

# On the Relationship of Diabetes and Sleep Apnea: Evolution and Epigenetics

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BSc honors

Molecular Biology

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## **Abstract**

Diabetes is the seventh leading cause of death in the United States today. Between sixty and ninety percent of diabetics also have sleep apnea. Although both sleep apnea and diabetes engender weight gain, the comorbidity of the two conditions is higher than can be explained by obesity alone.

In this study we explore the advantages of and evidence for the coevolution of diabetes and sleep apnea.

There is a metabolic shift that takes place when the cells of the heart need repair. Normally, hypoxic events cause a shift in heart-cell metabolism toward a high-glucose energy use. This shift mechanism is still fully functional in a diabetic heart cell, but because the underlying diabetes shifts the cellular metabolism to a primarily fatty-acid-based energy use, even a normally functioning hypoxia-induced cascade does not lead to full glucose metabolism or normal cellular repair.

So sleep apnea might serve a useful function in instigating heart tissue repair in cells. This suggests that sleep apnea and diabetes are not just frequently found together, but one condition may be causing the other.

After discussing some of the possible evolutionary drivers for co-adaptation of sleep apnea and diabetes, we examine some of the epigenetic marks associated with the two conditions, laying the groundwork for a better understanding of the underlying etiology.

## **Background I—Sleep Apnea and Diabetes**

Sleep apnea is a condition in which breathing stops during sleep, either because the brain is not correctly signaling the body to breathe (central sleep apnea, or CSA), or because of obstruction of the airway by the collapse of soft tissues, primarily the tongue, across the airway (obstructive sleep apnea, or OSA) (Lochan 2011). Sleep apnea is associated with high blood pressure, poor glucose control, obesity, heart disease and stroke. With so many negative consequences, why hasn't natural selection eliminated sleep apnea in the population? The strong correlation between sleep apnea and diabetes may provide some clues. Specifically, metabolic changes induced by sleep apnea may help counteract some of the damage from diabetes-induced hyperglycemia (high blood sugar). Indeed, a look at the literature reveals that patients with type I diabetes and patients with type II diabetes both experience a high rate of sleep apnea, and that this comorbidity is uncorrelated with obesity.

Mansor et al. (2016) describe a metabolic shift that takes place when the cells of the heart need repair, in their research on why the hearts of diabetic patients often fail to repair themselves at the same rate as those of nondiabetic patients. Normally, hypoxic events cause a shift in heart-cell metabolism toward a high-glucose energy use. Mansor et al. discovered that this shift mechanism is still fully functional in a diabetic heart cell, but because the underlying diabetes shifts the cellular metabolism to a primarily fatty-acid-based energy use, even a normally functioning hypoxia-induced cascade does not lead to full glucose metabolism or normal cellular repair. Hypoxic events can be caused by heart attacks or strokes, but also by temporary changes in breathing; if those breathing changes occur during sleep, they are classified as sleep-disordered breathing, or sleep apnea.

So sleep apnea might serve a useful function in instigating heart tissue repair in cells. That suggests that sleep apnea and diabetes are not just frequently found together: one condition may be causing the other.

We find other clues about this in the field of linguistics. The advent of fricatives in human speech corresponds with a softer diet, around the time of the first agricultural revolution (Blasi et al. 2019). Blasi et al. point out that softer foods can cause a difference in jaw development, leading to the modern human overbite and allowing fricatives such as "f" and "v" to enter human speech. Soft foods, such as grains (fermented and otherwise) and sweet fruit (more widely available when planted than when stumbled upon), would have been much more available after the first agricultural revolution than before. These soft foods are also much more likely to cause hyperglycemia, the primary diagnostic factor in diabetes.

Richard Wrangham theorizes that *Homo habilis*, *Homo erectus*, and *Homo neanderthalensis* all probably cooked some of their food (Wrangham 2017). That corresponds with smaller jaws and teeth in *Homo erectus* than in earlier hominids. So the final transition to talking came with the final transition to being dependent on cooking in the most recent hominids: *Homo sapiens*, also known as us.

Davidson et al. (2005) hypothesized that obstructive sleep apnea in humans is a side-effect of our capacity for speech. To evaluate this hypothesis, the authors recruited 123 men with sleep apnea and evaluated them for severity of sleep apnea; they also measured several areas between the face and pharynx/larynx corresponding to the human capacity for speech. They found a strong correlation between some of these measurements (especially cranial base angulation and laryngeal descent) and the severity of the subjects' sleep apnea; this correlation corroborates the theory that sleep apnea is a result of those same changes that allow speech.

So we see that paleoarcheological evidence in conjunction with modern research *allows* for the coevolution of sleep apnea and hyperglycemia in response to a softer, cooked diet, though of course it cannot *prove* any such thing.

### **Importance**

Diabetes is the seventh highest cause of death in the United States today. In addition, diabetes can cause nephropathy, neuropathy, retinopathy (including complete blindness), heart tissue damage, and loss of digits or even limbs. Sleep apnea causes significant loss of quality of life, as well as raising the risk of strokes, heart attacks, and car accidents. Whether or not sleep apnea and diabetes coevolved, knowing that these conditions are etiologically interactive could have a significant impact on the treatment of patients with either or both conditions.

### **Background II—Epigenetic Marks**

One place to look for evidence of etiological interaction is in the epigenome. Epigenetics is the study of heritable changes in gene expression that occur without alterations to the underlying DNA sequence. Epigenetic mechanisms regulate interactions between the genome and environmental factors such as infection and nutritional changes. The three primary epigenetic mechanisms currently being studied are DNA methylation, histone modifications, and noncoding RNAs.

