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EDITORIAL

Effects of Short-Term Proteinuria on the Incidence of Stroke in Patients With Different Glucose Tolerance Status

Ahlim Alsanani, MD; Joseph I. Shapiro, MD

Proteinuria has emerged as a potential risk factor for adverse cardiovascular events, including stroke.[1–4] It has been suggested that proteinuria not only reflects glomerular damage, but also is a sensitive indicator of systemic factors that initiate and maintain the atherosclerotic process.[5,6] Diabetes mellitus is among the most important systemic factors that are associated with atherosclerosis.[7–9]

See Article by Wang et al.

It is well known that albuminuria in diabetic patients is associated with higher risk of cardiovascular and cerebrovascular events.[10] Studies suggest that diabetes mellitus can cause pathologic changes in blood vessels that predispose to stroke. The major putative mechanisms by which diabetes mellitus can predispose to stroke are displayed in the Figure. Still unclear is whether hyperglycemia itself is a risk factor for stroke.[7]

A meta-analysis of 10 observational cohort studies involving 140 231 participants and 3266 strokes was recently performed.[1] Participants with proteinuria had a 71% greater risk of stroke compared with those without proteinuria (95% CI, 1.39–2.10). The authors concluded that there was a substantially greater risk of stroke in individuals with macroalbuminuria than in individuals with microalbuminuria. These findings clearly support an independent relationship between proteinuria and stroke. Unfortunately, this and other previous studies typically measured proteinuria only once and focused on the long-term effect of such proteinuria on long-term cardiovascular and cerebrovascular events. However, proteinuria often changes dynamically, and the impact of proteinuria on the concurrent risk of stroke was poorly understood[11] before the current study in this issue of the *Journal of the American Heart Association* (*JAHA*).

Wang et al[12] report on an observational cohort study of 82 938 participants who were free of myocardial infarction or stroke at the beginning of the study. These subjects all underwent fasting blood glucose and urinary protein measurements (using dipstick) at baseline and subsequent follow-up (annual for the urine dipstick). Time-dependent proteinuria was defined as the status of said urine dipstick test updated through the following year. The prevalences of pre–diabetes mellitus and diabetes mellitus were 19.69% (n=16 332) and 8.58% (n=7119), respectively. During a median follow-up of 8.37 years (interquartile range, 7.91–8.75 years), 2538 participants (3.06%) developed stroke. Further analysis deemed that 2047 were ischemic, 495 were hemorrhagic stroke, and only 65 were subarachnoid hemorrhage. Because of the low

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Correspondence to: Joseph I. Shapiro, MD, Department of Medicine, Marshall University, 1600 Medical Center Dr, Huntington, WV 25701-3655. E-mail: shapiroj@marshall.edu

