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Review Article

Metabolic syndrome, platelet activation and the development of transient ischemic attack or thromboembolic stroke

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ABSTRACT

Stroke is the second most common cause of mortality in the world today, where transient ischemic attack (TIA) is a period of focal ischemia, the symptoms of which resemble a thromboembolic stroke. Contrary to stroke, TIA symptoms typically last less than one hour and necrosis is absent. Stroke is often preceded by TIA, making it an important predictor of future ischemic events. The causal role of atherosclerosis in the development of TIA is well established, however, research indicates that the atherosclerotic process begins years earlier with the development of metabolic syndrome, which affects approximately 45% of the adult population worldwide. Metabolic syndrome is present if three or more of the following is present: increased waist circumference, increased triglycerides, decreased HDL, increased fasting glucose and hypertension. This syndrome causes systemic inflammation that activates the coagulation system and may cause the formation of pathological thrombi. The role of platelets in stroke has been studied and platelet activation pathways identified. ADP and thromboxane A_2 are the most common activators of platelets in normal physiology. Several pharmacological treatments have been employed to prevent the activation of platelets, the most common of which include aspirin and $P2Y_{12}$-inhibitors. Although treatment is administered strokes and subsequent TIAs are very common in individuals that suffered an initial event. This indicates that research needs to be done in order to elucidate new therapeutic targets, but also to better treat ischemic events to not only decrease the amount of recurring events but also decrease stroke mortality worldwide.

Contents

Abbreviations: ADP, adenosine diphosphate; AACE, American Association of Clinical Endocrinologists; cox-1, cyclo-oxygenase-1; CVD, cardiovascular disease; EGIR, European Group for the study of Insulin Resistance definition; GP, Glycoprotein; HDL, high density lipoproteins; IDF, International Diabetes Federation; IL-6, interleukin-6; mm Hg, millimeter mercury; mmol/l, millimole per liter; MRI, magnetic resonance imaging; NCEP ATP III, National Cholesterol Education Programme – Adult Treatment Panel III; PAI-1, plasminogen activator inhibitor-1; PAR, protease activated receptor; TF, tissue factor; TFPI, tissue factor plasminogen inhibitor; TIA, transient ischemic attack; TNF-α, tumor necrosis factor alpha; t-PA, tissue plasminogen activator; vWF, von Willebrand factor; WHO, World Health Organization.

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Introduction

Cardiovascular disease (CVD) is currently the leading cause of global mortality according to the 2010 WHO Global Status report on non-communicable diseases (NCDs). More than 36 million people died from NCDs in 2008 with 48% of these deaths caused by CVD [1]. Despite advances in medical therapy, the prognosis following a vascular event remains poor [2]. Nearly 80% of the CVD deaths occurred in low- and middle-income countries, where, on average, they now exceed communicable diseases as the major cause of disease burden [2–4]. CVD include all diseases of the heart or circulation such as stroke, transient ischemic attack (TIA) and coronary heart disease especially due to the presence of atherosclerosis [5,6].

Stroke is currently the second leading cause of CVD death worldwide, after ischemic heart disease. The number of people suffering a stroke every year is increasing, with a mounting global burden involving stroke survivors and stroke related deaths [7]. Several different etiologies can give rise to thromboembolic strokes such as cardio embolism, small vessel occlusion, arterial dissection, thrombophilic disorders as well as other undetermined etiologies. This manuscript however, will focus on large artery atherosclerosis brought on by metabolic syndrome as cause of cerebral thrombotic events. A close association exists between the occurrence of TIA and thromboembolic stroke, since thromboembolic strokes are often preceded by a TIA. TIA is thought to serve as a warning sign that a stroke could be imminent, with a subsequent stroke occurring in roughly a third of TIA patients [8,9]. TIA is therefore also classified as a thrombotic event [10]. The most recent definition of TIA is "a transient episode of neurological dysfunction caused by focal brain, spinal cord or retinal ischemia, without acute infarction" [11]. The major difference between a TIA and thromboembolic stroke is that brain damage (necrosis) due to ischemia, is only present in strokes since ischemia and the clot are resolved in TIAs [10,12–14]. These infarcts are visible when using neuroimaging techniques such as magnetic resonance imaging (MRI). A TIA typically lasts less than 1 hour and is caused by local brain ischemia, due to the occlusion of a cerebral vessel [8,15,16]. The blood clot causing the occlusion eventually dissolves or is dislodged, resulting in restored blood flow to the hypoxic area. In a thromboembolic stroke, however, the occlusion cannot be dissolved or dislodged resulting in permanent hypoxia and consequent necrosis [17].

