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DIABETES ASSOCIATED HYPERTENSION: PERSPECTIVES ON PATHOGENIC PATHWAYS AND EGCG AS A NOVEL TREATMENT

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ABSTRACT

The prevalence of diabetes associated hypertension is rapidly increasing and inflicts a huge burden on the healthcare worldwide. Diabetes mellitus is the major risk factor for increasing prevalence of high blood pressure. Hyperglycemia is a pathological clause linked with diabetes and hypertension. The pathogenesis of hypertension has been associated with hyperglycemia induced metabolic derangements, insulin resistance, reactive oxygen species, renin angiotensin aldosterone system, vascular alterations and related endothelial abnormalities. Long term hyperglycaemia bring out insulin resistance, alteration in glycation and non-glycation pathways moreover augmented oxidative stress as well as altered the advanced glycation end products activity, protein kinase C and vascular inflammation; all these interconnected for the cause and development of diabetes associated hypertension. Hypertension is appearing as another complication of type 2 diabetes that considers obligation for further study. Additionally, the characteristic of this review study is to highlight the perspective of diabetes related hypertension and EGCG-green tea catechin as a novel treatment option for counteracts the diabetes associated hypertension. Recently the beneficial effects of EGCG had been evaluated in numerous studies and widely accepted as antioxidant, anticancer, anti-inflammatory, antiviral, antibacterial, neuroprotective, antihyperglycemic, antihyperlipidaemic, and cardiovascular diseases. This review study concluded and highlights the functioning of pathogenic pathways implicated in the development of diabetes associated hypertension, moreover suggesting EGCG-green tea catechin as an emerging treatment and management strategy for the preventing comorbidity of diabetes and hypertension.

INTRODUCTION

Diabetes mellitus (DM) recognized as one of the main threats and a major challenge for public health worldwide because of its high prevalence and associated increased in morbidity and mortality [1, 2]. DM defined as an chronic disorder characterized by impaired metabolism of glucose and lipids either due to the progressive failure of pancreatic β-cell function therefore a lack of insulin production and/or insulin action (insulin resistance) [3,4]. Currently, DM is the leading cause for many serious complications such as cardiovascular, renal and other serious comorbidities [5], moreover progressive hyperglycemia leads to increase in tissue or vascular damage may results to oxidative stress, insulin resistance, obesity, endothelial dysfunction, and accumulation of harmful agents in the vascular endothelium causing development of microvascular and macrovascular complications [6, 7].

International Diabetes Federation (IDF) summarized that diabetes affects 382 million people worldwide and it is predictable to 592 million by 2035 [8]. DM is undoubtedly considered as one of the most challenging health problems in the 21st century, diabetic population is rapidly increasing due to stress, obesity, decreased physical activity and food habits [9-11]. Individuals can experience different signs and symptoms of diabetes, and sometimes there may be no signs. Characteristic symptoms of diabetes mellitus are thirst, polyuria, blurring of vision, and weight loss. The long-term effects of DM include progressive development of the specific complications such as retinopathy, nephropathy and neuropathy with risk of foot ulcers, amputation, Charcot joints and features of autonomic dysfunction including sexual dysfunction.

Diabetes mellitus affect people chronically; may contribute to the pathogenesis of diabetes related complications. As per macrovascular complications of DM, hypertension (HTN) is one of the illustrations of diabetes related complications results for the major cause of morbidity and mortality [12]. People with hypertension are at greater risk of increasing metabolic syndrome compared to non-hypertensive. Hypertension and diabetes are the main cause of heart failure considered as an important public health problem. If hypertension develops concomitant with diabetes, treatment problem of this comorbidity becomes more complex [13]. DM and HTN are two widespread diseases to often coexist. The co-existence of this comorbidity resulted to accelerate the microvascular and macrovascular complications and greatly increases the risk for cardiovascular diseases. Hyperglycemia emerges to be interconnected in the development of hypertension in diabetic patients. Hyperglycemia resulted in more expression of free radicals sources for additional complications such diabetic

hypertension. Insulin resistance has been shown to occur in approximately 50% of hypertensive patients as well as in diabetic patients insulin resistance seems to play a pivotal role in the pathogenesis of hypertension [16].

