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Mini Review

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Post-Meal Exercise may Attenuate the Glycemic Response to a Carbohydrate Load: Important Implications for Adults who are Obese, with Pre-Diabetes or Diabetes, and/or At-Risk for Dementia

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ABSTRACT

Obese individuals are at risk for insulin resistance and type 2 diabetes. Both obesity and diabetes are known risk factors for dementia, already a recognized global public health issue. Up to one-third of Alzheimer-type dementia may be attributed to potentially-modifiable risk factors such as the prevention of obesity and diabetes; physical exercise, particularly post-meal exercise, can play an important role in such prevention. This paper reviews research on the link between obesity and insulin resistance related to the conditions of pre-diabetes and diabetes, the consequences of elevated blood glucose (hyperglycemia) that result from a carbohydrate-rich diet and insulin resistance, the potential short and long term health consequences of elevated blood glucose, and the promising effects of post-meal exercise to stabilize blood glucose levels after consuming a carbohydrate load. Mitigating elevated blood glucose after consumption of snacks and meals in obese adults who are at-risk for, or who have diabetes, could improve glycemic control, decrease the need for medication (or decrease the dosages needed), delay the onset of long term complications of the diabetes, and decrease dementia risk. Further, facilitating stable levels of blood glucose in adults diagnosed with dementia through regular post-meal light exercise may positively affect mood and behavior, important aspects of dementia management, as well as physical health. If post-meal exercise does prove to effectively blunt the blood glucose spike after a meal, it could be a low-cost convenient method to prevent the damaging consequences of elevated blood glucose.

KEYWORDS: Diabetes; Dementia; Elevated blood glucose; Insulin resistance; Obesity; Post-meal exercise; Prevention.

ABBREVIATIONS: BG: Blood Glucose; OGTT: Oral Glucose Tolerance Test; HbA1c: Glycated Haemoglobin; IL-6: Interleukin-6; TNFα: Tumor necrosis factor alpha; CRP: C-reactive protein; ER: Endoplasmic Reticulum; ROS: Reactive Oxygen Species; AGEs: Advanced glycosylated end products; SFA: Saturated Fatty Acids; GI: Glycemic Index; GL: Glycemic Load; IDF: International Diabetes Federation; FFA: Free Fatty Acids; RBP4: Retinol-binding protein 4.

INTRODUCTION

Obesity, especially abdominal obesity, increases the risk for pre-diabetes and Type 2 Diabetes Mellitus (T2DM). Through changes in the microvascular and macrovascular systems, as well as inflammatory mechanisms, diabetes is a known risk factor for dementia, a progressive, neurological and life-limiting disease.[1-4] Midlife obesity is a further risk factor

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for developing dementia.[5,6] Thus, the rising tide of obesity, with its association with pre-diabetes and T2DM, has the potential to profoundly worsen the prevalence of dementia, already a recognized global public health issue.[7]

In 2012, 28 million Americans had T2DM, 86 million had pre-diabetes, and the prevalence of these conditions is increasing.[8] Pre-diabetes and diabetes are characterized by insulin resistance, in which case insulin is not optimally effective in inhibiting liver glycogenolysis (referred to as liver insulin resistance) or stimulating the transport of glucose from the circulation into skeletal muscle cells and adipocytes.[9-11] The end result of insulin resistance is elevated Blood Glucose (BG); hyperglycemia. Fasting BG, the Oral Glucose Tolerance Test (OGTT), and glycated hemoglobin (HbA1c) are used to diagnose pre-diabetes and diabetes. *Fasting* BG (measuring *plasma glucose* after not eating for at least 8 hours) is often the initial test done. The more substantial OGTT follows fasting BG and involves consumption of a beverage containing 75 gm of glucose with BG measured every 30 min for at least 2 hrs. The HbA1c test indicates a person's average blood glucose levels over the preceding 2-3 months. Blood test criteria to diagnose pre-diabetes and diabetes are shown in Table 1.

