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Associations among Visceral Obesity, Type 2 Diabetes, and Dementia

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Abstract

Obesity is a recognized global epidemic. Obese individuals are at increased risk for type 2 diabetes mellitus (T2DM), and both obesity and diabetes are known risk factors for dementia, another global public health issue. This paper reviews research on the link between obesity, and dementia, with an emphasis on visceral obesity. Some obese individuals, the metabolically healthy obese, do not appear to be at increased risk from excess body fat, but most eventually become metabolically unhealthy over time. Accumulation of visceral fat appears to be particularly problematic. Visceral obesity results in increased free fatty acid delivery to the liver, which, in turn, increases insulin resistance. Visceral obesity is associated with increased inflammatory adipokines which can promote cardiovascular disease and dementia. In addition, a long term complication of T2DM is dementia, due to the vascular complications and increased inflammatory status associated with the disease. These issues highlight the need for health professionals to work to prevent and treat obesity, especially visceral obesity, to optimize health and decrease the likelihood of developing debilitating chronic diseases such as T2DM and dementia. The Mediterranean diet may be useful in decreasing inflammation and dementia risk. Other dietary factors that reduce inflammation, insulin resistance, and cardiovascular risk (and thus dementia) independent of weight loss are addressed.

Keywords: Dementia; Elevated blood glucose; Insulin resistance; Obesity; Type 2 diabetes mellitus; Visceral fat

Introduction

Obesity, a recognized global public health issue, is associated with an increased risk for a number of health problems, including the metabolic syndrome, insulin resistance, type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD, including hypertension, coronary heart disease, abnormal blood lipids, and stroke), gallstones, orthopaedic issues including osteoarthritis, some cancers, and respiratory issues, including sleep apnoea and hypoventilation syndrome [1]. Although not included in most of the classic lists of health risks of obesity, evidence now supports obesity as a risk factor for cognitive decline and dementia, as well [2,3].

However, there is debate regarding the degree to which obesity increases health risk among individuals. Some health professionals and counsellors are proponents of the Health at Any Size movement, and may underestimate the degree to which obesity can increase health risk. Some individuals may not be at increased health risk due to obesity, while others may be at significantly greater health risk. Specifically, the metabolically healthy obese (MHO) phenotype, which comprises an estimated 10% to 40% of obese individuals (depending on the definition used for metabolic status) [4,5] seems to defy the presumed health risks associated with obesity. In fact, individuals with the MHO phenotype do not appear to exhibit hypertension, increased inflammation, abnormal blood lipids or elevated fasting glucose as expected in the obese population [5].

Although some studies indicate a lower risk of adverse health outcomes in the MHO phenotype compared to the at-risk obese population, other studies indicate that those with the MHO phenotype are still at greater risk for CVD and mortality than the metabolically healthy non-obese. Hinnouho et al. [6] compared the risk of CVD and T2DM among the MHO and metabolically unhealthy obese (MUO) phenotypes, as well as metabolically healthy and unhealthy normal weight individuals using data from the Whitehall II cohort study, which included 7,122 subjects followed for an average of 17 years, and included adults ranging in age from 39-63 years. To be considered metabolically healthy, subjects had to have none or only one of the following criteria: high triglycerides or lipid-lowering drugs; elevated systolic blood pressure or diastolic blood pressure or anti-hypertensive drugs; high fasting glucose or medications for diabetes; and low HDL-cholesterol. Note that inflammatory markers and waist circumference were not included in the criteria. Results indicated that although MUO subjects were more likely to develop T2DM than MHO subjects (HR 1.98, 95% CI: 1.39–2.83), they were not at greater risk for developing CVD than MHO subjects. Furthermore, risk for T2DM (HR 3.25, 95% CI: 2.32–4.54) and CVD (HR 1.97, 95% CI: 1.38–2.80) was greater in the MHO group than the metabolically healthy non-obese

