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Angiopoietin-2 in type 2 diabetes mellitus complication

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Abstract
Angiopoietin-2 is an important growth factor essential for endothelial physiology and has been implicated in vascular related diseases. Circulating Angiopoietin-2 levels have been reported to be elevated in type 2 diabetes mellitus compared to normoglycaemic people. These elevations lead to excessive or deficient angiogenesis with resultant diabetes mellitus complications. It's important to understand that targeting the molecular pathway of Angiopoietin-2 may become an effective anti-angiogenic therapy in type 2 diabetes mellitus complications.

Keywords: Angiopoietin-2, Endothelial physiology, Type 2 diabetes mellitus, Angiogenesis, Anti-angiogenic therapy

Introduction

Diabetes mellitus is a metabolic disease that consists of an array of dysfunction characterized by chronic hyperglycemia resulting from the inadequate insulin secretion, insulin action, or both [1]. The morbidity and mortality of diabetes mellitus, however is mainly attributed to the development of both microvascular and macrovascular complications. Microvascular complications like nephropathy, retinopathy and neuropathy are the major causes of diminished quality of life, while macrovascular complications such as peripheral artery disease, cerebrovascular disease and coronary artery disease, are the main causes of mortality. A report from a systemic review has shown that cardiovascular disease affects approximately 32.2% of patients with type 2 diabetes mellitus (21.1% with coronary artery disease, 10% with myocardial infarction, 7.7% with stroke and 14.6% with angina) and that cardiovascular disease accounts for the cause of death in 9.9% of patients with type 2 diabetes mellitus [3]. The key players that contribute to diabetes pathophysiology include: beta cell dysfunction, Insulin Resistance (defects of insulin signaling) in brain, skeletal muscles, and liver, accelerated lipolysis resulting in increased production of non-esterified fatty acids (NEFA), dysregulated production of adipokines, dysregulated action/production of incretin and gut hormones, hyperglucagonemia, subclinical inflammation through production of proinflammatory mediators, oxidative stress and excessive production of reactive oxygen species (ROS) [3].

Globally, 573 million people have diabetes mellitus in 2021, within the age range of 20- 79 years with the vast majority of them suffering from type 2 diabetes mellitus (T2DM), and the projected prevalence is estimated to reach 643 million people by the year 2030 and 783 million people by the year 2045. The prevalence in Nigeria was estimated to be 3.6% [1].

Prevalence of diabetes mellitus in each geopolitical zone of Nigeria was reported to be 5.9% in North east, 3.0% in North west, 3.8% in North central, 5.5% in South west 4.6% in South east and 9.8% in South-south was reported to be 9.8%, The overall pulled prevalence was put at 5.77% [4].

Risk factors of type 2 Diabetes Mellitus

Environmental and genetic factors play a crucial in the development of type 2 diabetes mellitus and its vascular complications. The risk factors for the development of diabetes mellitus include Family History, Unhealthy Diet, Urbanization, Cigarette Smoking, Physical Inactivity, Obesity [4], hypertension, hyperlipidemia, increased formation of advance glycation end products, increased oxidative stress. Dysfunctions in angiogenesis is been suggested to be a common origin of diabetic vascular complications [5].

The Endothelium

The endothelium (ED), is a monolayer of cell lining that covers the luminal surface of the blood, lymphatic vessels and heart is composed of approximately one trillion cells which extends over an area of 300 m^2 [6]. The vascular endothelium functions as a barrier between the vessel well and the lumen and it has been shown to secrete various cytokines and growth factors that regulate numerous vascular functions that include; vascular tone, proliferation of vascular smooth muscle, platelets aggregation, coagulation and fibrinolysis. Also, the endothelium mediates vasodilation by secreting mediators, such as Nitric oxide which is synthesized from L arginine by endothelial nitric oxide synthase. It regulates the endothelium derived relaxation of arteries), endothelium derived hyperpolarizing factor, prostacyclin and vasoconstriction by the following mediator's endothelin- 1, thromboxane A2 and Angiotensin II [7]. Thus, it serves as a gate keeper that maintains between vasodilation and vasoconstriction, anti- thrombosis and pro-thrombosis, anti-inflammation and pro-inflammation, antioxidation and pro- oxidation and vascular smooth muscle cell growth inhibition and growth promotion [3].

