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Review Article

ROLE OF HEREDITY IN DIABETES

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ABSTRACT

This review contains the details about what is diabetes, probability of genetic risk on diabetes, how to prevent it and phenotypic variation in the definition of diabetic microvascular complications as well as extent to which contributing pathophysiological mechanisms are similar among different ethnicities may, in part, explain lack of the results reproducibility.

Keywords: Heredity, Diabetes, Genetic, Hormones.

INTRODUCTION

What's Diabetes?

The medical term 'Diabetes Mellitus' is derived from the Greek words 'syphon' and 'sugar', describing symptoms of uncontrolled diabetes, passing huge amounts of urine containing sugar-glucose.

Diabetes is a condition characterized by high blood sugar (glucose) levels due to a lack or insufficient production of a hormone called insulin in the body. Insulin is responsible for decreasing the blood sugar levels and aids in producing energy for the cells. Without enough insulin, glucose obtained from the food builds up in the blood stream leading to a hike in blood sugar levels above than the normal limits. This causes many health complications.

It is a lifelong condition that can be managed with careful diet control and proper medication (either oral medication or insulin) under your physician's and dietitian's supervision.

Diabetes and genetic risk

The risk of developing diabetes is affected by whether your parents or siblings have diabetes.

The likelihood of developing type 1 diabetes or type 2 diabetes differ, as you can see below.

Type 1 diabetes and genetics - average risks

Related guides

Mother with diabetes increases risk of diabetes by 2%

Father with diabetes increases risk of diabetes by 8%

Both parents with diabetes increases risk by 30%

Brother or sister with diabetes increases risk by 10%

Non-identical twin with diabetes increases risk by 15%

Identical twin with diabetes increases risk by 40%

Type 2 diabetes and genetics - average risks

- If either mother or father has diabetes increases risk of diabetes by 15%
- If both mother and father have diabetes increases risk by 75%
- If non-identical twin has diabetes increases risk by 10%
- If identical twin has diabetes increases risk by 90%

Some other forms of diabetes may be directly inherited, including maturity onset diabetes in the young (MODY) and diabetes due to mitochondrial DNA mutation.

However, neither type 1 or type 2 diabetes may be entirely genetically determined.

Experts believe that environmental factors act as either 'initiators' or 'accelerators.'

Several genes are known as susceptibility genes, meaning that if an individual is carrying this gene they face greater risk of developing diabetes.

Similarly, other genes provide greater immune tolerance for non-diabetics

Is Type 2 Diabetes Caused By Genetics?

Several factors have to come together for a person to develop type 2 diabetes. Elements like nutrition and exercise are extremely important. However, type 2 diabetes also has a strong hereditary component.

If you have recently been diagnosed with type 2 diabetes, look around. There is a good chance that you're not the first person with diabetes in your family. According to American Diabetes Association, your risk of developing type 2 diabetes is:

- One in seven, if one of your parents was diagnosed before the age of 50.
- One in 13, if one of your parents was diagnosed after the age of 50.

- One in two, if both your parents have diabetes

However, not all of your type 2 diabetes risk is genetic. Major risk factors for type 2 diabetes also include obesity and a sedentary lifestyle.

That said, several gene mutations have been associated with type 2 diabetes risk. None of these genes cause diabetes on their own. Instead, they interact with environmental factors — for instance, toxins, viruses, and foods — and each other to increase your risk.

The Role of Heredity in Type 2 Diabetes

Type 2 diabetes is caused by both genetic and environmental factors. Understanding the role of genetics requires looking at other factors as well.

Genetic Mutations

Scientists have linked several gene mutations to a higher diabetes risk. Not everyone who carries a mutation will get diabetes. However, many people with diabetes have one or more of these mutations.

Lifestyle and Family Inheritance

It can be difficult to separate lifestyle risk from genetic risk. Lifestyle choices tend to run in the family. Sedentary parents tend to have sedentary children. Parents with unhealthy eating habits are likely to pass them on to the next generation. On the other hand, genetics play a big part in determining weight. Sometimes behaviors can't take all the blame.

Identifying the Genes Responsible for Type 2 Diabetes

Studies of twins have shown that type 2 diabetes might be influenced by genetics, according to the American Diabetes Association. However, these studies were complicated by the environmental influences that also affect type 2 diabetes risk.

Still, scientists have persevered. To date, numerous mutations have been shown to affect type 2 diabetes risk. The contribution of each gene is generally small. However, each additional mutation you have seems to increase your risk.