TIAs are usually associated with the presence of carotid artery atherosclerosis [18]. Atherosclerosis is caused by the progressive accumulation of cholesterol and lipids in blood vessel walls, resulting in secondary inflammation, repetitive fibrous tissue deposition, and eventually luminal surface erosions [19]. Disruption of atherosclerotic plaques leads to thrombus formation and arterial occlusion [20]; that can result in the development of mobile thrombi, resulting in an embolus and subsequent TIA or stroke [16]. Therefore, unpredictable and potentially life-threatening atherothrombotic sequence underlies clinical events such as angina and TIAs, and eventually the full consequences of thromboembolic ischemic stroke or myocardial infarctions. Central to the formation of the thrombus, and the development of atherothrombosis, is platelet activity and fibrin formation. Studies have shown that platelets are hyper-activated and prothrombotic in TIAs [21]. Platelet alterations in the presence of atherosclerosis may result in an increase in platelet adhesiveness, ultimately resulting in abnormal platelet aggregation and thrombus formation. Importantly, atherosclerosis, hypercoagulability, TIAs and thromboembolic ischemic stroke represent a spectrum of conditions dependent on similar prothrombotic processes, which could ultimately, if ignored, lead to death [22].

Current research, however, suggests that the development of atherosclerosis is not the first step in CVD, but rather that the entire process starts years earlier with the development of metabolic syndrome. It has been postulated that metabolic syndrome leads to atherosclerosis, which in turn could result in TIA [22]. Metabolic syndrome could therefore be central in the development of TIA and/or stroke. This review therefore focuses on the prevalence, etiology and pathophysiology of metabolic syndrome related to activation of platelets and the subsequent development of thromboembolic stroke and TIA. The central theme of this manuscript is summarized in Fig. 1.

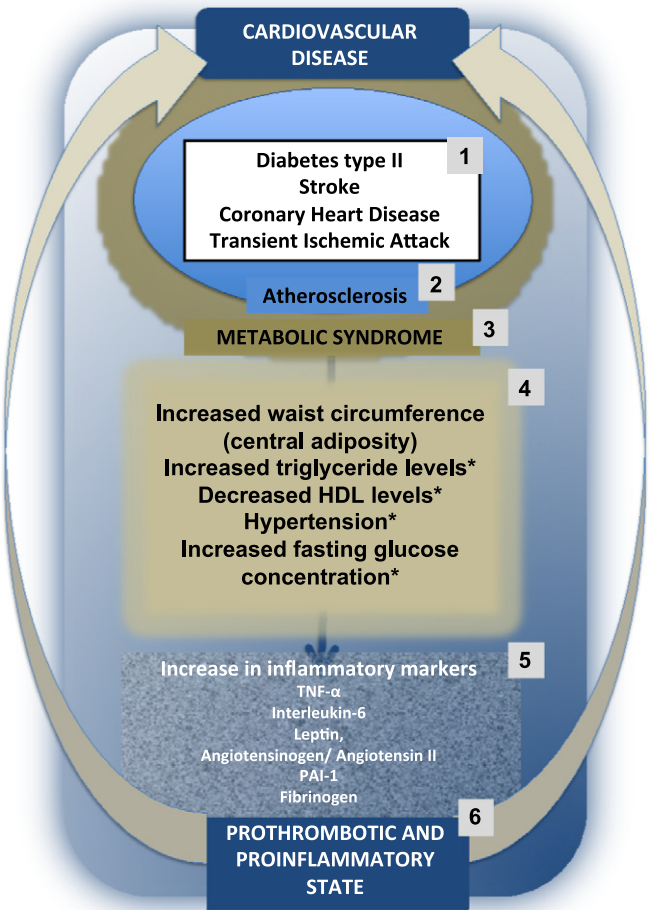

Fig. 1. Layout of this manuscript. ***1)*** Cardiovascular diseases such as *diabetes type II, stroke, coronary heart disease and transient ischemic attack (TIA) are associated with* ***2)*** *atherosclerosis that is now believed to be due to metabolic syndrome* ***3).*** *At least 3 of the list in* ***4)*** *needs to be present to be diagnosed with metabolic syndrome. Metabolic syndrome is characterized by an increase in inflammatory markers* ***5)****. This leads to a general prothrombotic and proinflammatory state* ***6),*** *which is fundamentally linked to cardiovascular disease.*