

Role of diabetes, hypertension, and cigarette smoking on atherosclerosis

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ABSTRACT

Hyperosmolar food causes atherosclerosis. Hyperosmolar food hypothesis encompasses all the factors involved under one heading and, that is, the generation of heat in the body. The involvement of cigarette smoking is obvious. High glycemic index food and diabetes result in high levels of blood glucose, which raises the core body temperature. The ingestion of hyperosmolar salt, glucose, and amino acids singularly or synergistically raise the core body temperature, forcing abdominal aorta to form an insulation wall of fatty material causing atherosclerotic plaques. The osmolarity of food, that is glucose, salt, and amino acids is reduced when water is ingested with food. The incidence of atherosclerosis goes down with increasing intake of water.

Key words: Atherosclerosis, cigarette smoking, diabetes, hypertension

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INTRODUCTION

People all over the world suffer from atherosclerosis. Therefore, etiology of the disease should be the same irrespective of geographical location. Mathur^[1-3] has described the effect of hyperosmolality of food consumed in the development of atherosclerosis. These articles state that the ingestion of caloric-rich food containing NaCl, amino acids, and glucose raises the core body temperature. As a result, arteries build insulatory layers of fatty material to protect themselves from temperature fluctuations caused by thermogenesis. Similarly, cigarette smoking raises lung temperature and leads to fatty deposits in arteries. Consumption of fat does not cause atherosclerosis because it does not raise core body temperature. Fatty deposits in arteries are not the cause but the manifestation of the disease. Furthermore, being overweight is also not the cause of disease, it just exacerbates the condition. In addition, diabetes mellitus causes atherosclerosis because it causes hyperglycemia, which leads to excessive thermogenesis. Now let us peruse the literature in the light of hyperosmolar food hypothesis.

THERMOGENESIS

Food intake stimulates the metabolic rate of the whole body

and increases core body temperature. This phenomenon has been called diet-induced thermogenesis (DIT), postprandial hyperthermia, and thermic effect of food. According to Jequier,^[4] thermic response to amino acids, glucose, and lipids are 30–40%, 6–8%, and 2–3% of energy infused, respectively. In another study, Westerterp^[5] showed that alcohol and protein play the biggest role in thermogenesis. Scott and Devore^[6] confirmed Westerterp's findings by demonstrating that 100% as well as 60% protein shakes produce higher DIT as compared with 60% fat, 30% protein, 10% carbohydrate and 60% carbohydrate, 30% protein, 10% fat, shakes. To determine the mechanism of thermogenesis, Osaka *et al.*^[7-9] infused hypertonic solution of glucose, NaCl, fructose, and amino acids in the intestine of urethane-anesthetized rats. A higher core body temperature was observed with increasing amounts of the above-mentioned nutrients. Furthermore, an intravenous injection (IV) of these nutrients also caused thermogenesis accompanied by an increase in plasma osmolality. However, thermogenesis caused by IV was lesser than that caused by the intestinal infusion of NaCl and the solutions of the other above-mentioned nutrients, suggesting an involvement of intestinal osmoreceptors. This further suggests that it is unlikely that IV and intestinal osmotic stimulation induces identical mechanisms of

thermogenesis. However, it does show that an increase in the plasma osmolality, within the physiological range, elicits thermogenesis. The mechanism of thermogenesis is not clear. However, it may involve intestinal osmoreceptors. The authors also found that food intake stimulated the metabolic rate of the whole body and increased the core body temperature. The core body temperature is measured by inserting a thermister in the anus. The skin or cutaneous body temperature is measured by a thermister taped to the lateral surface of a rat's tail. The mechanism of core and skin temperatures are regulated differently.^[10,11] It is this thermogenesis that is responsible for the generation of atherosclerotic plaque. Furthermore, it is only the core body temperature that plays the main role and not the whole body temperature or the atmospheric temperature. In addition, there is no evidence of this disease being more prevalent in people running high fever for a prolonged period of time or in those living in warm to hot climates.