In general, mutations in any gene involved in glucose regulation can affect your risk of type 2 diabetes. These include genes that control:

- Production of glucose
- Production of insulin
- How glucose levels are sensed in the body
- Regulation of insulin

Genes that have been associated with type 2 diabetes risk include:

- TCF7L2, which affects insulin secretion and glucose production
- The sulfonylurea urea receptor (ABCC8), which helps regulate insulin
- Calpain 10, which is associated with type 2 diabetes risk in Mexican Americans
- Glucose transporter 2 (GLUT2), which helps move glucose into the pancreas
- The glucagon receptor (GCGR), a glucagon hormone involved in glucose regulation

Genetic Testing for Type 2 Diabetes

Tests are available for some of the gene mutations associated with type 2 diabetes. However, the risk increase for any given mutation is small. Other factors are far more accurate

predictors of whether you'll develop type 2 diabetes, including:

- Body mass index (BMI)
- Family history
- High blood pressure elevated triglycerides and cholesterol levels
- History of gestational diabetes

Focusing on Prevention

The interactions between genetics and the environment make it hard to get a handle on the true cause of type 2 diabetes. That doesn't mean you can't reduce your risk. Strong evidence supports the fact that behavioral changes can reduce your risk of developing type 2 diabetes.

Diabetes Prevention Program study, a large study of people at high risk for diabetes, suggested that weight loss and increased physical activity can prevent or delay type 2 diabetes. Blood glucose levels return to normal level in some cases.

Although the genes you inherit may influence the development of type 2 diabetes, they take a back seat to behavioral and lifestyle factors. Data from the Nurses' Health Study suggest that 90 percent of type 2 diabetes in women can be attributed to five such factors: excess weight, lack of exercise, a less-than-healthy diet, smoking, and abstaining from alcohol.

Among 85,000 married female nurses, 3,300 developed type 2 diabetes over a 16-year period. Women in the low-risk group were 90 percent less likely to have developed diabetes than the rest of the women. Low-risk meant a healthy weight (body mass index less than 25), a healthy diet, 30 minutes or more of exercise daily, no smoking, and having about three alcoholic drinks per week.

Similar factors are at work in men. Data from the Health Professionals Follow-up Study indicate that a "Western" diet, levels in some cases.

Combined with lack of physical activity and excess weight, dramatically increases the risk of type 2 diabetes in men.

Information from several clinical trials strongly supports the idea that type 2 diabetes is preventable. The Diabetes Prevention Program examined the effect of weight loss and increased exercise on the development of type 2 diabetes among men and women with high blood sugar readings that hadn't yet crossed the line to diabetes. In the group assigned to weight loss and exercise, there were 58 percent fewer cases of diabetes after almost three years than in the group assigned to usual care. Even after the program to promote lifestyle changes ended, the benefits persisted: The risk of diabetes was reduced, albeit to a lesser degree, over 10 years. Similar results were seen in a Finnish study of weight loss, exercise, and dietary change, and in a Chinese study of exercise and dietary change.

Simple Steps to Lower Your Risk

Making a few lifestyle changes can dramatically lower the chances of developing type 2 diabetes. The same changes can also lower the chances of developing heart disease and some cancers.

Control Your Weight

Excess weight is the single most important cause of type 2 diabetes. Being overweight increases the chances of

developing type 2 diabetes seven fold. Being obese makes you 20 to 40 times more likely to develop diabetes than someone with a healthy weight.

Losing weight can help if your weight is above the healthy-weight range. Losing 7 to 10 percent of your current weight can cut your chances of developing type 2 diabetes in half.

Get Moving—and Turn Off the Television

Inactivity promotes type 2 diabetes. Working your muscles more often and making them work harder improves their ability to use insulin and absorb glucose. This puts less stress on your insulin-making cells.

Long bouts of hot, sweaty exercise aren't necessary to reap this benefit. Findings from the Nurses' Health Study and Health Professionals Follow-up Study suggest that walking briskly for a half hour every day reduces the risk of developing type 2 diabetes by 30 percent. More recently, The Black Women's Health Study reported similar diabetes-prevention benefits for brisk walking of more than 5 hours per week. This amount of exercise has a variety of other benefits as well. And even greater cardiovascular and other advantages can be attained by more, and more intense, exercise.

Television-watching appears to be an especially-detrimental form of inactivity: Every two hours you spend watching TV instead of pursuing something more active increases the chances of developing diabetes by 20 percent; it also increases the risk of heart disease (15 percent) and early death (13 percent). The more television people watch, the more likely they are to be overweight or obese, and this seems to explain part of the TV viewing-diabetes link. The unhealthy diet patterns associated with TV watching may also explain some of this relationship.

Tune Up Your Diet

Four dietary changes can have a big impact on the risk of type 2 diabetes.