	HbA1c [A1C] (percent)	Fasting Plasma Glucose (mg/dL)	Oral Glucose Tolerance Test (mg/dL)
Diabetes	6.5 or above	126 or above	200 or above
Pre-diabetes	5.7 to 6.4	100 to 125	140 to 199
Normal	About 5	99 or below	139 or below

Definitions: mg: milligram; dL: deciliter
For all three tests, within the pre-diabetes range, the higher the test result, the greater the risk of diabetes.
Source: Adapted from American Diabetes Association. Standards of medical care in diabetes-2012. *Diabetes Care*. 2012; 35(Supp 1): S12, Table 2.
Table 1: Blood test levels for the diagnosis of diabetes and pre-diabetes.

Short-term consequences of hyperglycemia include fatigue, blurred vision, poor wound healing, increased thirst and urination, numbness or tingling in the extremities, and increased infections. Long-term complications of T2DM can be devastating, and include cardiovascular disease, retinopathy, neuropathy, and nephropathy, as well as cognitive decline.[12]

THE LINK BETWEEN OBESITY, INSULIN RESISTANCE, AND DEMENTIA

Obese individuals are at increased risk for insulin resistance for a number of reasons, and the mechanisms are described in an excellent review article by Qatanani and Lazar.[13] Greater fat mass results in elevated levels of Free Fatty Acids (FFA), which affect the circulating levels of the secreted hormones collectively called "adipokines." Laboratory studies have shown that the adipokine resistin and Retinol-binding protein 4 (RBP4) are elevated with obesity[14,15] although the role in humans is uncertain at this point.[13] In a recent review, Kiliaan and her colleagues[16] identified investigations that describe the role of adipokines in the link between obesity and dementia. These investigations suggest that obesity, through impaired cerebral blood flow, is associated with brain atrophy and deep (subcortical) hemispheric white matter changes that affect neurons, glia, vascular cells, the permeability of the blood-brain-barrier and the production of axonal myelin by oligodendrocyte cells in the brain. The investigations raise the possibility that adipokines contain important clues to transient or permanent cognitive decline as a result of impaired neurovascular structure and function. Small vessel (white matter) infarcts are strongly associated with diabetes, insulin resistance, and hyperlipidemia.[17] These micro-infarcts, along with micro-bleeds, increase dementia risk and are associated with reduced glucose uptake in the frontal lobe and cortical atrophy. Weight control and maintaining blood glucose at an optimal level are among the recommended strategies to control vascular risk factors, promote vascular health and lessen the risk for dementia.[17]

Adipocytes (cells that comprise fat tissue) also produce the hormone cortisol when cortisone, the inactive form, is converted to cortisol by the enzyme 11β-hydroxysteroid dehydrogenase type 1 (11βHSD1). Adipocyte 11βHSD1 levels are increased in obese humans and contribute to obesity-related insulin resistance, resulting in increased influx of cortisol to the liver *via* the portal vein.[18] This may partly explain why visceral fat is associated with increased insulin resistance. Of equal importance, increased levels of cortisol in cerebrospinal fluid have been associated with faster cognitive decline in adults with Mild Cognitive Impairment and Alzheimer-type dementia, reflecting hyperactivity of the hypothalamic-pituitary-adrenal axis. This hyperactivity may precede clinical symptoms of dementia, and may be a particular issue for adults who carry the APOE ε4 allele, a genetic risk factor for dementia.[19]

Adipose tissue is now recognized as an important and active part of the immune system.[20,21] Consistent, strong evidence indicates that obesity-related chronic inflammation is linked to insulin resistance,T2DM, and dementia.[22-25] Inflammatory markers (cytokines; often linked with adipokines and termed adipocytokines) including Interleukin-6 (IL-6), Tumor necrosis factor alpha (TNFα), and C-reactive protein (CRP) are elevated in obese, insulin resistant individuals, and increased levels of these inflammatory markers are predictive of the development of T2DM and other pathological conditions.[13] Macrophages, which generate and secrete inflammatory cytokines, accumulate in adipose tissue.[26] Interestingly, inhibition of macrophage infiltration in adipocytes of obese rodents reduces insulin resistance.[27,28]