American Heart Association (AHA) defined Hypertension or high blood pressure (HBP) as a systolic blood pressure greater than 140 mmHg and/or diastolic blood pressure greater than 90 mmHg [14]. HTN is characterized by a normal cardiac output and elevated arterial pressure [15]. HTN in DM is described clinically by the symptoms such as: Severe headache, high blood pressure, nausea or vomiting, confusion and vision changes. HBP has been implicated as a cause for renal dysfunction in hypertensive patients. Diabetic hypertension recognized as one of the most challenging health problems and greater risk for human morbidity and mortality worldwide (responsible for 13% of global deaths) [17-20]. Globally, hypertension affects 972 million people in 2000 and it will project to a total of 1.56 billion by 2025 which is increase by 60% i.e., 29% of the adult population worldwide [17, 18, 21]. According to Centers for Disease Control and Prevention (CDCP), HTN is a common comorbidity in patients with T2DM, with approximately 67% of adults with T2DM having blood pressure (BP) ≥140/90 mmHg or treated with antihypertensive medication (Centers for Disease Control and Prevention) [22, 23].

COMORBIDITY OF DIABETES AND HYPERTENSION: A MAJOR RISK FOR GLOBAL HEALTH

The prevalence of comorbidity of diabetes and hypertension is rapidly increasing world-widely. However it is well-known that both genetic and environmental factors contribute to the development and progression of type-2 diabetes (T2DM) with associated hypertension [24, 25]. Moreover, diabetes remains the most important modifiable risk factor for a variety of cardiovascular diseases like myocardial infarction, peripheral vascular disease, coronary heart disease (CHD), stroke and end-stage renal disease [26, 27]. Diabetes and hypertension are widespread chronic disorders that often coexist [28]. Large epidemiologic studies showed that diabetes is associated with increased cardiovascular mortality and that HTN accelerates morbidity and mortality markedly in these patients [12]. The incidence of HTN is just about twofold as frequent in diabetic patients compared to non-diabetic population [29]. Cardiovascular diseases (CVDs) are the major causes of mortality in the diabetic population, also there are numerous factors such as HTN which furthermore contributes to this high prevalence of CVD [28, 30, 31]. Almost 90% of the patients with T2DM are obese [32]. Obesity is a well-recognized threat which causes and leads for the development of comorbidity of

diabetes and HTN [33]. In patients with T2DM, insulin resistance (IR) appears to play a pivotal role in the pathogenesis of hypertension [16, 34].

HTN is a common and costly complication of both type-1 diabetes mellitus (T1DM) and T2DM. There are four major molecular mechanisms implicated in glucose-mediated vascular damage viz. augmented polyol pathway flux; increased production of advanced glycation end-product (AGE); additionally the activation of protein kinase C (PKC), sorbitol, cytokines and prostanoids moreover increased hexosamine pathway flux [35]. Free radicals, reactive oxygen species (ROS) leads to several damaging pathways furthermore resulting in micro and macrovascular complications of diabetes which accelerates the formation of AGE products, polyol pathway and phospholipase C (PLC) [36, 37]. Moreover, oxidative stress has been implicated as the underlying cause of serious diabetic complications [38]. Accumulation of glucose and fatty acids within the muscles, adipose tissue and pancreatic cells combined with sedentary lifestyle furthermore leads to the generation of excessive reactive metabolites (RMs).

Oxidative stress and RMs are interrelated terms defined in general as excess formation and/or insufficient removal of highly reactive molecules such as ROS, reactive nitrogen species (RNS) and reactive thiyl species [39]. At this time favored hypothesis is oxidative stress which leading to IR, impaired glucose tolerance (IGT), β-cell dysfunction and ultimately plays an important role in pathophysiology of diabetic hypertension. Nitric oxide (NO) plays a fundamental role in the regulation of endothelial function and vascular tone in many organs including kidney [40]. Clinically, eNOS uncoupling has been allied with HTN, DM, atherosclerosis and hypercholesterolemia [41, 42]. Impaired production of NO leads to endothelial dysfunction furthermore contributes to the development of various pathologies such as T2DM, IR, chronic renal failure and cardiovascular (likely HTN and hypercholesterolemia) [43]. A causative link among hyperglycemia, oxidative stress, generation of mitochondrial ROS and the progression of complications has been suggested which plays a major role in the pathogenesis of diabetes and related CVDs [44, 45]. In healthy individuals both enzymatic and non-enzymatic antioxidant defense play important roles in scavenging ROS and RNS. Impaired antioxidant defense increases oxidative stress and contributes to the development of T2DM and associated cardiovascular diseases such as hypertension.

