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Effects of endothelins and matrix metalloproteinases in various pathological disorders and their antagonism at a better treatment modality in modern medicine

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ABSTRACT

Chronic disorders or diseases like hypertension, diabetes-mellitus, cancer, heart failure, pulmonary hypertension are becoming more prevalent nowadays even at a younger age. Various methods have been introduced to determine several diseases out of which the concept of measurement of endothelins and matrix metalloproteinases and the usage of endothelin receptor antagonist as a way of treatment either singly or combinedly with other drugs has achieved more importance. By the usage of serum matrix metalloproteinases (MMPs) and endothelins we can determine the people who are at risk of developing hypertension, type2 diabetes, heart failure, atherosclerosis, cancer, pulmonary hypertension and can also assess the range of complications that are going to occur in the individual. These elevated levels cause remodelling after a period of time. Hence, the detection is done through a method in which few factors like endothelins and MMPs of our body are measured through a blood sample, maximum benefits can be obtained in individuals who have a significant family history of developing hypertension and other conditions In this review we have discussed about various effects of endothelins in different conditions, and also to know if these conditions can be improved or not by using endothelin receptor antagonists.

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INTRODUCTION

Chronic disorders (diseases) like hypertension, diabetes-mellitus, cancer, heart failure, pulmonary hypertension are becoming more prevalent nowadays even at a younger age. In the past these conditions were confined to elderly individual but over past few decades the occurrence has shifted to early adult and middle-aged people. In the coming years it wouldn't be surprising, if these conditions are seen in late teenage and early twenties. Hence prevention can be done by concentrating on two things, firstly the way of living should be changed by heading towards positive health, but the drawback associated is, it is completely individual dependent which may be interrupted in between by various deviations like appetite etc. And the second thing is early identification and using early measures to prevent further progress of the disease condition in the patient. (Takahashi *et al.*, 2001) There are many ways in which hypertension, diabetes etc. can be

detected i.e for example, blood pressure measurement over a period, serum cholesterol. All these conditions can be seen\detected after a significant change has taken place. For example, elevated blood pressure can be measured and said to be elevated, only after blood pressure has been sustainably elevated over a period and by that time the changes which have taken place may be reversible or irreversible. If the patient is lucky enough, he\she acquainted with the knowledge about hypertension knows that they have elevated blood pressure can be adequately treated on time. (GALIE, 2004) On the other side the unlucky end up in complications of hypertension, which probably ends in causing diabetes and here for understanding rule of halves may or may not be applied here all chronic diseases can be explained by iceberg phenomenon, in which only few individuals with the disease condition are identified and probably treated while most of them remain undetected, similar to an iceberg in which visible part of ice berg is comparable to number of patients identified with the disease and the undermined part of the ice berg is comparable to the number of individuals who are undetected. (Lüscher *et al.*, 1993)

Various methods have been introduced to determine various diseases, out of which the concept of measurement of endothelins and matrix metalloproteinases and the usage of endothelin receptor antagonist as a way of treatment either singly or combinedly with other drugs has achieved more importance. (Matsui *et al.*, 2002) Here we take serum markers named endothelin and matrix metalloproteinases which help us in identifying the changes that are about to take place. These markers are responsible for knowing changes in blood vessel and their levels are increased in pathological states of various diseases. The elevated levels of these substances causes vascular remodeling after a period. Hence the detection is done through a method in which few factors like endothelins and matrix metalloproteinases (MMPs) of our body are measured through a blood sample, maximum benefits can be obtained in individuals who have a significant family history of developing hypertension and other conditions (As we know changes are sure to take place in these individuals). (Harris *et al.*, 2005)

Endothelin is involved in the pathogenesis of various diseases like pre-eclampsia, Alzheimer's, asthma, heart failure, cancer etc., Hence endothelin antagonists can be used as a mode of treatment. It has been noticed that better outcome has been achieved when endothelin antagonist have been used with the present available treatments than available standard treatments. (Abraham and Distler, 2007)

WHO proposed that hypertension prevalence would show a relative increase of 17% in spite of relative reduction by 25% after a decade By this information we can probably have a chance to understanding that, the present procedures which are being used for detection of hypertension etc haven't been sufficiently enough to identify patients who have increased risk of developing hypertension etc, and hence there is a need for new procedures or techniques which can have a better capacity of identification. We also may need newer and better drugs for better control of disease. (Fernandez-Patron *et al.*, 1999)

Epidemiology

Hypertension

Globally, an estimated 26% of the world's population (972 million) has hypertension and the prevalence is expected to increase to 29% by 2025 driven largely increase in economically developing nations.