HYPEROSMOLAL FOOD

The ingestion or intravenous infusion of food nutrients raises body temperature. Westerterp^[5] stated that the hierarchy in DIT descends from proteins to carbohydrates to fats, which is similar to macronutrient oxidation in postprandial state. Therefore, it seems that fat produces the least thermic response. This was further elucidated by Nagai *et al.*^[12] They found that high fat meals had lower thermic effects than low fat meals.

Osaka *et al.*^[7-9] confirmed low thermic response of fat by infusing 100% safflower oil into the duodenum of urethane-anesthetized rats. Safflower oil did not produce any thermic response as compared with 5–20% glucose, 2–4% NaCl, 20% fructose, and 5–10% solutions of various amino acids. Furthermore, infusion of 0.9% NaCl or distilled water also did not produce any heat. However, the thermic response increased with an increase in the osmolarity of glucose, fructose, amino acids, and NaCl solutions. Similar effects were observed in conscious animals and humans by Osaka and coworkers.

CONSUMPTION OF WATER

Amount of consumption of water is the single most important factor in the development of atherosclerosis. It can increase or decrease the osmolarity of food. The United States Department of Agriculture (USDA) recommends a water intake^[13] between 1 and 1.5 mL/kcal of energy expenditure, which translates to 2–3 L of water per day. In the United States and other western countries,

water is consumed more in the form of beverages rather than pure water. According to the USDA Nationwide Food Consumption Survey^[14] of 1977–1978, the median intake of water as such by a person was only 662 mL/day. In similar USDA surveys of 1994–1996 and 1998,^[15] drinking water consumption by adult males and females was 600 and 549 mL/day, respectively. These drinking water consumption figures were far below the USDA recommendations of 2–3 L/day.

Chan *et al.*^[16] in a remarkable cohort study discovered a strong negative multivariate association between the intake of water and the risk for fatal coronary artery disease and, in contrast, a positive association between the intake of fluids other than water and the risk for heart diseases. High intake of water (5 or more glasses/day) compared with low intake (2 or fewer glasses/day) were associated with a very high relative risk of 0.46 in men and 0.59 in women. At the same time, a high versus low intake of fluids other than water was associated with a relative risk of 1.46 in men and 2.47 in women. These statistics remained virtually unchanged in multivariate analysis adjusted for age, education, smoking, hypertension, body mass index, and hormone replacement therapy (in women only). Therefore, it is pertinent to look at the per capita consumption of fluids other than water, that is, sweetened beverages that increase the osmolality of food and also cause hyperglycemia. According to a survey between 1994 and 1996 conducted by Wright *et al.*,^[17] the mean consumption of soft drinks by adult males and females in the United States were 752 and 595 mL/day, respectively. This survey also shows that children aged between 2 and 5 years drank on average 266 mL of soft drink per day, which surpassed their water intake of 259 mL/day. Similarly, the consumption of soft drinks by people of other age groups was higher than their water intake. This may be one of the reasons for atherosclerotic plaques appearing in children aged 2–5 years. According to a study by Berenson *et al.*,^[18] all persons in the age group between 2 and 39 years had fatty streaks in the aorta. This study states that the prevalence of fatty streaks in coronary arteries increases with age from approximately 50% at 2–15 years of age to 85% at 21–39 years ($P = 0.01$). The statistics are alarming because 50% of all the children in the United States are already afflicted with the disease by the age of 15 years.

THE ROLE OF HYPERGLYCEMIA, HIGH GLYCEMIC INDEX FOOD, AND DIABETES MELLITUS

Ingestion of high glycemic index food creates postprandial hyperglycemia and creates physiologically a diabetic-like

condition in experimental animals.^[19] Coutinho *et al.*^[20] stated that postprandial hyperglycemia is an important risk factor for cardiovascular diseases not only among patients with diabetes, but also among the general population. Dickinson and Brand-Miller^[21] stated that several lines of evidence indicate that exaggerated postprandial glycemia puts individuals even without diabetes at greater risk of developing cardiovascular disease. Furthermore, Ceriello^[22] and de Vegt *et al.*^[23] stated that a high 2-hour postprandial glucose was independently associated with all-cause and cardiovascular mortality in a population even without diabetes.

