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Not all clots are created equal: a review of deficient thrombolysis with tissue plasminogen activator (tPA) in patients with metabolic syndrome

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Abstract

Metabolic syndrome is a cluster of cardiovascular risk factors associated with a prothrombotic, proinflammatory and hypofibrinolysis state. Although resistance to tissue plasminogen activator (tPA) in metabolic syndrome patients has been associated with a defective fibrinolytic system, the factors and mechanisms underlining such resistance is unclear. While there is a great debate on proposed mechanisms, fundamental questions regarding resistance to tPA in metabolic syndrome patients with ischemic stroke remain unanswered. This article reviews articles and documents published between 2001 and 2017, and provides an overview of metabolic syndrome, factors associated with tPA resistance in metabolic syndrome, conflicting evidence of insufficient dosing of tPA in overweight/obese patients and future directions for research.

Keywords

Metabolic syndrome; ischemic stroke; tissue plasminogen activator; thrombolysis; cardiovascular disease

Introduction

Cardiovascular diseases (CVDs) are a major cause of mortality and morbidity worldwide. Stroke is the fifth leading cause of death and disability in the United States [1,2]. On average, stroke occurs every 40 s and death from stroke every 4 min [1]. Ischemic stroke is responsible for 87% of all strokes and is associated with several risk factors, including metabolic syndrome [1]. According to a population-based study, metabolic syndrome is responsible for 19% of all strokes [3].

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To date, the treatment options for acute stroke are limited. Tissue plasminogen (activator tPA) is the only approved medication for the treatment of acute ischemic strokes administered within 3 to 4.5 h of onset of stroke [4]. With a growing body of evidence showing that metabolic syndrome is associated with a pro-inflammatory, pro-thrombotic and hypofibrinolytic state [5–12], it is of interest to understand why metabolic syndrome patients with ischemic stroke respond poorly to tPA.

This article reviews the relationship between metabolic syndrome and stroke, pathophysiological mechanisms of metabolic syndrome and coagulation cascade, factors associated with tPA resistance in metabolic syndrome, conflicting evidence and unanswered questions of insufficient dosing of tPA in overweight/obese patients and future directions for research. A pubmed search was done in June 2017 for full articles, review articles and documents published between 2001 and 2017 using the following MeSH terms: ‘cardiovascular diseases’, ‘metabolic syndrome’, ‘hemostasis/thrombosis’, ‘stroke’, ‘tPA, and pharmacodynamics/pharmacokinetics of tPA’. The MesH terms were later on combined as follows: ‘stroke and tPA’, ‘metabolic syndrome and stroke’, ‘resistance to tPA and metabolic syndrome’, ‘sex differences and metabolic syndrome’, and ‘patients with ischemic stroke’, ‘metabolic syndrome and ischemic stroke’, ‘metabolic syndrome and hemostasis/thrombosis’, and ‘metabolic syndrome and inflammation’. We narrowed down our search to studies conducted in humans (especially adults).

Metabolic syndrome

Epidemiology

Metabolic syndrome is a cluster of at least three cardiovascular risk factors that include high blood pressure, central obesity, hyperglycemia and dyslipidemia [13]. The 2009 to 2010 and 2011 to 2012 National Health and Nutrition Examination Survey (NHANES) reported a decrease in the prevalence of metabolic syndrome in youths aged 12–19 years old compared to earlier survey [1]. A similar trend was also seen in the adult population [14]. Despite the decreasing trend, metabolic syndrome progresses with advancing age in 76% of adults; with a faster progression in women and adolescents [1]. Another study in 2010 showed that metabolic syndrome was more common in women that in men [9,14]. Patients with metabolic syndrome have a fivefold increased risk of developing diabetes and a twofold increase risk of developing CVD. In addition, the risk of having a stroke is two to four times more likely in patients with metabolic syndrome [9,15,16].