Alterations in neurobiology in the obese may also contribute to insulin resistance. Circulating leptin (produced by adipocytes) and insulin (produced by the pancreas) levels are proportional to fat mass, and provide input to the regions of the hypothalamus involved in appetite regulation and substrate metabolism.[29,30] Both insulin and leptin receptors in the brain are necessary for normal insulin action.[31] Central administration of leptin in insulin resistant rodents attenuates insulin resistance,[32] and inhibition of hypothalamic insulin receptors results in liver

insulin resistance.[33]

Other possible explanations for the role of obesity in the development of insulin resistance include ectopic lipid storage in the liver and muscle, oxidative stress, and Endoplasmic Reticulum (ER) stress that suppresses insulin signaling.[13] Obesity also is associated with mitochondrial dysfunction that results in excessive intracellular lipid accumulation, excessive fat storage in liver and muscle tissue, increased fatty acid metabolites and Reactive Oxygen Species (ROS) that interfere with insulin signaling.

POTENTIAL HEALTH CONSEQUENCES OF ELEVATED BLOOD GLUCOSE: MECHANISMS

The health consequences associated with elevated Blood Glucose (BG) levels are well documented in the literature. Elevated BG levels increase the glycosylation of body proteins and lead to increased Advanced glycosylated end products (AGEs).[34-36] AGEs are associated with accelerated aging and the progression of numerous health conditions such as Alzheimer's disease, diabetes, cardiovascular disease, and stroke.[5-7,37-39] The consumption of sugar and refined carbohydrates results in BG elevation that is proportional to the accumulation of AGEs.[40]

Elevated blood glucose also can contribute to chronic inflammation.[41,42] Chronic inflammation is mediated by the immune system; cells of the immune system enter tissues and release chemicals that perpetuate the inflammatory state, resulting in damage to healthy tissues. A recent systematic review describes studies in which high glycemic load diets have been associated with higher concentrations of circulating inflammatory markers.[43] High blood glucose causes inflammation through several mechanisms that increase the production of free radicals and other pro-inflammatory chemicals. Chronic inflammation is associated with a number of chronic diseases, including cardiovascular disease, diabetes, cancer and Alzheimer's disease.[44-47]

Thus, prevention of T2DM is of utmost importance. For obese individuals, one of the recommendations to prevent pre-diabetes or progression to T2DM is to exercise at a moderate pace for at least 150 min per week.[48,49] It is well known that physical activity improves insulin sensitivity in both healthy and insulin resistant individuals.[50] However, compliance with current exercise recommendations is poor, with self-reported compliance rates of about 35% for those with T2DM.[51] Emerging evidence[52-59] suggests that a short bout of post-meal exercise in particular can attenuate the spike in BG after consumption of carbohydrates, which may be advantageous for those with and without diabetes, including those with dementia. Knowing that a short bout of exercise after consumption of a carbohydrate load could specifically decrease the spike in BG after carbohydrate consumption may be more motivating for compliance than exercising for general improvements in glycemic control.

Ideally, consumption of refined and simple carbohydrates would be avoided to prevent blood glucose spikes. However, it is difficult for many to restrict or eliminate such foods from the diet, especially in light of increasing evidence for sugar addiction.[60] Only about 50% of those with chronic illnesses adhere to recommended lifestyle changes.[61] Adherence rates to dietary recommendations in those with T2DM appear to be especially poor; a large multi-national study including North America, indicated a self-reported dietary adherence rate of 37% among those with T2DM.[51] Tan and colleagues found that only 16.4% of surveyed individuals with type 2 diabetes indicated they adhered to dietary regimens recommended by dietitians.[62] Vijan and colleagues found that people with type 2 diabetes rated strict diet as a major burden.[63] Moreover, adults with dementia tend to favor foods with simple carbohydrates, Saturated Fatty Acids (SFA) and simple sugars. Hsu and Kanoski[64] suggest that consumption of these foods can adversely affect the neuronal structure, plasticity, and function of the hippocampus, an area of the brain critically important for memory and learning. These investigators speculate that adverse effects result from elevated secretion of beta-amyloid in the small intestines, its increased circulation within the vascular system, and subsequent damage to the blood-brain-barrier. This in turn increases the vulnerability of the hippocampus to beta-amyloid build-up and other circulating toxins.