group. Kim et al. [7] found similar results in a 10-year longitudinal Korean Genome and Epidemiology Study, including 7,588 subjects without CVD or T2DM at the beginning of data collection. The same criteria to define metabolic health status were used as in the previously described study. Compared to the metabolically healthy normal weight group, both the metabolically unhealthy normal and MUO groups were at an increased risk for developing T2DM (HR 3.0, 95% CI: 2.5–3.6 and 4.0, 95% CI: 3.4–4.7, respectively) and CVD (HR 1.6, 95% CI: 1.3–2.0 and 1.9, CI: 1.5–2.4, respectively). The MHO group did have an increased risk for developing T2DM and CVD over the course of the study compared to metabolically healthy normal weight subjects, but the increased risk was small (HR 1.2 95% CI: 0.99–1.6, 1.4 95% CI: 0.99–1.8, respectively). Interestingly, those under age 45 at the beginning of this study had a higher risk for developing T2DM than those over 45 at the same study period. Furthermore, only approximately 15% of the MHO group remained metabolically healthy over the 10-year course of the study. However, since waist circumference and inflammatory markers were not included as metabolic risk factors, the percentage of MHO subjects who remained so may be an overestimate.

In a timely review, Roberson and colleagues [8] concluded that the cardiovascular and all-cause mortality risk for the MHO population was between the at-risk obese and the metabolically healthy non-obese. One problem with studies examining health risk of the MHO phenotype is the varying metabolic parameters used to define MHO. In any event, biochemical and physiological mechanisms that explain an increased health risk associated with obesity have been identified. The purpose of this commentary is to highlight the underlying mechanisms of the associations of obesity, particularly visceral obesity, T2DM, and dementia.

Defining Obesity

Although there is much controversy over the body mass index (BMI - weight in kg divided by height in m^2) as an indicator of adiposity, a BMI over 30 is generally accepted as the definition of obesity [9]. Clinical judgment must be used when assessing adiposity with BMI, as some with a large lean mass may be misclassified as obese by this definition. The National Institutes of Health, National Heart, Lung, and Blood Institute (NIH NHLBI) [9] further categorizes BMI as Class I (BMI 30-34.9), Class II (BMI 35-39.9), and Class III (BMI 40+) obesity, with health risk increasing with each class. Additionally, the organization classifies a waist circumference of over 35" for women and 40" for men as indicative of increased health risk due to excess abdominal fat. However, some suggest that waist circumference-to-height ratio may be a better indicator of abdominal obesity, as height corrects for errors in classification that may be incurred if a person is taller or shorter than average [10].

Subcutaneous *vs.* Visceral obesity

Adipose (fat) tissue located under the skin is referred to as subcutaneous body fat. This fat depot differs from adipose located in the abdominal cavity, which is in close proximity to internal organs. The fat depot within the peritoneum is referred to as intra-abdominal or visceral adipose tissue (VAT) [11].

Accumulation of excess adipose in the abdominal region is associated with a male hormone profile, and is often called central or "android" obesity, although women can certainly accumulate excess fat in this region, especially after menopause. Accumulation of excess fat subcutaneously is associated with a female body fat pattern and is often referred to as peripheral or "gynoid" obesity [11]. Some may accumulate fat in both regions, so although waist-to-hip ratio was used in the past to determine if one exhibited the android or gynoid body fat distribution, waist circumference alone is now used. This differentiation is important as intra-abdominal fat accumulation is associated with greater health risk than subcutaneous accumulation [9,11]. It is also important to note that waist circumference is an indirect measure of visceral fat mass, as it includes both visceral fat and subcutaneous fat in the abdominal area. CT and MRI scans can accurately measure visceral fat, but are not practical in clinical and community settings.

In the 1980s, researchers first noticed that there was a distinct difference between subcutaneous and intra-abdominal fat, and found that they posed different health risks. In fact, subcutaneous fat accumulation in physically active individuals was not found to be associated with the adverse metabolic parameters associated with increased health risk [12]. In contrast, central obesity was found to be associated with an increased risk for CVD and T2DM.

In terms of physiological differences between visceral and subcutaneous fat tissue, VAT has greater vasculature, a larger number of immune system cells, and more inflammatory cells. The fat cells are larger with more glucocorticoid and androgen receptors [11]. This fat depot contains monocytes that differentiate into macrophages. The macrophages may result in fat dysfunction including the secretion of excess free fatty acids, inflammatory markers (adipocytokines), and a decreased capacity to store fat in subcutaneous depots [13,14]. In addition, the visceral depot drains through the portal system directly to the liver. As VAT cells are more metabolically active and are able to generate more free fatty acids than subcutaneous fat, there is a greater influx of free fatty acids to the liver with increased VAT. According to Kihara and Matsuzawa [12], this influx of free fatty acids may increase hepatic lipid synthesis and promote insulin resistance, with potential end results including hyperlipidaemia, insulin resistance, glucose intolerance, CVD, and other chronic pathological conditions.