Diabetes

The number of people with diabetes has risen from 108 million in 1980 to 422 million in 2014 and the global prevalence of diabetes among adults over 18 years of age has risen form 4.7% in 1980 to 8.7%in 2014 associated more with rapidly increasing burden by the middle and low economic income countries.

Chronic Kidney Disease

850 million people worldwide have kidney disease, which is occurring as a hidden epidemic- as per health day news, 2018

Heart Failure

Researchers found out that population ageing contributed to an estimated 55% increase in cardiovascular deaths globally and population growth contributed to 25% increase.

Pulmonary Hypertension

Each year between 10 and 15 people per million populations are diagnosed with pulmonary hypertension.

Cancer

Approximately 38.4% of men and women will be diagnosed with cancer at some point of time based on 2013-2015 data.

All the above-mentioned diseased conditions are chronic in nature and the prevalence always is going to increase thereby there is a need to determine better methods to reduce the burden in the population.

Here is one of the method that needs to be taken into consideration for better treatment and prognosis by

estimating the levels of endothelins and matrix metalloproteinases (MMPs) and blocking their action as the mode of treatment in early as well as in acute states by various drugs (some have shown promising effects and some are still under trial moving towards positive side). (Gupta *et al.*, 2017)

Endothelin and MMPS

Endothelin

(ET-1) is a 21 amino acid peptide that is produced by the vascular endothelium from a 39 amino acid precursor, big ET-1, through the actions of an endothelin converting enzyme (ECE) found on the endothelial cell membrane. ET-1 formation and release are stimulated by angiotensin II (AII), antidiuretic hormone (ADH), thrombin, cytokines, reactive oxygen species, and shearing forces acting on the vascular endothelium. ET-1 release is inhibited by prostacyclin and atrial natriuretic peptide as well as by nitric oxide.

The endothelin family consists of three peptides ET type 1,2 and 3. It acts primarily as paracrine / autocrine peptide and not as a circulating hormone by binding to ET-A and ET-B receptors. It has a very small half-life of less than five minutes in plasma with the main clearance in lungs and kidneys. (Yanagisawa *et al.*, 1988)

"Matrix metalloproteinases (MMPs), also known as matrixins are usually calcium- dependent zinc-containing endopeptidases. They belong to a larger family of proteases known as the metzincin super family". They are classified based on their composition and the organization of their structural domains into collagenase, gelatinases, stromelysins, matrilysins, membrane type (MT)-MMPs etc. (Kedzierski and Yanagisawa, 2001)

Production of Endothelin and MMPs and Their Actions

Endothelin-1 is produced by endothelial and smooth muscles, air-way epithelial cells, macrophages, fibroblasts, cardiac myocytes, brain neurons and pancreatic islets. (Kedzierski and Yanagisawa, 2001)Figure 1

Endothelin-2 is expressed by ovaries and intestinal epithelial cells. (Mulvany, 2002)

Endothelin-3 is found in endothelial cells and intestinal cells (whose action is mediating release of vasodilators including NO and prostacyclin). (Mulvany, 2002)

Endothelin production is stimulated by hypoxia, catecholamines, angiotensinogen-2, epinephrine, vascular shear stress, inflammation, thrombin, insulin, cyclosporine, inflammatory mediators and oxidative stress. (Mulvany and Alkjaer, 1993)

Endothelin production is inhibited by nitric oxide, nitric oxide drug donors, dilator prostanoids via increase in cellular cGMP and natriuretic peptides via an increase in cAMP levels. (Mulvany, 2002)

MMP's in broad are produced by leucocytes, vascular smooth muscle and fibroblasts. (Mulvany, 2002)

MMP-2, and **MMP**-9 which are involved in vascular remodeling are secreted by a variety of vascular and non-vascular cell types such as endothelial cells, podocytes, fibroblasts, myofibroblasts and resident macrophages. (Dupuis *et al.*, 1996)