Endothelial Dysfunction and Diabetes Mellitus

The inability of the endothelial cells to maintain vascular homeostasis as a result of disturbed balance between endothelium derived pro- atherosclerotic factors and anti-atherosclerotic in favor of pro-atherosclerotic factors leading to the initiation and progression of vascular complications is termed endothelial dysfunction. Vascular disease can occur due to chronic hyperglycemia according

to multiple studies in patients and animal models. Endothelial metabolism and functions are altered by hyperglycemia, leading to vascular injury that contributes to all diabetic complications in all the forms of diabetes mellitus. Prolonged and repeated exposure to other cardiovascular risk factors additionally cause serious damage to the endogenous protective mechanisms within the endothelial cells. As a consequence, the endothelium may become dysfunctional and may lose its vasomotor properties [8]. Endothelial dysfunction which is an early event of atherosclerosis also plays a critical role in its progression leading to the development of vascular complications. Diabetes mellitus is associated with endothelial dysfunction usually due to increased nitric oxide inactivation and/or decreased nitric oxide production from the endothelium resulting in decreased nitric oxide bioavailability [3].

Mechanism Underlying Endothelial Dysfunction in Diabetes Mellitus

Vascular endothelium functions as a structural barrier between the vessel wall and the lumen. Endothelial dysfunction plays a crucial role in the pathogenesis of diabetic macroangiopathy and microangiopathy, a common cause of morbidity and mortality in patients with diabetes mellitus. Studies have implicated endothelial function as an early marker of atherosclerosis proceeding ultrasonic evidence of atherosclerotic plaque and an event seen in patients with prediabetic condition [7].

Over the past two decades, substantial studies have focused on mechanism provoking endothelial dysfunction. These mechanisms include Reactive oxygen species (ROS) mediated endothelial nitric oxide synthase (eNOS) uncoupling, loss of nitric oxide bioavailability and hyperglycemia induced apoptosis of the vascular endothelium which will ultimately result in the impairment of vascular relaxation, a common biomarker of endothelial dysfunction [7].

The Role of Insulin

Insulin, is a hormone that plays a vital role in maintaining vascular homeostasis where it stimulates the muscle tissue and liver to store excess glucose in form of glycogen. And. The impairment of biologic sensitivity and/or responsiveness to insulin stimulation in muscle, adipose tissue and liver which are its target tissue is insulin resistance (IR). Numerous studies support IR as an important pathophysiologic impairment responsible for both metabolic and cardiovascular disorder. A disturbance in insulin signaling will ultimately lead to glucose intolerance, dyslipidemia, diabetes mellitus and coronary artery diseases [9].

Insulin binds to its cell surface receptor called the insulin receptor leading to its activation. The activated insulin receptor phosphorylates intracellular substrates, such as insulin receptor substrates (IRS) family members, Shc protein and Gap- 1 [7]. Three isoforms of IRS- 1, 2 and 4 has been identified in humans and they all play varying important roles depending on the cell type and metabolic condition. The phosphorylated insulin receptor substrates tyrosine activates phosphoinosisitide-3 kinase (PI3-K) thereby converting phosphatidylinositol (3,4)-biphosphate (PIP2) to phosphatidylinositol (3,4,5)-triphosphate (PIP3). A cascade of serine kinases is initiated by PIP3 which results in the recruitment of phosphoinositide-dependent kinase-1 (PDK-1) and Akt to the membrane where they were activated. The activation of Akt influences cellular functions by controlling nitric oxide production, glucose metabolism and angiogenesis. An alternative insulin signaling pathway proceeds from Shc that causes the activation of the small GTP binding protein Ras that initiates a cascade of phosphorylation involving mitogen activated protein kinase (MAPK). The MAPK pathway is associated with endothelial cells, mediating the secretion of endothelin- 1 [7]. The MAPK pathways are weakly associated with regulation of metabolic function, while PI3-kinase dependent pathway functions as a crucial branch to mediate the metabolic actions of insulin. Deficiencies in the metabolic action of insulin results in Insulin resistance. Disorders associated with PI3-K/Akt pathway results in a lack of insulin sensitivity in the peripheral tissues, this leads to the strong activation of the MAPK pathway with compensatory hyperinsulinemia with the production of inflammatory mediators (vascular cell adhesion molecule, E- selectin and ICAM) when the PI3-K/Akt axis is downregulated [10].

