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Metabolic Syndrome and its Profound Effect on Prevalence of Ischemic Stroke

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Abstract

Ischemic stroke represents a leading cause of death worldwide and the leading cause of disability in the United States. Greater than 8% of all deaths are attributed to ischemic stroke. This rate is consistent with the heightened burden of cardiovascular disease deaths. Treatments for acute ischemic stroke remain limited to tissue plasminogen activator and mechanical thrombolysis, both of which require significant medical expertise and can only be applied to a select number of patients based on time of presentation, imaging, and absence of contraindications. Over 1,000 compounds that were successful in treating ischemic stroke in animal models have failed to correlate to success in clinical trials. The search for alternative treatments is ongoing, drawing greater attention to the importance of preclinical models that more accurately represent the clinical population through incorporation of common risk factors. This work reviews the contribution of these commonly observed risk factors in the clinical population highlighting both the pathophysiology as well as current clinical diagnosis and treatment standards. We also highlight future potential therapeutic targets, areas requiring further investigation, and recent changes in best-practice clinical care.

Keywords

Ischemic Stroke; Metabolic Syndrome

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Introduction

Ischemic stroke has been recognized as a leading cause of morbidity and mortality in the United States.[1] Disruption of cerebral blood flow causes activation of neuroinflammatory cascades, which can ultimately disrupt brain metabolism and lead to decreased neuronal survival. These chronic changes account for why ischemic stroke is the leading cause of disability in the United States.[2] Several risk factors are associated with the occurrence of ischemic stroke. Risk factors fall into two categories: modifiable factors such as hypertension and diabetes and non-modifiable factors such as age and gender. While age remains the greatest risk factor for stroke, evident by the exponential increase in risk with each decade,[3] modifiable risk factors such as smoking, hypertension, diabetes, dyslipidemia, and obesity are contributing to a significantly heightened risk for ischemic stroke.[4] In fact, population-based analysis suggests that the metabolic syndrome may account for approximately 19% of all strokes.[4] By understanding the factors that increase the risk of ischemic stroke and are associated with poor outcomes, alternative therapeutic targets may be identified.

Hypertension and Stroke

Classification

Hypertension can be classified as either primary or secondary hypertension. Secondary hypertension can be caused by medical conditions or as the result of various medications.[5] Unlike secondary hypertension the cause of primary hypertension is idiopathic. Primary hypertension is responsible for 95% of all hypertension cases and negatively affects multiple organ systems.[6] Several factors may contribute to the 20% increase in hypertension cases from 1976–2004[7]. One factor is the increased screening for hypertension following the United States Preventive Services Task Force (USPSTF) 1996 recommendation for sphygmomanometry readings for all adult patients.[8] Other factors that account for the increase in hypertension may include increased alcohol consumption, high salt intake, obesity, high cholesterol, stress, and advanced age. The VIPER-Bp clinical study reported that successful management of hypertension in the clinic involves early diagnosis, a multi-drug treatment approach, and eliminating environmental and social factors that lead to an increase in hypertension.[9]

Hypertension Outcomes

Age is one of the most predominant risk factors for hypertension according to a recent National Health and Nutrition Examination Study report. This is of particular relevance as the median age across the nation increases.[10] By the year 2040, the population over the age of 65 is predicted to double.[11] The rate of hypertension for individuals over 60 was 65.4% which dwarfs the 28.7% overall rate for the general population.[12] One of the reasons for this large difference may be due to the body's response to aging including but not limited to an increase in inflammatory reactivity. Aging affects blood pressure through age-related changes in blood vessel structure. Elevated blood pressure increases the shear force placed on artery walls as blood is pumped throughout the body.[5] This pressure change can cause damage to the vascular wall as well as smooth muscle thickening, decreased elasticity, and a

narrowed lumen. Patients with diagnosed hypertension during mid-life have increased susceptibility for ischemic injury as they age.[10]

Pathophysiology

In addition to thrombosis, cardiovascular disease (CVD) is a suggested secondary effect of primary hypertension. The major cells of the vessel wall that play a role in CVD are the endothelial cells (EC). These cells line the vessels in every organ system and have the ability to control secretory, synthetic, metabolic, and immunologic functions.[13] The regulation of blood flow in the body is partly orchestrated through a wide variety of molecules acting on membrane bound receptors. These molecules include coagulant and anticoagulant proteins, metabolites, cytokines, lipid transporting proteins, and hormones.[13] In correct proportions these molecules help maintain homeostasis, but in excess or scarcity may lead to damage. Damage initiated through dysregulated signaling pathways can have detrimental consequences on any organ in the body.