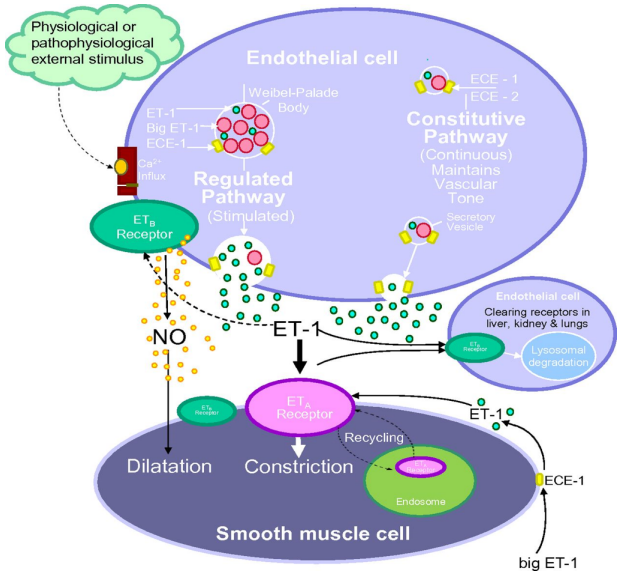

Figure 1: Synthesis of ET-1

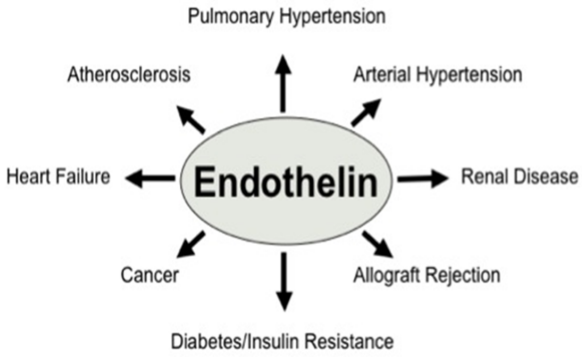

Figure 2: Role of Endothelin in various diseases

MMP production is kept in check: By the endogenous tissue inhibitors of metalloproteinases (TIMP's) which reduce excessive matrix degradation by the metalloproteinases. Alteration in the levels of MMPs/TIMPs causes various vascular diseases like aortic aneurysm, varicose veins, hypertension and pre-eclampsia. (Wang and Khalil, 2018)