The imbalance between these two signals leads to endothelial dysfunction characterized by the decreased production of vasodilating substance (nitric oxide), and increased generation of vasoconstricting substances (endothelin- 1) in endothelial cells [7].

The Role of Oxidative Stress

Oxidative stress is referred to as a disturbed balance between the antioxidant system and reactive oxygen species (ROS) derived from molecular oxygen in favor of ROS. Various enzymatic sources such as Xanthine dehydrogenase/oxidase, Nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, uncoupled endothelial nitric oxide synthase are involved in the production of ROS. ROS includes free radical specie such as superoxide anion radical, peroxyl radical, alkoxyl radical, non-radical species such as singlet molecular oxygen, hydrogen peroxide, ozone [11]. Insufficiencies in the balancing the effects of the antioxidant system result in a harmful effect of ROS such as inhibition of signal transduction pathways or normal cellular functions through the damage of cellular DNA, protein or lipids. Interaction occurs between endothelial function and oxidative stress [13]. Superoxide anion radical, a free radical specie produced through the removal of one electron from molecular oxygen directly inactivates nitric oxide with a high affinity resulting in the decrease of nitric oxide bioavailability. With a concomitant production of peroxynitrite, a highly potent oxidant that can cause lipid peroxidation DNA damage, protein tyrosine nitration and call death [13]. Tetrahydrobiopterin (BH_4) an essential cofactor for eNOS is also oxidized by peroxynitrite to its biologically inactive form resulting in reduced BH_4 availability. Insufficiencies in BH_4 leads to the production of Superoxide anion radical from uncoupled eNOS instead of nitric oxide [14].

When an oxidative condition is established, impairment of endothelial function continues through a vicious cycle of increased superoxide anion radical and reduced nitric oxide bioavailability.

Hyperglycaemia and Oxidative Stress

Glycolytic process, generates pyruvate in the cytosol and the pyruvate is utilized for the synthesis of ATP by oxidative phosphorylation in the mitochondria. After its transportation in the mitochondria, pyruvate is oxidized by the tricarboxylic acid (TCA) cycle to produce H_2O, CO_2, nicotinamide adenine dinucleotide (NADH) and 1,5-dihydro flavin adenine dinucleotide ($FADH_2$) The electrons generated from the mitochondrial NADH and $FADH_2$ are used for the synthesis of ATP by the electron transport chain in the inner mitochondrial membrane.

In hyperglycemic state, increased production of NADH and $FADH_2$ by the TCA cycle leads to increased transportation of NADH and $FADH_2$ (serve as electron donors) to the electron transport chain resulting in an enhanced electron transfer and proton pumping which results in an increase in electron leak from the electron transfer chain and subsequent increased in superoxide anion radical production in the mitochondrial [3].

Glyceraldehyde 3- phosphate dehydrogenase (GAPDH) is a glycolytic enzyme that is important for maintaining glycolysis. Hyperglycemia induced over production of mitochondrial superoxide anion radical partially inhibits its activity leading to the accumulation of glycolytic metabolites upstream of GAPDH and the increased flux of upstream metabolites into pathways of glucose overutilization [3]. The increase in flux of glucose into the polyol pathway results in an increase in the consumption of NADPH which is required for the generation of reduced glutathione.

