

## Epidemiology and Pathophysiology of Diabetes Mellitus

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### Abstract:

Diabetes mellitus (DM) is a metabolic disorder affecting the insulin production and resistance of the human body. Type I-DM commonly affects children and has a high genetic disposition. Type II-DM develops more commonly in adults and is heavily related to the overall health of the person. Risk factors for diabetes include obesity, stress, and environmental factors such as arsenic, mercury, BPA, and phthalates. Other factors such as gender and race are out of one's control. 10.6% of women and 13.6% of men in the US suffer from diabetes. Men are more likely to develop diabetes from weight gain, while women are more likely to develop it due to stress. The cause of diabetes depends on the type, there are genetic alleles for human leukocyte antigen (HLA) known to be involved in causing diabetes. These include HLA-DR3-DQ2, HLA-DR4, and DQ8. Ultimately all forms of diabetes result from either the decreased production of the anabolic insulin hormone, or from increased insulin resistance.

**Key Words:** diabetes, gender differences, pathophysiology, obesity

### I. Introduction

Diabetes is an epidemic disease becoming increasingly common across the world. Diabetes mellitus is a group of disorders caused by the improper function of the insulin hormone produced in the beta-cells of the islets of Langerhans of the pancreas. Though diabetes is not an uncommon disease, and educational programs are in place to create a conscious society, the number of people developing diabetes continues to increase and the age of diagnosis is decreasing, affecting children at a younger age. To better understand who diabetes affects, what can place a person at greater risk, and what causes diabetes to develop, research was conducted using several databases. PubMed, MedLine, and Biomedical Reference Collection - Comprehensive were utilized with search words such as diabetes mellitus, gestational diabetes, risk factors, gender differences, environmental factors, stress, and obesity. Not all of the articles resulting from my search were used, mostly due to the fact that some were far too outdated and more current research addressing the same topics were available. Some studies were localized in certain areas of the world and did not give overall comprehensive information about how diabetes works in diverse populations. Ultimately, 17 of the articles were found to provide an understanding of diabetes in several areas. Included in this review are gender specific, age-specific, and race-specific facts and theories.

### II. Incidence & Prevalence

Diabetes Mellitus affects 382 million people worldwide and is estimated to affect more than 592 million people by the year 2035. This means 8.3% of adults in the world have diabetes and this number will increase to 10% in the next 15 years [1]. In the United States alone, the prevalence of diabetes increased from 5.5% to 9.3% in 2010, affecting 30.3 million People by 2015. Of these cases, approximately 95% are diagnosed as type 2 diabetes, and less than 5% are type 1 diabetes.

### Age

Diabetes mellitus can affect people of any age and increases in cases have been seen in all age groups. Most cases of diabetes occur in older adults, this includes type 1 diabetes, which was thought to be a juvenile form of the disease. Type 1 and type 2 diabetes has increased in youth. Overall, there has been an annual increase of 1.8%, from 2002 to 2012, in the youth in America. For type 2 diabetes, the annual increase in the same time period was of 4.8% [2]. This is in accordance with research done, which estimated 3-5% annual increase in diabetes incidence in Europe and North America [3]. That study also stated that the age of diagnosis has decreased, creating an increase in new cases for children under the age of five. As for adults, 90% of cases were diagnosed as type 2 diabetes and onset occurred at an older age, usually above 40 years of age [4]. The senior population in America is increasingly affected by diabetes, with twelve million or 25.2% of seniors over the age of 65 having some form of the disease, including diagnosed and undiagnosed cases [5].

### Gender

According to the Center for Disease Control, from 2007 to 2010, 13 million (10.6%) women had diabetes, and another 48 million women (39%) had pre-diabetes. Men had a slightly higher occurrence with 13.6% of men being affected [6]. Unexpected differences do exist between genders. Women were found to have worse survival rates, increased risk of cardiac and renal complications and blindness when compared to men [7]. Gestational diabetes is a form of diabetes that affects women during pregnancy. Sex hormone imbalances can have several manifestations related to diabetes, including vascular function, metabolism, and inflammatory reactions. Due to this, women with excess androgens and men affected by hypogonadism experience different metabolic complications [8]. More women than men were found to have cases of

diabetes related to being overweight or obese. African American women, especially, are more susceptible, with twice the likelihood of developing the disease than white women are. A study found that diabetes symptoms can differ in women and men. Women reported experiencing more drug mouth and abdominal pain than men did. The same study also revealed women were less efficient with their diabetes care than men were [9].

