHC will stimulate antibody production. Genes encoded on the MHC are associated with IDDM, particularly the human leukocyte antigen (HLA) class II alleles, DQ and DR (1). Although the HLA-DQ locus appears to be the best single marker for susceptibility among Caucasians, at least 40% of family-related diabetes cases have combinations of both DQ and DR alleles (2,3). DQ and DR alleles are almost always found together on a chromosome and the risk is associated with them not being in equilibrium. Many combinations have been documented, some showing both increased and decreased susceptibility, however it has been difficult to determine the contribution of HLA-DQ independent of DR. The insulin gene region at chromosome 11 is also associated with IDDM risk.

Studies conducted in the 1970's established an HLA association and contribution of IDDM while comparing siblings with the disease (4,5,6). When comparing the relationship between family members, results are inconsistent. Current estimates suggest that HLA is 40-50% related to genes passed down by family members (7,5). The risk of developing IDDM for a twin of someone who already has the disease is about 70%, and this rises depending on the specific HLA alleles that the twins share (8). When comparing the risk of developing the disease for first-degree relatives vs. the US population, the risk is 1/20 and 1/300, respectively (1). Research in the area of HLA has been extremely difficult. Definitive answers cannot be drawn because not everyone holding these "susceptible" genes develops IDDM. Actually, less than 10% of genetically susceptible individuals progress to diabetes, implying that other factors are responsible for progression of the disease. Researchers have explored these other factors, particularly environmental factors such as early introduction of cow's milk, dysregulation of the gut immune system, viral infections, drinking water and a number of others.

Cow's Milk

Several population studies have found a link between exposure to cow's milk and increased risk for IDDM in genetically susceptible individuals. A few studies have also shown an increased risk for infants exposed to cow's milk or cow's milk based formulas within the first 3 months, and also later in life. It has been found that infants fed cow's milk had increased levels of bovine insulin anti-bodies compared to those that were

breast-fed (9,10,11). Bovine insulin is found in the milk of cows. The antibodies binding to bovine insulin appear to cross-react with human insulin (9,10). Bovine insulin is considered immunogenic because it differs from human insulin by 3 amino acids.

Insulin-specific antibodies (ISA), those specific for IDDM, and increased T cell levels from exposure to cow's milk have been found in those carrying diabetes associated HLA risk alleles. Of all the studies to date however, levels of insulin binding antibodies seem to decrease as the child approaches 9-18 months. This suggests that the infant is building a tolerance to dietary antigens (12). However, Vaarala et al. discovered that infants who developed ISA's, also had increased levels of bovine insulin antibodies, suggesting that insulin specific immune responses in children prone to develop autoimmunity cannot be prevented (12). Other studies have found bovine insulin antibody levels to decrease when human insulin was presented in the body.

Early weaning (2-3 months) from breast milk has been shown to increase the risk for IDDM. Maternal milk contains colostrum, a light fluid that contains a variety of protective factors for the infant. Infants have an immature and easily penetrable gut system allowing food, in this case cow's milk, to easily cross into the bloodstream. The gut system works in one of two ways: it will either accept (build tolerance to) or reject (develop immunity to) food and its dietary components (13). Several cow's milk proteins have been shown to be related to IDDM such as bovine albumin, beta−lactoglobulin, and beta casein (14,15,16)

A study by Karjalainen et al. in 1992 was conducted to assess whether bovine serum albumin (BSA) was a trigger for IDDM (14). Researchers measured the levels of anti-BSA and anti-ABBOS (specific part of the albumin protein) antibodies in the serum of children with newly diagnosed IDDM, children without IDDM, and blood donors' (14). Antibodies that react to the ABBOS also react with a beta cell surface protein that may represent a target for autoimmune attack (14). All children in the study with IDDM had the highest amount of both antibodies, especially ABBOS, compared to the children without IDDM and blood donors' (14). Antibody levels declined after one or two years of exposure to cow's milk (14). This suggests that albumin has a section that is capable of reacting with "beta-cell specific surface proteins", which could contribute to islet cell dysfunction because of molecular mimicry (14). What is molecular mimicry?

When an antigen is present in the body, T cells latch onto a short segment, consisting of about 10 amino acids. T cells then present the antigen to macrophages that engulf it and break it down into smaller protein fragments. The macrophages bring the fragments to the cell surface where capable T cells can bind to it. This activates the T cells, leading to stimulation in other areas to attack all proteins with similar amino acid segments. Bovine serum albumin has a short amino acid sequence similar to a beta cell surface receptor ICA69 (17) and beta casein shares a similar sequence with a glucose transporter. If molecular mimicry occurs here, then presentation of BSA or beta casein in the body would lead to autoimmune destruction.

Contrary to Karjalainen et al.'s study, Vaarala et al. found no association with BSA, but did find an increased risk for newly diagnosed IDDM with beta-lactoglobulin, another cow's milk protein (15). A study conducted by Cavallo et al. found an association with increased risk of newly diagnosed IDDM with beta casein, another milk protein (16). However, no differences were noted with BSA and other proteins assessed (16). Despite these conflicting results, it does appear that some form of "cross-reactivity" may

occur with cow's milk proteins and islet-cell antigens, leading to "auto-attack" of the beta cells.