Visceral obesity, type 2 diabetes, and dementia

Obesity, especially abdominal obesity, is associated with an increased risk for chronic pathological conditions including pre-diabetes and T2DM, a known risk factor for dementia [3]. Obesity occurring at midlife (45-65 years) is also a known risk factor for dementia [3]. Thus, the chronic disease consequences of obesity, particularly visceral obesity, have the potential to profoundly worsen the prevalence of dementia, another recognized global public health issue [15].

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Increased understanding of the link between obesity, T2DM and dementia centres on the fact that adipose tissue is actively involved in the immune system and that there is a positive correlation of inflammatory adipokine levels with the amount of visceral fat [16,17]. Adipokines include the pro-inflammatory adipokines plasminogen activator inhibitor type 1 (PAI-1), tumor necrosis factor (TNF)-alpha, monocyte chemo attractant protein (MCP)-1, and resistin, which also have been associated with an increased risk for CVD. Adpiponectin, derived from VAT, is inversely correlated with the amount of VAT. Hypoadiponectin has been observed in those with T2DM and CVD [18-23]. The associations are complex but highlight the important role of obesity-related chronic inflammation.

Visceral fat is associated with increased insulin resistance, and the elevated blood glucose that is characteristic of T2DM also can contribute to the chronic inflammation that is associated with this disease, as well as CVD, cancer, and Alzheimer's disease [24-32]. Further investigations suggest that adipokines also may contain important information about cognitive decline as a result of their role in adverse obesity-related effects on the structure and function of cerebral arteries affecting blood flow to the brain, particularly blood flow deep within the brain [23]. Resultant neuronal damage and cerebral atrophy are characteristic of vascular dementia. Once considered rare, vascular dementia is now viewed as a major type of dementia that can co-occur with and compound the effects of Alzheimer's disease [33].

Prevention and treatment of obesity to reduce T2DM and dementia risk

Given the physiological mechanisms linking obesity to T2DM and dementia, effective modalities to prevent and treat obesity, especially abdominal obesity, should be employed. However, despite decades of public health campaigns, implementation of different treatment strategies including medically supervised programs, weight loss medications, weight loss surgery, as well as a vast array of commercial weight loss programs, the incidence of both obesity and T2DM has increased [34,35]. Obesity itself is a complicated health problem, with genetic, environmental, psychosocial, economic, medication, lifestyle, and other factors contributing. Long term treatment of obesity has been abysmal, with a high recidivism rate among those who lose weight [36] It is clear that a "one size fits all" approach to weight management will not be effective. Multidimensional efforts must continue to promote the prevention and treatment of obesity. As clinical investigators in the fields of nutrition and dementia, we agree with the recently released position statement on the prevention and treatment of obesity in adolescents by the American Academy of Paediatrics: that a focus on healthy lifestyle, rather than weight or restrictive dieting, is a desirable approach to address obesity that would translate to all age groups, minimize the stigmatization of obesity, reduce the likelihood of body image disturbances and weight obsession, and decrease the likelihood of chronic diseases such as T2DM and dementia [37].

Because a common thread in the link between obesity, T2DM, and the development of dementia is inflammation, lifestyle adjustments that reduce inflammation independent of weight loss might mitigate, to a degree, the risk of dementia due to visceral obesity and T2DM. The Mediterranean diet, emphasizing the consumption of fruits, vegetables, whole grains, nuts, and olive oil, while minimizing red meat and sweets has been shown to reduce the risk for dementia [38]. Scarmeas et al. found that in older adults, higher compliance to Mediterranean diet guidelines was associated with reduced risk of developing mild cognitive impairment and Alzheimer's disease over time [38]. In the Washington Heights–Inwood Columbia Aging Project (WHICAP) longitudinal study, adherence to the Mediterranean diet was scored using a validated method in 1,393 participants without cognitive impairment. Two hundred and seventy-five participants developed mild cognitive impairment in the follow-up period of 0.9-16.4 years. Compared with participants in the lowest diet adherence tertile, those in the highest tertile had a lower risk of developing mild cognitive impairment (HR 0.72; 95% CI: 0.52- 1.00). Of the 482 subjects with MCI at the beginning of data collection, 106 developed Alzheimer's disease during the follow-up period. Compared with participants in the lowest adherence tertile, subjects in the middle tertile had a 45% lower risk (HR 0.55; 95% CI: 0.34-0.90) and those in the highest tertile had 48% lower risk (HR 0.52; 95% CI: 0.30-0.91) of developing Alzheimer's disease.

