The Dutch Hunger Winter: Epigenetic Effects on Metabolic and Heart Health

by
Kuei-Chiu Chen
Premedical Education
Weill Cornell Medical College–Qatar

Preparation

Videos

To prepare for this case study, watch the following two videos to learn about the basics of diabetes.

- *What Is Diabetes?*
  This video focuses on type 1 diabetes in children. Running time: 4:11 min. Produced by Phoenix Children's Hospital, 2018. <https://youtu.be/9tvD2sMl9hI>
- *Pathophysiology – Type II Diabetes*
  This video focuses on type 2 diabetes and covers the concept of insulin resistance. Running time: 7:43 min. Produced by Matthew McPheeters for Khan Academy, 2015. <https://youtu.be/RlLrvnnTDDU>

Questions

Find a body mass index chart to answer the following questions. Bring your chart to class for discussion.

1. What is considered a normal range of birth weight in pounds?

2. Convert the weights from pounds to grams and record it here:

Reading

Since the beginning of the 20th century it has been noticed that diabetes, particularly type 2 diabetes, is very common in various parts of the world. Being a devasting disease, the prevalence of type 2 diabetes in many populations has raised the question about why it exists in human populations. There are three main hypotheses to explain its occurrence in human populations.

Thrifty Genotype Hypothesis

Proponents of the thrifty genotype hypothesis (Neel, 1962) suggest that type 2 diabetes occurs in a non-random fashion and has a genetic basis. The argument is that the long history of human evolution as hunter-gatherer involved cycles of feast or famine (Neel, 1962). Certain genotypes perhaps provided protection in being efficient in fat storage when food availability was uncertain. Civilization has made food availability much more stable and the change in the environment has caused the thrifty genotype to lose its advantage and instead leads to diabetes when the diet is

abruptly switched to one that is high in calories. The mismatch of the thrifty genotype in civilized societies is similar to sickle cell disease in places where there is no malaria (Neel, 1962). More recently, studies that support this hypothesis cite evidence from many indigenous populations that switched over to the more "Western lifestyle" (e.g., as reviewed by Diamond, 2003). This includes evidence from the observation of high (100%) concordance of type 2 diabetes in identical twins compared to much lower (20%) in fraternal twins (Diamond, 2003). With the advent of genome-wide association studies (GWAS) many attempts have been made to identify the thrifty gene(s), as reviewed by Sandholt *et al.* (2012). However, despite at least 36 gene variants having shown statistically significant association with type 2 diabetes, their collective impact can only explain about 10% of the heritability of the disease (Herder & Roden, 2011), making the role that genes play in the clinical relevance of type 2 diabetes very low (Marullo *et al.*, 2014).

Thrifty Phenotype Hypothesis

A few decades after the thrifty genotype hypothesis was proposed, the thrifty phenotype hypothesis (Hales & Barker, 1992) was set forward to instead draw connections between *in utero* and infant nutritional conditions with type 2 diabetes. Specifically, this hypothesis suggests that low nutrition availability during early stages of growth hinders the development of beta-cells in the islets of Langerhans and possibly innervation in the pancreas (Hales & Barker, 2001). This consequently reduces the capacity of insulin secretion and insulin response, leading to impaired glucose tolerance. If combined with obesity and physical inactivity the early deficiency of nutrition becomes the predictor of type 2 diabetes later in life (Hales & Barker, 2001). Children exposed to maternal undernutrition often have lower than normal birthweights. This would not impact the metabolic health if the individual maintains a lower body weight. However, type 2 diabetes may be triggered by obesity through excessive caloric intake and inactive lifestyle in these individuals.

The thrifty phenotype hypothesis, when compared to the thrifty genotype hypothesis, reignited the nature-versus-nurture debate by emphasizing developmental plasticity from fetal and infantile exposure to environmentally induced effects rather than predisposition at the genetic level. The direct impact of nutrition in early life stages on adult health has been supported in many studies, linking poor nutrition to a plethora of adult diseases, including impacts on both physical and mental health. Overall, these studies have expanded the connections between environmental conditions in early stages of growth and the phenotypes of adults and demonstrated the phenotypic plasticity resulting from exposure or experience during the development of the individuals.

Thrifty Epigenotype Hypothesis

Despite the strong association and plausible causality between the environment and the phenotype suggested in many studies, the underlying mechanisms for the thrifty phenotype remain unanswered. This includes diabetes and other health issues in those conceived during the Dutch famine (e.g., Lumey *et al.*, 2007). While examining the possible underlying mechanism for this fetal programming it was noticed that differential methylation at a few critical genes coding for transcription factors involved in fetal growth may have contributed to diabetes risks in the population (Heijmans *et al.*, 2008; Tobi *et al.*, 2009). Since the cause is connected to gene expression rather than the effect of nucleotide sequences, the thrifty epigenotype hypothesis was proposed (Stöger, 2008). This hypothesis connects specific cellular and molecular mechanisms to the thrifty phenotype (Demetriou *et al.,* 2015). Among the epigenetic mechanisms, methylation is the most studied, and in particular on genes involved in the regulation of cellular metabolism such as *IGF2* and mitochondrial genes (e.g., Jia *et al.*, 2013; Ding *et al.*, 2018).

It is advantageous for organisms to exhibit flexibility in phenotype as a response to the environment. However, this adaption did not anticipate a feast immediately following a famine. The mismatch of undernourishment early in life and nutritional excess in later life stages is an unintended evolutionary consequence that is at the core of the thrifty phenotype discussion. The most explored mechanism, DNA methylation, as well as histone modification have been supported in animal models for their role in the thrifty epigenotype (Sandovici *et al.,* 2011; Jiménez-Chillarón *et al.,* 2012).

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