The reduction in the intracellular concentrations of reduced glutathione results in enhancement of intracellular oxidative stress and eventually endothelial dysfunction [3]. Increased flux of glucose into the hexosamine pathway may lead to endothelial dysfunction. In this pathway, Fructose-6-phosphate is converted to glucosamine-6- phosphate in resulting in an increase in UDP-N- acetyl glucosamine, a metabolite required for reactions such as proteoglycan synthesis, and O- linked glycoprotein formation. As a consequence of the increased UDP- N- acetyl glucosamine formation, transcriptional factors, nuclear protein, cytoplasmic proteins are modified resulting in the alteration of protein and gene function. For example, eNOS activity is inhibited by O- acetyl glucosaminylation of eNOS protein at the Akt site leading to the reduced nitric oxide production and consequent endothelial dysfunction. Activation of Protein Kinase C (PKC) induced by hyperglycemia through an increase in diacylglycerol has a number of pathogenic effects such as decreased eNOS expression, increased Endothelin- 1 expression, increased plasminogen activator inhibition- 1 (PAI- 1) expression, NF- KB activation and NADPH oxidase activation leading to endothelial dysfunction [3]. Advanced glycation end products (AGEs), generated *in vivo* as a normal consequence of metabolism are enhanced under conditions of hyperglycemia, increased oxidative stress and hyperlipidemia. AGEs are highly reactive and can trigger inflammation by generating TNF- α and interleukin 6 (IL- 6). In addition, Advanced glycation end products can activate the receptor binding site of RAGE in endothelial cell, monocytes and macrophages resulting in the accumulation of MAPK and NF- KB. They can also enhance oxidized low-density lipoprotein (OxLDL) formation and in a hyperglycemic state the expression of LOX-1 on monocyte and macrophages are increased. These processes facilitate the uptake of OxLDL by macrophages thus increasing inflammation [3].

Role of Inflammation

Subclinical inflammation, a hallmark sign of diabetes mellitus is characterized by elevated levels of tumor necrosis factor alpha (TNF-α), C-reactive protein (CRP), interleukins (most notably IL-1, IL-6, IL-18). These factors have the ability to interact with different receptors that converge in their mediators that increase oxidative stress and activate nuclear factor kappa B in the endothelial cells which eventually lead to endothelial dysfunction [3]. The levels of CRP are significantly higher in diabetes mellitus, which has been proven to induce endothelial function in cultured endothelial cells. Its role in in endothelial dysfunction is related to the presence of other agents like oxidized low-density lipoprotein (ox-LDL). CRP also interacts with lecithin-like ox-LDL receptor 1 (LOX 1) and complement proteins to induce inflammation in cultured endothelial cells. CRP effects are also mediated by the IgG Fc receptor where it abolishes insulins activation of eNOS by inhibiting Akt phosphorylation at Ser473, and also, it disrupts endothelial progenitor cells migration, adhesion and proliferation thereby instigating apoptosis and necrosis of endothelial progenitor cell [3].

The Angiopoietins

Angiopoietin/Tie Signaling pathway system is among the tightly controlled biological processes that are involved in vascular morphogenesis and homeostasis [15]. Angiopoietins (Ang), the bona fide ligands of Tie-2 receptor, are a family of secreted glycoproteins which are approximately 70 kDa in weight and acts primarily on the vasculature to control blood vessel development and stability. Earlier, Angiopoietins comprised of four members, Angiopoietin 1 (Ang1), Angiopoietin 2 (Ang2), Angiopoietin 3 (Ang3), and Angiopoietin 4 (Ang4); however, the family currently consists only of Ang1, Ang2, and Ang4. Ang3 is locus to mouse and does not exert significant biological effects on human endothelial cells [16].

Angiopoietin 1

Angiopoietin 1 are secreted primarily by the perivascular cells and smooth muscle cells and it acts in a paracrine manner on the endothelium. It activates Tie2 receptor and its downstream targets leading to the stabilization and maturation of blood vessels. It is an anti-inflammatory cytokine [15].