1. Choose whole grains and whole grain products over highly processed carbohydrates.

There is convincing evidence that diets rich in whole grains protect against diabetes, whereas diets rich in refined carbohydrates lead to increased risk. In the Nurses' Health Studies I and II, for example, researchers looked at the whole grain consumption of more than 160,000 women whose health and dietary habits were followed for up to 18 years. Women who averaged two to three servings of whole grains a day were 30 percent less likely to have developed type 2 diabetes than those who rarely ate whole grains. When the researchers combined these results with those of several other large studies, they found that eating an extra 2 servings of whole grains a day decreased the risk of type 2 diabetes by 21 percent.

4. Limit red meat and avoid processed meat; choose nuts, whole grains, poultry, or fish instead.

The evidence is growing stronger that eating red meat (beef, pork, lamb) and processed red meat (bacon, hot dogs, deli meats) increases the risk of diabetes, even among people who consume only small amounts. The latest support comes from a "meta analysis," or statistical summary, that combined findings from the long-running Nurses' Health Study I and II and the Health Professionals Follow-Up Study with those of six other long-term studies. The researchers looked at data

from roughly 440,000 people, about 28,000 of whom developed diabetes during the course of the study. They found that eating just one daily 3-ounce serving of red meat—say, a steak that's about the size of a deck of cards—increased the risk of type 2 diabetes by 20 percent. Eating even smaller amounts of processed red meat each day—just two slices of bacon, one hot dog, or the like—increased diabetes risk by 51 percent.

The good news from this study: Swapping out red meat or processed red meat for a healthier protein source, such as nuts, low-fat dairy, poultry, or fish, or for whole grains lowered diabetes risk by up to 35 percent. Not surprisingly, the greatest reductions in risk came from ditching processed red meat.

Why do red meat and processed red meat appear to boost diabetes risk? It may be that the high iron content of red meat diminishes insulin's effectiveness or damages the cells that produce insulin; the high levels of sodium and nitrites (preservatives) in processed red meats may also be to blame. Red and processed meats are a hallmark of the unhealthy "Western" dietary pattern, which seems to trigger diabetes in people who are already at genetic risk.

If You Smoke, Try to Quit

Add type 2 diabetes to the long list of health problems linked with smoking. Smokers are roughly 50 percent more likely to develop diabetes than nonsmokers, and heavy smokers have an even higher risk.

Alcohol Now and Then May Help

A growing body of evidence links moderate alcohol consumption with reduced risk of heart disease. The same may be true for type 2 diabetes. Moderate amounts of alcohol—up to a drink a day for women, up to two drinks a day for men—increases the efficiency of insulin at getting glucose inside cells. And some studies indicate that moderate alcohol consumption decreases the risk of type 2 diabetes. If you already drink alcohol, the key is to keep your consumption in the moderate range, as higher amounts of alcohol could increase diabetes risk. If you don't drink alcohol, there's no need to start—you can get the same benefits by losing weight, exercising more, and changing your eating patterns.

Hyperglycemia and diabetic complications

Type 2 diabetes (T2D) is a complex, multifactorial, metabolic disorder characterized by impaired insulin secretion and action, which ultimately lead to chronic hyperglycemia (Lyssenko et al. 2008). Chronic hyperglycemia is associated with increased risk of progression to micro- (nephropathy, retinopathy and neuropathy) and macrovascular complications (cardiovascular disease (CVD)) of diabetes. Several studies have suggested the preventive effect of controlling blood glucose on developing microvascular complications (The Diabetes Control and Complications Trial Research Group 1993; UK Prospective Diabetes Study (UKPDS) 1998; Aiello and Group 2014; Di Landro et al. 1998). Although it is commonly believed that hyperglycemia induces damage to the particular cell subtypes, e.g., mesangial cells in the renal glomerulus, capillary endothelial cells in the retina, and neurons and Schwann cells in peripheral nerves, the exact mechanisms underlying these damaging defects are not yet well understood.