DIETARY CARBOHYDRATE AND BLOOD GLUCOSE LEVELS: CONSEQUENCES OF POST-MEAL HYPERGLYCEMIA

After consumption of a carbohydrate source, blood glucose levels rise, reaching a peak about 1hr after ingestion, but this peak could be 30-min to 2 hrs, depending on the composition, quantity, and timing of the meal or snack.[65] The pancreas releases insulin in response to an elevation in BG, which facilitates glucose entry into cells and glucose storage as glycogen in the liver, lowering BG to maintain glucose homeostasis. Some foods result in a slower rise and a lower peak of blood glucose than others. Glycemic Index (GI) reflects the degree to which different foods ingested in amounts that provide 50 gm carbohydrate increase blood glucose. Some prefer to consider foods in terms of Glycemic Load (GL) which is calculated as GI×grams of carbohydrate consumed/100.[66] Foods that are high in simple and refined carbohydrates have the highest GIs. Consumption of high GI foods results in higher and more rapid increases of blood glucose than lower glycemic index, which could influence inflammation and AGEs. Studies have shown that low glycemic index diets decrease inflammation and formation of AGEs.[40,41,67]

In a healthy individual, BG elevates no higher than 140 mg/dL after a carbohydrate load.[68,69] A value above that would be considered post-meal hyperglycemia. Post-meal hyperglycemia is very common in those with T2DM, but can occur before clinical diagnosis.[70] The International Diabetes Federation (IDF) has concluded that post-meal hyperglycemia is harmful, associated with increased risk for macrovascular disease, retinopathy,

cancer, impaired cognitive function in the elderly with T2DM, increased carotid intima-media thickness, decreased myocardial blood volume and blood flow, and increased oxidative stress, inflammation, and endothelial dysfunction.[70] Furthermore, the IDF contends that implementation of strategies to lower post-meal BG in those with post-meal hyperglycemia is important, but at this point, only low glycemic load diets and medications have been investigated as potentially effective strategies.

MITIGATING THE GLYCEMIC EFFECT OF FOOD WITH EXERCISE

In order to decrease inflammation and AGEs, limitation of high glycemic index foods in the diet would be ideal; however, implementation of this is difficult. Since some people may be unwilling or unable to limit their consumption of high GI foods, alternative means of blunting the BG spike of high glycemic index foods would be useful. Post-meal exercise may be one method for attenuating the BG increase associated with such foods. Glucose is a primary fuel for exercise and is used preferentially before fat stores are mobilized.[48] Insulin is necessary to stimulate the translocation of the GLUT4 glucose transport protein from inside the cell to the cell surface in order for glucose to enter a muscle cell in the rested state. Exercise stimulates the translocation of GLUT4 transport proteins without insulin, facilitating glucose uptake from the blood into cells.[48] Exercise plus insulin has an additive effect to some degree in the facilitation of glucose uptake by muscle cells. Previous research has shown that cycling (30 minutes at 70% maximum heart rate) blunts the BG spike after consumption of cornflakes (1 gm carbohydrate per kg body weight),[53] and another study[54] indicated that slow post-meal walking reduced the BG response to a meal of cornflakes (1 gm carbohydrate per kg body weight).Recent research determined that 30 min of light exercise (walking) reduced the blood glucose spike following consumption of a Milky Way candy bar, a typical snack, compared to the spike in BG that occurred when subjects sat after consuming the candy bar.[52]