Definition of metabolic syndrome

Metabolic syndrome can be diagnosed using a set of risk factor criteria established by scientific/clinical organizations [17]. While three of the four organizations (World Health Organization (WHO), European Group for Study of Insulin Resistance (EGIR), and the American Association for Clinical Endocrinologists (AACE)) define metabolic syndrome as an insulin resistance syndrome, the International Diabetes Federation (IDF) defines metabolic syndrome as a syndrome characterized by central obesity [17]. Interestingly, the WHO definition of metabolic syndrome included microalbuminuria as one of its five risk factors [17]. The AAEC considered abnormal uric acid metabolism, hemodynamic changes,

pro-thromobotic factors, markers of inflammation and endothelial dysfunction in addition to traditional risk factors of metabolic syndrome (obesity, hyperglycemia, dyslipidemia and hypertension) [17].

Despite the existing differences in the definition of metabolic syndrome, the National Cholesterol Education Program-Adult Treatment Panel III (NCEP ATP III) uses a different multidimensional approach [17,18]. According to NCEP ATP III, metabolic syndrome is defined by the presence of at least three of five components (low high-density lipoprotein, high triglyceride levels, visceral obesity, hypertension and high fasting glucose) [17,18]. Among all the components of metabolic syndrome, insulin resistance seems to be the common underlining pathophysiological mechanism [19].

Pathophysiology – Metabolic syndrome and inflammation

Metabolic syndrome is a significant contributor to the pathophysiology of ischemic stroke. It is associated with three main processes (pro-inflammatory, pro-thrombotic and hypofibrinolysis) that interact to create a favorable environment for ischemic stroke [7,8,10,11]. With regards to inflammation, a close relationship exists between inflammation and the fibrinolytic system in patients with metabolic syndrome [8]. Increased adiposity in metabolic syndrome contributes to adipocyte hypertrophy that leads to tissue hypoxia and release of adipocytokines such as tumor necrosis factor, IL-6, leptin, angiotensinogen, angiotensin II and plasminogen activator inhibitor-1 (PAI-1) [17].

Tumor necrosis factor-α (TNF-α) results in oxidative stress, induces plasminogen activator inhibitor-1 (PAI-1) and leptin production, promotes the expression of endothelial adhesion molecules and reduces the secretion of adipocytokines [7,17]. In addition to inducing the release of substances that potentiate a prothrombotic state, TNF-α has a direct and an indirect role in initiating insulin resistance [7]. TNF-α initiates insulin resistance directly by inhibiting insulin receptor activity [7]. Through an indirect mechanism, TNF-α initiates insulin resistance by enhancing the production of non-esterified fatty acid [7].

IL-6 induces insulin resistance, increasing platelet count and platelet aggregation, and promotes thrombosis by increasing synthesis of fibrinogen [7,10]. IL-6 is also known to increase expression of endothelial adhesion molecules [7]. Besides suppressing food intake, leptin promotes platelet aggregation, and increases the secretion of CRP by acting on IL-6 receptors in the liver and thus creates a self-perpetuating chronic inflammatory cycle [7].

Angiotensinogen/angiotensin increases the production of reactive oxygen species, inflammatory cytokines and adhesion molecules. The release of these substances eventually leads to vasoconstriction and smooth muscle proliferation that increase the probability of plaque rupture [7,10].

Plasminogen activator inhibitor-1 (PAI-1) is produced by the liver, adipose tissue and spleen [7]. It inhibits tissue plasminogen activator and thus leads to a thrombotic state by decreasing the clearance of fibrin. PAI-1 has also been shown to be directly correlated with obesity, tumor growth factor β, angiotensin II, TNF-α, insulin and free fatty acids [7,11,20].

Pathophysiology – Relationship between metabolic syndrome and coagulation/platelet function

As mentioned previously, metabolic syndrome is associated with a pro-coagulant and hypofibrinolytic state. Endothelial dysfunction is the driving force behind the pro-coagulant and hypofibrinolytic state associated with metabolic syndrome [21]. Endothelial dysfunction leads to the release of pro-thrombotic, pro-inflammatory and hypofibrinolytic substances that in turn increase the expression of adhesion molecules [21]. Other factors that play an important role in potentiating the pro-thrombotic, pro-coagulant and hypofibrinolytic state in metabolic syndrome include insulin resistance with decreased tissue plasminogen activator, increased PAI-1 level, and increased production of factor VII, factor VIII, fibrinogen and tissue factor (TF) [21,22]. In addition, increased levels of factor XIII and triglycerides, and a decrease in HDL-C levels have also been associated with activation of the coagulation cascade [21,23]. The pro-inflammatory, pro-thrombotic, hypo-fibrinolysis, and increased platelet aggregability associated with metabolic syndrome predispose patients to atherosclerosis, thrombosis and other cardiovascular diseases including ischemic stroke [7,17].

