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Review article

Molecular mechanisms underlying some major common risk factors of stroke

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ABSTRACT

Ischemic and hemorrhagic strokes are the most common known cerebrovascular disease which can be induced by modifiable and non-modifiable risk factors. Age and race are the most common non-modifiable risk factors of stroke. However, hypertension, diabetes, obesity, dyslipidemia, physical inactivity, and cardiovascular disorders are major modifiable risk factors. Understanding the molecular mechanism mediating each of these risk factors is expected to contribute significantly to reducing the risk of stroke, preventing neural damage, enhancing rehabilitation, and designing suitable treatments. Abnormalities in the structure of the blood-brain barrier and blood vessels, thrombosis, vasoconstriction, atherosclerosis, reduced cerebral blood flow, neural oxidative stress, inflammation, and apoptosis, impaired synaptic transmission, excitotoxicity, altered expression/activities of many channels and signaling proteins are the most knows mechanisms responsible for stroke induction. However, the molecular role of risk factors in each of these mechanisms is not well understood and requires a lot of search and reading. This review was designed to provide the reader with a single source of information that discusses the current update of the prevalence, pathophysiology, and all possible molecular mechanisms underlying some major risk factors of stroke namely, hypertension, diabetes mellitus, dyslipidemia, and lipid fraction, and physical inactivity. This provides a full resource for understanding the molecular effect of each of these risk factors in stroke.

1. Introduction

Stroke is a cerebrovascular disease that is caused by the interruption of the blood supply to the brain. Globally, stroke is a leading cause of death and disability among the affected subjects and is common in both males and females of all ages [1]. Based on the etiology, stroke can be classified into ischemic or hemorrhagic subtypes. The ischemic stroke accounts for the majority of cases (80–87%) and results from the vascular occlusion of any of the cerebral arteries due to thrombosis, cardio-embolism, or atherosclerosis and platelets plug (focal) or due to a complete reduction in blood flow to the brain such as in cardiac arrest (global) [2]. Also, ischemic stroke could be fatal or non-fatal. On the other hand, hemorrhagic stroke develops due to a ruptured blood vessel following hypertension, cerebral amyloid deposition, aneurysms, or traumas [3]. Typical clinical manifestations of stroke are motor, visual, and speech abnormalities including numbness, non-orthostatic vertigo; aphasia and altered speech, diplopia, and sudden unilateral weakness that is contralateral to the affected brain hemisphere [1, 4]. However, atypical symptoms include headache, confusion, amnesia (loss of memory), stridor, blindness, anosognosia (cognitively unaware), isolated vertigo, dysarthria (a motor speech disorder), dysphagia, and altered consciousness [1, 3, 4].

According to the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) classification, the ischemic stork can be divided into 5 types including 1) the large arteries thrombotic stroke that is caused by large atherosclerotic plaque in the large arteries (20%), 2) small penetrating artery thrombotic (lacunar) stoke (25%), 3) cardiogenic embolic stroke in which one or more vessels in the brain are affected (microatheromatosis) (15%), 4) cryptogenic unknown which is identified as the stroke of unknown causes (5–10%), and 5) stroke of other causes such as due to infection and illicit drugs (20–25%) [5]. Another classification of the stroke is the ASCOD phenotyping system which classifies the ischemic stroke into different subtypes [4, 6, 7]. Accordingly, type A is for strokes of atherosclerotic origin, type S for small-vessel disease, type C for cardiogenic strokes, types O for the stroke of unknown causes, and type D for dissection. On the other hand, hemorrhagic stroke is classified according to

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the etiology and the affected site [8]. Hemorrhagic stroke can be classified into two major types, namely subarachnoid hemorrhage and intracerebral hemorrhage (ICH) [3]. Supratentorial ICH is the most common site of hemorrhagic stroke that occurs in about 85–95% of patients [4]. Among these numbers, deep supratentorial intracerebral hemorrhage is the most common type seen in 50–75% of the patients whereas the lobar supratentorial intracerebral hemorrhage is less common with a rate of 25–40% [4]. However, hypertension is the most common cause of intracerebral hemorrhage that occurs in about 30–60% of the total cases followed by cerebral amyloid angiopathy, anticoagulation which is seen at a rate of 10–30% and 1–20%, respectively [4, 8].

Moreover, stroke of both types can occur during early or late life and is associated with many clinical manifestations and disabilities. A perinatal stroke occurs often during the last 20 weeks of gestation and one month after birth. It is currently estimated that the incidence rate of perinatal stroke is higher than 1/3500 per birth, and is a major cause of hemiparetic cerebral palsy [9, 10]. It has been reported by Kirton and Deveber that infant survivors also suffer from other neurological sequelae and manifestations that last for their entire life including; behavioral disorders, cognitive deficits, intellectual disabilities, and epilepsy. On the other hand, common disabilities seen in adult stroke survivors are cognitive, intellectual, and motor dysfunction; including unilateral paralysis and weakness, diplopia, imbalance and coordination problems, poor memory, thinking and learning functions, loss of speech, language, and visual problems, nausea, dizziness, and ataxia [11].

Reducing the burden of stroke required identifying the underlying risk factor and placing potential therapy. Understanding and early identifying the modifiable risk factor is imperative as it helps significantly to reduce the risk of stroke after immediate diagnosis and intervention [12]. During the last decades, several experimental, cross-sectional, epidemiological, and clinical studies have been conducted to identify the risk factors of both ischemic and hemorrhagic stroke. These factors and their proper management are listed and described in excellent reviews [4, 5, 13, 14]. Despite this, physicians find some frustrations in the diagnosis, treatment, and management of stroke which was attributed to a lack of knowledge of the precise molecular mechanisms underlying each risk factor, especially in the presence of other comorbidities. Understanding such mechanisms will help to identify therapeutic targets and develop protective molecules during the onset of stroke and recovery. To date, the literature lacks a comprehensive review that summarizes the overall molecular mechanisms mediating both types of strokes.

Therefore, in this review, the author aimed to revise the literature and issue a comprehensive update to discuss the role of major risk factors in the development of ischemic and hemorrhagic strokes. In particular, age, ethnicity, hypertension, diabetes mellitus, lipids, and physical activity. In addition, this paper gave a special focus on the overall molecular mechanisms underlying these risk factors.

2. Materials and methods

In this study, a comprehensive literature review search for all risk factors related to stroke was conducted using the major search engines including PubMed, Medline Plus, Medscape, PubMed central, The Cochrane Library, and Google Scholar. All experimental, subclinical clinical, clinical, epidemiological, cases report, and thesis were included. The following Keywords and terms were used in conjugation with the word Stroke: Ischemic Stroke, Haemorrhagic stroke, Diabetes, Hyperglycaemia, Hyperinsulinemia, Blood pressure, Hypertension, Dyslipidaemia, Hypercholesterolemia, Cholesterol, LDL-C, HDL-c, Triglycerides, Smoking, Alcohol, Exercise, Physical activity, Race, Epidemiology, Risk Factors, and Geography.

3. Results and discussion

3.1. The global prevalence of stroke

The global population provenance of stroke is obtained from large population-based studies and WHO reports. However, due to the rapid change in stroke epidemiology, these estimated studies should be continuously repeated over time, especially in poor countries where resources are still very limited. The Global Burden of Diseases (GBD) study, set up in 1992 by the Institute for Health Metrics and Evaluation at the University of Washington, remains the comprehensive population-based study that continuously quantifies and updates the global, country, and regional stroke burden in more than 188 countries around the world [15]. Within this view, GDB estimated the global burden of stroke by sex, age, and location in terms of prevalence, incidence, number of deaths, years of disability, and disability-adjusted life-years (DALYs). According to the most recent GDB report published in 2016 (1990–2016) and extended the terminal age to 95 years old, 80.1 million cases were reported globally with stroke in which 5.5 million deaths and 116.4 million DALY were reported. There was a significant decrease in the global age-standardized mortality rate, DALY, and incidence by 36.2%, 34.2, and 8.1% respectively [15]. However, despite these declines, the global burden of stroke is still high. Indeed, over the same period (1990–2016), the incidence rate of stroke has doubled in countries with low and medium-income and decreased by more than 42% in high-income countries over the same period, indicating an increase in the social-economic burden [15].