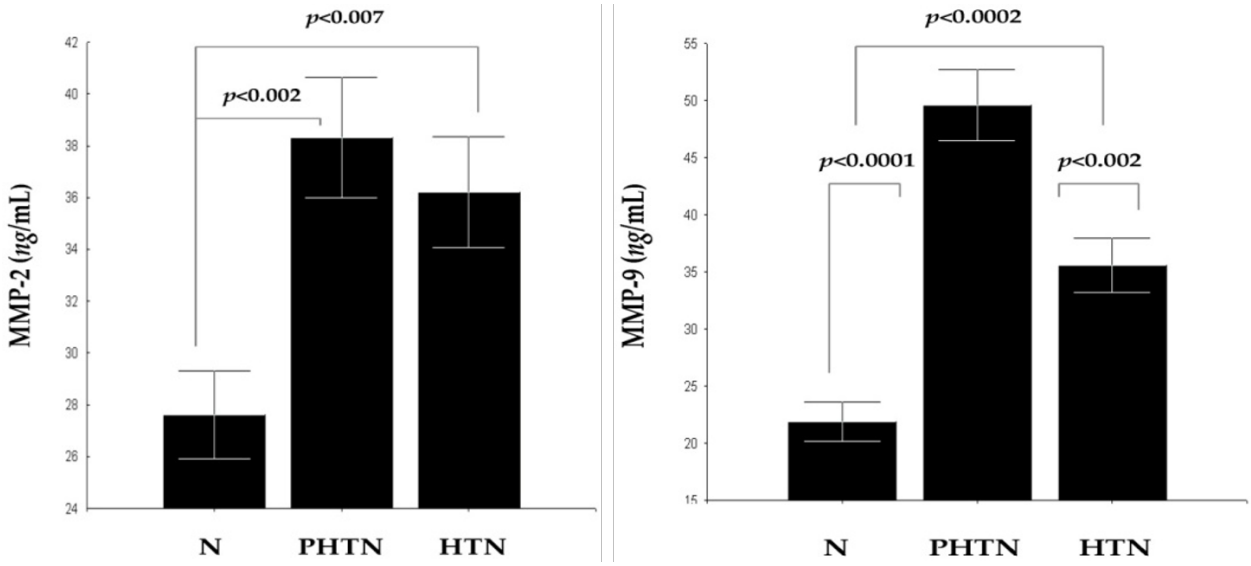

Figure 3: Levels of MMP-2 & 9 in pre-hypertensive and hypertensive states

Though there are different types of endothelins produced (ET-1, ET-2, ET-3) Each of these possesses a set of pharmacological activities of different potency. The main type of endothelin produced is ET-1 which shows its actions through receptors. There are two types of endothelin receptors ET-A and ET-B. The receptors can be differentiated by their affinity in the order of ET-1≥ET-2>ET-3, whereas ET-B show similar affinity for all the three isopeptides. ET receptors are distributed in various cells and tissues, but with different level of expression. They elicit biological response by various signal transduction mechanisms including the G-coupled activation of phospholipase-c and the activation of voltage dependent ca+ channels. Thus, different subtype of endothelins receptors may use different type of signal transduction mechanisms. ET-A increases cAMP and stimulates protein kinase –A activity, on the other hand ET-B inhibits cAMP and stimulates the formation of phosphoinositide (Kawanabe and Nauli, 2011)

ET-A receptors are located on vascular smooth cell, which when activated cause vasoconstriction which is slow in onset. ET-B receptors are located on both endothelial and vascular smooth cells, which when get activated cause vasodilation by the release of vasodilators acting on vascular tissue and inhibit cell growth and vasoconstriction by functioning as a clearance receptor. (Jaiswal *et al.*, 2011)

The actions of ET-A are vasoconstriction of smooth muscles, increased myocardial activity and aldosterone secretion mediated by ET receptor subtype-A (RET-A). Thus, on chronic stimulation of RET-A and persistent increase in endothelins, vascular proliferation and vascular smooth muscle hypertrophy of cardiomyocytes occurs because ET-1 acts as a mitogen responsible for pathological remodeling of vessels. In case of heart failure low density lipoprotein (LDL) reduces NO release via inhibition of arginine transporter of endothelial cells and endothelin induced vasoconstriction through nonselective Ca+ channels. (Raffetto and Khalil, 2008)

MMPs possess a destructive action on the basement membrane by damaging the collagen in it and has role in vascular smooth muscle migration, proliferation, Ca+ signaling and contraction. There by it is known to play an important role in vascular tissue remodeling during various biological process such as inflammation, angiogenesis, embryogenesis, morphogenesis and wound repair. (Lüscher *et al.*, 1993)

Effects of Endothelin

Vasoconstrictor effect

ET-1 causes vasoconstriction by acting through its receptor ET-A, which is the most dominant action of endothelin. (Mulvany and Alkjaer, 1993)

Vasodilatory Effect

By increasing the production of nitric oxide and prostaglandins by acting through ET-B receptor [Endothelin on overproduction loses its property of producing nitric oxide or if produced its production is insignificant compared to the levels of vasoconstrictors produced at that point of time] (Wang and Khalil, 2018)

Lipid Meatabolism

Increases the LDH-receptor and lipoprotein lipase which leads to atherogenic property. (Wang and Khalil, 2018)

Increase The Inflammatory Mediators And Reactive Oxygen Species Endothelin produces TNF-alpha, IL-1,6, 8 and induces a low-grade inflammation. It also induces the production of reactive oxygen species by stimulating NADPH oxidase which together act like a vicious cycle. (Sakurai *et al.*, 1990)

Growth Factors

It increases the production of IGF, Transforming Growth Factor, Colony stimulating factor and vascular endothelial growth factor. (Masaki *et al.*, 1999)

Procoagulant Factors

Increases the production of von Willebrand factor, thromboxane A2, factor 5, platelet activating factor and plasminogen activating factor inhibitor.