Relationship between metabolic syndrome and ischemic stroke

In general, there is a strong relationship between metabolic syndrome and CVD. According to the third National Health and Nutrition Examination Survey (NHANES III), metabolic syndrome is associated with increased risk of both ischemic stroke and myocardial infarction [24]. In another study, metabolic syndrome was also associated with increased cardiovascular mortality [25]. Koren and colleagues in a prospective study involving 14,284 metabolic syndrome patients without diabetes, and 3500 with diabetes reported that the odds of having a transient ischemic stroke (TIA) or ischemic stroke was more than 2-fold higher for the diabetic group compared to 1.49 for patients with metabolic syndrome without diabetes [18]. Additionally, women were found to have higher odds of TIA or ischemic stroke [18].

With insulin resistance being the common underlining pathophysiological mechanism in metabolic syndrome [17,19,26], Koren-Morag et al. also reported that, impaired glucose tolerance and hypertension were the greatest predictors of TIA or ischemic stroke [18]. Hypertension damages the endothelium; increasing oxidative stress and expression of adhesion molecules, and thus predisposing patients to increased risk of thrombosis and ischemic stroke [2,17]. Advanced glycosylated end products produced in diabetes also damage the endothelium; increasing the risk of ischemic stroke [2,16,27]. It is important that the risk of ischemic stroke increases with the number of components of metabolic syndrome [11,18].

tPA and treatment of acute ischemic stroke

To date, the only treatment approved by the food and drug administration (FDA) for acute ischemic stroke is tissue plasminogen activator (tPA) administered within 4.5 h of symptom onset [28,29]. In 2009, the treatment rate of acute ischemic stroke with intravenous tPA in the United States was 3.4 to 5.4% [28]. Tissue plasminogen activator, as the name indicates, activates plasminogen to plasmin. Plasmin dissolves the clot in the brain and reestablishes

recanalization of the occluded blood vessel [30]. Tissue plasminogen activator reestablishes recanalization of the occluded vessel in 10 to 25% of the cases and has a very short half-life [31,32]. The main side effects associated with tPA during treatment of ischemic stroke include intracerebral hemorrhage, hemorrhagic transformation, and bleeding in other organs [30].

Clot composition and metabolic syndrome: not all clots are created equal

In addition to increased levels of PAI-1 activity [5,18], one theory that might explain decreased tPA effect in patients with metabolic syndrome is clot density. High levels of PAI-1 and factor XIII are significant contributors of dense clot formation in metabolic syndrome patients; thus increasing the risk of stroke and decreasing tendency of clot dissolution [23,26]. Clot lysis depends on concentrations of fibrinolysis inhibitors, structure of the clots, and binding properties of the fibrin clot to plasminogen or tPA [17,33]. In general, fibrin clots are made up of an aggregate of laterally arranged protofibrils branching into a three-dimensional structure [34]. There are two types of fibrin clots; dense and light fibrin clots. Lighter clots are made up of thick arranged fibrin fibers. Dense clots on the other hand are made up of thin and densely packed fibrin fibers [33]. Carter et al. (2007) also showed that patients with metabolic syndrome had denser clots that lysed more slowly than clots from patients without metabolic syndrome, and clot density increases with increasing number of cardiovascular risk factors [33].

Metabolic syndrome and treatment of ischemic stroke with tPA; misconceptions and unanswered questions

Although it is established that metabolic syndrome is associated with a prothrombotic, proinflammatory and hypofibronolytic state, there are still gaps in knowledge regarding the effect of metabolic syndrome on the effectiveness of tPA in acute ischemic stroke [10,17,21]. While many questions remain unanswered, the impact of metabolic syndrome in patients with ischemic stroke has been associated with a few conflicting evidence. For example, it was believed that obese patients had a better clinical outcome (obesity paradox) following treatment with tPA [35]. However, a recent study showed that, the protective effect disappeared after adjusting for age, stroke severity and stroke sub-type [36]. Seet et al. (2014) therefore suggested that other components of metabolic syndrome (especially hypertension and insulin resistance) be considered crucial factors that affect acute and long-term outcomes following tPA treatment rather than obesity alone [36].