On the other hand, the prevalence and burden of stroke (mortality and morbidity) are much higher in the south Pacific, eastern Europe, central Africa, and North Asia [5]. The regional prevalence of hemorrhagic and ischemic stroke depends on the risk factors. A piece of accumulating evidence has shown that the prevalence of hemorrhagic stroke was significantly higher relative to that of ischemic stroke in developing countries where hypertensive disorders are more common [13]. However, controlling hypertension with the significant demand on the western diet has resulted in an epidemiological transition toward ischemic stroke due to the development of ischemic heart disorders (IHD). A typical example of such epidemiological transition occurred in Beijing, China between the years 1984 and 2004 where a 1.7% decline in the incidence of hemorrhagic stroke with a parallel 8.7% increase in the incidence of ischemic stroke were observed and were coincided with a significant decline in cerebrovascular disorders and an increase in ischemic heart disorders [16].

3.2. Common risk factors and triggers of stroke

Risk factors for hemorrhagic and ischemic stroke are almost similar with some notable differences. These include modifiable and non-modifiable risk factors. The non-modifiable factors of stroke include sex, age, ethnicity, and genetics [12]. However, the modifiable risk factors include diet and other comorbid conditions such as diabetes mellitus (DM), hypertension, infection, stress, smoking, alcohol, obesity, physical inactivity, and hyperlipidemia [4, 5, 13, 14] (Figure 1). These modifiable and non-modifiable risk factors could act in short (e.g. stress and infection), medium (e.g. hyperlipidemia and hypertension), and long-term (e.g. race and sex) [13]. According to the international INTERSTROKE case-control study conducted in 22 nations, smoking, hypertension, alcohol consumption, western diet, and higher waist-to-hip ratio (obesity) are the major risk factor for intracerebral hemorrhagic stroke [17] (Figure 1). However, physical inactivity, diabetes mellitus, cardiovascular disorders (CVDs), depression, psychosocial stress, and higher levels of apolipoprotein B are the common risk factors for ischemic stroke [13] (Figure 1). These factors increase the risk of stroke by 90% [13]. At the pathological level, most of these modifiable risk factors can act by altering the vascular structure and function, promoting morphological changes (i.e, hyperplasia and atherosclerosis), reducing the cerebral blood flow (CBF) perfusion, impairing the cerebrovascular autoregulation, increasing the intrinsic susceptibility to damage, and amplify the neural damage after an ischemic episode [18, 19]. Of note, known molecular mechanisms mediating ischemic and hemorrhagic stroke, in general, include over-production of reactive oxygen species (ROS), scavenging nitric oxide (NO), and promoting oxidative stress,

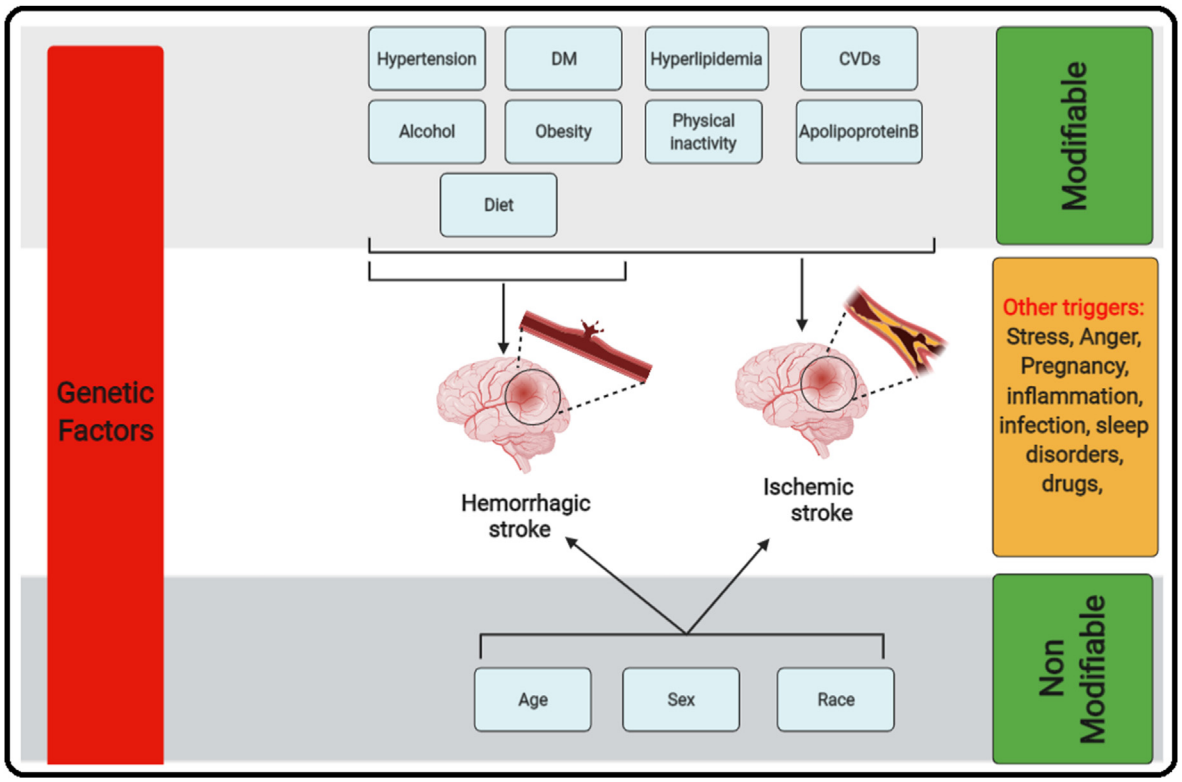

Figure 1. Modifiable, non-modifiable risk factors and triggers of ischemic and hemorrhagic strokes.

inflammation, and endothelial dysfunction [20]. On the other hand, sickle cell disease (SCD), is an independent pathological risk factor for stroke [21]. The destruction of the red blood cells increases the risk of hemorrhage up to 400 folds [5, 21, 22]. Also, the risk of recurrent stroke is increased by 2–25% in 1 year and by 20–40% in 5 years after a previous stroke [5, 17]. In addition to the above-mentioned risk factors, some other modifiable factors known as ***stroke triggers*** could accelerate the development and progression of stroke (Figure 1) [20, 23, 24]. These include anger, pregnancy, chronic inflammation, infection, migraine, the use of illicit drugs, puerperium, long working hours, depression, psychosocial stress, and sleep disorders [4, 5, 20]. Up-to-date, the precise mechanisms by which stroke triggers act is still unknown but is believed to be most likely due to inflammation [20].

3.3. Non-modifiable factors

3.3.1. Age and sex

Concerning age, the incidence of stroke is doubled at an age higher than 55 with the highest rates in Asia and China (331–378/100000), followed by Europe (181–218/100000) – GBD 2015 [25, 15]. The lowest incidence rate of stroke is seen in Latin America (85–100/100000). The stroke rate is doubled in both men and women every 10 years after the age of 55 [25, 26, 27]. Interestingly, a sudden significant increase of about 5.7% (from 12.9 to 18.6%) in all stroke cases was observed in subjects aged between 20 to 54 years, indicating an alarming sign. Nonetheless, the current incidence and severity of stroke are higher in women than men. In the GBD study (2019), 51.3% of all stroke cases were seen in females (41.1 million) as compared to 48.6% in males (39.0 million). In Europe, a study conducted in 18 countries showed that the yearly increase in stroke incidence is 10 % in women compared to 9% in men [28]. Besides, the mean severity of stroke in males was almost 8 compared to 10 in females [28]. Although the occurrence of stroke is also more common in young females, it increased with older ages in men. Such an increase in the stroke incidence and severity among females was attributed to several unique female factors including longer ages, pregnancy, hormonal replacement therapy, the use of contraceptive drugs, preeclampsia, migraine, atrial fibrillation (AF), higher fatality rate, and refuse to show complain or receive help [29]. Furthermore, the common forms of stroke seen in females are cardiometabolic and subarchidonic types whereas brain fraction and intracerebral hemorrhage are frequently observed in males [15, 28, 30, 31].