ROLE OF VARIOUS PATHWAYS IN PATHOPHYSIOLOGY OF DIABETIC ASSOCIATED HYPERTENSION

There may be multiple etiologies which account for the various hypertensive stages seen in patients with diabetic complications. Hyperglycemia undoubtedly plays a key role in the development of diabetic hypertension as well as the other diabetic macrovascular complication. Reasonably then, furthermore investigations into the molecular and biochemical pathophysiology of diabetic hypertension have focused on metabolic pathways, dysfunctions and complications related to diabetes (figure 1).

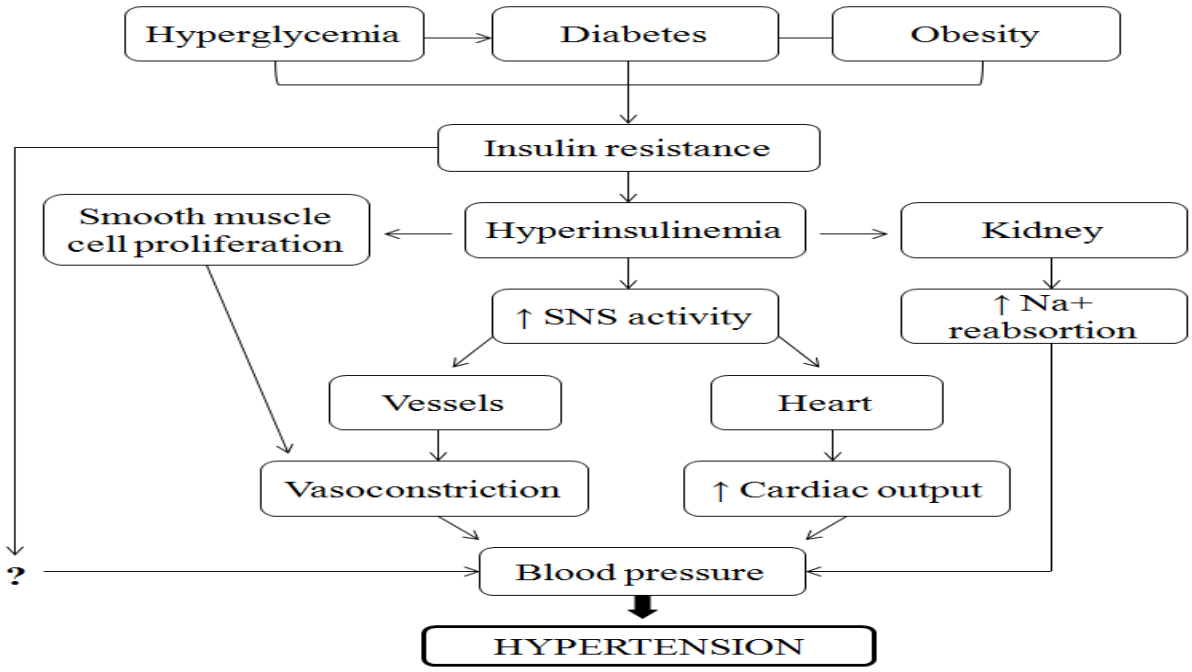

Figure 1: Interactions by which hyperglycemia, obesity and insulin resistance might lead to type 2 diabetes induced hypertension (Abbreviations: Na+, sodium; SNS, sympathetic nervous system).

