Against the Grain: Diet and Alzheimer's Disease

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Alzheimer's disease (AD) is a progressive neurological disorder characterized by neurodegeneration and loss of cognitive functions. Although its etiology is not yet clear, evidence suggests that AD, diabetes, and obesity may share a common pathophysiology of disordered insulin signaling. Currently, there is growing evidence that hyperinsulinemia may play a key role in the development of AD, with some researchers dubbing it as "type 3 diabetes". This paper addresses the recent increasing incidence of AD by adopting an interdisciplinary approach that unites anthropological, biological, and psychological research to create a holistic understanding of how an evolutionary mismatch between our ancestral and current environment contributes to development of lifestyle diseases. Lastly, this paper discusses the theoretical implications of using nutritional therapy to treat cognitive symptoms of AD.

Keywords: Alzheimer's disease, insulin, carbohydrates, fat, diet, evolution

Alzheimer's disease (AD) is a neurodegenerative disease marked by impaired memory and cognitive deficits (Bird, 2014). Described as the pandemic of the 21s century (Jellinger, 2006), statistics indicate that around 24 million people in the world were afflicted with dementia in 2001, with predictions that numbers would rise to 42.3 million in 2020 and 81.1 million by 2040 (Ferri et al, 2005). The increasing prevalence of AD and an aging population has led many western countries prioritize it as a public health concern (Weiler, 1987).

Worryingly, statistics on other lifestyle diseases such as type 2 diabetes (T2D) and obesity are also rising. According to Statistics Canada (2016), approximately two million Canadians have (T2D) in 2014, an 8.4% increase from 2010. More than 14 million of adult Canadians are also either overweight or obese, an estimated 8% increase from 2010 (Statistics Canada, 2016). AD is highly comorbid with both diabetes and obesity (Profenno, Porsteinsson, & Faraone, 2010). Patients with T2D who have a history of multiple hypoglycemic episodes are also at an increased risk of developing dementia later in life (Whitmer, Karter, Yaffe, Quesenberry, & Selby, 2009). Metabolic syndrome, a set of risk factors for cardiovascular disease and diabetes, is also associated with late-onset dementia and AD (Frisardi et al, 2010). Currently, metabolic syndrome is diagnosed as having three of the following symptoms: High waist circumference, high plasma triglycerides, high fasting glucose, low high-density lipoprotein cholesterol, and high blood pressure (Alberti, Zimmet, & Shaw, 2005).

Notably, incidence of metabolic syndrome was relatively rare or almost absent in hunter-gather societies that followed a traditional diet (Cordain et al, 2005; Schaeffer, 1971; Trowell & Burkitt, 1980). Historical data indicates that such

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cultures were also free from common maladies such as dental cavities, myopia, gall bladder disease, acne, obesity, and cancer that were prevalent in European societies at the time (Cleave, 1974). Early observations classified such symptoms under the umbrella of "saccharine disease", noted for its association with a diet rich in refined starches and sugar (Cleave, 1974). Subsequent researchers adopted the term "syndrome X" or "diseases of civilization" to address the cluster of symptoms that were especially prevalent in western civilizations but relatively rare in traditional societies (Burkitt, 1973; Cleave, 1974; Reaven & Laws, 1999). Although the definition of metabolic syndrome has fluctuated over the years, its connection to a westernized diet remains robust. According to Schaeffer (1971), the development of diseases of civilization was directly associated with the westernization of dietary habits.

In light of both old and new research that invites insight into traditional lifestyle of hunter-gatherer societies, this paper proposes that the primary contribution to the increasing prevalence of AD and its sequelae of metabolic abnormalities is an evolutionary mismatch between our ancestral and modern food environment. Currently, research has investigated diabetes, obesity, and AD as separate but related constructs. This paper proposes that a common pathophysiology of dysregulated insulin signaling may unite each disease as different points on a single continuum of hyperinsulinemic disorders. Lastly, this paper discusses the therapeutic implications of using a low-carbohydrate diet to treat AD and its comorbid disorders.

Insulin and Diseases of Civilization

Lifestyle disease such as diabetes, obesity, and AD often occur sequentially and share a common pathophysiology of disordered insulin signaling. Insulin is a key hormone responsible for the partitioning of nutrients and energy (Ludwig, 2002). The pancreas releases insulin upon ingestion of a meal. There are many factors that determine how much insulin is secreted, one of which being the glycemic load of foods (Ludwig, 2002). The higher the glycemic load, the steeper the blood sugar rises, and more insulin secreted to bring it back down. Regular consumption of high glycemic load carbohydrates have been linked to increased risk for metabolic disorders such as: Cardiovascular disease (Liu et al, 2000), T2D (Krishnan et al, 2007), and obesity (Bell & Sears, 2003).