Angiopoietin 2

Angiopoietin-2, a growth factor produced primarily by the endothelial cells belongs to the Angiopoietin/Tie (tyrosine kinase with Ig and EGF homology domains), an important pathway that is involved in angiogenesis. It was discovered shortly after Angpt1 through a cDNA library screening with 496 amino acid long proteins. It shares approximately 60% amino acid homology with Ang1 and lacks of the nine-cysteine found in a matured Ang-1. Ang-2 has an NH_2-terminal coiled domain, a COOH- terminal fibrinogen like domain and a secretion signal peptide. It acts in an autocrine manner with a highly regulated expression unlike Ang1. Similar to Ang1, it binds to the Tie2 receptor with the same affinity inducing its antagonistic [17], thereby interrupting the functions of Ang1 thereby destabilizing an established vasculature [15]. Ang-2 expression is triggered by

inflammatory mediators, such as thrombin, hypoxia and cancer [17]. In the presence of vascular endothelial growth factor (VEGF), Ang-2 promotes the proliferation and migration endothelial cells. It was recently shown that Ang-2 has context-dependent agonist activities and inflammatory signals were found to regulate the switch between the agonistic and antagonistic activity of Ang-2.

In pathological-free conditions, there is activation of Tie1 which triggers Ang-2 to act as an agonist to promote Tie2 phosphorylation. However, in inflammatory conditions, there is cleavage of Tie1 (inactivated) to convert Ang2 into an antagonist thereby inhibiting Tie2 activation. The cleavage of Tie1 therefore, induces Ang-2 switching from agonist to antagonist. Ang2 acts as a context-dependent agonist/antagonist of Tie2 and a dynamic regulator for endothelium [18].

Tie 2 Receptor

Tie2, together with Tie1, make up the Tunica Interna Endothelial (Tie) family of receptor tyrosine kinases (RTKs). The Tie 2 receptor, is highly expressed in the endothelial cells and it demonstrates strong kinase activity. It becomes phosphorylated on several cytoplasmic tyrosine residues resulting in the activation of pathways related to the inhibition of de novo blood vessel growth and vascular hyperpermeability such as PI3/Akt and ERK [19].

The Angiopoietin/Tie Signaling System

The second endothelial growth factor receptor signaling pathway that functions in angiogenesis and lymph angiogenesis and a critical regulator of endothelial cell function. It functions to regulate blood and lymphatic vessel remodeling after VEGF- VEGFR driven phase of active angiogenesis. It contributes to vascular homeostasis, by regulating endothelial barrier function, inflammation, vessel remodeling as well as pathological angiogenesis and lymph angiogenesis in matured tissue [20]. The translocation and activation of the Tie receptors is induced by Angiopoietins in some subcellular compartments, and is dependent on the cell microenvironment, this explains the versatile functions of angiopoietins during vessel quiescence and remodeling.

For Endothelial cells (ECs), that are in the quiescent vasculature, the formation of Tie receptor signaling complexes in trans across the EC–EC junction is induced by angiopoietins. These junctional Tie complexes mediate cell survival signals via the PI3K-Akt pathway, leading to the activation of the endothelial nitric oxide synthase (eNOS) [21].

Activation of Tie2results in the inactivation of Foxhead box protein O1 (FOXO1), and induction of Akt-dependent phosphorylation, this suppresses the expressions of genes involved in endothelial destabilization and apoptosis, thereby maintaining junctional integrity, and enhancing cell survival, capillary stabilization, and sprouting. Ang2 also competes with other Ang for binding to Tie2 thereby downregulating the Tie2 phosphorylation, promoting FOXO1 activity leading to disruption of endothelial quiescence [21]. In some circumstances, such as tumor models, lymph angiogenesis, pathogen-free conditions, or when Ang1 is absent, Ang2 can function as an agonist of Tie2 signaling thereby promoting Tie2 phosphorylation. Researchers found out recently that vascular endothelial protein tyrosine phosphatase (VE-PTP) can dephosphorylate Tie2 and reduce its activity. VE-PTP is upregulated in diabetic animals and inhibition of VE-PTP activates endothelial nitric oxide synthase and decreased FOXO1 and its downstream pro-inflammatory and profibrotic targets. A new drug targeted to VE-PTP induced a reduction in proteinuria which may protect the kidney from diabetic injury [18].

Angiopoietin 2 gene

The Angiopoietin 2 gene (Angpt2) belong to the Angiopoietin family of growth factor and encodes for the protein Angiopoietin 2 an antagonist of Angiopoietin 1. Angpt2 is located on human chromosome band 8 (8p23.1), comprising of 8 introns and 9 exons that codes for 496 amino acids.