Renard *et al.*^[24] stated that diabetes causes atherosclerotic lesions regardless of diet. They also discovered that diabetic mice had significantly higher cholesterol on a cholesterol-free diet as compared with nondiabetic mice, which could be attributed only to hyperglycemia in diabetic mice. Therefore, this study suggests that the synthesis of cholesterol is endogenous because it is not coming from the diet. In another study using an animal model, Kunjathoor *et al.*^[25] showed that hyperglycemia and not hyperinsulinemia is responsible for the development of atherosclerosis. Therefore, both diabetes mellitus and high glycemic index food can increase blood sugar and cause excessive thermogenesis.

Sartippour and coworkers^[26,27] stated that lipoprotein lipase (LPL) produced by macrophages in vascular walls may favor the development of atherosclerosis by promoting lipid accumulation within the atherosclerotic lesion. They demonstrated that high glucose concentration stimulated *in vitro* murine and human macrophage LPL production. They measured macrophage LPL mRNA expression, immunoreactive mass, and activity in normotriglyceridemic subjects and patients with type 2 diabetes. Monocytes isolated from healthy control subjects and patients with type 2 diabetes were differentiated into macrophages in RPMI media containing 20% autologous serum. After culturing for 5 days in diabetic sera, macrophage LPL mRNA expression increased significantly as compared with its expression in control subjects. Differentiation of macrophages of diabetic patients in sera obtained from control subjects significantly reduced these anomalies. Conversely, culturing macrophages of control subjects in sera of diabetic patients significantly increased the LPL mass, and its activity in these cells. The authors concluded that diabetes may contribute to the development of atherosclerosis.

CONSUMPTION OF SODIUM CHLORIDE

A positive correlation between salt intake and cardiovascular diseases has been known to exist for a long time. Menton

et al.^[28] stated that epidemiologic, migration, intervention, and genetic studies in humans and animals provide very strong evidence of a causal link between high salt intake and high blood pressure. Furthermore, Miura and Nakagawa^[29] stated that a reduction in salt intake remarkably decreased blood pressure in the elderly, the middle-aged, and the younger generation in Japan. It is also known that obesity and diabetes mellitus increase a patient's risk for stroke. The risk for atherosclerosis is even higher when a diabetic patient has high blood pressure. The most plausible explanation again is that both NaCl and glucose in blood synergistically raise both osmolarity of blood and core body temperature, resulting in atherosclerotic plaque formation.

Because hypertension is a major risk factor for atherosclerosis, Ketonen *et al.*^[30] tested whether high salt intake would aggravate endothelial dysfunction and promote atherosclerosis in apolipoprotein E-deficient mice (ApoE(-/-) mice) and their littermate controls. Their findings suggest a detrimental role of high salt (7%) intake in the development of atherosclerosis and underscore the importance of increased oxidative stress in the pathogenesis of salt-induced vascular damage. Similarly, Weiss and Taylor^[31] tested whether atherosclerosis was increased in the setting of a low renin model of hypertension. They observed a dramatic increase in the atherosclerotic lesion areas in the setting of either a low- or high-fat diet. In the hypertensive animals, they observed an increase in angiotensin II staining that was localized to adventitial macrophages. The increase in atherosclerosis was inhibited by the administration of an angiotensin receptor antagonist, an angiotensin-converting enzyme inhibitor, or a renin inhibitor. These data suggest that even in the setting of hypertension, which is not associated with the activation of the systemic renin-angiotensin system, local generation of angiotensin II within the arterial walls may be of pathophysiological relevance to the development of atherosclerosis.

CONSUMPTION OF PROTEINS, FATS, AND CARBOHYDRATES

Contrary to current theories, high fat diet does not cause atherosclerosis. It is further substantiated by French paradox.^[32] In France, there is a high intake of saturated fat but low mortality from coronary heart disease. It is high carbohydrate and high protein intake that leads to atherosclerosis. In addition, Karst *et al.*^[33] have shown that in DIT, protein was at least 3 times as large a thermic contributor as isocaloric carbohydrate supply. These investigators also discovered that dietary fats produced no

evident thermic response. The doubling of energy from either casein or hydrolyzed starch led to an approximate doubling of thermic effect. Kurowska and Carroll^[34] have shown that in rabbits, the elevation of cholesterol is produced by feeding a cholesterol-free, semi-purified diet containing 30% casein amino acid mixture or 14.7% casein amino acid mixture, which corresponds to a normal level of dietary protein. Therefore, a diet high in salt, protein, and carbohydrate will maintain an elevated core body temperature and lead to atherosclerosis plaque formation.