Increase Matrix Products

Fibronectin, laminin, collagen and proteoglycans. It also potentiates the effects of angiotensin-2, phenylephrine and serotonin, i.e vasoconstrictor activity. (Skalska *et al.*, 2009)

Other Effects Of Et-1

ET-1 also directly regulates cardiac output, central and peripheral nervous system activity, renal sodium and water excretion, systemic vascular resistance and venous capacitance. Also increases fibrosis and atherogenicity by simulating the production of fibroblasts and others. (Romero *et al.*, 2010)

Effects of MMP's

Due to their effect on arterial remodeling and angiogenesis these lead to various pathological disorders such as HTN, atherosclerosis, varicose veins etc. To be specific MMP-2 and MMP-9 degrade collagen type 4 of the vascular membrane. (Piechota *et al.*, 2010)

Role of endothelin and MMPs in various diseases

The role of endothelins has been shown in various diseases as depicted in Figure 2.

Endothelin In Hypertension

Over expression of endothelin induces low grade inflammatory response by increasing the expression of proinflammatory mediators like interleukins 1,6 and 8 this increases the activation of NK-K beta which in turn increases the expression of transcription factors which further increase the production of endothelin -1. Endothelins stimulate ROS in human endothelial and vascular smooth by increasing NADPH oxidaseàincrease in inflammatory response and oxidative stress and forms a vicious cycle causing endothelial dysfunction which further result in active increase in the production of endothelin. Increased endothelins suppress the production of nitric oxide synthesis through the receptor ET-B thereby reducing the vasodilatory effect leading to increase in the vasoconstrictor action of blood vessels thereby increasing blood pressure and the probability of hypertension. (Sakurai *et al.*, 1990)

Endothelin In Diabetes

ECE-1 is known to increase in diabetes type-2 in response to high glucose levels in endothelial cells along with ET-1. An increase in ET-1 causes an imbalance between endothelial relaxing factors and endothelial constricting factors leading to endothelial dysfunction including microangiopathy. Several studies have shown that endothelial dysfunction is the precursor of type -2 diabetes indicating that vascular endothelial dysfunction precede insulin resistance.

One of the most important features of endothelial dysfunction is elevated levels of ET-1(found in type-2 diabetes) which induces reduction in the sensitivity of insulin. An increase in insulin resistance is due to production of ROS (Reactive oxygen species) and also activation of NADPH oxidase which is done by ET-1 and likewise it is also known to cause diabetic nephropathy, neuropathy and retinopathy. (Savoia *et al.*, 2011)

Endothelin In Pulmonary Hypertension

Pulmonary arterial hypertension is caused due to sustained increase in pulmonary vascular resistance. Pulmonary vascular smooth muscles and endothelial cells are known to increase ET-1 in lung in response to increased pressure, hypoxia and particularly when stimulated by cytokines. In patients with pulmonary arterial hypertension there is a significant correlation between serum levels of endothelin, pulmonary vascular resistance, right atrial pressure and oxygen saturation. (Takahashi *et al.*, 2001) There is an increase in receptors in lungs leading to over expression of ET-1 localized to medial layer of pulmonary arterial tree. Inhibitors of ET-A receptor are effective in reducing PAH reducing pulmonary arterial pressure and inhibiting vascular remodeling. ET-A receptor antagonist Sitaxentan was granted approval in 2006 for class-3 and 4, class-3 are those that do not respond even to vasodilators. (Ruetten and Thiemermann, 1997)

Endothelin In Systemic Hypertension

ET-A receptor antagonist can substantially reduce the blood pressure in hypertensive patients with chronic kidney disease , It is also known that the mechanism involved in the development of glomerulosclerosis—particularly those which are responsible for podocyte injury with an emphasis on

potential capacity of endothelin receptor blocker to reverse this process, there is a strong evidence that ET-1 has a central role in pathogenesis of proteinuria and glomerulosclerosis via ET-A receptor (Hofman *et al.*, 1998) and also prevents vascular hypertrophy and attenuates left ventricular hypertrophy, as well as blockade of endothelial receptors reduces diet induced hypercholesterolemia and atherosclerosis in apolipoprotein-e deficient mice (Browatzki *et al.*, 2000)