## Ethnicity

How diabetes affects different ethnicities is constantly being studied, especially in nations with large immigrant populations such as the United States and Canada. A study done in Canada observed that when compared to white and non-white ethnicities, individuals of South Asian descent had an increased likelihood of developing diabetes[10]. Another study done states African-Americans and Hispanics are more likely to develop diabetes than white individuals are - Hispanics having a prevalence of 8% versus 4% in non-Hispanic white adults. Prevalence in the Hispanic community, however, did differ depending on the region in the United States, it was 10.7% in Puerto Rico, 4.1% in the Northeast, and 5.8% in the Southwest, and 4.9% in the South/Southeast. Based on these figures Hispanics in Puerto Rico were almost 3 times more like to develop diabetes than non-Hispanic Whites, and those in the Southwest are twice as likely. Hispanics also showed worse glucose control, and more severe retinopathy than white adults [11]. This study also stated that there are differences in how individuals of different ethnicities are treated. African Americans were more likely to be treated with insulin than Mexican Americans and non-Hispanic whites. They were also less likely to self-monitor their glucose levels, even when they were found to have received the most patient education. European populations have a higher likelihood of developing diabetes, and in accordance with this diabetes guidelines recommend Hispanics, Aborigines, Asians and people of African descent be targeted for screening[10].

## III. Risk Factors and Causes

### Obesity

More often than not, obesity is listed as a common risk factor for diabetes. Obesity is defined as the excess accumulation of adipose tissue, causing physical and psychosocial impairment to human health [12]. The accumulation of fat differs in healthy and obese individuals. Adipose tissue in obese people tends to accumulate in the central region of the body, including the chest and abdomen. This intra-abdominal fat is mostly related to genes and proteins used in the production of energy. Intra-abdominal fat is also more lipolytic than peripheral fat and responds poorly to the anti-lipolytic function of insulin, increasing insulin resistance, which could ultimately lead to diabetes. Obesity also contributes to the development of diabetes by increasing the amount of nonesterified fatty acids (NEFAs) that are secreted from adipose tissue. Research showed that as serum levels of NEFAs increased, insulin tolerance in humans began to develop. When NEFAs were reduced glucose monitoring and insulin uptake in peripheral tissues improved. Constant exposure of beta-cells to NEFAs causes reduced insulin production, and therefore affects the regulatory pathways insulin is involved in to keep serum glucose levels balanced. This becomes a cycle, since a compensatory mechanism for damaged beta-cells is to increase lipid secretion of NEFAs [12]. Obesity is often determined by the use of body mass index (BMI). Though obesity is correlated to diabetes in both men and women, women were more frequently diagnosed with diabetes in relation to obesity, whereas men were diagnosed at lower BMIs. Body mass index in men can often overestimate fat mass and forget to consider that men have more fat free muscle in comparison to women [8].

### Stress & Sleep Deprivation

Several studies have found stress can be a factor increasing the risk for diabetes. Stress may result from a person's occupation or

responsibilities. Even a study done in 1909, showed occupations that involve mental strain, worrying, or excitement increased the possibilities of diabetes onset [13]. A more recent study done in Germany, agreed stating that men and women with strenuous jobs had 45% higher risk of developing diabetes[8]. Stress was also said to result in women whose husbands had diabetes. These women ultimately also developed the disease themselves[13]. Similarly, today, even in educated societies, women were more susceptible to the sustained stress of unpaid household duties and demands[8]. A manifestation of stress can be sleep deprivation, where a person gets less than 5 hours of sleep. The risk of women suffering insomnia is 40% higher than in men. This lack of rest is associated with obesity and insulin resistance. Though men gain more weight from lack of sleep and night work, females experience stronger effects earlier. These include greater risk for type 2 diabetes. Ultimately stress and lack of sleep increase a person's risk for developing diabetes. Since only 20% of the diabetes cases caused by stress were related to obesity, the bettering of factors such as stress are suggested to patients.