According to Cordain, Eades and Eades (2003), peripheral insulin resistance is the first stage in the development of T2D. T2D is an endocrine disorder featuring progressive deterioration of carbohydrate metabolism, usually over several years (Weyer, Bogardus, Mott, & Pratley, 1999). Researchers propose that a defect in insulin signaling marks the early stages of T2D (Pimenta et al, 1996), but the lack of longitudinal studies have made it difficult to pinpoint the exact temporal sequence of such deterioration (Weyer, Bogardus, Mott, & Pratley, 1999). Peripheral insulin resistance is the physiological condition in when peripheral tissues such as muscles, adipose tissues, and liver become unresponsive to insulin signaling. One possible cause for peripheral insulin resistance is insulin receptor downregulation in response to exposure to high concentrations of serum insulin (Khan & Flier, 2000), or hyperinsulinemia. To compensate for receptor downregulation, the pancreas secretes additional insulin to bring blood sugar back down (Cordain, Eades, & Eades, 2003). Although the organism will a maintain normal level of blood sugar as long as the pancreas is able to maintain this extra output of insulin, this state of "com-

pensatory hyperinsulinemia" (Cordain, Eades, & Eades, 2003) can lead to many metabolic abnormalities distributed throughout the body.

One consequence of hyperinsulinemia may be abnormal adipose growth in genetically susceptible individual. Obesity is a metabolic disorder characterized by excessive accumulation of fat tissue. Research indicates that patients with obesity also have elevated levels of basal insulin and exaggerated insulin response to food intake (Grey & Kipnis, 1971). As both obesity and T2D feature abnormal insulin signaling, the two may be sequentially related. In other words, obesity is the disorder in which adipose tissues remain insulin sensitive and grow disproportionately in response to elevated insulin levels. In turn, T2D is the latter stage in which insulin receptors in the peripheral tissues have downregulated to the effects of chronic hyperinsulinemia; the pancreas ceases to maintain the additional output of insulin, leaving blood sugar level pathologically elevated. Notably, both diabetes and obesity are comorbid with Alzheimer's disease (Profenno, Porsteinsson, & Faraone, 2010). People with abdominal obesity are three times more likely to develop dementia later in life, compared to people with a low waist circumference (Whitmer et al, 2008). As abdominal obesity is a marker for both glucose intolerance and insulin resistance (Després & Lemieux, 2006), this suggests that these three disorders may share a common causal mechanism that is also temporally related.

Chronic hyperinsulinemia may exert effects beyond diabetes and obesity. The brain uses glucose as its primary fuel source. The brain is also an insulin-sensitive organ, with distributed insulin receptors maintaining glucose metabolism and neuronal growth (Frölich et al, 1998). According to Craft and Watson (2004), peripheral insulin resistance may affect the functioning of the central nervous system. Additional research found that insulin crosses the blood-brain-barrier (Reinhardt & Bondy, 1994) and is involved in cognition, learning, memory (Biessels, Bravenboer, & Gispen, 2004). One connection between hyperinsulinemia and AD lies in the insulin-degrading enzyme (IDE) (Qiu & Folstein, 2006). According to Qiu and Folestein (2006), IDE is an enzyme that works on two substrates: insulin and amyloid-β peptide (Aβ). As amyloid-β peptide is neurotoxic, the role of IDE is to regulate its levels in the brain's neuronal and microglial cells (Qiu & Folstein, 2006). Qiu and Folstein hypothesized that hyperinsulinemia may promote pathogenesis of AD by disrupting the activity of IDE, as both insulin and Aβ competes for IDE. Further research points to that metformin, a common insulin-sensitizing drug used in T2D, improve cognitive symptoms in patients with AD (Alagiakrishnan, Sankaralingam, Ghosh, Mereu, & Senior, 2013).

Lastly, there is evidence showing that risk of cognitive decline does not only increase in patients with T2D, it also increases in patients with pre-diabetes and metabolic syndrome (Luchsinger, Tang, Shea, & Mayeux, 2004). One study on patients with type 1 diabetes found an inverse correlation between the number of hypoglycemic episodes and performance on cognitive tests such as reaction time (Langan, Deary, Hepburn, & Frier, 1991). As the brain depends on a steady supply of glucose transported through the blood-brain-barrier, maintaining glycemic homeostasis may be instrumental in preventing cognitive deficits commonly seen in patients with AD.