For example, ECs respond to the surrounding environment and release vasoconstrictors and vasodilators in order to maintain the appropriate blood pressure and proper blood flow. When ECs are healthy they prevent platelet adhesion to the vessel wall by favoring release of vasodilators such as nitric oxide (NO) and prostacyclin (PGI_2).[13] On the other hand, during inflammatory driven responses due to shear and other physiologic processes, ECs may become damaged due to oxidative stress and cytokine mediated responses. Damaged ECs have a lower availability of NO and PGI_2 and an increased level of vasoconstrictors and platelet enhancers such as platelet activation factor (PAF) and Thromboxane A2 (TXA2) (Figure 1). This change in balance has a series of effects ultimately leading to the development of hypertension and increased risk of thrombosis. Inflamed ECs produce cytokines and adhesion factors such as intercellular adhesion molecule 1 (ICAM-1) and vascular cell adhesion molecule (VCAM) leading to leukocyte adhesion to the underlying damaged tissue.[14] During this process circulating platelets create a hemostatic plug by interacting with adherent platelets and other adhesion factors already on the EC surface. This interaction induces the generation of thrombin which leads to the formation of a fibrin clot aiding vessel wall repair.[13] Unfortunately, this process is also known to be the earliest stages of atherothrombosis. Atherothrombosis is the cause of 50% of ischemic strokes, which comprise approximately 80% of all strokes. Furthermore, stroke is the second most common cause of death worldwide.[15] Therefore, continuous high blood pressure is associated with chronic vessel wall damage and indicates an increased likelihood for future stroke, necessitating close management of hypertension as a preventative measure.

Diagnosis and Treatment

Unfortunately, no clear signs of primary hypertension exist and hence it is sometimes referred to as a silent killer. At the time of discovery, treatment involves basic lifestyle modifications such as diet alterations, increasing physical activity, lowering sodium and alcohol intake, lowering LDL cholesterol, smoking cessation, and reducing stress. If lifestyle modifications are not sufficient, antihypertensive medications such as beta blockers, calcium channel blockers, angiotensin converting enzyme inhibitors, and diuretics may be prescribed.[16] Based on previous studies, only 34% of patients with hypertension are

controlled, indicating a clear shortcoming in current management and/or screening/prevention efforts. Since hypertension is a silent killer, few people understand its severity as a risk factor for ischemic vascular events. With increased focus on improving patient understanding of the disease, the percentage of controlled cases will increase and more people will get screened. The USPSTF suggests that adults be screened a minimum of every 2 years and more frequently in the elderly. Therefore, increased emphasis on screening and prevention programs, particularly those that target elderly populations, may reduce the burden of ischemic stroke.[17]

Diabetes Mellitus and Stroke

Diabetes Mellitus Classification

Type II diabetes (T2D) is one of the fastest growing diseases in terms of new diagnoses around the world. It is characterized by insulin resistance and insulin deficiency. The CDC has claimed that 7% of the American population has the disease.[18] T2D has been linked to lifestyle habits as well as certain genetic patterns. The growing number of individuals affected by the disease is due to limited health service access, socioeconomic factors, and the restricted amount of nutritional resource availability in commercially packaged foods. The growing levels of obesity are directly associated with the increasing prevalence of T2D.[19] T2D has been linked as a leading risk factor for ischemic stroke.[20]

T2D Stroke Outcomes

Both stroke and T2D are typically diagnosed in the aging population. Aging contributes to a heightened state of inflammatory response and microglia activation.[21] Inflammatory cytokines, such as interleukin-6 (IL-6), have been shown to increase concomitantly with increasing levels of blood glucose.[22] It has become well known that inflammatory cytokines play a major role in neural injury. The increasing release of inflammatory cytokines associated with ischemic stroke in T2D patients has been shown to exacerbate the damage caused by the stroke,[23] and lead to worsened outcome.[24] While T2D is not the sole cause of stroke, it does negatively affect the outcome of ischemic injury.