3.3.2. Race and ethnicity

Ethnicity is an independent risk factor for stroke. Stoke is more prevalent in adult blacks and Hispanic Americans as compared to their white and Asian counterparts [32]. In a study performed in 2005 in the USA; the prevalences of stroke among the Alaskan natives, blacks, Hispanics, whites, and Asians were 6.0%, 4.0%, 2.6% 2.3%, and 1.6%, respectively [32]. Also, the incidence of stroke was higher in black American and Hispanic dialysis patients and those with Systemic Lupus Erythematosus (SLE) as compared to whites [32]. In the same line, the Northern Manhattan Stroke Study (NOMAS) has shown that blacks American and Caribbean Hispanics, living in the same geographically defined community, are 3 folds higher for developing stroke than whites mainly due to the prevalence of hypertension and diabetes mellitus but not due to atrial fibrillation, chronic heart disease (CHD), or physical inactivity [33]. The findings from the National Health and Nutrition Examination Survey (NHANES) have shown that blacks are at higher risk for developing ischemic and hemorrhagic strokes due to the prevalence of hypertension, diabetes mellitus, peripheral vascular disease, and C-reactive protein [34, 35]. Indeed, blacks develop stroke risk factors, especially hypertension and diabetes at younger ages and experience greater rates of mortality (28% higher) as compared to whites [36]. In this study, a 38% significant decrease in the black mortality rate was observed after adjusting for sex and family income [36]. On the same page, blacks had greater severity of stroke at hospital admission than whites which was attributed to the variations in the socioeconomic factors, low income, and poor health care [37]. The same authors have also shown that black survivors have a greater limitation of the post-stroke physical activity (i.e walking, carrying, etc) and showed poorer

functional outcomes following rehabilitation compared to white survivors, after adjusting the for sociodemographic factors and other comorbidities [37]. In the USA, a 17-year follow-up study was conducted on 126 018 women participants (11389 black and 114629 white women) who are free of any cardiovascular disease and stroke, at the baseline, and after adjusting for the socioeconomic variables, black women are moderately at higher risk of having a stroke (47%) as compared to white American whereas the racial disparities were greater at women aging between 50 to 60 years old [38]. Other studies including the NOMAS and the Atherosclerosis Risk in Communities (ARIC) have also reported that black women are at a 3-fold higher risk to have a stroke compared with white mates [33, 39].

3.3.3. Genetic factors

The conventional risk factors including hypertension, diabetes mellitus, and cardiovascular diseases are not the only risk factors for stroke [5, 40, 41]. Accumulating data have demonstrated a key role of genetic factors in the development of both ischemic and hemorrhagic strokes [5, 13, 42, 43]. The contribution of hereditary causes to the risk of both types of stroke could be modifiable and non-modifiable factors. Currently, tens of gene mutations are implicated to contribute directly or indirectly to increasing stroke risk. This has been discussed in excellent studies and reviews and was shown to be involved at different levels [13, 44, 45, 46, 47, 48]. On one hand, stroke could be the only and unique manifestation of an autosomal dominant or recessive single gene mutation. These include the cerebral autosomal dominant/recessive arteriopathy with subcortical infarcts and leukoencephalopathy and the autosomal dominant Familial amyloid angiopathy and Collagen 4 (COL4A1) mutations [13]. On the other hand, stroke can be just one clinical manifestation of other multi-system autosomal dominant, x-linked, and autosomal recessive single-gene disorders such as sickle cell anemia, Ehlers–Danlos type 4 disorder, Fabry disease, Marfan syndrome, and smooth muscle α-actin mutation–associated disorders [13]. Also, increased stroke risk is associated with other common and rare variants of genetic polymorphisms such as TSPAN2, FOXF2, ABO, HDAC9, and ZFHX3 [13]. Furthermore, the increase in stroke risk is linked to some genes which are also involved in mediating other chronic disorders such as diabetes mellitus, atrial fibrillation, and hypertension [49, 50].

3.4. Modifiable risk factors and triggers

3.4.1. Hypertension

Hypertension is the leading cause of both hemorrhagic and ischemic stroke and is a major contributor to increased mortality among affected subjects [51]. Hypertension is increased with age and more than two-thirds of individuals older than 65 years are hypertensive [52]. Also, hypertension is more prevalent in patients with large arteries and small vessels but less prevalent in patients with cardioembolic stroke [53]. Besides, hypertension is more prevalent in African Americans (44% in females vs. 41% in males). The relationship between stroke risk and blood pressure is a very strong, linear, and continuous relationship [13, 51, 52, 54, 55]. Patients having a history of the disease or having a blood pressure (BP) $>$ 160/190 mmHg have a predisposition to have a stroke by 54% [13, 17]. Other studies have also shown that hypertensive people are 3–4 times at higher risk to develop stroke [5, 52]. African Americans are more likely to develop hemorrhagic stroke due to hypertension by 50% [12, 14, 52]. According to the most recent INTERSTROKE study which investigated the associations of knowledge, awareness, and treatment of hypertension with the risk of stroke and its subtypes in 32 countries between 2007 and 2015, ischemic stroke was evidenced in 77.3% of the total patients compared to 22.7% cases Intracerebral hemorrhage [17]. However, reducing blood pressure in young and aged individuals by 5–6 mmHg decreased the risk of stroke by 42% [56, 57, 58].

According to guideline recommendations from the Eighth Joint National Committee (JNC 8), age was considered a major factor in treating hypertension. In this regard, patients aged more than 65 years should be treated for hypertension if their blood pressure is greater than 150/90 while those under this age should be treated if their blood pressure is higher than 140/90 [59]. Opposing this is the guidelines established by the American Heart Association (AHA) which have considered age as a nonsignificant contributing factor in treating hypertension [60]. Accordingly, irrespective of the patient's age, the treatment should start if stage 1 hypertension appeared (i.e., SBP = 140–159 mmHg and DBP = 90–99 mmHg). However, both guides emphasized the importance of changing lifestyle through exercise and diet regimens.

Nonetheless, mechanisms by which hypertension promotes stroke and expansion of the infarct have been studied in several animal models and were shown to include, at least, promoting structural changes in the smooth muscles of cerebral blood vessels (i.e. hypertrophy; rarefaction, and inward remodeling), stiffness, vasoconstriction (scavenging nitric oxide (NO), thrombosis, and atherosclerosis, as well as diminishing the cerebral blood flow (CBF) (i.e. vasoconstriction and hypoperfusion) [61, 62, 63, 64, 65, 66, 67, 68]. The molecular mechanism underlying these effects was attributed mainly to the activation of angiotensin II (ANG II) and the subsequent increase in the production of reactive oxygen species (ROS) and the activation of phospholipase C (PLC) [67, 69, 70, 71, 72, 73, 74]. Each of these pathways may activate a particular mechanism to increase the risk of stroke. In this review, I have examined all these separate studies and pathways and withdrawn a single figure that summarized and connect all these hypertensive molecular pathways and how they collaborate to induce stroke (Figure 2). In brief, increasing intraluminal pressures stimulate muscle contraction and vasoconstriction by activating phospholipase C (PLC) and subsequent production of inositol triphosphate (IP3) and intracellular Ca+2 which in turn stimulate vasoconstriction. On the other hand, ANG II mediates the majority of the above-mentioned effects of hypertension through activating NADPH oxidase and increasing the production of (ROS). The cellular effects of ROS include: 1) activating the caveolin-1 (Cav-1)/PI3K/Akt axis; 2) promoting inflammation by activating NF-κB and upregulating several adhesive molecules and inflammatory mediators; 3) increasing the generations of peroxynitrite (ONOO-) which leads to reduce the generation of nitric oxide generation (NO), upregulating the vasoconstrictor endothelin-1 (ET-1), and activating poly-ADP-ribose polymerase (PAR-P)-induced Ca^{2+} overload, 4) activating of the matrix metalloprotease-9 (MMP-9); 5) changing antioxidants including manganese superoxide dismutase (MnSOD) and glutathione (GSH); 6) increasing the oxidation of low-density lipoprotein cholesterol (ox-LDL) which promotes atherosclerosis; and 7) downregulating and inhibiting of small- and intermediate-conductance calcium-activated potassium (SK_{Ca}/IK_{Ca}) and potassium ($Kir_{2.x}$) channels; and 8) inducing endoplasmic reticulum (ER) stress.