Endothelin In Heart Failure

The circulating levels of endothelins have been correlated to the with severity of hemodynamic and with symptoms in patient with congestive heart failure. ET-1 contributes to acute and chronic increase in the vascular resistance of the blood vessels, by vascular and ventricular remodeling. It is known that ET-A receptors are up regulated, and ET-B receptors are down regulated in heart failure. There is evidence of increase in for ET-1 mediated vasoconstriction in chronic heart failure. Acute hemodynamic and neurohumoral effects of selective ET-A receptor blocker in patients with congestive heart failure has been observed towards positive health. The dual endothelin receptor antagonist tezosentan, acutely improvers hemodynamic parameters in patients with advanced heart failure, (Mohazzab *et al.*, 1994) the clinical safety trials of dual receptor antagonist tezosentan in patients with advanced heart failure, and in patients with type-3 and type-4 advanced congestive heart failure are under study probably having a positive effect. (Kamata *et al.*, 2004)

Endothelin In Cancer

Endothelins are known to play a relevant role in tumor growth and metastasis by regulating mitogenesis, cell survival, angiogenesis, bone remodeling, stimulation of nociceptor receptor, epithelial to mesenchymal transition, tumor infiltrating immune cells, invasion and metastatic dissemination.

Endothelin-1 has role in various cancers like prostatic, ovarian, renal, pulmonary, colorectal, cervical, breast, bladder, Kaposi sarcoma, brain tumors, melanoma and bone metastasis. (Kanie and Kamata, 2002) Endothelin-1 shows its action via transforming growth factor (TGF-beta). Most of the cells contain TGF-beta type-1 receptor known as ALK-5 which is having role in endothelial cell migration and proliferation. Antagonism of ET receptors partially reverted the effect of TGF-beta, indicating a significant portion of anti-proliferatory and anti-migratory action of this cytokine is mediated through ET-1 through its autocrine mode of action. (Ergul, 2011) ET-1 causes the transactivation of vascular endothelial growth factor receptor-3 through ET-B receptor and modulates cell migration. These effects were similar to the effects mediated by the hypoxic inducible factors. (Kalani, 2008) ET-1 is elevated in almost all primary and metastatic ovarian tumors, especially in grade 3 and 4. High levels of endothelin-1 are also found in the ascitic fluid of the patients with ovarian cancer, suggesting a potential role for ET-1 in tumor growth promotion or maintenance through a possible autocrine and paracrine action. As well endothelin acts synergistically with other factors such as VEGF, EGF etc and ET-1 induces mitogenic signaling in human ovarian carcinoma cells. Furthermore ET-1 also induced cyclooxygenase-1 and cyclooxygenase-2 which increases prostaglandin release which causes again trans activation of epidermal growth factor receptor. (Spinella *et al.*, 2004)

Endothelins In Pre-Eclampsia

It has been suggested that there is increase in production of endothelins and NO and decrease in the production of prostacyclins, which promote hyperlipidemia and lipid peroxidation that contributes to endothelial damage aggravating further endothelial dysfunction. Endothelin has shown to increase the ca+ by activating ca+ permeable non-selective cation channels and also enhances adhesion molecules in endothelial cell. (Kawanabe *et al.*, 2002)

Endothelins Role in Some Other Disease Conditions

In Alzheimer's

It's a neuro-degenerative disorder in which there is increased amount of presence of beta-amyloid which is known to stimulate ECE and increase the production of ET-1. It is a vasoconstrictor and reduces blood flow àvasoconstriction àreduces the cerebral blood flowàhypoperfusion of the brainàand hence reduces the clearance of the A-beta and other toxic metabolites from the brain and also increases the production of A-beta(this continues as a cycle deteriorating the condition as the time progress Hypoperfusion is also known to cause dementia. (Kohan *et al.*, 2011)

In Bone Metabolism And Metastasis

IN: ET-1 is known to have effects on the osteoprogenitor proliferation and known to have effects on the(the action of endothelins is receptor dependent , and the receptor expression was under the control of vitamin D3) osteoblast cells ,hence involving in growth and remodeling of bone (Rodríguez-Pascual *et al.*, 2011) and hence known to be involved in bone metastasis in various cancers e.g. breast cancer etc.

In Sickle Cell Anemia

Sickle cell anemia is a vaso-occlusive phenomenon and has shown that the levels of endothelins are elevated by activating calcium channels and calcium dependent potassium channels located on RBCs which are known to cause cell dehydration. (Intengan and Schiffrin, 2001)

In Chronic Pain

Endothelins shows its effects through its receptors located both in central nervous system and peripheral nervous system, mediated by type-c pain fibers causing pain for a long time. Endothelins also increase serotonin, formalin and capsaicin. At lower doses, capsaicin induced hyperalgesia via ET-A receptor has been seen. Activation of ET-B which is opposite in action with ET-A reduces hyperalgesia.