CIGARETTE SMOKING

The association between long-term cigarette smoking and coronary artery disease is well established. Furthermore, diabetics who smoke develop more severe cardiovascular diseases early in life. In cigarette smoking, lungs inhale hot smoke because at the time of puff, the temperature at the tip of the cigarette is around 950°C.^[35] The smoke also carries numerous chemicals that adversely affect the elasticity of lungs and the hot smoke raises the lung temperature and in turn raises the core body temperature. The lungs become incapable of performing one of their vital physiological functions, that is, cooling or removing the heat from the body. Karim *et al.*^[36] have illustrated that smoking is associated with subclinical atherosclerosis in diabetics and interacts with the duration of diabetes to accentuate atherosclerosis. The association between carotid intima-media thickness and the duration of diabetes increases with both the frequency and duration of smoking. The examination of the Framingham Heart Study by Wolf *et al.*^[37] revealed that regardless of smoking status and sex, hypertensive subjects had twice the incidence of stroke. Furthermore, smoking was determined to be a significant independent contributor to risk of stroke generally and brain infarction specifically. This study also revealed that the risk of stroke increased with the number of cigarettes smoked. The report further states that after cessation of cigarette smoking, the risk significantly dropped in 2 years and was at the level of nonsmokers in 5 years. This study suggests that the harmful effect of smoking is reversible as far as the stroke is concerned.

TEST OF HYPEROSMOLAL FOOD HYPOTHESIS

Okinawa centenarians^[38] come closest to getting a perfect score on hyperosmolal food hypothesis test. Okinawa centenarians consume food that has very high water content, such as cereals, roots, beans, fish, vegetables, and others. Their beverage is mainly tea, which is close to 99% water. However, they consume about 4 g of NaCl per day,

which is too high. In spite of this, they are least affected by cardiovascular diseases as compared with the rest of the world.

CONCLUSION

It is well known that diabetes, excessive salt intake, obesity, and a host of other factors lead to atherosclerosis. However, till now no general theory existed that could explain the involvement of all the above factors in the development of atherosclerosis, but now hyperosmolal food hypothesis explains the etiology of the disease remarkably well. Thus, only this hypothesis can explain the development of atherosclerosis all over the world. The details of hyperosmolal food hypothesis have been described elsewhere.^[1]

FUTURE PERSPECTIVE

In perspective, research on atherosclerosis currently is in disarray. The scientists require a paradigm shift in their thinking. We already know that fat intake does not cause atherosclerosis. Lowering blood cholesterol level does not protect people from becoming a prey to the disease. People on low fat diet are also not spared from the disease because the human body is capable of synthesizing cholesterol if needed by the body for insulation from heat. Thus, they too get heart attacks anyway. Furthermore, patients after coronary artery bypass graft (CABG) surgery relapse 50% of the time because the atherosclerotic plaque continues to build up in the grafted arteries and elsewhere. Patients are advised to stay away from fatty foods, which obviously does not help because fatty meal is not the cause for atherosclerosis. Therefore, the researchers should first examine the cause of the disease before trying to cure it; otherwise, we will be treating symptoms rather than curing the disease itself. Likewise, research foundations should increase funding on causal analyses and reduce financial grants on finding cures at this time.

However, there is some good news. The rate of cardiovascular diseases is slowing down, but it is not because of statins or CABG surgery. It is because of the advent of bottled mineral water. Luckily, it has become fashionable to carry a bottle of mineral water anywhere you go. It is this water consumption, which is diluting the hyperosmolar foods we eat.

Finally, this field requires some broad theories and hypotheses explaining the involvement of foods, diabetes, hypertension, cigarette smoking, and others in the

formation of atherosclerotic plaque. We have a mission but are lacking the vision. That is why we have not made any progress even though we have worked on it for more than 50 years.

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