3.4.2. Diabetes mellitus

Prediabetes and diabetes including type 1 and type 2 DM (T1DM and T2DM, respectively) are the second most known contributing factors to a stroke which lead double the risk of stroke, increases mortality by 20%, and are associated with poor prognosis and slower recovery [75, 76, 77, 78, 79, 80]. The prevalence of prediabetes and diabetes mellitus in stroke patients ranges between 28% and 45% [81]. Like hypertension, diabetes also increased with age and raised the risk of stroke by 60% in elderly patients [82]. In the USA, more than 50% of Americans aged higher than 65 years are pre-diabetic [13]. Moreover, DM is increased in young blacks which accounts for the increase in the prevalence of stroke among the young population [13]. However, T2DM patients usually are presented with additional risk factors for stroke such as hyperlipidemia, atrial fibrillation, hypertension, insulin resistance (IR), and obesity [79, 83, 84]. However, T1DM could amplify the risk of stroke through these mechanisms but to a lesser degree [79]. Of note, lacunar stroke or small vessel disease, identified as a small stroke in size that $<$15 mm in diameter is the most common type of stroke seen in diabetic patients and involves small penetrating arteries [85].

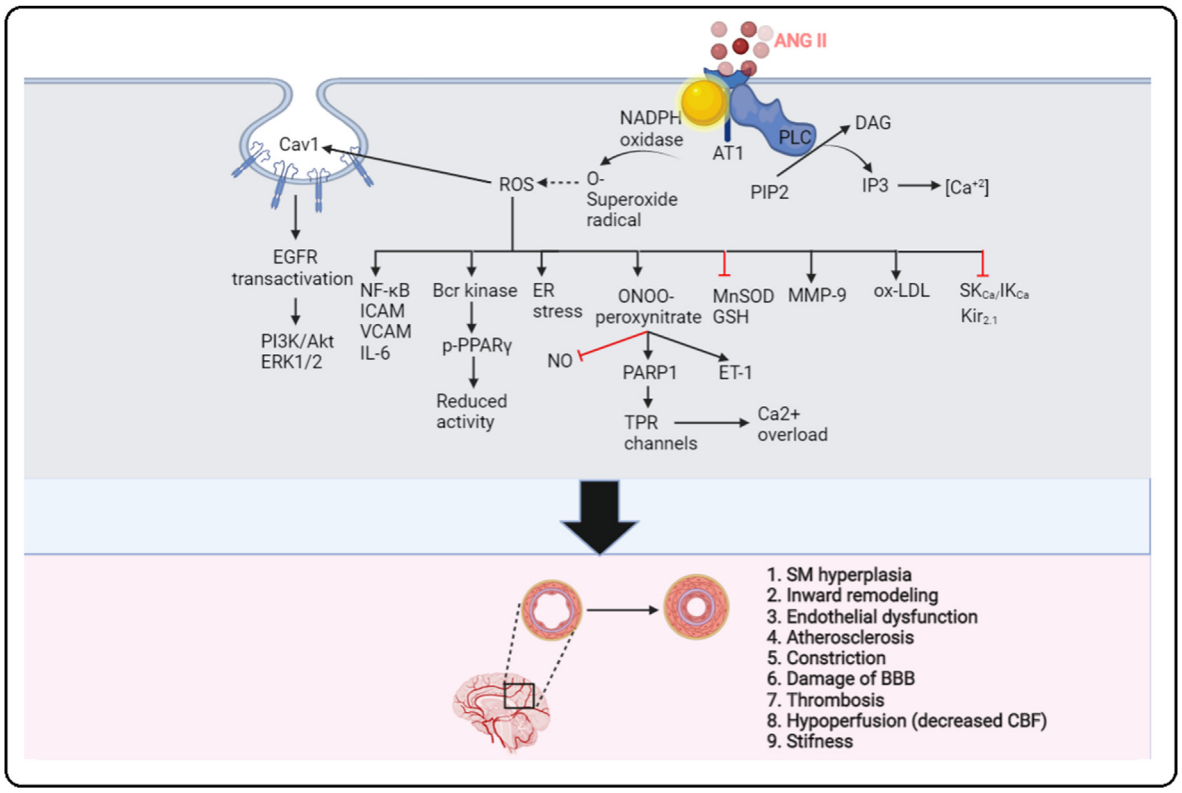

Figure 2. Molecular mechanisms by which hypertension increases the risk of stroke through modifying the structure and function of the cerebral blood vessels. Diverse mechanisms include increasing smooth muscle hypertrophy, inward remodeling, promoting endothelial dysfunction, atherosclerosis, vasoconstriction, thrombosis, and vessel stiffness, and reducing cerebral blood flow (CBF). Increasing intraluminal pressures stimulates muscle contraction and vasoconstriction by activating phospholipase C (PLC) and subsequent production of inositol triphosphate (IP3) and intracellular Ca^{2+} which induces vessel vasoconstriction. However, ANG II generates large quantities of reactive oxygen species (ROS) through activating NADPH oxidase. In turn, ROS induces vessel structural changes, apoptosis, inflammation, and vasoconstriction by activating the caveolin-1 (Cav-1)/PI3K/Akt axis, stimulating NF-κB and the expression of diverse adhesive and inflammatory cytokines, inducing vasoconstriction through the further generation of scavenging nitric oxide (NO) and peroxynitrite oxidants (ONOO-), upregulating endothelin-1 (ET-1), and activating poly-ADP-ribose polymerase (PARP), upregulating the matrix metalloprotease-9 (MMP-9), scavenging antioxidants like manganese superoxide dismutase (MnSOD) and glutathione (GSH); increasing the oxidation of low-density lipoprotein cholesterol (ox-LDL) which promotes atherosclerosis; downregulating and inhibiting of small- and intermediate-conductance calcium-activated potassium (SK_{Ca}/IK_{Ca}) and potassium ($Kir_{2.x}$) channels; and inducing endoplasmic reticulum (ER) stress. EGFR: epidermal growth factor receptor, IL-6: interleukin-6; ICAM: intracellular cell adhesion molecule, VCAM: vascular cell adhesion molecule, AT-1: angiotensin receptor type 1.

At the molecular level, T1DM and T2DM and their associated hyperglycemia, hypo/hyperinsulinemia, and IR can increase the risk of stroke by promoting hyperlipidemia, atherosclerosis, hypertension, arrhythmia, atrial fibrillation, microvascular complications, and diabetic cardiomyopathy (DC) [79, 86]. Several mechanisms mediate these effects including, at least, generation of reactive oxygen species, promoting oxidative stress, inflammation, and mitochondria dysfunction, inducing endothelial dysfunction and hyperkalemia, increasing Na^+ absorption, and stimulating the renin/ANGII system [79, 86, 87, 88, 89]. A summary of these mechanisms is shown in Figure 3. In brief, some studies have confirmed that hypoinsulinemia that is seen in T1DM suppresses the activity of Na^+/K^+ ATPase and leads to hyperkalemia which can induce arrhythmia, atrial fibrillation, myocardial infarction, and other forms of cardiovascular diseases [90]. On the contrary, hyperglycemia, and hyperinsulinemia are typically seen in metabolically impaired individuals and patients with T2DM which stimulates hypertension in several ways. In this view, the higher levels of insulin stimulate the tubular NA^+ reabsorption in the kidneys which leads to hypervolemia [86, 91]. In the same way, hyperosmolarity and subsequently water volume both are relatively increased by hyperglycemia and higher circulatory glucose levels [86, 92]. Also, hyperinsulinemia leads to activating the sympathetic nervous system (SNS) which ultimately ends up with sustained activation of the renin/ANG II system, thus raising the cardiac output and the peripheral resistance which increase the blood pressure [86, 93].