T2D and an increased stroke risk have also been linked with hypertension. T2D can potentially exacerbate hypertension, due to added stress placed on the arterial walls, thereby also increasing the risk of thromboembolic stroke.[25, 26] Unfortunately, most patients at risk for stroke present with a metabolic syndrome consisting of T2D, hypertension, and obesity.[27] The metabolic syndrome has been linked to poor cardiovascular outcomes in adults as well.[28] According to a recent study, a person with hypertension is 2.4 times more likely to have cerebrovascular disease.[29] The synchrony of clinical data reveals a stark comorbidity between stroke and diabetes; however, the underlying mechanism behind this relationship has yet to be fully unveiled.

Pathophysiology

T2D causes acute microvasculature changes such as retinopathy, and contributes to macrovascular changes related to atherosclerosis.[30] After ischemic stroke, hyperglycemia is an acute indicator of endocrine stress and neuroinflammation.[31] Sustained hyperglycemia

leads to the formation of advanced glycosylated end products, which trigger the release of reactive oxygen species.[32] Advanced glycosylated end products also lead to increased vascular permeability and decreased vascular dilation, thus worsening ischemic stroke outcome. Controlling hyperglycemia has been shown to have a 42% relative risk reduction for ischemic stroke.[33] The appropriate management of T2D is therefore an urgent necessity.

Diagnosis and Treatment

Diagnosis of T2D consists of either fasting plasma glucose above 126 mg/dl or an HbA1c above 6.5%. Appropriate management of T2D is lowering the HbA1c below 6.5%. The most successful treatment regimens include a combination of healthy diet, regular exercise, and anti-hyperglycemic therapy.[34] 50% of T2D patients however, are not adequately managed. Long terms results of unmanaged T2D include optic retinopathy, diabetic neuropathy, and increased risk for ischemic stroke. A clear need exists for an increase in prevention and monitoring programs based on the high prevalence of diabetes across the nation.[35] When considering ischemic stroke specifically, management and control of diabetes may lessen the impact of stroke. Rapid and sufficient correction of hyperglycemia has been shown to reduce infarct development and expansion in ischemic stroke.[36] Furthermore, diabetes increase rates of intracerebral hemorrhage following tPA administration, emphasizing the need for blood-glucose control upon patient arrival.[37, 38]

Obesity and Stroke

Obesity Classification

The obesity epidemic continues to plague the United States, where nearly 70% of Americans are overweight (Body Mass Index (BMI) ≥ 25) and 35% are obese (BMI ≥ 30).[39] Moreover, health problems including diabetes, coronary artery disease, ischemic stroke, respiratory failure, and cancer are strongly associated with excess weight gain.[40]

Obesity is a multifactorial disease influenced by many variables including environment, social structures, genetics, behavior, and diet. Furthermore, twin, adoption, and family lineage studies suggest that heritable factors contribute to 40–70% of inter-individual variation seen in the obesity population.[41, 42] At the simplest level, obesity can be defined as a state of positive energy balance. This positive energy balance is in part fueled by our current environment, which encourages overeating and discourages physical activity. Recent data suggests the adult population is consuming an excess of 100kcal/day.[43]

A substantial body of evidence has documented that increased adiposity is associated with an increased risk of stroke.[44–47] A meta-analysis found that between the BMI ranges of 25 to 50, each increase of 5 on the BMI scale was associated with a 40% increased risk of stroke mortality. There was no relationship in the lower BMI ranges.[48] Recently, the American Heart Association and American Stroke Association recommended that the treatment of obesity is critical for both primary[5] and secondary[49] stroke prevention.

Obesity Stroke Outcomes

Interestingly, inconsistent results about the association between obesity and stroke risk have been reported. A recent analysis showed that BMI and abdominal obesity do not increase cardiovascular disease risk when data about systolic blood pressure, history of diabetes, and lipid dysfunction are accounted by controlling for confounding.[50] On the other hand, while one study reported that BMI was associated with an increased risk of stroke in both sexes and abdominal obesity only in men[51]; another study reported women aged 35 to 54 years are more likely to be obese and morbidly obese than in the previous decade and their abdominal obesity however was an independent risk factor for stroke.[52] Abdominal obesity may be a stronger risk factor of stroke than BMI in future studies considering the current trends.[53] Apart from stroke morbidity, a recent study has proposed a paradoxical "protective" effect of obesity in acute stroke survivors.[54] This inverse relationship between obesity and outcome was first documented in those recovering from an intracerebral hemorrhage[55] as well as those suffering from chronic diseases.[56] Clearly, further research is needed to sufficiently assess the best measure of obesity on stroke risk and to find better tests to predict likelihood of stroke mortality.