The Angpt2 has been found to be highly polymorphic in exon 2 at position 759, position 1233 in exon 5 and 1087 in exon 4 (this has been associated with diabetes mellitus and diabetic nephropathy, of the cDNA sequence of Angpt2. These polymorphisms include the (rs2442598 and rs 3020221). Genetic variant in the Angpt2 may affect its expression or vascular angiogenesis [23].

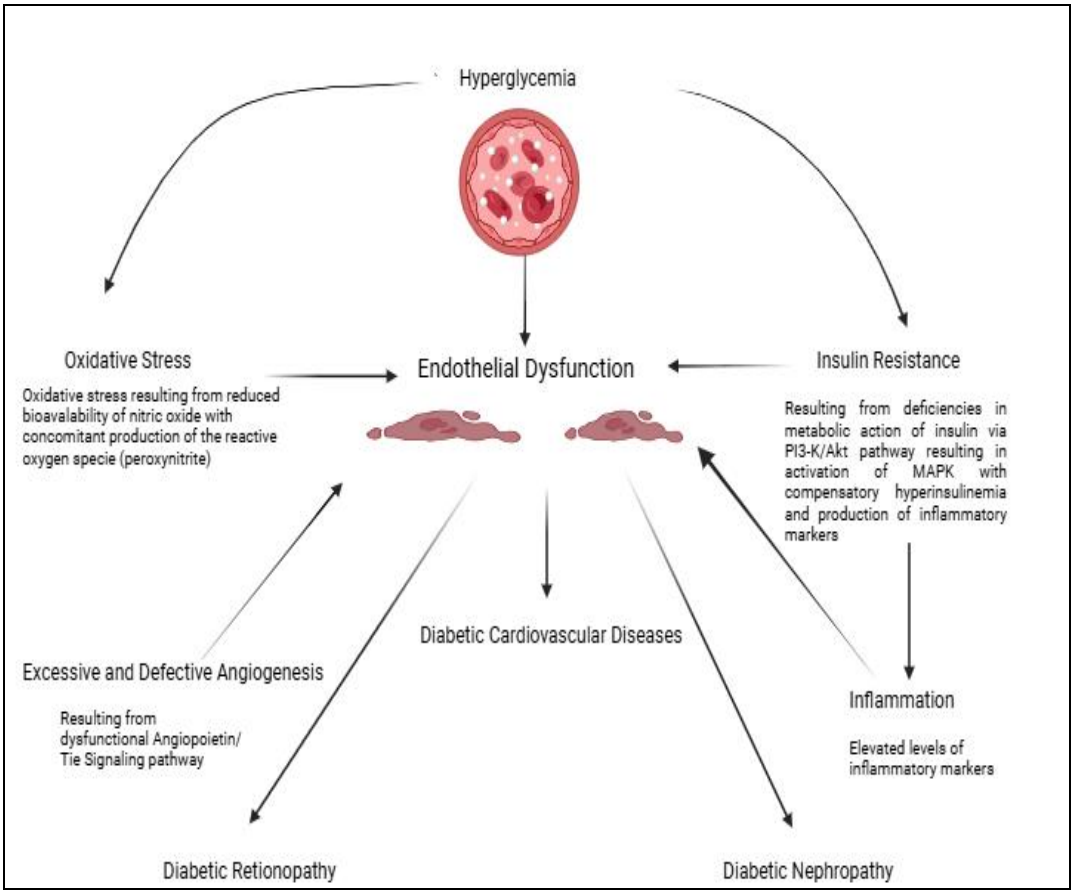
The rs2442598, an intron SNP and one of the most studied variants of the Angpt2 and has been associated with diabetic retinopathy [19], coronary artery disease [23] and cardiovascular disease [24]. The Angiopoietin 2, 1087 G>A rs3020221 Single Nucleotide Polymorphism is located at exon 4 [25].