Role of Oxidative stress in comorbidity of diabetes and hypertension: The generation of free radicals is a major factor in development of diabetes induced hypertension through increased glycolytic process. Simultaneous with generation of free radicals during the glycolytic process, moreover oxidative stress harms the mitochondrial DNA, proteins, and membranes [46, 47]. Oxidative stress and reactive oxygen species (ROS) link the physiological mediators and metabolic initiators implicated in progressive vascular damage, dysfunction, and loss in diabetic hypertension. It is well accepted that kidneys regulate blood pressure by controlling water and electrolyte balance and secreting hormones such as angiotensin-II [48]. Redox signaling inside the central nervous system (CNS) is well known in neuronal control

of blood pressure (BP), which is associated to ROS dependent HTN. Montezano & Touyz and Sedeek et al. showed that NADPH oxidase (Nox) enzymes are a primary source of superoxide in angiotensin-II (Ang-II) induced neuronal activity [49, 50]. Additionally, it has been exposed that local oxidative stress reduces NO bioavailability in humans with coronary endothelial dysfunction. An additional mechanism linking ang-II to elevated ROS production can be attributed to Nox-mediated activation of mitochondrial ROS production. Similar to the CNS, ang-II-induced Nox activation has been noted to increases mitochondrial ROS production in aortic endothelial cells [51]. Superoxides (O_2-) are the short-lived molecules which undergo enzymatic dismutation to yield hydrogen peroxide (H_2O_2) [52]. H_2O_2 produced by enzymatic dismutation of O_2- is further converted to highly reactive hydroxyl radical (OH-) by Fenton reaction, well-known to cause DNA damage. Superoxide provokes the vascular dysfunction in hypertension by interaction with NO [37]. It has been shown that high salt intake along with L-buthionine sulfoximine (BSO) treatment causes vascular dysfunction by reducing NO levels and eNOS activity in rats [53].

Moreover, superoxides oxidized the proteins and lipids; react with endothelium-derived nitric oxide (NO) in order to create the RNS peroxynitrite (ONOO-) [54]. The peroxynitrite and other RNS subsequently oxidize the proteins, lipids, and also the critical enzymatic cofactors; leads enhance the oxidative stress [55]. The homeostatic levels of ROS have been considered important in normal cellular signaling and normal reactions to stressors [56, 57]. Various studies implicate ROS in the multiple kidney functions, moreover the deregulation contribute to HTN and end organ damage, which accompanies hypertension [58, 59]. Oxidative stress in coincidence with hyperglycemia furthermore activates poly ADP-ribose polymerase (PARP) additionally; it leads to cleaves nicotinamide adenine dinucleotide (NAD+) to nicotinamide and ADP-ribose residues [4]. This process continues by a link to nuclear proteins and results in changes of gene transcription and expression, NAD+ depletion, oxidative stress, and distraction of glycolytic intermediates to other pathogenic pathways such as PKC and advanced glycation end products (AGEs) [46]. Individually, the polyol pathway, AGEs, PARP, PKC, hexosamine and all contribute to vascular and neuronal damage mutually.

The polyol pathway and AGEs modify the redox capacity of the cell either through weakening of necessary components of glutathione recycling or by direct production of ROS. The PKC, PARP and hexosamine pathways are representatives of damage mediated through expression of inflammatory proteins [46]. In support, animal studies have also demonstrated the development of HTN with associated increase in oxidative stress and impaired vasodilation in

rats exposed to a high-salt and oxidant containing diet [60]. Additionally, different animal models of HTN including spontaneous hypertension, renovascular hypertension; salt-sensitive hypertension and obesity-related hypertension have been associated with excessive oxidative stress, moreover substantiates that excessive ROS is a common factor in the pathogenesis and morbidity of hypertension [9, 46, 47].