Pathophysiology

A possible mechanism linking obesity and stroke involves the pleiotropic effects that cytokines secreted by adipose tissue may exert on insulin resistance, inflammation, and changes in the vascular wall. An accumulation of lipids in adipocytes and the expansion of adipose tissue initiate a host of inflammatory processes. The hypertrophic adipocytes produce proinflammatory cytokines such as tissue necrosis factor alpha (TNF-α), interleukin-6 (IL-6), and monocyte chemotactic protein-1 (MCP-1) as outlined in Table 1. Local endothelial cells respond with an up-regulation of adhesion molecular synthesis and increased vascular permeability, which along with the chemokines serve to recruit circulating monocytes. Together, the endothelial cells, adipocytes, and immune cells create an inflammatory milieu that induces a state of local and systemic insulin resistance and increase the risk for atherosclerosis.[57] In addition, the dysfunction of adipose tissue may lead to the dysregulation of cytokines acting on the sympathetic nervous system, renin-angiotensin axis, and endothelial cells. These changes increase the risk for hypertension,[58] which is the number one modifiable risk factor for stroke.

Diagnosis and Treatment

The need for appropriate diagnosis of obesity is necessary to prevent serious long-term consequences. The relative risk for ischemic stroke after 10 years of obesity is 1.64.[59] If obesity is diagnosed early, effective treatment options can be implemented to prevent serious long-term outcomes such as stroke.[60] Diagnosis of obesity is more likely when patients are referred to a cardiology specialist.[61] Furthermore, preventing obesity has gained widespread support, and the NIH is sponsoring consortiums to find effective interventions for children and adolescents.[62] Current treatment includes lifestyle modifications, followed by phentermine-topiramate or lorcaserin, and as a last resort bariatric surgery.[63] Unfortunately, only 50% of obese patients attempt to lose weight.[59] Patients diagnosed as obese instead of simply being classified as overweight have a higher likelihood of participating in weight loss

programs.[61] Several novel approaches for treating obesity such as encouraging patients to watch less television and to walk after eating are currently being investigated with randomized control trials.[64]

Future Directions

As highlighted in the previous sections, comorbidities contribute substantially to ischemic stroke risk. Due to the limited success of translating compounds from preclinical trials to FDA approved ischemic stroke treatments, it will be necessary to promote preventative care. Preventive approaches must incorporate healthcare professionals, research scientists, and members of the local communities. A three tier approach should be implemented. Tier one incorporates focused research to improve our understanding of stroke pathophysiology. The goal is to ascertain how subsets of patients presenting with different comorbidities may respond to individualized therapies and focused treatment plans that will lower the risk for ischemic stroke. Inherent to this goal is early diagnosis and treatment. Tier two is an educational approach that engages the community to encourage healthy food availability, to teach about comorbidities, and to improve recreational and park resources. Regular physician check-ups should be emphasized in these educational meetings. In order to create an environment more conducive to healthy lifestyles, tier three requires physician led advocacy for changes in social infrastructure. One such change is encouraging regulations on nutrient-poor food and drinks. Other changes include improving transport protocols from tertiary care centers following stroke, and increasing the number of care facilities in areas with high ischemic stroke prevalence.

Conclusion

In summary, ischemic stroke is the leading cause of disability and a major cause of mortality worldwide. It is predominantly seen in the elderly and in patients with the metabolic syndrome.[65, 66] We looked specifically at the pathophysiology of hypertension, T2D, and obesity. Continued research is necessary to improve our understanding of exactly how the aforementioned comorbidities increase ischemic stroke risk. A stroke is a devastating event for the individual, family, and local community. Currently, those at risk for stroke have limited understanding of why they are at risk. To adequately address the overall lack of awareness, it will be important for an interdisciplinary healthcare team to implement the three tiers mentioned in the future direction section. Tier 1 requires early diagnosis, adequate treatment, and focused preclinical and clinical research. Tier 2 provides educational resources in easy accessible formats such as through school assemblies or town-hall meetings. Simple targets should be highlighted: improving nutritional food choices, increasing physical activity, and scheduling annual physical exams. Tier 3 involves physician led advocacy for nutritional regulations. Furthermore, when a stroke does occur, it is critical that patients know how to activate the emergency response system and where to go to receive help.[67] It is also important for limited care facilities to initiate transport protocols quickly and efficiently in order for patients to receive the best care available.[68] Although the need for improved care for stroke patients is dire, the potential for better preventive measures orchestrated through the three tier approach offers to be promising.