Nonetheless, hyperglycemia seen in both types of DM stimulates the production of massive quantities of reactive oxygen species (ROS), suppresses insulin-stimulated expression of the endothelial NO synthase (eNOS), increases the generation of numerous inflammatory cytokines, adhesive molecules, and atherogenic factors through activating NF-κBp65 (metabolic memory), depletes Glutathione (GSH) and antioxidant defense enzymes, impairs the mitochondria function and induces endoplasmic reticulum (ER) stress [79, 87] (Figure 3). Mechanisms behind these include activating the NADPH oxidase and other several damaging pathways including the hexosamine, polyol; protein kinase C (PKC), and advanced glycation product pathways [79, 94, 95]. These events have several adverse effects such as increased blood pressure, promoting diverse microvascular complications, inhibiting NO-dependent endothelium relaxation, inducing atherosclerosis, and diabetic cardiomyopathy [79, 87] (Figure 3).

3.4.3. *Dyslipidaemia*

The effect of dyslipidemia on stroke incidence and the post-stroke outcome has been extensively studied during the last decades [96, 97, 98, 99, 100, 101]. However, complicated, mixed, and conflicting results still exist. In general, available data suggest that the risk of dyslipidemia during stroke depends on stroke type and lipid fraction [98, 102, 103, 104, 105].

3.4.3.1. TC and LDL-c. In the majority of the experimental, epidemiological, observational, and meta-analysis studies, a strong positive

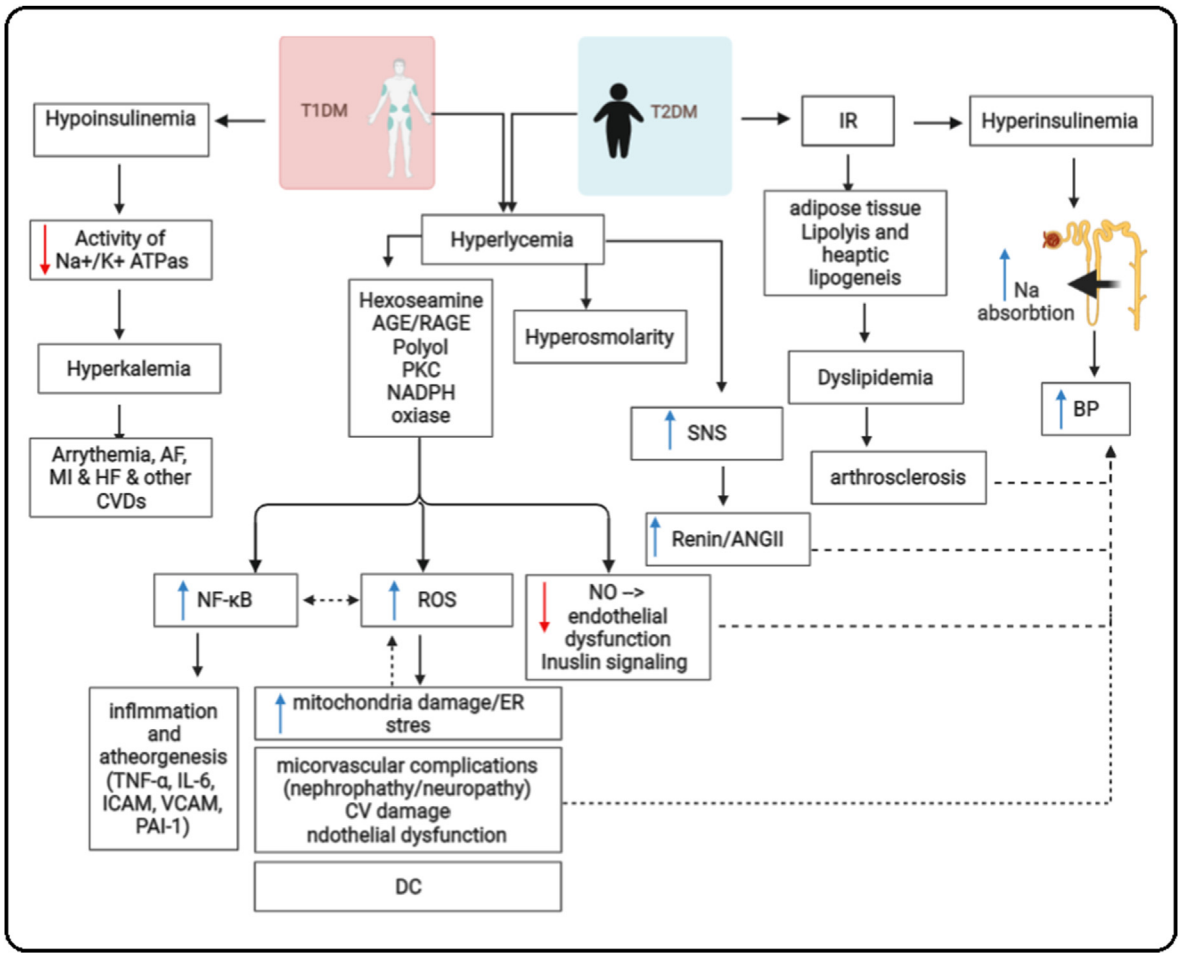

Figure 3. Molecular mechanisms by which type 1 and type 2 diabetes mellitus (DM) (T1DM and T2DM) increase the risk of ischemic and hemorrhagic strokes. In the figure, T2DM is mainly associated with insulin resistance (IR) and hyperinsulinemia which increases blood pressure (BP) through stimulating sodium (Na^{+}) resorption and promoting dyslipidemia and atherosclerosis. On the other hand, T1DM1 increases the risk of arrhythmias, atrial fibrillation (AF), myocardial infarction (MI), heart failure (HF), and other cardiovascular disorders (CVDs) by hypoinsulinemia-induced impairment in the function of Na+/K + ATPase and promoting hyperkalemia. However, hyperglycemia-induced by both types of DM can increase blood pressure by inducing hyperosmolarity and activating the sympathetic nervous system (SNS). In addition, hyperglycemia can promote cardiovascular disorders such as diabetic cardiomyopathy (DC) and atherosclerosis and raises blood pressure by promoting inflammation and oxidative stress and through overproduction of reactive oxygen species (ROS), activating NF-κB, and scavenging nitric oxide (NO). Mechanisms behind the effects afforded by hyperglycemia include activating numerous damaging pathways such as NADPH oxidase, hexosamine, polyol; protein kinase C (PKC), and advanced glycation products.