In Asthma

Endothelins cause obstruction in the airway by increasing mucous secretion, Bronchoconstriction, edema etc. All of which play a pivotal role in the pathogenesis of asthma. (Keynan *et al.*, 2004)

Matrix-Metalloproteinases (MMPs)

Over expression of MMPs result in overproduction of endothelins by increasing the conversion of big ET-1 to Active ET-1 which have a higher vasoconstrictor activity.

MMPs are involved in physiological as well pathological roles, In physiological role it is considered to cause good vascular remodeling and as we know anything in excess leads abnormalities, so does it happen in case of MMPs leading to pathological remodeling of vascular tissue. MMP'S can contribute to weakening of the atherosclerotic plaques which is a major cause of acute cardiovascular events. (Takahashi *et al.*, 2001)

In moderate to severe hypertensives, the increased production of endothelins leads to fatal effects such as increased risk of stroke, atherosclerosis, myocardial infarction etc. As we know that the vascular cells are very sensitive to the hemodynamic changes so any change in blood pressure is sensed by structural modification within the vascular wall. In case of hypertension increase in arterial stretch stimulates vessel thickening which requires modification of the extracellular matrix, which is done by the help of extracellular proteases i.e., MMPs. (Corder *et al.*, 1995)

Both MMPs and TIMPs (tissue inhibitors of matrix metalloproteinases (TIMPs) that controls the function of MMP'S by inhibiting their action on matrix degradation are involved in tumor cell progression , angiogenesis and also known to promote cell adhesion molecules (increase in cell adhesion molecules can be seen in conditions like pregnancy, pre-eclampsia, cancer). (Nootens *et al.*, 1995)

DISCUSSION

The levels of MMPs (type 2 & 9) are known to be elevated in pre hypertensive states when compared to normotensive and hypertensive state of an individual hence there is a need to measure the levels of MMPs in pre hypertensive state of an individual or if the individual has the probability of developing hypertension. Figure 3 This would help us in determining whether the individual is really at risk of developing hypertension or not. It also should be noted that the levels of MMPs fall in hypertensive individuals when compared to prehypertensive individuals but are higher than that of the normal individual.

The concentration of ET-1 has shown to be increased in the hypertensive individuals and are almost similar in normotensive and pre-hypertensive. There by it also can be used as an individual method to identify whether the individual is at risk or not, if he is at risk (i.e a known hypertensive since a considerable time) then, the amount of risk can also be calculated by comparing or measuring the amount of elevated levels of endothelins when compare to that of the normal individual endothelin concentration levels.

The specificity can be increased by measuring the levels of both MMPs and ET-1, combinedly.

Example - In hypertensive patients, the levels of ET-1 are significantly high, but the levels of the metalloproteinases may reduce when compared to prehypertensive stage [this can be taken as index that several changes have taken place due to increased levels of endothelins and metalloproteinases and are at risk of developing complications. The faster the care is provided the better is the prevention of complications.] (Barst *et al.*, 2004)

In this rapidly developing world, people have less time to take care of their health and find ways to obtain food in less time like juices, beverages, soft drinks, fast foods etc., which when often taken increase the blood glucose above the baseline, causing hyperglycemia which is a stimulant for ET-1 production. This in turn causes insulin resistance and show various effects by acting as a vicious cycle (as described above in pathophysiology of diabetes caused by ET-1) and finally lead to endothelial dysfunction and thus landing up in diabetic vasculopathy etc.

These individuals concomitantly develop hypertension too in a timely period or vice-versa. Hence

providing information about why juices and other drinks should not be taken on a chronic note and to what extent prolonged intake of those substances can cause damage to the individual taking them can be a better step for prevention.

The probability of developing atherosclerosis is due to increased endothelins action on the LDL-receptor and lipoprotein lipase and aided by increase in the procoagulant factors, disturbed matrix balance and increased vasoconstrictor effect. The action of MMPs may weaken the plaque that probably gets dislodged and leads to increased chance of occurrences of myocardial infarction and stroke.