The aforementioned studies were conducted with healthy subjects. In addition, Manohar and colleagues[55] found that light activity after meals blunted the glycemic response to meals in both healthy individuals and those with type 1 diabetes (the less common, but more severe type of diabetes in which the pancreas produces no insulin). Studies examining the effect of post-meal exercise on the glycemic response to a meal in those with pre-diabetes and T2DM have garnered similar results. A recent study indicated that short bouts of exercise after meals improved the 24hr glucose control (measured *via* continuous BG monitoring) in older individuals at high risk for impaired glucose tolerance (pre-diabetes).[56] Colberg and colleagues examined the effect of 20 min of moderate walking before or after meal consumption in individuals with T2DM.[57] They found that post-meal exercise resulted in lower plasma glucose levels at the end of exercise compared to values at the same time point when subjects had walked pre-meal. Additional studies found post-meal exercise (1 hour moderate exercise[58] or a short bout of intense exercise)[59] resulted in reduced hyperglycemia in those with T2DM; however, the exercise did not commence immediately after meal consumption. Additionally, subjects with higher pre-exercise BG levels in both studies benefited the most from post-meal exercise.

Although avoiding spikes in BG is important for people without diabetes, it is especially important for those with diabetes. It is well recognized that exercise in general improves insulin sensitivity[50] and can improve glycemic control (indicated by HbA1c) in people with type 2 diabetes.[71] HbA1c provides an indication of average BG levels over the previous 2-3 months. However, this test does not indicate if BG levels were relatively stable over that period of time, which would be ideal, or if the individuals experienced frequent peaks and valleys, which would be an unhealthy pattern. Mitigating spikes in BG after consumption of snacks and meals in people with diabetes could improve glycemic control, decrease the need for medication (or decrease the dosages needed), and delay the onset of the long term complications of diabetes. Further, facilitating stable levels of glucose in adults diagnosed with dementia through regular light exercise, particularly after meals, may positively affect mood and behavior, important aspects of dementia management, as well as physical health.[72]

CONCLUSION

Obese individuals, with or without cognitive impairment, are at risk for insulin resistance and T2DM. Post-meal hyperglycemia often precedes clinical diagnosis of the disease. Further, elevated BG in a person without diabetes may have adverse health consequences, as a diet high in refined carbohydrates and simple sugars is associated with increased accumulation of AGEs and greater levels of inflammatory markers. To date, the primary strategies to attenuate the spike in BG after a carbohydrate load have been low glycemic load diets and medication. However, low glycemic load diets can be difficult for many to adhere to, and avoidance of simple and refined carbohydrates at all times is not realistic for most. Thus, one approach to mitigate the post-meal spike in blood glucose after a carbohydrate load may be exercise commencing after consumption. Much additional research is needed to clarify the effect of post-meal exercise on the glycemic response to a carbohydrate load, including studies that examine different types, durations, and intensities of exercise, and studies that include obese subjects at-risk for insulin resistance as well as those with T2DM. In addition, the effect of mitigating the spike in BG after carbohydrate consumption on health outcomes needs to be further assessed. In a pivotal recent paper, Norton and colleagues[73] documented that up to one-third of Alzheimer-type dementia may be attributed to potentially-modifiable risk factors such as the prevention of obesity, vascular disease, and diabetes and stressed the importance of physical exercise. If post-meal exercise does prove to effectively blunt the BG spike after a meal, it could be a low-cost

convenient method to prevent the damaging consequences of elevated BG.

CONFLICTS OF INTERESTS

Both authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. No funding sources were involved in the development of this article.

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AUTHOR'S CONTRIBUTIONS

Associate Professor Heiss conceptualized and synthesized this review. Dr. Goldberg contributed her knowledge of issues in adults with dementia and contributed to the synthesis of the manuscript.

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