association between total cholesterol (TC) and low-density lipoproteins (LDL-c) and large arteries ischemic stroke has been reported in both males and females [98, 99, 103, 106, 107, 108, 109, 110, 111]. Also, menopausal women having high total cholesterol levels are at 56% higher risk of ischemic stroke than those with lower levels [112]. In addition, ischemic stroke risk, but not a hemorrhagic stroke, is increased with a higher LDL-c/HDL-c ratio [101, 113]. Indeed, higher levels of TC and LCL-c levels are positively correlated with cerebral atherothrombotic infarction but negatively associated with those derived from cardioembolism [104]. On the other hand, lower levels of TC and LDL-c are associated with an increased risk of hemorrhagic stroke [114, 115, 116]. In the recent meta-analysis of 23 studies, lower levels of total cholesterol were associated with an increased risk of intracerebral hemorrhage, in a dose-response manner [117]. Observational studies in patients who utilized statins as a potential therapy have shown no effect of reducing TC and LDL-c on the risk of intracerebral hemorrhage but showed a large reduction in the risk of total and ischemic stroke [110, 118, 119]. Stain therapy has been suggested to increase the risk of intracerebral hemorrhage [120, 121]. In addition, stroke patients with high levels of LDL-c had higher mortality rates [122]. Also, higher levels of TC and LDL-c negatively affected the post-actuate stroke outcome in patients who were treated with mechanical embolectomy or received thrombolytic agents, whereas cholesterol-lowering drugs improved these outcomes [123]. In the same line, cholesterol-lowering drugs improved neurological outcomes in patients post-stroke [103]. Opposing these studies, some other studies did not show any relationship between dyslipidemia and embolic lacunar stroke [104, 105]. No association between high total cholesterol levels and ischemic stroke was seen in the Eurostroke study [108]. On the same page, the Korean Medical Insurance Corporation Study (KMICS) has shown no association between low total cholesterol levels and hemorrhagic stroke [124]. Moreover, no association between LDL-c levels and stroke incidence was noticed in the atherosclerosis Risk in Communities (ARIC) study which was held on middle-aged men and women [106]. Furthermore, some other investigations have shown a protective effect of hyperlipidemia in reducing the mortality rate in stroke patients [38, 125]. Such contradiction could be explained by many contributing factors including the lack of laboratory data on cholesterol subtraction and variations in patient sex groups, genetic, and demographic factors [99]. In addition, other authors have argued that the protective effect of statins is independent of their hypolipidemic effects and is mainly mediated by improving the vascular integrity through its independent antioxidant abilities which can inhibit lipid peroxidation and improve endothelial function [126, 127].

3.4.3.2. HDL-c. The effect of high-density lipoprotein-cholesterol (HDL-c) on stroke incidence remains mixed. In some studies, reduced levels of HDL-c are associated with an increased risk of ischemic stroke [110]. In the Cardiovascular Health Study (CHS), the higher levels of HDL-c were associated with a reduced risk of ischemic stroke in men but not in women [128]. In the Northern Manhattan Stroke Study (NOMASS), circulatory HDL-c levels less than 35 mg/dl (0.9 mmpl/L) were associated with an increased risk of ischemic stroke [129]. Similarly, increasing HDL-c levels by 10 mg/dL reduced the incidence of ischemic stroke by 11–15% [110]. Also, a 47% decrease in hemorrhagic stroke was associated with increasing circulatory HDL-c levels by 1 mmol/L [33]. However, medications that increase circulatory HDL-c levels showed no benefit in reducing the risk of ischemic stroke [108]. This has been further explained by the effects exerted by HDL-c sub-fractions (large and less-dense HDL (HDL-c type 2) and the smaller more-dense HDL-c (HDL-3), rather than the total HDL-c [98]. In this regard, HDL-c type 3 acts on the endothelium to protect against atherosclerosis by suppressing LDL-c oxidation [98]. Also, HDL-c type 2 seems to increase the plaque thickness whereas HDL-c type 3 reduces this [130]. In addition, higher HDL-c type 3 was not associated with stroke risk but the medium and higher levels of HDL-c type 2 are associated with a reduced risk of ischemic stroke [131].

3.4.3.3. TGs and FFAs. Concerning triglycerides (TGs), the most epidemiological, cohort, and large-scale meta-analysis studies have also indicated a positive association between circulatory levels of triglycerides and ischemic stroke [132, 133]. Higher circulatory levels of triglycerides are associated with a reduced risk of hemorrhagic stroke [134, 135]. However, the precise mechanisms underlying this effect are still inconclusive. Opposing this, the ARIC study (The atherosclerosis risk in communities) has shown no association between serum levels of triglycerides and ischemic stroke [106]. Concerning free fatty acids (FFAs), elevated circulatory FFAs are associated with an increased risk of ischemic stroke possibly through their role in promoting other comorbidities including obesity, insulin resistance, hypertension, atherosclerosis, and ischemic heart disease (IHD), arrhythmia, and other cardiac toxicities [101].

On the other hand, the mechanisms by which dyslipidemia and low circulatory levels of HDL-c induce stroke involve the induction of atherosclerosis, thrombosis, endothelial dysfunction, and blood-brain barrier (BBB) damage, reducing cerebral blood flow CBF, and promoting neural apoptosis [96, 99, 136, 137, 138, 139, 140, 141, 142]. Besides, hyperlipidemia increases the risk of stroke by inducing hypertension, insulin resistance, obesity, and cardiovascular diseases [101]. However, it is currently well-accepted that vascular shear stress and inducing oxidative stress and inflammation in the endothelium, macrophages, and other tissues, as well the subsequent endothelial dysfunction and apoptosis are the major mechanisms by which hyperlipidemia activates the above mentioned vascular and neural damaging pathways in the brain and cardiac damage [143, 144, 145, 146, 147, 148, 149]. The role of oxidative stress and inflammation in promoting atherosclerosis, endothelial dysfunction, cell survival, and endothelium-dependent vasodilation is reported in many reviews. In this context, a higher lipid profile is associated with increased generation of reactive oxygen species (ROS) from the mitochondria due to excessive impairment in the process of oxidative phosphorylation and fatty acid (β)-oxidation. Besides, hyperlipidemia can generate ROS and ONOO- through activating many ROS-generating enzymes including NADPH oxidase, myeloperoxidase (MPO), xanthan oxidase (XO), uncoupling the endothelial nitric oxide synthase, depleting antioxidants, and upregulating the activated transcription factor-3 (ATF-3) [147,150–155]. Also, hyperlipidemia can disturb cerebral blood flow by decreasing the synthesis and the release of the vascular endothelial growth factor (VEGF) [156]. In addition, higher total cholesterol, LDL-c and TGs levels stimulate the cellular inflammation and macrophage infiltration and disturb the blood-brain barrier (BBB) by stimulating several inflammatory pathways such as ATF-3, NRLP3 inflammasome, NF-κB, tumor necrosis factor-α (TNF-α), and interleukine-6 (IL-6), as well as increasing the expression of several enzymes (e.g. MMP9), chemokines (e.g. CXCL-1 and CCL3), and adhesive molecules (e.g. as VCAM-1, CD11c/CD18, and P-selectin) [145, 147, 157, 158, 159, 160, 161, 162, 163, 164]. Moreover, hyperlipidemia activates neural and endothelial cell apoptosis by upregulation of MMP2/9 and myeloperoxidase (MPO), and PCSK9, as well as activating the intrinsic cell death (i.e. Bax, cytochrome C/caspase-3 axis) [143, 146, 165]. It also induces vascular stiffness via increasing Ca^{+2} overload in a ROS-dependent mechanism [166]. Hyperlipidemia, and through increasing endothelial oxidative stress and inflammation, increases the permeability of the blood-brain barrier (BBB) through activating calpain-1/2, matrix metalloproteinase-2/9, and RhoA [167]. A full description of all these mechanisms is shown in Figure 4.

3.5. Physical inactivity

Physical activity is a term that indicates any movement in skeletal muscles that increases whole-body energy expenditure [168]. Physical activity can be also identified as a group of planned, repetitive, and structured physical activities to maintain body fitness [169]. However, exercise is not the same as physical activity and can be identified as planned, regular, repetitive, and structured physical activities to improve physical fitness [168, 170]. Physical activity is classified into either occupational physical activities (daily activities such as dressing, sports, cooking, etc.) or leisure-time physical activities (i.e. exercising and recreational walking) [169]. Available global data indicate that 23% of adults and 81% of adolescents are not physically active which increases mortality of all types (Global action plan on physical activity 2018–2030, 2018) [171]. However, hundreds of epidemiologic studies have indicated that adherence to regular physical activity reduces the mortality rates by at least 30%, thus indicating a curvilinear relationship (Physical Activity Guidelines Advisory Committee, 2008).