Therefore, measuring the level of ET-1 and MMPs (as they play a significant role in pathogenesis) at the earliest possible and blocking their actions by antagonists would significantly reduce the occurrence of stroke, acute coronary disease, etc

Endothelin antagonists may benefit in improving renal hemodynamics and reducing proteinuria, and also data is emerging to suggest a synergistic role for ET receptor antagonist with angiotensin converting enzyme inhibitors in slowing Chronic Kidney Disease progression. (Dhaun *et al.*, 2006)

As shown above in pathogenesis of cancer, endothelins have a variable effect in promoting tumor growth and progression in various types of cancer in which endothelin promote angiogenesis by promoting the production of TGF-beta, VEGF, EGF and others, and also metastasis by increasing the production of cellular adhesion molecules. Thereby using ET antagonists along with other chemotherapeutic agents are known to show a good and better prognosis, compared to chemotherapy alone even in prostatic cancer. Some of the substances like green tea polyphenol epigallocatechin-3-gallate has been known to show tumor growth inhibition in ovarian carcinoma cells by inhibiting ET-1, ET(A) receptor and its expression. (Goddard *et al.*, 2004)

Endothelial axis deregulation promotes cancer, Atrasentan is a novel agent that effectively targets this pathway and can inhibit or reverse several of those events by acting as an endothelial-receptor blocker. Atrasentan represents a new therapeutic option in the management of cancer even for refractory adenocarcinomas. Certain studies have shown that preclinical anticancer activity of specific endothelin A receptor antagonist ZD4054 delayed the onset of metastatic events. (Barton, 2008)

Measurement of ET-1, MMP-2, 9 & ET-A

measurement is done by obtaining blood sample and determined by indirect ELISA results are obtained, in the form of graph as shown in Figure 3. (Moreau *et al.*, 1997)

CONCLUSIONS

Since MMPs and ET are measured by indirect ELISA which is a costly procedure and may not be affordable to all and even may not be available at all places especially in developing countries. So, there is a need for developing more cheaper and more available way of determining the levels of MMPs and ET. And the most important thing is to educate and popularize about the widespread effects of endothelin in various diseases and to make the current generation understand how important it could be in the future as an application for pathogenesis of various diseases. At present, even doctors may not have proper knowledge about endothelins and its use. There is also a need to do research and promote research regarding endothelin and its use in the treatment for various diseases/disorders, as most of the performed results are promising to provide a good result when compared with the previously commonly used drugs alone.

Usage of endothelial receptor blockers can be alone given for treatment alone or along with other drugs for various disease conditions like hypertension, diabetes type-2, atherosclerosis, pulmonary hypertension, heart failure, cancer etc. which have shown a good response in pre-clinical and clinical trials. But there is need for more data for support with a stronger evidence especially in cancer so that these drugs can be used commonly as other drugs being used because the studies have shown better prognosis and better out come when treated with ET receptor antagonists. And there is a need to spread the idea and concept of role of endothelins in cancer for awareness, their widespread use and to provide better prognosis by use of these drugs. ET has been recognized as a multifunctional peptide and cardiovascular related studies have shown promising clinical conditions about the therapeutic efficacy of ET antagonists.

ET receptor antagonist, use has not been able to prove that ET-antagonist improves asthmatic conditions in a poorly controlled asthma patient. But the role of endothelins in the pathogenesis of asthma has been elucidated clearly as described above, so it might be useful and confirmatory if more experiments are done to know if endothelin receptor blockers can be useful or not for improving the condition of the patient.(More better and beneficial if done in a larger population or group.)ET-A antagonists have shown good results in treating sickle cell disease, but lack number of drug trails that needs to be focused to provide a better treatment and to

increase the life span in people suffering with sickle cell disease.

Disclosure of Interest

The authors declare that there are no conflicts of interest involved in this review. The authors alone are responsible for the content and writing of the paper.

Author's Contribution

Prashant P: the lead author and synthesis of the literature.

Ramu G, Tallapaneni V: Involved in drafting.

Karri V V S R: Conceptual input, design, and critical revision of the manuscript.

All authors read and approved the final paper.

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Ethical Approval

This article does not contain any studies with human or animal subjects performed by any of the authors

Conflict of Interest

None.

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