### Environmental Factors: Arsenic, Mercury, POPs, BPA, phthalates

Chemicals in the environment have been linked to several components of diabetes mellitus. Mercury, for instance, is a non-degradable toxic heavy metal that causes oxidative stress that kills pancreatic beta cells, affecting the insulin signaling pathway. Cadmium is soft metal commonly found as a protective coating around other metals because it resists corrosion, or as a part of rechargeable batteries [14]. Heavy exposure to this metal interferes with calcium reabsorption, which is necessary for the secretion of insulin from beta cells. Arsenic is another chemical that affects the development of diabetes. Residents with chronic exposure to arsenic had an incidence 2 to 5 times higher than those who weren't chronically exposed. In vitro, chronic arsenic exposure caused oxidative stress and decreased the amount of insulin secreted. In adipocytes, arsenic increased insulin resistance and decreased glucose uptake.

Persistent organic pollutants (POP) are defined by the EPA as toxic chemicals that adversely affect health and the environment. They can be spread by wind or water and persist for long periods of time while moving from species to species. Some POPs include polychlorinated biphenyls, dioxin, and oligo-chlorine pesticides [15]. POPs are resistant to biodegradation and their lipophilicity causes them to accumulate in adipose tissue. They are also known as endocrine disrupting chemicals because they interfere with secretion of sex hormones, thyroid hormone, and glucocorticoids. Though POPs were banned several decades ago, their effects continue to persist and can still be found. POPs in fish oil increases insulin resistance and elevates total cholesterol levels.

Other chemicals affecting diabetes levels are BPA and phthalate, which are used in the making of plastic containers many of us use today. These chemicals can seep into water or food stored in these containers. Constant exposure to these affects glucose homeostasis and are more strongly related to Type II-DM [12].

### Autoimmune Disorder

Type I-DM makes up approximately 10% of diabetic cases. It is characterized by autoimmune destruction of beta cells. Destruction tends to happen faster in children and adolescents when compared to adults. Genetic and environmental factors have been found that cause Type I-DM. There are more than 60 genes linked to DM, but the most important to Type I-DM is the human leukocyte antigen (HLA) which is found on chromosome 6, the most important alleles being HLA-DR3-DQ2, HLA-DR4, and DQ8. The heterozygous presentation of HLA-DR3-DQ2 and HLA-DR4 has the highest likelihood of developing Type I diabetes. A study showed that siblings that shared HLA-DR3 and HLA-

DR4 had a 55% chance of developing Type I-DM by the age of 12, whereas those who didn't only had a 5% chance.<sup>16</sup> These mutations are thought to cause the autoimmune response marked by T-cells that destroys beta cells, and the antibodies produced that also attack. Islet Cell Antibodies (ICA) serve as a biomarker, and these antibodies target the antigen located within the cytoplasm of islet cells of the pancreas and lead to the destruction of the cell. Insulin Antibodies (IA) are found in other autoimmune diseases, but it is their concurrence with ICAs that causes the highest risk for Type I-DM. The same study, previously mentioned, stated that with the heterozygous there was a 63% chance of developing these antibodies by the age of 12, and those lacking the heterozygous form only had a 20% chance of developing by the age of 20. Type II-DM is said to be called a "geneticist's nightmare", but the fact that there is a genetic factor is commonly accepted especially since family penetrance supports this. Environmental factors relating to the cause of diabetes include viruses such as rubella, mumps, and coxsackie virus B [4].

### Gestational Diabetes Mellitus

Gestational diabetes can be defined as the intolerance to glucose first diagnosed during pregnancy. The incidence of gestational diabetes can be as high as 22% depending on the population and is increasing as factors such as obesity, maternal age, and changes to urban lifestyles are increasing [17]. This form of diabetes is caused by the mother's inability to increase insulin production to maintain euglycemia [4].