Further, another theory about the poor response to tPA in metabolic syndrome patients is insufficient dosing. In general, patients presenting with ischemic stroke receive 0.9 mg/kg of alteplase; with a 90 mg dose limit [37,38]. In this light, it was believed that metabolic syndrome patients (with a weight >100 kg) receiving the 90 mg dose limit may theoretically be getting less than recommended for the treatment of stroke, and thus insufficient thrombolysis [38]. Diedler et al. showed that patients weighing >100 kg, and receiving the 90 mg dose limit of intravenous tPA (a lower dose per kilogram) had similar 3-month outcomes, and response to thrombolysis than those weighing <100 kg [39]. However, the group weighing >100 kg had higher rates of intracranial hemorrhage, implying that the current dose limit should not be increased for obese patients (or metabolic syndrome).

Contrary to the above findings, Garavaglia et al. conducted a retrospective analysis of 301 patients with 21% receiving the standard 0.9 mg/kg and 79% receiving the maximum dose (90 mg) of tPA and found no significant difference in 90-day Modified Ranking Scale Score, asymptomatic hemorrhage and symptomatic hemorrhage [37].

There are additional unanswered questions regarding increased resistance to tPA seen in metabolic syndrome patients with stroke. One of the unanswered questions is whether resistance to tPA in metabolic syndrome patients is related to unusual tPA pharmacokinetics and pharmacodynamics. Although volume of distribution in the central compartment is lower in ischemic stroke patients than in healthy subjects [40], it is unclear whether volume of distribution, plasma clearance and metabolism of tPA are affected by metabolic syndrome [40]. However, since metabolic syndrome is associated with other comorbidities such as diabetes, fatty liver disease, hypertension and other vascular dysfunction [38], metabolic syndrome may mediate resistance to tPA by indirectly affecting volume of distribution, plasma clearance and metabolism of tpA. It is therefore of great interest to understand the pharmacodynamics/pharmacokinetics of tpA in metabolic syndrome patients with strokes compared to their healthy weight counterparts.

Another important unanswered question is the gender difference in response to tPA in metabolic syndrome patients. Metabolic syndrome patients (especially women) have a 2.2-fold probability of resistance to tPA; with resistance occurring as early as 2 h following administration of tPA [19,20,28]. The reasons for such resistance have not been fully elucidated. Factors that may play a role include increased levels of plasminogen activator inhibitors, increased clot density and lysing time, poor leptomeningeal collateral circulation, endothelial dysfunction, platelet activation and pro-inflammatory state associated with metabolic syndrome [41–43]. Key findings from both clinical and population-based studies are provided in table 1.

Conclusion

Metabolic syndrome is associated with a proinflammatory, prothrombotic and hypofibrinolytic state. This paper reviews complex interactions between metabolic syndrome and ischemic stroke; emphasizing how the epidemiology of both conditions contributes to understanding the pathophysiology of ischemic stroke, and factors responsible for resistance of intravenous tPA in metabolic syndrome patients. Key questions that remain unanswered include differences in pharmacokinetics/pharmacodynamics of tPA in ischemic stroke patients with metabolic syndrome compared to healthy weight patients, reasons for gender difference in clot dissolution with intra-veinous tPA, and clot structure, burden and density in ischemic stroke patients with metabolic syndrome compared to their healthy weight counterparts.

Future directions

This review article identifies four main issues that should be considered for future research. First, from a clinical standpoint, prior knowledge of metabolic syndrome patients showing increased resistance to tPA can inform clinicians to identify and stratify patients who may

benefit from early thrombectomy. This may help decrease patient morbidity and healthcare expenditure in the long run. Second, it will be interesting to examine whether there is a gender difference in clot composition in metabolic syndrome patients resistant to tPA. Third, further studies should also assess sex differences and recanalization time (early vs. late recanalization). Fourth, we need to examine the impact of metabolic syndrome and hemorrhagic transformation following administration of tPA. Finally, there is a need to understand whether the pharmacokinetics/pharmacodynamics of tPA in metabolic syndrome patients differs from their healthy weight counterparts.