Role of Renin-Angiotensin-Aldosterone System (RAAS) in comorbidity of diabetes and hypertension: The renin angiotensin system and its major components, regulators of renin release and the primary effects of ang-II excluding the ang-II receptors plays a vital role in the regulation of BP. Renin may play a critical role in the pathogenesis of most HTN [61]. Although, low renin levels are predictable in essential HTN, the majority of patients among essential hypertension do not have low suppression renin angiotensin levels but "inappropriately" normal or even elevated PRA levels. Indeed, when renin profiling is correctly performed and indexed in patients with essential HTN, about 20% are found to have high renin values, and about 30% have low renin values, with the remaining half distributed between these two extremes. It seems likely that this mechanism is abnormally activated in many patients with essential HTN and DM, and at least three mechanisms have been offered: nephron heterogeneity, non modulation, and increased sympathetic drive [62, 63]. Furthermore, nephron heterogenecity with unsuppressible renin secretion and impaired natriuresis as cause of comorbidity of DM and HTN: Within the kidneys, there exists a functional and structural basis for the abnormal renin secretion and impaired Na+ excretion that are characteristic of hypertensive states [64, 65].

Role of Sympathetic Overactivity in comorbidity of diabetes and hypertension: An excess of renin angiotensin activity could interact with the sympathetic nervous system (SNS) to mediate most of its results. Alternatively, stress may stimulate the SNS directly and SNS over-activity in turn, may interact with high sodium intake; furthermore the renin-angiotensin system and IR among the other possible mechanisms. Considerable evidence supports increased SNS activity in early HTN and even more impressively, in the still normotensive offspring of HTN parents, among whom a large number are likely to develop HTN.

Stress: People exposed to repeated psychogenic stresses may develop HTN more frequently than otherwise similar people not so stressed. Annual rate of developing HTN is 5-6 times greater in traffic controllers, work under high level of psychological stress than non professional pilots. People may become hypertensive not just because they are more stressed, it may be because they react differently to stress. Greater cardiovascular and sympathetic

nervous reactivities to various laboratory stresses have been documented in hypertensives and in normotensive at higher risk of developing HTN [66], extending even to a greater anticipatory BP response while awaiting an exercise stress test. Despite the rather impressive body of literature, the role of mental stress in the development of HTN remains doubtful. Effects mental stresses are likely to depend on an interaction of at least three factors: nature of stressor, perception of stressor by individuals and the individual's physiological vulnerability. It proposes that HTN has two phases: an early phase in which elevations in BP are mainly episodic and are mediated by a hyperactive SNS or RAS, and a second phase in which BP is persistently elevated and that is primarily mediated by an impaired ability of the kidney to excrete salt, NaCl. The transition from the first phase to the second occurs as a consequence of catecholamine induced elevations in BP that preferentially damage regions of the kidney (juxtamedullary and medullary regions) that do not autoregulate well to changes in renal perfusion pressure.

In conclusion, this hypothesis links early, episodic, salt independent HTN with the later development of a persistent salt dependent HTN with the new concept that it is mediated by acquired tubulointerstitial and peritubular capillary injury. Strength of the hypothesis is that it unites many prior hypotheses into one pathway including that of Julius on the role of the SNS in early HTN [68]; Cowley et al on the role of medullary ischaemia, Sealey and Laragh on activation of the renin-angiotensin system [69], on impaired pressure natriuresis [64] and on enhanced TG feedback [68].

Role of Baroreceptor dysfunction in comorbidity of diabetes and hypertension: The baroreceptors when activated by a rise in BP or central venous pressure, respectively, normally reduce heart rate and lower blood pressure by vagal stimulation and sympathetic inhibition. When HTN is sustained, these reflexes are reset rapidly from both structural and functional changes so that given increase is BP evokes less decrease in heart rate [70]. Shepherd postulates that the decreased inhibition of the vasomotor center resulting from resetting of arterial baroreceptors (mechano receptors) may be responsible for increased sympathetic out flow and thereby in the perpetuation of HTN.

Role of Peripheral resistance in comorbidity of diabetes and hypertension: Multiple factors affect peripheral resistance. Main determinant of sustained elevated BP is increase in peripheral resistance which resides in precapillary vessels with a lumen diameter of less than 500 μm [71]. In human HTN and in experimental animal models of HTN, structural changes in these resistance vessels are normally observed. In patients among essential HTN and DM, the