One mechanism for the protective effect of the Mediterranean diet is reduced inflammation. Those with better adherence to the Mediterranean diet had lower markers of inflammation including lower CRP, IL-6, fibrinogen, and homocysteine levels than those with lower adherence in one study [39]. In addition to reducing inflammation, the Mediterranean diet has been associated with reduced blood glucose, insulin resistance, as well as vascular disease, [40] which may also explain why this diet may be brain-protective. In a randomized control trial of people with the metabolic syndrome, subjects following the Mediterranean diet for two years had significantly lower levels of the inflammatory markers IL-6, IL-18, and C-reactive protein than the control group, who were instructed to follow a "prudent" low fat diet. Insulin resistance was also lower in the Mediterranean diet group than the control group, and endothelial function improved in the Mediterranean diet group over the course of the study, but not in the control group. The high antioxidant content of the Mediterranean diet may also contribute to its protective effect [41].

If compliance with a special diet, such as the Mediterranean diet, is not feasible, modifications in diet or addition of supplements that reduce inflammation, oxidative stress, and protect vascular health may be more realistic. The omega-3 fatty acids docosohexanoic acid (DHA) and eicosopentanoic acid (EPA) are anti-inflammatory, [42] and can be increased in the diet via foods high in omega-3 fatty acids, such as high fat fish (DHA and EPA) or by omega-3 fatty acid supplements. Reducing the omega-6 to omega-3 fatty acid ratio in the diet, which is currently about 15-20:1 vs. the 1:1 ratio that human ancestors consumed, [43] would be a further strategy to reduce inflammation. Interestingly, the increase in omega-6 to omega-3 ratio has been linked to the increased prevalence of obesity over the past several decades by a variety of proposed mechanisms

[44]. An article from Oregon State University's Linus Pauling Institute Micronutrient Information Centre describes the anti-inflammatory effects of arginine, vitamins B-6, D, E, and C, magnesium, multivitamin supplements, carotenoids, flavonoids, and resveratrol, and a low glycaemic-index diet [45]. Dietitian generally recommend that nutrients be consumed in food form rather than as supplements, as nutrients may act differently in supplement vs. food form, so caution must be exercised when recommending supplements. Many of the dietary factors that reduce inflammation also reduce the risk for T2DM and cardiovascular disease. Ensuring adequacy of folate and vitamin B-12 aids in the prevention of hyperhomocysteinemia, and these vitamins have been implicated in brain health independently of their role in reducing levels of the inflammatory molecule homocysteine [45]. In a review of nutrition and cognitive function in the Linus Pauling Institute Micronutrient Information Centre, the author emphasizes that although nutrient deficiencies have been associated with compromised cognitive functioning, it remains unclear if vitamin/mineral supplementation is beneficial [46].

Conclusion

Some have suggested that obesity is not necessarily associated with increased health risk. Certainly, some individuals in the normal BMI range are metabolically unhealthy, as some in the obese range are metabolically healthy. Unfortunately, evidence is mounting that most metabolically healthy obese individuals eventually develop the metabolic parameters that increase health risk. The metabolism of VAT makes accumulation of intra-abdominal fat particularly damaging to health, including cognitive health. Individuals with abdominal obesity are at increased risk for insulin resistance and T2DM. Both obesity and elevated BG, characteristic of T2DM, result in increased inflammation which has the potential to facilitate the development of dementia. In addition, both obesity and T2DM increase the risk for CVD which could decrease cerebral blood flow, resulting in cognitive impairment, compounding the risk for dementia.

Thus, prevention of obesity and T2DM is important for decreasing the risk for many chronic diseases, including dementia. Health professionals need to be proactive about obesity prevention and treatment by informing people of the risks associated with obesity, stressing the importance of a healthy lifestyle, assisting individuals to find approaches that facilitate nutrition and behavioural changes that will promote healthy weight achievement, and regardless of weight status, recommending dietary strategies that are easy to implement to reduce the risk of developing T2DM and dementia.

Conflicts of Interest

Both authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper. No funding sources were directly involved in the development of this article. Dr Goldberg's work is supported by the JO and JR Wicking Trust.

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