Role of Angipoietin-2 in Diabetes Mellitus

Angiopoietin- 2 plays a crucial role in diseases that are connected to vascular permeability and angiogenesis. It has a vascular disrupting property which became evident when Ang2 over expressing transgenic mice were embryonically lethal due to poorly formed blood vessels [26]. Earlier studies reported elevated levels of Ang2, soluble Tie-2 receptor (sTie-2), vascular endothelial growth factor in patients with type 2 diabetes mellitus [5, 2[7]. A selective increase of plasma levels of Ang2, sTie-2, but not Ang1 is accompanied by neovascularization and endothelial abnormalities [28]. Ang2 is important for the initiation of inflammatory response. It has been positively associated with inflammatory biomarkers such as hsCRP, white blood cell count, leading to the notion that it can be considered as an inflammatory marker [29].

Diabetic Retinopathy

One of the characteristics of diabetic retinopathy is vascular leakage and it can lead to macular oedema and vision loss. Significantly elevated levels of Ang2 were found in type 2 diabetes mellitus with both proliferative and non-proliferative diabetic retinopathies when compared with diabetic patients without retinopathy [30]. In an early streptozotocin induced diabetic retinopathy model, increased Ang2 levels led to astrocyte loss and vascular leakage, both of which were blocked by an intravitreal injection of Ang2 neutralizing antibody [31]. Diabetic retinopathy is associated with pericyte loss. Ang2 transcription is induced hyperglycemia leading to apoptosis and migration of retinal pericyte through Tie2 activation, thus regulating the activation and death of pericyte. This was not observed in Ang2 deficient mice, thus demonstrating the impact of Ang2 in diabetic retinopathy and the potentials of Ang2 inhibition for a therapeutic intervention [28].



Diabetic Nephropathy

At physiologic conditions, Angiopoietins are important for glomerular capillaries, where they play an important role in permeability of the vascular wall and blood flow regulation. The imbalance of the different growth factors angiopoietins inclusive, promotes endothelial dysfunction and it has been linked to the early pathological changes in the functions of the glomerulus in diabetes mellitus namely; changes in blood flow and vascular wall permeability [33]. This was based on a study on streptozotocin induced diabetic rats, where the authors concluded that diabetes mellitus was associated with a disproportionate increase in Ang2 compared to Ang1 and that Ang1 expression was decreased in the diabetic kidney after eight (8) weeks of experiment.

Similarly, only the mRNA level of Ang2 was elevated in the whole glomerular endothelial cells of the diabetic mice when compared to the controls. No changes were observed in Ang1 [33]. In addition, high blood glucose was proven to lead to the down regulation of Ang1 mRNA in high glucose treated podocyte when compared to normal glucose treated cell. In humans, studies reported the negative role of Ang2 on the glomerulus, where Ang2 mRNA expression was increased in glomeruli isolated from patients with diabetes mellitus when compared to controls [34]. Also, urinary Ang2 concentration was increased in patients with type 2 diabetes mellitus associated with albuminuria [35]. This information supports the hypothesis that Ang1/2 may take part in diabetic glomerular disease onset and progression [33]. Elevated levels of Ang2 have been linked to systemic inflammation in patient's chronic kidney disease and it may predict mortality [38]. Recently, it was proven that elevated serum concentration of Ang2 is independently associated with increased risk of major adverse cardiac events (MACE) or all-cause mortality in patients with diabetic nephropathy and that Ang2 could be a potential predictive factor for MACE in patients with diabetic nephropathy at increased risk of microvascular complications [39].

Cardiovascular Disease

Ang2 has been implicated in endothelial physiology and cardiovascular remodeling. Endothelial dysfunction usually associated with cardiovascular risk factors and cardiovascular remodeling is associated with the modification of the vascular structure, a percussor of cardiovascular disease (CVD).

Elevated Ang2 levels have been reported in most cardiovascular disorders such as coronary artery disease, congestive heart failure, peripheral artery disease, chronic kidney disease, in most cases, was reported as a biomarker [17]. On the other hand, decreased Ang2 expression combined with increased Ang1 expression is thought to contribute to vascular remodeling, and this was targeted through human umbilical cord mesenchymal stem cell conditioned medium post stroke treatment [38].