characteristic findings include: decreased lumen diameter and, increased ratio of the diameter of vascular smooth muscle layer of the vessel (tunica media) to lumen diameter, referred to as the media to lumen ratio. According to Poiseulle's law, vascular resistance is positively related to both the viscosity of blood and the length of arterial system and negatively to the fourth power of the luminal radius. Furthermore, Since neither viscosity nor length are much, if at all, altered and the small change in luminal radius can have such a most important effect, it is evident to the increased vascular resistance seen in established HTN must reflect changes in the calibre of the small resistance arteries and arterioles. The increase in media to lumen ratio of the resistance vessels occurs by the addition of material to the outer or inner surfaces of the blood vessel wall [71]. This process has need of growth (either hyperplasia or hypertrophy) of the cellular components of the blood vessel wall and results in an increase in its cross-sectional area. An alternative process referred to as vascular remodeling, which can result in an augmented media to lumen ratio through the rearrangement of the existing material without an increase in the cross sectional area of the vessel. During human essential HTN, there is mounting evidence to support the view that vascular remodeling rather than growth is the predominant change occurring in resistance vessels.

Role of Cell membrane alterations in comorbidity of diabetes and hypertension: There is a body of evidence that shows that the cell membranes of hypertensive animals and, less convincingly, of hypertensive people are altered in a primary manner, allowing abnormal movements of ions and thereby changing the intracellular environment to favour contraction and growth. These primary alterations are differentiated from the secondary inhibition of the Na+/K+-ATPase pump by ouabain, which is secreted after increase volume and as illustrated previously, is a possible mechanism for renal sodium retention. Abnormalities of the physical properties of the membrane and multiple transport systems have been implicated in the pathogenesis of diabetes associated hypertension [72]. Most relate to vascular smooth muscle cells, but since such cells are not available for study in humans, surrogates such as red and white blood cells are used. The transport systems present in cell membrane of erythrocytes that control the movement of sodium and potassium to maintain the marked differences in concentration of these ions on the outside and inside of cells; furthermore provides the elector chemical gradients needed for various cell functions. Evidently, the sodium hydrogen exchanger is stimulated in hypertensive patients either by an increased cellular calcium load or enhanced external calcium entry. An increased Na+/H+ exchanger could play a significant role in the pathogenesis of HTN; both by stimulating the vascular tone and cell growth,

possibly by increasing sodium reabsorption in renal proximal tubule cells [73]. RBC membranes from hypertensives have increased cholesterol: phospholipid ratio in association with high sodium lithium transport (SLC) and increased ratios of fatty acid metabolites to precursors compared to those from age matched normotensives [72]. Such changes in lipids produce a high membrane microviscosity and decrease in fluidity, which may be responsible for increased permeability to sodium and other alterations in sodium transport[73].

Role of Endothelial dysfunction in comorbidity of diabetes and hypertension: Nitric Oxide (NO) is the primary endogenous vasodilator. Although, the role of NO in the regulation of BP is doubtful; several studies have reported its influence on BP and renal haemodynamics [69]. In healthy human subjects, inhibition of NO synthase by N-monomethyl L-arginine intensely increased BP, fractional excretion of Sodium (Na+) and the peripheral vascular resistance. NO is tonically active in the medullary circulation, so that reducing NO production or vascular reactions reportedly increases the pressure natriuresis response followed by reductions in papillary blood flow, renal interstitial hydrostatic pressure and Na+ excretion by approximately 30% without consequent changes in total or cortical RBF or GFR [69]. This mechanism may contribute to the blunted pressure natriuresis reported in experimental models. Vascular and nerve blood flow is reduced in diabetic cardiovascular complication (macrovascular) perhaps mediated via NO. Overproduction of superoxide anion by the mitochondrial electron transport chain (ETC) in diabetic hypertension leads to binding of this anion to NO to form the strong oxidant peroxynitrite, lethal to endothelial cells. The endothelial cells, as well generate NO which acts as a vasodilator and antagonizes the thrombosis. NO also shields against inflammation by adjusting (Na+/K+)-ATPase or inhibiting the production of potent vasoconstrictor peptide endothelin-1 (ET-1) [74, 75]. In addition, hyperhomocysteinemia is associated with impairment of endothelial function, moreover providing a mechanism for its possible involvement in diabetic cardiovascular complications. There is a synergistic effect between AGEs and homocysteine in the initiation of endothelial damage [74].