Hyperglycemia and microvascular complications

Glycated hemoglobin and duration of the disease are known to be the major risk factors associated with progression to diabetic complications (Pirart 1977; Stolar 2010). The Diabetes Control and Complication Trial (DCCT) (The Diabetes Control and Complications Trial Research Group 1993) and United Kingdom Prospective Diabetes Study (UKPDS) (Skyler 1996) demonstrated a clear association between HbA1c and development of microvascular complications in patients with T2D. There are several hypotheses on mechanisms responsible for the development of hyperglycemia-induced micro- and macrovascular complications. The main hypothesis involves the increased flux into the aldose reductase (AR) or polyol pathways due to the increased intracellular glucose concentrations. AR is upregulated as a result of hyperglycemia and catalyzes conversion of glucose to sorbitol, which later oxidizes to fructose. Activation of the AR and polyol pathways increases consumption of NADPH and leads in depletion of glutathione (GSH), which is one of the main antioxidant mechanisms in the cell (Brownlee 2001). As a result, the cells exert increased susceptibility to oxidative stress. AR is highly expressed in the lens compared with other tissues. Sorbitol is also believed to contribute to development of cataract (Kinoshita 1974) and osmotic vascular damage (Gabbay 1975) in the microvascular cells. Other suggested mechanisms involve increased formation of reactive oxygen species (ROS) and advanced glycation end product (AGE), increased flux into the hexosamine pathway and activation of the protein kinase C (PKC) pathway (Sheetz and King 2002)

CONCLUSION

The field of genetics of diabetic complications is still in its infancy, and most of the genetic associations reported in the literature were not reproducible in different populations. In contrast to the immense progress made in genetic discoveries in the field of both T1D and T2D, most of the studies aiming at dissecting genetic factors of diabetic complications had modest sample size and therefore were underpowered to reproducibly report genetic effects at genome-wide significance level. However, a substantial amount of work has already been done and a number of large GWAS meta-analyses are now on their way. Also phenotypic variation in the definition of diabetic microvascular complications as well as extent to which contributing pathophysiological mechanisms are similar among different ethnicities may, in part, explain lack of the results reproducibility. A new genetic approach (integrative genomics studies) will be greatly helpful for understanding the heterogeneity of diabetic complications. Integrative genomic methodologies are supported by the basic hypothesis that polymorphisms (non-disease causing genetic variation) and/or mutations in or near genes have an effect on the expression of the causative gene and are also associated with the trait under study. It is possible for a gene to have a coding mutation, which may affect protein function, but not directly influence gene expression, and could thus escape detection. Performing integrate studies on different layers of DNA and RNA sequences of the genome, epigenetic modifications (DNA methylation and histone modification),

proteomics, metabolomics and other biomarkers will aid in identification of genetic markers (Ware et al. 2013). In conclusion, until now only a handful number of genetic variants were reported to be associated with either nephropathy (ACE, ELMO1, FRMD3, and AKR1B1) or retinopathy (VEGF, AKR1B1, and EPO), and only a few studies were carried out for genetic susceptibility to CVD (ADIPOQ, GLUL) in patients with diabetes. It is, therefore, obvious that the accumulation of more data from larger studies and better phenotypically

Characterized cohorts is needed to facilitates genetic discoveries and unravel novel insights into the Pathogenesis of diabetic complication

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REFERENCES

1. American Diabetes A. Economic Costs of Diabetes in the U.S. in 2007. *Diabetes Care*. 2008; 31:596-615
2. Narayan KMV, Boyle JP, Geiss LS, Saaddine JB, Thompson TJ. Impact of Recent Increase in Incidence on Future Diabetes Burden: U.S., 2005-2050. *Diabetes Care*. 2006; 29:2114-2116.
3. Shaw JE, Sicree RA, Zimmet PZ. Global estimates of the prevalence of diabetes for 2010 and 2030. *Diabetes Res Clin Pract*. 2010; 87:4-14.
4. Centers for Disease Control and Prevention. Deaths: Preliminary Data for 2008 (PDF). Released December, 2010.
5. National Diabetes Statistics fact sheet: general information and national estimates on diabetes in the United States. U.S. Department of Health and Human Services, National Institute of Health.
6. Search for Diabetes in Youth Study Group. The Burden of Diabetes Mellitus Among US Youth: Prevalence Estimates From the SEARCH for Diabetes in Youth Study. *Pediatrics*. 2006; 118:1510-1518.
7. Total prevalence of diabetes & pre-diabetes. American Diabetes Association.
8. Hu FB, Manson JE, Stampfer MJ, et al. Diet, lifestyle, and the risk of type 2 diabetes mellitus in women. *N Engl J Med*. 2001; 345:790-7.
9. Van Dam RM, Rimm EB, Willett WC, Stampfer MJ, Hu FB. Dietary patterns and risk for type 2 diabetes mellitus in U.S. men. *Ann Intern Med*. 2002; 136:201-9.
10. Knowler WC, Barrett-Connor E, Fowler SE, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med*. 2002; 346:393-403.
11. Knowler WC, Fowler SE, Hamman RF, et al. 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet*. 2009; 374:1677-86.