Elevated plasma concentration of Ang2 has been associated with arterial stiffness, a known risk factor for cardiovascular mortality in type 2 Diabetes mellitus [39]. Rasul *et al.* [5], reported that subjects with diabetic macrovascular complications, in particular with the CVD, had higher serum Ang2 concentration than those without these complications and also in an *invitro* study, proving that hyperglycemia may lead to an increase in Ang2 concentration, causing increased myocardial apoptosis, increased infarction size, and impaired myocardial angiogenesis [40].

Laboratory and Clinical Diagnosis

WHO (1999) has described the clinical diagnosis for diabetes mellitus to includes:

Polyuria, Polydipsia, Polyphagia, Weight loss, Blurred Vision, Lower extremities Paresthesia while the laboratory investigations for diabetes mellitus are [41]

- Fasting Plasma Glucose ≥ 7.0mmol/L, 2HrPP ≥ 11.1 mmol/L, Random plasma glucose ≥ 11.1mmol/L, HbA1c ≥ 6.5%, lipid profile levels
- Markers of Inflammation (HsCRP)
- Markers of ED (Nitric Oxide, Endothelin-1)
- Markers of Angiogenesis (Ang 1, Ang 2, Soluble Tie 2 Receptor, Vascular endothelial growth factor).

Management of Endothelial Dysfunction in Diabetes

Life style Modification

1. Medical nutrition therapy, an evidence based medical approach to treating certain chronic conditions through the use of individually tailored nutrition. The goal is to achieve and maintain: Blood glucose level in the normal or close to normal levels, and reduction HbAIc levels. A lipid and lipoprotein profile that reduces the risk of vascular diseases.
2. Normal blood pressure levels or ass close to normal as safely as possible. Provide adequate calories for achievement of reasonable body weight. To decrease the complications of DM and CVD by promoting healthy food choices and physical activities leading to moderate weight loss that is maintained slowing the rate of DM and cardiovascular disease complications [43].
3. Use of metformin as the optimal first line drug unless contraindicated. After metformin, the use of 1 or 2 additional oral or injectables, with the goal of minimizing adverse effects if possible. Ultimately, insulin therapy alone or with other agents if needed to maintain blood glucose control [43]. Others include Sulfonylureas, Glinides, SGLT2 inhibitors Thiazolidinediones etc. [3].

Therapeutic Strategies with Angiopoietin

The involvement of the Ang/Tie system in the pathophysiology of several disorders has made Ang2 a potential therapeutic target, some therapeutic approaches targeting Ang2 have also provided promising results. Vasculotide, an Angiopoietin based peptidomimetic compound, binds the Tie2 receptor thereby eliciting downstream signaling, it also promoted angiogenesis both *in vivo* and *in vitro* and it also accelerated wound healing in diabetic mice.

Vasculotide, was also successful in blocking vascular leakiness, protecting the endothelial monolayer from sepsis-associated permeability, and polymicrobial abdominal sepsis-induced lethality. Inhibition of vascular leakiness was verified in other models, where it preserved microvascular integrity during hemorrhagic shock and cardiopulmonary bypass [17]. Ang 2 blocking antibodies have been shown to reduce plasma triglycerides levels and decreased the formation of intimal fatty streaks in mouse model of hypercholesterolemia induced atherosclerosis thus suggesting a beneficial effects of Ang 2 depletion during the early phase of arteriosclerosis [44].

Conclusion

Angiopoietin 2 is vital for endothelial cell physiology and plays a central role in vascular-related diseases by regulating endothelial permeability and angiogenic functions. Patients with diabetes mellitus are at risk of both macrovascular and microvascular complications. A selective increase in Ang2 concentration may favor abnormal neovascularization and disrupt the endothelium, which is linked to both atherosclerotic vascular complications and microvascular in Type 2 diabetes mellitus. Since Ang2 plays a role in vascular diseases, targeting Ang/Tie signaling pathway may perhaps become a therapeutic approach because anti-angiogenic therapies are considered to be promising treatment methods in this field, especially towards restoring macrovascular and microvascular integrity.

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