Endothelin: Endothelin is among the vasoconstrictors yet to be identified. Its actions are mediated through two types of receptors, endothelin A (ET-A) and endothelin B (ET-B); which are located on the vascular smooth muscle. Bosentan, an orally active mixed endothelium receptor antagonist reduced BP in hypertensive patients to a level that was comparable to enalapril. Bosentan has also been reported to block the effects of an infusion of

ang-II on BP and renal blood flow in rats [76]. This raises the issue of whether a component of these ang-II actions may be mediated by endothelin.

Role of Obesity in comorbidity of diabetes and hypertension: The prevalence of HTN is more common in obese people [32]. Obese individuals have higher cardiac output, stroke volume, and central and total blood volume and lower peripheral resistance than non obese individuals with similar blood pressure [61]. The increase in cardiac output is proportional to the expansion of body mass and may be the primary reason for the rise in BP. The prevalence of diabetes associated hypertension increased equally with increasing BMI, degree of upper body obesity, and fasting insulin levels [77]. Insulin resistance and hyperinsulinaemia higher insulin levels are associated with more hypertension, and many possible mechanisms may explain the association. HTN that is more common in obese population may arise in large part from the insulin resistance and resultant hyperinsulinaemia those results from the augmented mass of fat. Nevertheless, somewhat unexpectedly, IR may also be involved in HTN in non-obese people as well. The explanation for IR found in as many as half of non-obese hypertensives, however is not obvious and may involve one or more aspects of insulin's action.

Effects of hyperinsulinaemia on BP: There are three ways by which the hyperinsulinaemia that develops as a consequence of insulin resistance and reduced clearance could induce hypertension. Other mechanisms have been proposed. Of these, impaired endothelium-dependent vasodilation may be particularly important Insulin normally acts as a vasodilator [65]. It has been shown that although insulin increases sympathetic activity, the effect is normally overridden by the direct vasodilatory effect of insulin. Proposed mechanisms by which insulin resistance and/or hyperinsulinaemia may lead to increased blood pressure: Enhanced renal sodium as well as water reabsorption, Increased BP sensitivity toward dietary salt intake, Expansion of the pressure and aldosterone reactions to ang-II, Changes during transmembrane electrolyte transport are: increased intracellular sodium, decreased Na+/K+ -ATPase activity, increased intracellular Ca2+ pump activity. Increased intracellular Ca2+ accumulation leads to stimulation of growth factors, especially in vascular smooth muscle. Activation of sympathetic nervous activity, Decreased synthesis of vasodilatory prostaglandins (PGs), impaired vasodilation and increased secretion of endothelin.

Epigallocatechin gallate (EGCG): A Green Tea Catechin as novel treatment for Comorbidity of Diabetes and Hypertension

In recent times, the search and investigation for an appropriate hypoglycemic, hypolipidemic and blood pressure lowering agents has been focused on the natural traditional-remedies because natural products that may be better treatments as compared to currently used drugs. Hence, various studies have been conceded to assess natural products including plant materials, as an alternative treatment for oxidative stress induced diseases. Plants are rich sources of hypoglycemic, hypolipidemic and antioxidant agents such as flavonoids, phytosterols, gallotannins, and other related polyphenols [78]. Tea is the one of the most common drinking beverages worldwide after water. Epigallocatechin gallate (EGCG) has been reported to possess strong antioxidant properties [79]. Oral administration of EGCG is capable of protecting several organs such as liver, kidney, testes, heart and brain against oxidative stress induced by free radicals [80-84].

Various mechanism of EGCG have been reported are: inhibition DNA damage decrease ROS generation and decrease formation of Peroxynitrates[85] decrease expression of PPARϒ, decrease Interleukines (IL) formation and TNF alpha[86] Suppress the Phosphorylation of Epidermal growth factor receptor (EGFR) regulate JAK/STAT, MAPK, PI3K/AKT activating killer Caspases, decrease in ATP generation and Suppressing oncogenic transcription factors[87] angiogenesis by suppressing the activity of VEGF, phosphorylation of VE-cadherin and activity of matrix metalloproteinase. GT catechins reduce production of inflammatory cytokines, in part by suppressing the "master switch" of inflammation called nuclear factor-kappaB (NF-kB) [88]. It prevents expression of a vascular endothelial growth factor (VEGF), which is required for generation of new blood vessels to feed the growing tumor.