In general, physical activity is a part of a healthy lifestyle prevention strategy that also includes reducing body weight and preventing alcohol and drug uptake, as well as stopping smoking [168]. Indeed, it has been suggested that maintaining healthy physical activity should be combined with a restricted adherence to a healthy lifestyle including avoiding unhealthy diets, smoking, and alcohol [172, 173]. Women and men who maintained healthy lifestyle choices with an optimum physical activity of at least 30 min/day for 1 year were less likely to have a stroke than those uncommitted women and men by 80% and 70%, respectively [174]. In the same line, Swedish women who adhered to a lifestyle with low-moderate physical activity (bicycle = 40 min/day & exercise 1 h/day) are 62% less to have cerebral infarction [173]. Similarly, a 32% reduction in stroke incidence was reported in men and women who participated in the European Prospective Investigation into Cancer and Nutrition (EPIC-Heidelberg) study [172]. On the other hand, women, not men who are physically inactive and not committed to the other lifestyle factor have a higher risk of stroke as compared to those who are physically active [175]. Also, adherence to lifestyle factors with moderate to high activity is associated with a reduced risk of total and ischemic strokes with a trend to reduce the risk of hemorrhagic stroke [176].

During the last decades, several cohorts, prospective, and meta-analysis studies have been conducted to identify the effect of physical activity on stroke prevention in all age groups. The majority of all these studies showed a reduction in the incidence of the total, ischemic, and hemorrhagic strokes, as well as in the prevention of stroke rehabilitation in physically active men and women of all ages with some variations between both genders [168, 177, 178, 179, 180, 181, 182, 183, 184, 185, 186, 187, 188, 189]. Both occupational and leisure-time physical activities are associated with a reduced risk of stroke [184]. However, the benefits were seen in moderate to highly active individuals [168]. In a meta-analysis of individual cohort studies and case-controlled studies, moderate and highly active individuals are at a low risk of 25% and 64% to have a stroke as compared to low active partners, respectively [182].

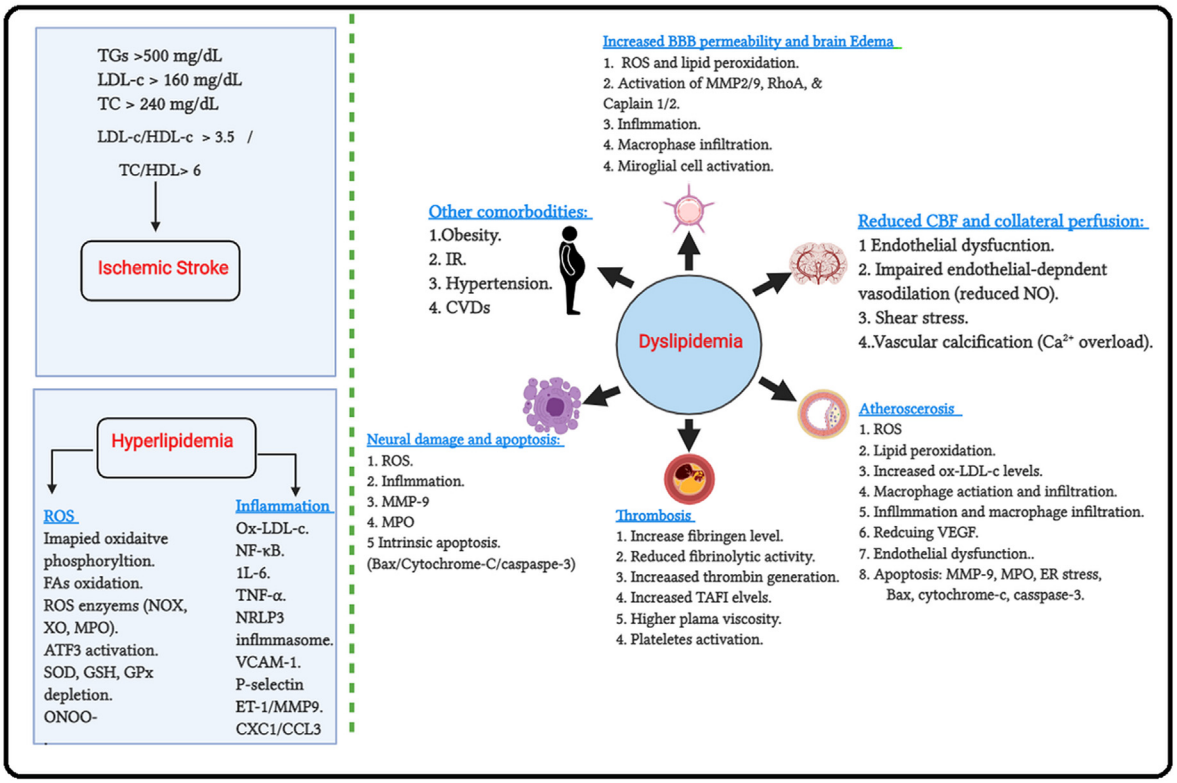

Figure 4. Molecular mechanisms by which hyperlipidemia increases the risk of stroke. Ischemic stroke risk is increased with triglycerides (TGs), low-density lipoprotein cholesterol (LDL-c), and total cholesterol levels higher than 500, 160, and 240 mg/dl, respectively. Also, LDL-c/HDL-c > 35 or TC/HDL ratio >35 and 6, respectively increase the risk of ischemic stroke. inflammation and increased production of reactive oxygen species (ROS) are the major underlying mechanisms leading to ischemic stroke. The mechanism by which hyperlipidemia induces oxidative stress and inflammation is shown in the left lower panel of the figure. On the other hand, the major pathways involved in hyperlipidemia-induced ischemic and hemorrhagic strokes include promoting thrombosis and atherosclerosis, and neural damage and apoptosis, reducing cerebral blood flow, increasing blood-brain barrier (BBB) permeability, and promoting obesity, hypertension, cardiovascular disorders (CVDs) and insulin resistance IR. The underlying mechanisms of all these pathways are shown in the figure.

However, those highly active individuals are 27% less likely to have a stroke when both cohort and case-control studies were combined [182].

The variation in the percent of reduction of stroke incidence between males and females was attributed to the variations in the physical activity intensity, type of exercise, and duration [187]. For example, men who are moderately and highly physically active have reduced stroke risk by 17% and 25% respectively [182]. In the Framingham Heart Study (FHS), old men but not women who are moderately physically active had reduced stroke incidence [179]. In the Northern Manhattan Study, low-intensity exercise reduced the risk of stroke in both men and women whereas vigorous exercise showed a reduction in stroke risk only in men [185]. In the same line, vigorous physical activity was not associated with a reduction in the risk of stroke in women who were included in the Reasons for Geographic and Racial Differences in Stroke (REGARDS) study [190]. On the contrary, moderate-intensity exercise reduced the risk of stroke in women but not men in the Spanish EPIC cohort study [191]. Experts in this area of research suggest that women need higher levels of physical activity to reach the same reduction in stroke risk as men [187]. This can be achieved by increasing the duration, frequency, and strength of the physical activity (i.e. from low to moderate and increasing walking hours to more than 3.5 h/week) [187].

On the other hand, physical activity and exercise pre-conditioning have many protective effects on stroke prevention and rehabilitation. In this regard, beneficial effects were many and included both vascular, neural, and systemic effects. In general, the beneficial effects of exercise were attributed to its ability to lower the risk of other comorbidities including obesity, hyperlipidemia, insulin resistance, and hypertension which are associated with a reduced risk of stroke. The neuroprotective benefits of exercise were also reported in the brain of animal models after stroke and were shown to be mediated by enhancing the synaptic plasticity, neurogenesis, and angiogenesis, improving endothelial function and cerebral blood flow, decreasing inflammation, preserving the blood-brain barrier integrity, and modulating the excitatory mechanism [192, 193, 194]. Besides, exercise can improve cognition and memory function, functional recovery, and have anti-depressing effects after stroke [195, 196]. A brief presentation of all molecular pathways underlying the protective effect of exercise on preventing stroke and improving stroke outcomes is shown in Figure 5.

