Research
a dietetic practice group of the
eat right. American Dietetic Association

TheDigest

Endothelial Function and Obesity: What is the Connection?

Melanie Mott MS, RD

Introduction

Even in the age of increasing emphasis on preventive healthcare and advanced medicines and technology, cardiovascular disease (CVD) continues to be this nation's number one cause of death[1], making early detection crucial. One technique being used in research to provide early identification of arterial disease is the evaluation of the vascular endothelium. This single layer of cells plays an important role in maintaining homeostasis and normal physiological functioning of the vasculature. Endothelial cells produce a number of paracrine factors, including endothelium-derived nitric oxide (EDNO) that maintains vascular tone, inhibits platelet and cell adhesion, promotes fibrinolysis, and limits vascular proliferation[2]. Dysfunctional endothelium occurs when the normal mechanisms of the endothelial cells are lost, due to decreased nitric oxide bioavailability and/or reduced utilization of nitric oxide. This event is associated with the initiation and progression of arterial disease[3]. Research by our group and others has shown that the state of the endothelium provides prognostic information of future cardiovascular risk[2]. This link between endothelial dysfunction and arterial disease makes it an ideal target for prevention and detecting CVD.

The most popular method for measuring endothelial function is with the use of a high-resolution vascular ultrasound. EDNO is measured indirectly by occluding the brachial artery with a blood pressure cuff for five minutes. Once the blood pressure cuff is released, the resulting hyperemic blood flow causes nitric oxide to be released by the endothelium, creating vasodilation of the brachial artery. This change in brachial artery diameter is called flow mediated dilation (FMD)[3]. Repeated measurements of FMD can determine the influence of excess adiposity on the endothelium.

Obesity and Endothelial Dysfunction

Nearly 65% of the U.S. population is classified as overweight[4], therefore it is important to understand the role excess adiposity plays on health. Besides the traditional cardiovascular risk factors, such as hypertension, diabetes, insulin resistance, and hypercholesterolemia, endothelial dysfunction has also been recently associated with obesity. The Framingham Heart Cohort, one of the largest studies to evaluate this link, found an inverse relationship between BMI and FMD in over 2,500 participants[5]. Additionally, this association has been confirmed in cross-sectional studies evaluating the differences between lean and overweight children[6]. Furthermore, FMD is shown to become progressively impaired as the degree of obesity increases[7]. While BMI is a strong correlate, waist-to-hip ratio appears to produce an even stronger correlation to FMD and has been used to evaluate a relationship in recent publications[8,9].

Continued on page 2

In this issue:

Endothelial Function and Obesity: What is the Connection?

Continued from page 1

Several possible mechanisms for the role of obesity in endothelial dysfunction are related to adipose depots as a source of proinflammatory and proatherogenic cytokines. These include immune signals, such as interleukin-6 (IL-6) and C-reactive protein (CRP), as well as adipokines that raise the propensity for thrombosis and impair vascular tone, such as plasminogen activator inhibitor (PAI-1) and angiotensinogen[2]. The adipocyte hormone, adiponectin, is reduced in a state of excess adiposity and low levels have been associated with impaired FMD[2]. Adipose tissue's other possible mechanism is the increased level of free fatty acids that reduce nitric oxide production by decreasing endothelial nitric oxide synthase (eNOS) activity[10].

While obesity has been linked to endothelial dysfunction in previous research, there is emerging data to suggest that some individuals can be obese and yet have no cardiovascular risks[11]. To explore this interesting phenomenon, The Whitaker Cardiovascular Institute divided 77 obese subjects into two groups based on targeted immunohistochemistry of subject's subcutaneous adipose tissue. Fifty subjects presented with an inflamed adipose phenotype characterized by tissue macrophage accumulation in crown-like structures (CLS). This CLS phenotype was associated with systemic hyperinsulinemia, insulin resistance, and impaired endothelium-dependent FMD and was linked to higher CRP compared to the 27 subjects with non-inflamed adipose tissue. Interestingly, there were no significant differences in waist circumferences, body mass indexes, ages, medications, and medical conditions between the two groups. This study is one of the first clinical studies linking adipose tissue inflammation to vasculature problems[12] and may help provide a way to identify overweight individuals at increased risk for developing CVD.

Weight Loss and Endothelial Dysfunction

Currently, there are no published data regarding the effect of weight loss between individuals with and without CLS. The information that is available relates to weight loss across populations. Research has shown that using a low calorie diet alone, or exercising three times per week, appears to improve endothelial function in studies less than six months in duration[13,14], supporting the notion that excess adiposity is associated with endothelial dysfunction. This improvement in endothelial function has been shown to occur in as little as two weeks[15]. Furthermore, The Whitaker Cardiovascular Institute found that weight loss with medical nutrition therapy or gastric bypass surgery improves endothelial function; however, this improvement was related to altered glycemic status rather than weight reduction[16]. The long-term implications of weight loss on endothelial function need to be elucidated.

While it appears weight loss improves endothelial dysfunction, the question of which macronutrient composition most effectively improves endothelial function remains controversial. Two short-term studies of less than eight weeks in duration produced conflicting results. In the first study, researchers from the Medical College of Wisconsin randomized participants to either a low fat diet (30% kcals from fat modeled after the American Heart Association guidelines) or a low carbohydrate (20 grams of carbohydrate modeled after the Atkins' diet recommendations). Both diets were designed to have participants consume 750 calories less than their typical intake. After six weeks, FMD improved in the low fat group, but worsened in the low carbohydrate group[17]. An eight-week isocaloric study evaluating a low carbohydrate diet (35% energy from protein, 61% as fat, 20% as saturated fat, and 4% as carbohydrate) versus a low fat- high carbohydrate diet (24% energy from protein, 30% as fat, <8% as saturated fat, and 46% as carbohydrate), showed that FMD trended toward improvement in both groups. Although the low fat group lost an average of 6.5 kilograms (kg) and the low carbohydrate group 7.9 kg, there were no statistically significant differences[18]. The important concept to consider is that regardless of macronutrient composition, weight reduction appears to improve FMD and consequential cardiovascular risk profile.

Conclusion

Given that obesity is linked to cardiovascular disease, evaluating the endothelium could provide a mechanism for assessing risk. Creating a growing understanding of the mechanisms of this relationship will be paramount. Future studies of the differences between CLS phenotypes will further develop this understanding. The long-tem outcomes of weight loss on endothelial function needs to be explored further, as does the role of macronutrient content of weight loss diets on improving FMD. Finally, while many questions have yet to be answered, dietitians are currently in a position to continue to provide individuals with the tools to lose weight and potentially reduce their risk for cardiovascular disease through an improvement in FMD.

References

1. Centers for Disease Control and Prevention. Heart Disease. Available at: *http://www.cdc.gov/heartdisease/*. Accessed August 8, 2008.
2. Meyers MR, Gokce N. Endothelial dysfunction in obesity: etiological role in atherosclerosis. *Curr Opin Endocrinol Diabetes Obes.* Oct 2007;14(5):365-369.
3. Widlansky ME, Gokce N, Keaney JF, Jr., Vita JA. The clinical implications of endothelial dysfunction. *J Am Coll Cardiol.* Oct 1 2003;42(7):1149-1160.
4. Ogden CL, Carroll MD, Curtin LR, McDowell MA, Tabak CJ, Flegal KM. Prevalence of overweight and obesity

Continued on page 3