Diet and Evolution

Regular consumption of refined grains and sugar is a dietary anomaly for most of human evolutionary history. Indeed,

on an evolutionary time scale, the practice of agriculture and animal husbandry was introduced as recently as 10 000 years ago, an "eyeblink" compared to five to seven million years of hominin evolution (Wills, 2008, p.50). Food processing techniques that enabled the mass-production of sugar were introduced as recently as the Industrial Revolution (Yudkin, 1972). Indeed, evidence indicates that for most of human existence, sustenance was largely limited to low-glycemic foods such as wild plants and animals (Cordain et al, 2005).

In the human ancestral environments, insulin spikes are an adaptive response for appropriating energy storage, and this would have been a self-regulating cycle as most traditional diets featured a limited range of low-carbohydrate foods. Sugar intake would also have been limited to seasonal fruits, its glycemic impact reduced by fiber. Modern food processing techniques have disrupted this self-limiting cycle, making it possible to access sugar year-round in increasing quantities (Yudkin, 1972). To date, sugar and refined starches take up 36% of the calories consumed by the average American (Cordain, Eades, & Eades, 2003). Data indicates that sugar consumption in the U.S. had increased by 64% from 1909 to 1999 (Gerrior & Bente, 2002) – an unprecedented amount that would have been unthinkable to our hunter-gatherer ancestors.

Indeed, contrast to the "short, nasty, brutish" adage that has plagued the popular description of ancestral humans, paleontology research shows that most pre-agricultural societies lived on a diet that was ample in nutrients, such as iron, zinc, magnesium, and folate, and exhibited little to no chronic diseases observed in contemporary Western society (Cordain et al, 2002). Symptoms of metabolic syndrome were rare or entirely absent in native cultures who consumed a traditional low-carb, high-fat diet (Cleave, 1973; Fouche, 1923; Schaeffer, 1971). Indeed, anthropological research on the nomadic group Masai indicated that they enjoyed good health despite their largely carnivorous diet of high-fat diet of milk, blood, and meat (Orr & Gilks, 1931). The Eskimos, whose diet based on blubber and animal meat, were also free from symptoms of diabetes or coronary heart disease (Cleave, 1974). Incidence of cancer was also extremely rare in the native African populations that consumed a traditional, hunter-gatherer diet (Fouche, 1923). Symptoms of physical deterioration did not emerge until the native population settle in colonized areas and adopted a westernized diet predominant in flour and sugar (Schaeffer, 1971).

In contrast to modern dietary guidelines that recommend a low fat, plant-based diet to prevent age-related cognitive decline (Barnard et al, 2014), Crawford (1992) observed that both fat and protein were imperative for the massive growth in brain size during human evolution. Other research indicated that energy derived from meat and fat was important for maintaining the higher metabolic costs of bigger brains (Leonard, Robertson, Snodgrass, & Kuzawa, 2003; Aillo & Wheeler, 1995). Myelin is the fatty sheath that wraps around nerve cells to speed up neurotransmission. High levels of cholesterol are critical for myelin growth and maintenance (Saher et al, 2005). The most bioavailable sources of dietary cholesterol are in animal foods, such as egg yolks and liver (USDA Food Composition Database, 2016). Zinc, a trace mineral found predominately in animal foods, is also critical for normal neuronal development during gestation (Wallwork, 1986).This suggests that for most of human evolutionary history, an animal-based diet was integral in the evolution and development of complex human nervous systems.

In addition, a comparative anthropo-

logical analysis on the Masai and Kikyu tribe also revealed the former, whose diet was mainly carnivorous, consisted of relatively high intake of protein and calcium, averaged five inches taller than the Kikyu tribe, whose diet was mainly vegetarian, and subsisted on millet, legumes, and roots such as plantains (Orr & Gilks, 1931). Other research on hunter-gatherer diets indicates that despite geographic variation in carbohydrate ratios – ranging from 30% in tropical areas and 15% in high altitudes – they were all markedly lower than the 60% ratio recommended today (Strohl & Han, 2011). In sum, this suggests that the displacement of dietary protein and fat by grains and sugar in the westernized diet may have played a key role in the development of lifestyle diseases commonly observed today.

One common controversy in the relationship of AD and diet is the role of fat intake. When it comes to the association between diet and AD, the lipid-hypothesis has its evidence largely based on rodent models where high-fat diets is used to induce brain inflammation (Morrison et al, 2010; Panthan et al, 2008; Pistell et al, 2010). One limitation of contemporary AD research is the use of rodent models to simulate the effects of high-fat consumption in humans. Although animal models provide valuable insight into how diseases emerge, humans and mice have diverged considerably in their evolutionarily natural diets. Whereas humans have evolved to a mixed diet of protein and fat, rodents are opportunistic omnivores that have evolved to a high-carb diet of grains and cereal (Clark, 1982). As such, the dietary recommendations drawn from such experiments are limited in its application to humans.