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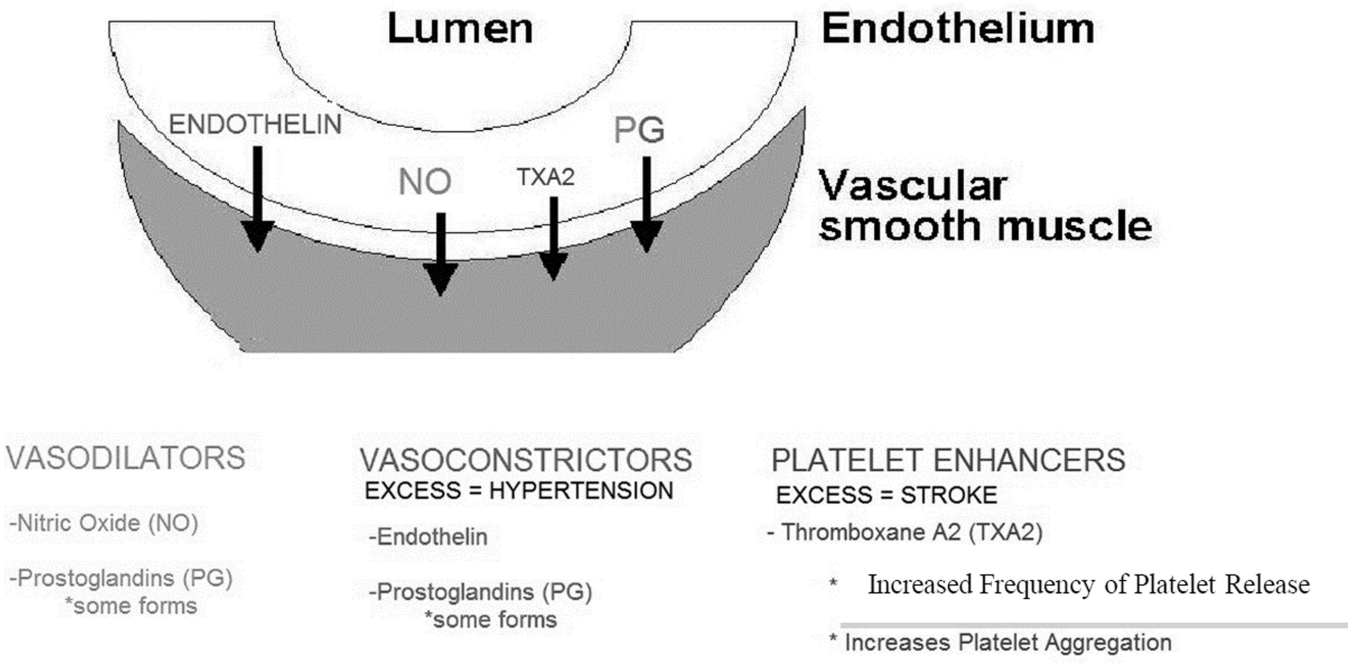

Figure 1.

Balance of vasodilator-associated and vasoconstrictor-associated signaling molecules is altered in hypertension. Damage to endothelial cells can lead to the development of hypertension and vice-versa. Further damage can result in release of pro-thrombotic factors leading to platelet adhesion and thrombosis, producing ischemic stroke.

Table 1

Cytokine secretion from adipose tissue and the role of these cytokines in the development of insulin resistance.[39]

Cytokine	Function	Role in insulin resistance
TNF-α	Inflammatory cytokine	Plays role in insulin resistance by stimulating intracellular signaling through NF-κB activation; knockout mice have shown improved insulin sensitivity and insulin signaling
IL-6	Inflammatory cytokine	Implicated as pathogenic mediator of insulin resistance; human polymorphism in *IL6* gene, with resulting decrease in circulating IL-6 levels, is associated with increased insulin sensitivity
resistin	Inflammatory cytokine	Plays role in insulin resistance by stimulating intracellular signaling through NF-κB activation; knockout mice have shown improved glucose tolerance on high-fat diet
MCP-1	Chemoattractive protein that recruits immune cells to sites of inflammation	Expression in adipocytes have resulted in hepatic steatosis and insulin resistance in liver, muscle and fat
PAI-1	Inhibitor of plasminogen activators, which converts plasminogen into plasmin during fibrinolysis	Knockout mice have shown improved insulin sensitivity