12. Tuomilehto J, Lindstrom J, Eriksson JG, et al. Prevention of type 2 diabetes mellitus by changes in lifestyle among subjects with impaired glucose tolerance. *N Engl J Med.* 2001; 344:1343-50.
13. Lindstrom J, Ilanne-Parikka P, Peltonen M, et al. Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet.* 2006; 368:1673-9.
14. Pan XR, Li GW, Hu YH, et al. Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. *Diabetes Care.* 1997; 20:537-44.
15. Li G, Zhang P, Wang J, et al. The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet.* 2008; 371:1783-9.
16. Rana JS, Li TY, Manson JE, Hu FB. Adiposity Compared With Physical Inactivity and Risk of Type 2 Diabetes in Women. *Diabetes Care.* 2007; 30:53-58.
17. Grøntved A, Hu FB. Television viewing and risk of type 2 diabetes, cardiovascular disease, and all-cause mortality: a meta-analysis. *JAMA.* 2011; 305:2448-55.
18. Tanasescu M, Leitzmann MF, Rimm EB, Hu FB. Physical activity in relation to cardiovascular disease and total mortality among men with type 2 diabetes. *Circulation.* 2003.
19. Hu FB, Sigal RJ, Rich-Edwards JW, et al. Walking compared with vigorous physical activity and risk of type 2 diabetes in women: a prospective study. *JAMA.* 1999; 282:1433-9.
20. Krishnan S, Rosenberg L, Palmer JR. Physical activity and television watching in relation to risk of type 2 diabetes: the Black Women's Health Study. *Am J Epidemiol.* 2009; 169:428-34.
21. de Munter JS, Hu FB, Spiegelman D, Franz M, van Dam RM. Whole grain, bran, and germ intake and risk of type 2 diabetes: a prospective cohort study and systematic review. *PLoS Med.* 2007; 4:e261.
22. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA.* 2002; 287:2414-23.
23. Villegas R, Liu S, Gao Y-T, et al. Prospective Study of Dietary Carbohydrates, Glycemic Index, Glycemic Load, and Incidence of Type 2 Diabetes Mellitus in Middle-aged Chinese Women. *Arch Intern Med.* 2007; 167:2310-2316.
24. Krishnan S, Rosenberg L, Singer M, et al. Glycemic Index, Glycemic Load, and Cereal Fiber Intake and Risk of Type 2 Diabetes in US Black Women. *Arch Intern Med.* 2007; 167:2304-2309.
25. Sun Q, Spiegelman D, van Dam RM, et al. White rice, brown rice, and risk of type 2 diabetes in US men and women. *Arch Intern Med.* 2010; 170:961-9.
26. Schulze MB, Manson JE, Ludwig DS, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA.* 2004; 292:927-34.
27. Malik VS, Popkin BM, Bray GA, Després JP, Willett WC, Hu FB. Sugar-sweetened beverages and risk of metabolic syndrome and type 2 diabetes: a meta-analysis. *Diabetes Care.* 2010;33:2477-83.
28. Palmer JR, Boggs DA, Krishnan S, Hu FB, Singer M, Rosenberg L. Sugar-sweetened beverages and incidence of type 2 diabetes mellitus in African American women. *Arch of Intern Med.* 2008; 168:1487-1492.
29. Ludwig DS, Peterson KE, Gortmaker SL. Relation between consumption of sugar-sweetened drinks and childhood obesity: a prospective, observational analysis. *Lancet.* 2001; 357:505-508.
30. Vartanian LR, Schwartz MB, Brownell KD. Effects of soft drink consumption on nutrition and health: a systematic review and meta-analysis. *Am J Public Health.* 2007; 97:667-75.
31. Am I at risk for type 2 diabetes? (2014, July 9). Retrieved from <http://diabetes.niddk.nih.gov/dm/pubs/riskfortype2>
32. Dean, L., & McEntyre, J. (2004). The genetic landscape of diabetes. National Center for Biotechnology Information, chapter 3. Retrieved from <http://www.ncbi.nlm.nih.gov/books/NBK1668/>
33. Genetics of diabetes. (2014, May 20). Retrieved from <http://www.diabetes.org/diabetes-basics/genetics-of-diabetes.html>
34. National diabetes statistics report, 2014. (2014). Retrieved from <http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf>
35. Walston, J., Silver, K., Bogardus, C., Knowler, W. C., Celi, F. S., Auston, S., Shuldiner, A. R. (1995, August 10). Time of onset of non-insulin dependent diabetes mellitus and genetic variation in the B(3)-adrenergic receptor gene [Full article]. *New England Journal of Medicine*, 333(343-347). Retrieved from <http://www.nejm.org/doi/full/10.1056/NEJM199508103330603#t=articleTop>

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