### IV. Pathophysiology

Diabetes mellitus is a disorder dealing with hormone regulation of glucose metabolism. Glucose is one of the main sources of energy for the human body. We can acquire glucose from carbohydrates, which human bodies completely metabolize into glucose. Proteins and fats also serve as sources of glucose, though their effect on blood glucose levels is less impactful. Essentially, this means everything we eat contains glucose. In order to regulate the amount of glucose consumed, there are transporters in place to move glucose into tissues such as muscle or liver tissue. This transport of glucose is facilitated by insulin hormone. Insulin is produced by the pancreas, an organ with both endocrine and exocrine functions. Exocrine functions of the pancreas are to secrete digestive enzymes into the gastrointestinal tract to improve absorption of nutrients. Endocrine functions of the pancreas are to produce hormones that aid in metabolism. Islets of Langerhans are endocrine regions of the pancreas containing alpha cells, which produce glucagon, and beta cells, which produce insulin [4].

Glucagon and insulin work in balance to regulate the metabolism of glucose depending on the condition and needs of the individual. Glucagon is the main catabolic hormone in the body. It is released into blood when levels of glucose are low and causes liver cells to convert glycogen into glucose via glycogenolysis. The glucose is then released to elevate blood glucose levels and to be used as energy. Beta cells are essential as they sense when glucose levels are too elevated. The mechanism used to sense glucose levels involves several steps. To begin, glucose uses GLUT transporters to move into the beta cells. Once glucose is in the cytoplasm, it undergoes glycolysis, releasing ATP. As more glucose enters the cell, levels of ATP increase and are sensed by sulfonylurea receptors (SUR1) of potassium channels, which consequently close. Depolarization of the cell causes calcium channels of the beta cells to open and calcium binds to proteins, triggering the release of insulin-containing granules. Insulin released into the blood stream increases the glucose uptake by muscle and adipose cells up to twenty-fold. Insulin also directs glucose conversion into glycogen, pyruvate, lactate, and fatty acids [4].

When the balance maintained by glucagon and insulin is interrupted by deficiencies in or resistance to insulin the result is hyperglycemia. In Type I-DM the main issue is the insufficiency of the insulin produced. This reduced amount of insulin is the result of an autoimmune response

where T-cells react to islet cell antigens presented by HLA Class II. T cells destroy these beta cells and then present them to B-cells of the immune system for the production of antibodies that will keep destroying. Destruction of the beta cells must be significant since 10-20% of beta cells can produce enough insulin to cover clinical symptoms.

Type II-DM is an insulin resistant form of diabetes where the body loses its ability to produce insulin as the need for insulin increases. In addition to this the receptors for insulin of fat and muscle cells do not respond adequately to the insulin being produced.

### V. Discussion

Diabetes mellitus is a disorder affecting the entire world. Obesity, stress, pollutants are things advised against everyday, but despite constant conversation and education efforts made to alert the public of what an endemic disorder this is, rates of obesity continue to increase. Unfortunately, these rates are extending to the younger population affecting children early on. The impact diabetes has on women is extensive compared to that it has on men. Women in today's world have responsibilities as home makers, breadwinners, and whatever else comes their way. This lifestyle adds on stress and often a busy schedule that doesn't allow for healthy eating. Examining the factors contributing to the increasing diabetes incidence in women and men should cause some kind of spark in the medical field to address these issues. Women and children have been made targets for diabetes screening, but perhaps another part of this should be ensuring this is a service provided to people of all socioeconomic status. There should be availability for all residents, citizens, and even undocumented immigrants. Politics can have many loopholes, but physicians are there to care for people's health around them. Perhaps clinics should make an effort to extend potentially life-saving screening and education to underserved areas.

Environmental chemicals were briefly discussed. BPA and phthalates should be more of a concern today. Few people are aware of the impact these chemicals can have on hormonal health and balance. Promoting the use of glass bottles could be a useful preventative measure.

Many diseases aren't as concerning today as they were when first discovered. One of these is HIV, but like HIV, diabetes should not be accepted as a growing disorder simply because there are medications to treat it. People should have awareness of what they consume, the materials they use and the stresses they take on.

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