Indeed, several lines of evidence have shown that exercise can stimulate neurogenesis, synaptic plasticity, neuronal excitability, synaptic transmission, glutamate release at the post synapse, and long-term potentiation through improving energy metabolism by increasing the levels of the brain-derived neurotrophic factor (BDNF), insulin-like growth factor (IGF-1), ghrelin, and VEGF levels [192, 193, 194, 197, 198, 199]. In this regard, exercise can stimulate BDNF by upregulating the expression of the hypoxia-inducible factor (HIF) which stimulates the BDNF/TrkB/CREB axis and the synthesis of multiple synaptic proteins including Tau, GAP-43, PSD-95, and synapsin 1 (SYN-1) [200]. In the same line, the stimulatory effect of exercise on BDNG and VEGF were also shown in clinical and pre-clinical studies and were associated with improved recognition and functional recovery after stroke [195, 196, 201]. Besides, exercise can inhibit neural apoptosis by stimulating the phosphatidylinositol-3-kinase/protein B (PI3K/Akt) survival pathways, increasing antioxidant levels, and improving mitochondria function. Exercise can improve the brain's energy metabolism by stimulating the BNFD/AMPK axis [202]. Also, exercise attenuated oxidative stress after stroke and during rehabilitation which afforded neuroprotection and reduced the risk of thermogenesis and thrombosis activities [203]. In

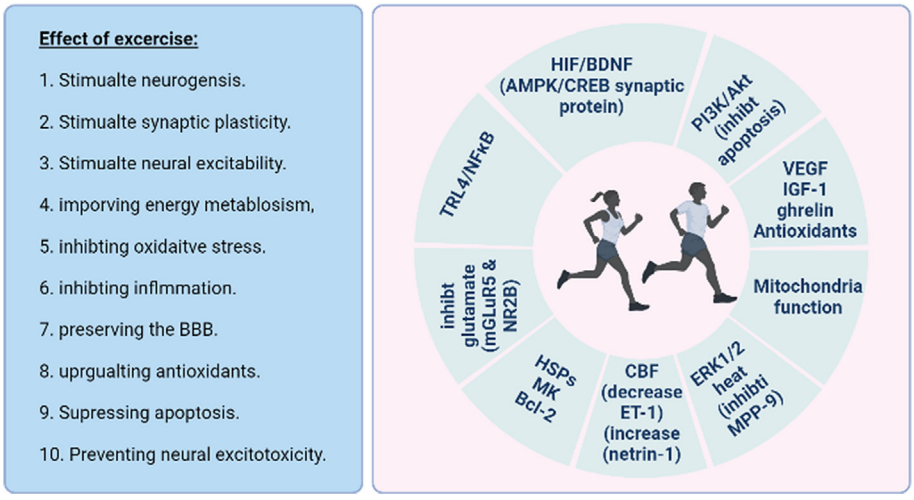

Figure 5. Molecular mechanisms mediating the neuroprotective effect of exercise in preventing stroke and improving post-stroke outcome. Accordingly, major effects of exercise are shown on the left panel. However, exercise can stimulate neural synaptic plasticity, excitability, and neurogenesis by stimulating the expression of BDNF, vascular endothelial growth factor (VEGF), and insulin-like growth factor (IGF-1). BDNF seems to be a key signaling molecule that further stimulates the synaptic protein expression by stimulating the CREB/synaptic protein axis. In addition, BDNF stimulates neural energy metabolism and suppresses oxidative stress, inflammation, and apoptosis by increasing the activation of AMPK. In addition, exercise stimulates cell survival and inhibits cell apoptosis by activating the PI3K/Akt survival axis, as well as upregulating antioxidants, heat shock proteins (HSPs), and the anti-apoptotic protein (Bcl2). Also, exercise preserve the integrity of the blood-brain barrier (BBB) by suppressing the activation of the myeloperoxidase-9 (MPP-9). Furthermore, exercise increases cerebral blood flow (CBF) by downregulating endothelin-1 (ET-1) and increasing the expression of netrin-1 and its receptors, the uncoordinated gene 5B (Unc5B), and the deleted in colorectal cancer (DCC). Lastly, exercise prevents neural excitotoxicity by downregulating the metabotropic glutamate receptor 5 (mGluR5) and N-methyl-D-aspartate receptor subunit type 2B (NR2B).

addition, regular physical exercise preserved the structure of the blood-brain barrier by decreasing stimulating collagen VI in the basal lamina and inhibiting MMP-9 by activating the ERK1/2 pathway [204, 205]. Also, exercise can increase cerebral blood flow by decreasing the expression of ET-1 and stimulating the neural and vascular expressions of netrin-1 and its receptors, the uncoordinated gene 5B (Unc5B) and the deleted in colorectal cancer (DCC) [206]. In addition, exercise inhibits neural apoptosis and stimulates survival through stimulating energy metabolism activating HIF-1α and AMPK, the expression of GLUT1/3, and the activation of the enzyme phosphofructokinase (PFK) [202]. This could be due to the activation of the HIF-1α/BDNF axis which is a potent activator of AMPK. Moreover, exercise can prevent neural inflammation, apoptosis and inhibits the activation of MMP-9 by several mechanisms including upregulating/activating ERK1/2, heat shock proteins (HSP-70 and HSP-20), midkine (MK), and Bcl2, as well as reducing the expression of Bcl-x, Bax, and Campaspe-3 [207, 208, 209, 210, 211]. Furthermore, exercise preconditioning prevents systemic and neural inflammation and oxidative stress and subsequently stimulates neural survival, endothelial function, cerebral blood flow, blood-brain barrier integrity by inhibiting the TLR4/NF-κB axis and the downstream generation of diverse inflammatory cytokines, as well as reducing the generation of reactive oxygen species, and increasing antioxidant enzymes [212, 213, 214]. Also, exercise preconditioning prevented neural excitotoxicity and subsequent increase in Ca^{+2} overload, oxidative and nitrosative stress, mitochondria and endothelial dysfunction, and neural apoptosis by inhibiting glutamate release, inhibiting the expression of the metabotropic glutamate receptor 5 (mGluR5) and N-methyl-D-aspartate receptor subunit type 2B (NR2B) [176, 215]. Although the upstream regulation of these mechanisms is not shown yet, it could be largely attributed to upregulating BDNF which exerts similar mechanisms. Further investigation on this is required mechanism are not been shown to decrease glutamate release and inhibit the expression of glutamate receptors, following middle cerebral artery occlusion MCAO [176, 215].

4. Conclusion

Stroke remains one of the major common disorders that is associated with the socioeconomic burden. Ischemic stroke remains the most dominant form of stroke even, some studies indicate an increase of hemorrhagic strokes in the future. However, major risk factors involved in both types of stroke include age, ethnicity, DM, hypertension, dyslipidemia, and physical inactivity. These factors may act as a synergistic mechanism to activate numerous damaging pathways and comorbidities. Therefore, advanced understanding of the molecular mechanisms underlying the pathophysiology of each of these contributing risk factors provides a novel approach for preventing and treatment of future stroke, enhancing the recovery after stroke, and developing effective therapeutic drugs. In general, it seems that structural abnormalities in the blood brain barrier and blood vessels, as well as activation of neural generation of reactive oxygen species, oxidative stress, inflammation, and apoptosis due to activation of several cellular signaling pathways, are the major mechanisms by which risk factors contribute significantly for stroke development and progression. In this review, I have presented a more comprehensive edit and collected all pieces of evidence from previously published studies to illustrate all possible molecular mechanisms underlying each of these risk factors and explained how they may affect stroke, stroke comorbidities, prevalence of each type of stroke, and patient's rehabilitation. In addition, this review also discusses how are these risk factors are connected. Despite this, this review did only discuss some major contributing risk factors of stroke, however, many other risk factors and triggers such as diet, gut microbiota, infection, pregnancy, etc, may play also a significant role in the pathogenesis of stroke. This was not included in this study and may be considered in future studies.

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