The role of cow's milk related to IDDM is not clear. The hypothesis of molecular mimicry has been questioned. Few studies have found a link between cellular immunity to BSA and IDDM. A recent study found that reactivities to beta casein were similar between newly diagnosed individuals with IDDM, their immediate relatives without the disease, and non-related healthy subjects. One confounding factor of the previous study was the lack of appropriately matched subjects, because researchers failed to use HLA matched relatives. Also, when comparing breast-feeding vs. cow milk formula, it is unclear at what point there is an increased risk, as well as the actual amount needed to induce an immune response. Despite all of the evidence presented here, exposure to cow's milk and risk for IDDM is only suggestive because the exact cause is unknown (18).

Viral Infections

Viral infections have been considered to be "more" responsible for diabetes development, than milk proteins. Identifying the exact virus responsible has been extremely daunting for several reasons. Individuals are exposed to many viral infections within their lifetime. Although IDDM is primarily a juvenile disease, by the time the disease is diagnosed, children have been exposed to many viruses. Thus, pinpointing the exact one would be every difficult, if not impossible to link. Another problem is that immunological damage often occurs after the virus is gone, leaving no trace of the virus responsible. However, large population studies, as well as human and mice studies, have led to some possible viruses responsible.

Coxsackie B Virus

Coxsackie B virus is an enterovirus, a virus part of a group of picornaviruses, related to those that cause polio. Several studies have found that after or with exposure to Coxsackie B that individuals developed IDDM. Also, large population studies have found antibodies against the virus in children with newly diagnosed IDDM. Coxsackie B viruses have been isolated from the pancreas in children who have developed IDDM very rapidly. Plus, inducing certain mouse strains with the virus has caused these mice to develop the disease.

Molecular mimicry has been postulated in the case of Coxsackie B virus. The virus increases the expression of an enzyme GAD in the pancreas. GAD is a highly potent autoantigen of the autoimmune response in humans and mice models. Coxsackie B and GAD share a similar sequence that may lead to cross reactivity.

Other, but not limited to, factors that may be responsible for Coxsackie B and IDDM are altered immune system regulation because of viral infection, altered memory of the T cells causing them to forget which are "self" and "not self" in the presence of viral infection, and persistent infection of the beta cells because of viral antigens expressed within them.

Although this all sounds promising, several other studies have not found conflicting results such as no difference in Coxsackie B antibodies between those with IDDM and those without it, along with no differences in prevalence and amount of antibodies responsible.

Rubella Virus

About 12-20% of fetal infected individuals with rubella will develop diabetes within 5-20 years (19,20). In some adults, development of diabetes has occurred after infection with rubella. Although this poses a threat to genetically susceptible individuals, vaccination programs have decreased the amount of rubella cases.

Cytomegalovirus (CMV)

There have been individual case reports of children developing IDDM after exposure to CMV. There have been recent studies done showing that newly diagnosed individuals with IDDM were recently exposed to CMV. It has been suggested that molecular mimicry may be partly responsible because CMV proteins share a resemblance with a protein in the islet cells of the pancreas. Pak et al. discovered that about 20% of individuals with IDDM have CMV DNA in the islet cells (21). Despite all this evidence however, a large Swedish study found no correlation between CMV infection and risk for IDDM (22). Besides all of this, vaccinations against the virus have lowered the prevalence of CMV infections.

Epstein-Barr Virus (EBV)

Individual cases have been noted where those infected with EBV develop diabetes. However, IDDM development as a result of EBV infection is probably not responsible for the disease in the majority of subjects. Little research and single cases are not enough to consider this a major cause.

Other Viruses

There have been reports of individuals developing IDDM after exposure to influenza, hepatitis A, varicella zoster, mumps, measles, rotavirus, polio, and Coxsackie A virus.

Other Environmental Factors

Recent studies have found a positive association between zinc levels in drinking water and protection against diabetes. Magnesium levels in tap water have been shown to be related to diabetes protection as well, however conflicting evidence resides with this. The protections that zinc may provide is unclear. Despite possible relationships with heavy metals and diabetes, more research must be done to ascertain the actual relationship.

Of all the evidence presented here, researchers have been unable to find the exact cause for development of IDDM. What we do know is that genetically susceptible individuals have an increased risk for diabetes. As displayed here, researchers have located genes that seem to predispose individuals to diabetes. Genes are not enough however, because not everyone who has these genes develops diabetes. Environmental factors are another part of the picture. Whether it is milk proteins, viral infections, or impaired gut function, those with genetic susceptibility tend to develop the disease after exposure to these. Identifying which factor is responsible has been difficult because exact mechanisms of the body are still unclear and tests to determine these things may not be specific or have not yet been developed. Plus, isolating one factor is not reasonable because there are a lot of overlaps in immune functions and genetics. All in all, research is headed in the right direction, but for now there is still no known cause for IDDM.

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