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Table 1.

Summary of key findings on metabolic syndrome, stroke and use of tPA.

Year	Key findings	Study population	References
2003	People with the metabolic syndrome had more atherosclerosis, CVD and elevated plasminogen activator inhibitor-1 compared with people without the metabolic syndrome	1276 Adults of South Asian, Chinese, European, and Native Indian ancestry from four communities in Canada	[5]
2004	High baseline plasminogen activator inhibitor-1 was an independent predictor of thrombolysis resistance. High PAI-1 levels interfered with tPA-induced recanalization in stroke, predicting a higher susceptibility towards clot-lysis resistance and poor outcome	44 Consecutive patients with acute proximal middle cerebral artery occlusion were studied, including assessment of transcranial Doppler artery patency.	[40]
2006/2007	Risk for incident ischemic stroke increases with increasing number of components of metabolic syndrome, all of which have been individually associated with an increased risk for future cerebral ischemic events. Insulin resistance represents the common underlying mechanism of metabolic syndrome	Population-based cohort study of 1131 men with no history of cardiovascular disease and diabetes at baseline.	[6,12]
2007	Individuals with the metabolic syndrome had significantly higher levels of high-sensitivity C-reactive protein, fibrinogen and factor VIII activity compared to those without. Metabolic syndrome is associated with a two-fold risk of venous thromboembolism	A total of 116 patients and 129 (age and sex-matched) controls were enrolled	[22]
2008	Forty-two (42%) patients showed resistance to clot dissolution, and 53 (53%) had poor clinical outcomes. Metabolic syndrome was identified as independently associated with resistance to thrombolysis	100 Consecutive patients with ischemic stroke with middle cerebral artery occlusions on prebolus transcranial Doppler (TCD) examination treated with tPA	[26]
2009	Resistance to clot lysis with tPA at 24h was observed in 53 (42%) patients. Metabolic syndrome was associated with a significantly higher odds of resistance to thrombolysis in women than in men	A total of 125 patients (75 men, 50 women; mean age, 67.6 ± 11 years) were included	[19]
2011	Patients who weighed > 100 kg received a lower per-kilogram alte-plase dose compared to those who weighed <100 kg. Neurological improvement and functional independence was similar in both groups. There was a higher incidence of symptomatic intracerebral hemorrhage in patients who weighed > 100 kg despite the lower per-kilogram recombinant tissue plasminogen activator dose.	27,910 Patients registered in Safe Implementation of Treatment in Stroke-International Stroke Thrombolysis Register (SITS-ISTR; 2002–2009) were included, and considered for analysis.	[39]
2014	There were no significant associations between the number of risk components of metabolic syndrome with respect to symptomatic intracranial hemorrhage. Age, baseline stroke severity, and the number of risk components of the metabolic syndrome accounted for 52% variation in functional recovery after intravenous thrombolysis	A total of 169 patients (mean age 75 years; baseline National Institutes of Health Stroke Scale score 11) were included and outcomes after recombinant tissue plasminogen activator treatment were compared between obese, overweight, and normal weight patients	[36]
2015	Metabolic syndrome was an independent predictor of resistance to thrombolysis and absence of dramatic neurological improvement. Metabolic syndrome also conferred poorer functional outcome, higher symptomatic intracerebral hemorrhage rate, and increased infarct volume. These associations disappeared after adjustment for covariates.	A prospective and observational study in consecutive stroke involving a total of 234 patients with MCA occlusion treated with IV tPA patients. One hundred and forty six (62.4%) fulfilled metabolic syndrome criteria	[17]
2017	64 (21%) received <0.9mg/kg dosing of tpA. There was a statistically significant association toward a good outcome for increases in tPA dose rate when compared against a poor outcome	A total of 301 patients were included in a single center retrospective analysis to assess the dosing rate and 90-day outcomes comparing maximum dosage (90 mg) and standard dosage (0.9 mg/kg) of tPA	[37]