Furthermore, research on human participants has shown that a low-carb diet provides an effective strategy for treating metabolic syndrome (Volek & Feinman, 2005). Because carbohydrates is one of the most insulinogenic macronutrient out of the three (Kopp, 2003), its reduction can help improve insulin sensitivity (Volek & Feinman, 2005). A low-carb diet was also more effective than a low-fat diet in inducing weight loss in patients with obesity (Samaha et al, 2003; Yancy, Olsen, Guyton, Bakst, & Westman, 2004). A low-carb, high fat ketogenic diet also holds promise for treating a variety of neurological disorders, including but not limited to dementia, epilepsy, and Alzheimer's disease (Rho & Stafstrom, 2012). The classic ketogenic diet is a high-fat diet with a 4:1 ratio of fat to carbohydrates, but therapeutic benefits were found with less restrictive forms such as a modified Atkins diet (Dhamija, Eckert, & Wirrell, 2013). The ketogenic diet works by restricting carbohydrates intake, inducing the body to enter a state of ketosis in which ketone bodies become the predominant energy source (Rho & Stafstrom, 2012). A ketogenic diet has found to improve memory performance in patients with AD (Reger et al, 2004). Although it is not yet clear how the ketogenic diet works, some possible mechanisms may involve ketone bodies' modulation of potassium channels (Ma, Berg & Yellen, 2007), and glutamate metabolism (Yudkoff et al, 2004).

Conclusion

The classic adage goes "Nothing in biology makes sense except in light of evolution" (Dobzhansky, 2013, p. 87). In other words, the use of evolutionary theory as a meta-framework can reveal important insights regarding human nutrition and etiology of diseases. The theory of evolution can be the "universal acid" (Dennet, 1995) that erodes the dogmatic barriers between disparate fields of scientific research, explaining ultimate causations that would not be possible otherwise. In light of new

research that has emerged over the last couple of decades, evidence suggests that hyperinsulinemia is the central component that underlies many of the chronic diseases associated with metabolic syndrome. Thus, it may be necessary to revise current nutrition guidelines to promote higher intake of fat in its natural forms, such as butter, cream, and coconut oil, in favour of processed carbohydrate such as grains, cereal, and bread.

Such policy revisions will be difficult to implement for four reasons. First, it requires a substantial revision of government nutritional guidelines that have become entrenched as official dogma over the last few decades. At the time of this writing, the current Canadian food guide is still recommending a diet based on a foundation of grains and cereals. Although a complete reversal may be unlikely, it may be helpful to increase public awareness about the glycemic index and empower them to make healthier choices.

Secondly, additional longitudinal studies may be necessary for fully investigating the causal links between diabetes, obesity, and AD. This methodological design may be problematic due to several reasons. Longitudinal studies are often costly and time-expensive. In addition, such study designs are vulnerable to volunteer bias – that is, patients with the most severe symptoms may be too sick to participate, thus leaving researchers to underestimate the potential relationship between T2D, obesity, and AD.

Thirdly, this would also require the medical system to shift toward a preventative and integrated model of care. Possible psychological interventions may include periodical cognitive screening for high-risk individuals, such as patients with T2D (Whitmer et al, 2008). Such measures ensure that patients in the prodromal phase of AD can be detected and benefit from early treatment. Other possibilities include integrated healthcare settings where psychologists, physicians, and dieticians work together to provide continuity of care.

Lastly, this would require psychology to shift toward a medical model in its practice. In other words, psychological interventions such as CBT may benefit from incorporating pharmacological and nutritional therapy in treating patients. Specifically, the use of CBT to treat anxiety and depression in patients with AD (Spector et al, 2014; Walker, 2004) may yield limited results as it neglects the physiological aspects of a diseased nervous system. For example, patients with uncontrolled hypoglycemia experience symptoms of anxiety and negative rumination (Wredling et al, 1992), not unlike a patient with generalized anxiety disorder. Such patients may benefit from using nutritional therapy to correct the underlying blood sugar fluctuations, rather than solely using CBT to target rumination symptoms. Of particular interest is also the connection between endogenous insulin resistances in patients with psychotic depression (Okamura et al, 2000). This suggests that psychological interventions that solely target the abnormal thought patterns and emotions associated with brain diseases, such as AD, may be insufficient for a therapeutic approach. Possible future intervention may include the addition of nutritional or pharmacological therapy to CBT for better patient outcomes.

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