Antidiabetic activity of EGCG: EGCG, the major bioactive constituent of green tea (C.sinensis) has been reported to demonstrate various pharmacological effects, including antihyperlipidaemic and antihyperglycemic activities against a broad spectrum of research [87, 89]. Administration of EGCG resulted to substantial decrease in blood glucose levels and hepatic G6PD activity along with improvements in hepatic glycogen content and hexokinase activity. The increase in hexokinase activity could be due to an insulin restoratory potential of EGCG [90]. In recent years, beneficial effect of EGCG have been reported blood glucose lowering capacity, reduced cholesterol level, triglycerides as well as enhances insulin activity [91, 92]. These antihyperglycemic activities of EGCG could be ascribed to the secondary

metabolites (polyphenols and flavonoids) present in green tea. Polyphenols are well recognized to inhibit the glucose absorption in the gut, inhibit glucose uptake in peripheral tissue by glucose transporters [93], moreover inhibit insulin resistance and shield pancreatic β-cells [94]. Flavonoids are reported to possess antidiabetic potential, furthermore attributed to an increase in pancreatic insulin secretion or its release from bound insulin [95]. The rich polyphenolic fiber contents of green teas contained dietary EGCG found to increase cholesterol excretion by interfering with the enterohepatic circulation of bile acid and cholesterol. The existence of flavonoids and polyphenols in EGCG also could be responsible for the antihypercholesterolaemic effects.

Antihypertensive activity of EGCG: In recent years, beneficial effect of EGCG have been reported enhances insulin activity and reduced the blood pressure [92]. EGCG decreases ROS level and reduces oxidative stress as well as it enhances the bioavailability of beneficial NO by promoting the coupling of eNOS results in vasodilation [16, 91, 92]. EGCG acts powerfully to improve endothelial dysfunction, as it may enhance production of beneficial NO, which in turn signals vessel walls to relax and dilate in response to blood flow [16]. GT desensitizes calcium-signaling channels through effects on the troponin (cardiac enzyme), improving the function of heart during relaxation (diastolic) phase. It decreases the RAAS activity, AGE/RAGE interaction and reduces the activity of PKC pathway in diabetic condition and plays a pivotal role in reduction of blood pressure [96]. Also EGCG have dose-dependent blood pressure lowering effect [97, 98]. It has found that GT extracts also inhibit angiotensin-converting enzyme (ACE), which bumps up blood pressure results in lowering BP [97, 99]. In conclusion, the present investigation depicts that the administration of EGCG decreases the ROS mediated metabolisms in liver tissue lipid profiles and restored the regulatory enzymes involved in the carbohydrates, protein, lipids and lipoprotein metabolism and maintains at a normal level. Therefore, in contrast of our literature survey, we conclude that EGCG could be used as a component in foods to promote the health of people living in endemic diabetes associated hypertension.

CONCLUSION

Diabetic associated hypertension is a significant complication of diabetes, with increase allegation in patient morbidity and mortality. It is one of the major alarming illnesses mainly to elderly people. After elongated time of searching, at rest a need to find out emerging treatment and management strategies for the prevention of comorbidity of diabetes and hypertension. Evidently, additional elementary research is required the molecular, cellular,

systemic, and behavioral levels. There is a considerable bunch of evidence implicating production oxidative stress and endothelial dysfunction moreover RAAS as a key factor in the development of diabetic associated hypertension and the normal aging process furthermore through this evidence, is an important pathologic state for research and treatment of the disease. This review study concluded the perspective of pathogenic pathways of diabetes related hypertension and EGCG-green tea catechin as a novel treatment option for counteract the diabetes associated hypertension. The current review is to highlights the functioning of various pathways implicated in the pathophysiology of diabetes associated hypertension moreover suggesting EGCG-green tea catechin as an emerging treatment and management strategy for the preventing comorbidity of diabetes and hypertension.

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