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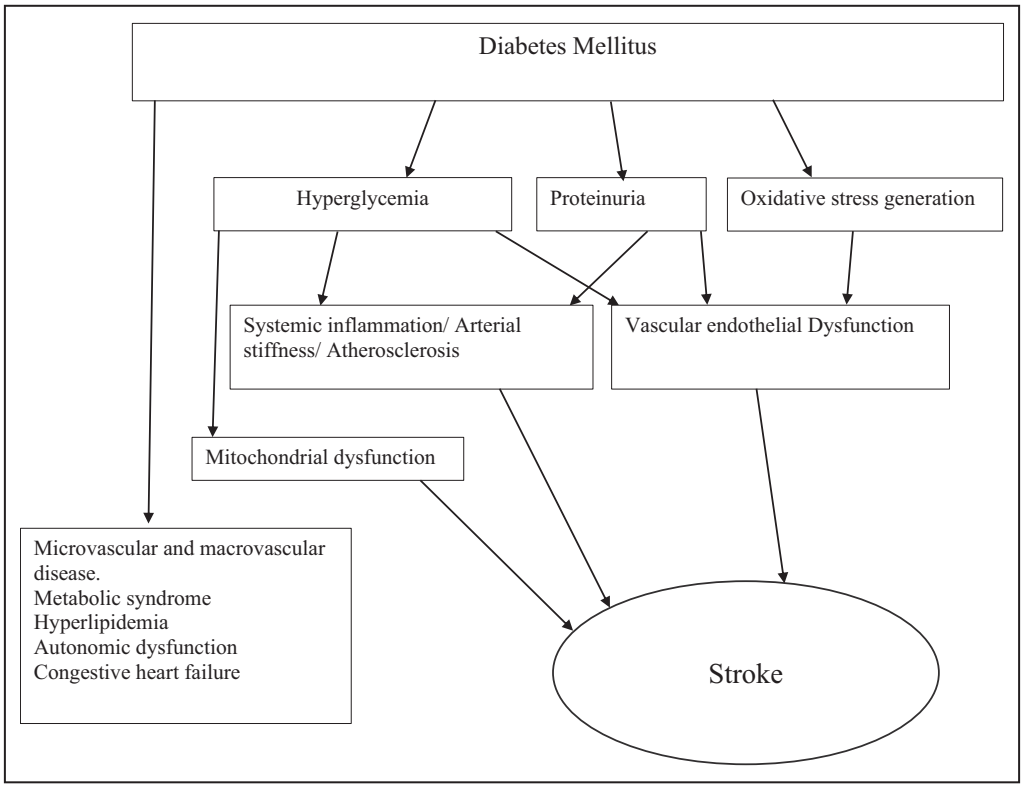

Figure. Putative mechanism by which stroke occurs in diabetic patients.
One mechanism is proteinuria, which is the topic of the article under discussion. Proteinuria can increase the risk of stroke through its effects on the coagulation system, systemic oxidant stress, and inflammation as well as by potentiation of atherosclerosis and other mechanisms.[5] In diabetic patients, other processes, such as hypertension, hyperlipidemia, vascular congestion, and microvascular and macrovascular disease, are probably operant.[7] In addition, the hyperglycemia itself in diabetics may be involved through direct and indirect mechanisms.[7–9]

numbers in the subarachnoid hemorrhage group, this group was not analyzed independently.

Wang and colleagues found that patients with time-dependent proteinuria demonstrated a higher risk for stroke in a dose-dependent manner.[12] Somewhat surprisingly, the relative risk of stroke was actually higher in nondiabetic and prediabetic patients compared with those with frank diabetes mellitus. Unfortunately, it is difficult to ascertain from the data reported whether this represents a greater stroke risk for those subjects with diabetes mellitus, which is less increased by proteinuria, or whether the absolute stroke risk is actually higher in nondiabetic proteinuric patients. On this note, it is believed that the risk of thromboembolism is higher in patients with some specific forms of nephrotic syndrome, especially those with membranous nephropathy.[13] Whether this is because patients with membranous nephropathy have substantially higher sustained levels of proteinuria than those with other proteinuric renal diseases or for other reasons (or if it is even true) is still a topic of some debate.[14–16] Stroke risk with proteinuria is believed caused, at least in part, by hypercoagulability from the glomerular loss of anticoagulants (eg, antithrombin III) along with increased liver procoagulant synthesis (fibrinogen, factor V, and factor VIII).[15,17] Increased platelet activation and aggregability, decreased fibrinolytic activity, and localized clotting activation in the kidney have also been implicated.[18]

In summary, Wang et al[12] reported that time-dependent proteinuria was actually a more significant risk factor of stroke in the normoglycemic and prediabetic populations than those with frank diabetes mellitus. Although these findings clearly support the concept that proteinuria is an independent risk factor of stroke, further work to better understand the interactions between the diabetic and proteinuric milieu is clearly necessary.

ARTICLE INFORMATION

Affiliations
From the Marshall University, Huntington, WV.

Disclosures
None.

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