DNA methylation is a covalent addition of a methyl group to the cytosine residues in CpG (5'-C-phosphate-G-3') dinucleotides. While hypomethylation of CpG islands is associated with gene activation, DNA methylation of promoter CpG islands is associated with gene repression. In addition to transcriptional regulation, DNA methylation is critical for maintaining genome integrity, most of the genome being highly methylated. DNA methylation is not a stable epigenetic modification; it changes throughout the lifespan of the organism, sometimes very rapidly, and dynamic DNA

methylation remodeling occurs during development and cell differentiation. DNA methylation is catalyzed by DNA methyltransferases (DNMTs): DNMT3A and DNMT3B are *de novo* methyltransferases. DNMT1 is involved in the maintenance of DNA methylation after replication. Hydroxymethylation via 10–11 translocase (Tet) is the main mechanism for demethylation.

Histone modifications alter chromatin compaction and the recruitment of transcriptional regulators, modifying gene expression. Histone modification primarily refers to the acetylation or methylation of the N-terminal tail of a histone. Histone acetylation on lysine residues leads to increased gene expression. H3K9ac, H3K14ac, and H4K5ac are all marks associated with active transcription. Histone methylation is more stable. Histone methylation can cause activation or repression of genes, depending on the location of histone modification. H3K36me<sub>2/3</sub> is transcriptionally active, but H3K9me<sub>3</sub> and H3K27me<sub>3</sub> are repressive marks. There are many families of histone-modifying enzymes, including histone deacetylases (HDACs), acetyltransferases (HATs), methyltransferases (HMTs), and demethylases.

Noncoding RNAs include small noncoding RNAs, also known as miRNAs, which are 21–25 nucleotides in length; the category of noncoding RNAs also includes long noncoding RNAs, or lncRNAs, which are more than 200 nucleotides in length. miRNAs can bind to the 3' untranslated region of target mRNA transcripts, disrupting translation or leading to degradation. miRNAs provide a rapid but reversible regulation of about 60% of protein-coding genes. lncRNAs can control mRNA degradation and, unlike miRNAs, can impact gene expression by means such as recruiting epigenetic modifier proteins (such as transcription factors).

## Overview

This paper will discuss possible rationale for the evolution and evolutionary retention of sleep apnea; possible evolutionary correlation between heart attacks, sleep

apnea, and diabetes; general concepts of epigenetics and epigenetic inheritance; and finally an analysis of the epigenetic marks and changes found in the conditions and their possible overlap. Data will be pulled from published literature and evaluated for evidence of epigenetic marks corresponding to these conditions. Epigenetic marks associated with each condition will be correlated to determine overlapping, counteracting, or cascading marks. Overlapping marks are those in which the same mark affects the same part of the genome in two conditions. Counteracting marks are those in which a mark associated with one condition (e.g. methylation at a particular locus) counteracts the effects of a mark associated with another condition (e.g. acetylation of a histone at that locus). Cascading marks are those in which a mark associated with one condition (e.g. a miRNA) triggers a change associated with another condition (e.g. down-regulation of a particular gene product). Learning more about epigenetic changes associated with diabetes and sleep apnea can help us better identify the underlying etiology of both conditions, which should lead to better disease management and improved patient outcomes.

### **Thesis committee and qualifications**

1. Dr. Steven Johnson, faculty advisor. Dr. Johnson studies epigenetics, primarily in *C. elegans*, in his lab here at BYU, where I have been working as a research assistant for the last two years.

2. Dr. Byron Adams, faculty reader. I started to notice the importance of the connections between diabetes and sleep apnea writing a paper for a class, "Evolutionary Medicine," which Dr. Adams was teaching.

3. R. Paul Evans, Honors Coordinator. I have taken three classes from Dr. Evans, and he is clearly very well qualified to mentor in this field.

IRB approval: Since I'm using already published data, IRB approval is unnecessary.



**Culminating experience**

I expect to share my research at the Roseman Symposium at Roseman University, and at the Utah Conference of Undergraduate Research at the University of Utah in Logan. I will take advantage of further presentation or publication opportunities as they arise.

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**September**

1. Write abstract
2. Submit proposal
3. Start building comparative data table

**October**

1. Continue working on comparative data table

**November**

1. November 1 Abstract submission deadline for UCUR (Utah Conference on Undergraduate Research)
2. November 8<sup>th</sup> thesis proposal deadline
3. November 25 UCUR notification of acceptance
4. November 25 UCUR Registration Opens

**December**

1. December 2 Roseman Symposium registration opens; submit application
2. Draft poster for thesis
3. Finish comparative data table
4. Write first draft of text

**January**

1. Write final draft of abstract
2. January 8 UCUR Registration Deadline

**February**

1. UCUR Conference: February 7, 2020
2. Feb 15<sup>th</sup> Graduation application deadline

**March**

1. March 28<sup>th</sup> Thesis poster due
2. Roseman symposium

**April**

1. April 23 Honors graduation ceremony

**May**

1. 15<sup>th</sup> Thesis defense information form due

**June**

1. 10<sup>th</sup> last day for thesis defense
2. 12<sup>th</sup> last day to submit thesis submission form
3. 18<sup>th</sup> University graduation date
4. 19<sup>th</sup> Thesis Final PDF due
5. 19<sup>th</sup> Thesis publication - printed and submitted to ScholarsArchive