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CONTEMPLATIVE STUDY OF RISK FACTORS ASSOCIATED WITH VASCULAR ENDOTHELIAL DYSFUNCTION

Parkhi Rastogi[1,2], Gunjan Singh[1]*, Arpit Singh[3], Vaibhav[4], Vikrant Verma[2]

[1]School of Pharmacy, Sharda University, Greater Noida (UP) India -201310

[2]Faculty of Pharmacy, Swami Vivekanand Subharti University, Meerut (UP) India-250005

[3]Department of Pharmacy, Dr. KN Modi University, Niwai, (Raj) India- 304021

[4]Department of Pharmacy, Dr. KN Modi Institute of Pharmacceutical Education and Research , Modinagar, Ghaziabad (UP) India- 201204

Corresponding Author

Gunjan Singh

Abstract:

Endothelial Dysfunction is a condition in which the Endothelium adverse effects are seen and there is disarray of poise homeostasis due to Endothelium on vascular tree leading to severe vasoconstriction ascribed to increased presence of vasoconstrictive autacoids. There are copious pivotal risk factors associated in pathobiology of vascular endothelium dysfunction. The pathogenesis of vascular endothelial Dysfunction is multi-factorial and the pinpoint mechanisms is still ambiguous . In current review, various risk factors associated with vascular endothelial Dysfunction in terms of development and progression have been discussed. The study summarize that Oxidative stress, TGF beta, TNF alpha, renin angiotensin aldosterone system and Protein kinase C are closely associated with vascular endothelial dysfunction. There are limited therapeutic interventions available in the market, among all statins are observed to be the standard drug so far for management of the disease.

Key Words: Vascular endothelial dysfunction, oxidative stress, RAAS, TGF beta, TNF Alpha, Protein kinase C

INTRODUCTION:

Endothelium being a functional barrier between blood stream and vessel wall, around 1,000 m^2 occupied the total human vascular and capillary system which is further covered by endothelial cells. Endothelium is tight cell to cell junction and membrane which separates the tissue and muscular system from the blood stream in the body (Patel JC, 2001). It is permeable to certain substances and non-permeable to numerous substances. Endothelium plays an important role in cardiovascular homeostasis, platelet aggregation on the walls of blood vessels, coagulation,

inflammatory responses, and mainly either vasodilation of vessels or vasoconstriction of vessels. Endothelium plays a vital role in binding of anticoagulant factors with its receptors thus maintaining blood flow homeostasis. Endothelium cells or the endothelial cells are involved in maintaining the homeostasis upon internal or external disturbances. The relationship of leukocyte and platelet interaction with the endothelium have been observed, where endothelial cells play vital role in rolling of platelet-leukocyte interaction upon external stimuli such as mechanical injury, or mechanical stress. Dysfunction of Endothelium system or vascular endothelium dysfunction disrupts the homeostasis of release of mediators resulting in balanced vasodilation and balanced vasoconstriction, leading to various series of cardiovascular events, such as heart attack or hypertension.(Barton M, et al., 2012). It has been realized that endothelial cells are also involved in development of cell proliferation and new blood vessels across the body. Furthermore endothelium dysfunction is a condition in which the endothelium adverse effects are seen and there is disruption of balanced homeostasis due to Endothelium on vascular tree leading to severe vasoconstriction due to increased presence of vasoconstrictive autacoids (F. Ribeiro, et al.,2009) Various diseased condition and pathological conditions are responsible for endothelium dysfunction such as Smoking, Obesity, and Cardiovascular Diseases and cardiovascular events. As of now various markers in form of progenitor cells can be used in order to detect endothelium dysfunction in the body or at the site of pathophysiological conditions. In endothelium dysfunction more of vasoconstriction is observed due to increased presence of vasoconstrictive autacoids at the site of pathophysiological event (R. J. Gryglewski, 2008).

For better understanding vascular endothelium dysfunction can be explained as a is a disease where there is imbalance of vasodilation and vasoconstriction in the body and is a condition in which the endothelium loses its control over the balance or homeostasis in vascular system of the body and hence disrupting the endothelium in the body resulting in wide varieties of pathophysiological events, resulting in wide range of diseases. It has been studied from the pre-clinical and clinical studies that patients suffering from vascular endothelial dysfunction shows narrowing of vessels which could result in chest pain. Chest pain during emotional stress or physical activity, pain in chest during menstruation, shortness of breath and several other symptoms are characterized by vascular endothelial dysfunction (Cerami, C et al., 1997). Mainly vascular endothelium dysfunction results in wide variety of diseases related to blood vessels in the body without blocking of the blood vessels itself. Means it's a non-blockage dependent reason for wide variety of pathological and cardiovascular events. It results in high rate of vasoconstriction without blocking the blood vessels due to aggregation of platelets or thrombosis. It has been observed that vascular endothelium dysfunction is the main reason for wide variety of human diseases. Like Insulin resistance, Kidney disturbances, heart attack, Stroke, Diabetes, Chronic Kidney Failure, and several viral infectious related diseases. Hence, any pathological event related to the flow of blood throughout the body has its pathogenesis related to the endothelium. And the disease of endothelium, which is endothelium dysfunction, is main reason for various damaging events in the body related to the blood flow across the body.

PREVALENCE

One important understanding regarding the vascular endothelium dysfunction is that, this pathological event has been observed to occur in more women as compared to males. Endothelium Dysfunction can be reversed by using various drugs used for cardiovascular diseases, and role mainly the statins has been observed significantly in reversing the diseased condition of Endothelium Dysfunction in the body (Y. Hirata, et al.,2010)

RISK FACTORS:

From background studies it has been observed that vascular endothelial growth factor, transforming growth factor- (TGF), renin angiotensin aldosterone system (RAAS), (Koh, K.K et al., 2010) protein kinase C (PKC), (Xu, X. et al., 2001), Rho-kinase and tumour necrosis factor (TNF), Enddothelin I (Thorin, E. and Clozel, M., 2010) are involved in the induction as well as progression of vascular endothelial dysfunction, these culprits associated with dysfunction are involved in enhancing the intensity of oxidative stress and also affected pathways via oxidative stress. Figure 1 elucidates correlation of above risk factors in pathogenesis of vascular endothelial dysfunction by eventually abating the bioavailability of nitric oxide. Figure 1 manifest the correlation of TGF beta, TNF alpha, RAAS, Oxidative stress and Protein kinase C in alleviation of nitric oxide availability, even by following different mechanism leading vascular endothelial dysfunction. Which can be cause by the imbalanced lifestyle or by any disorder.

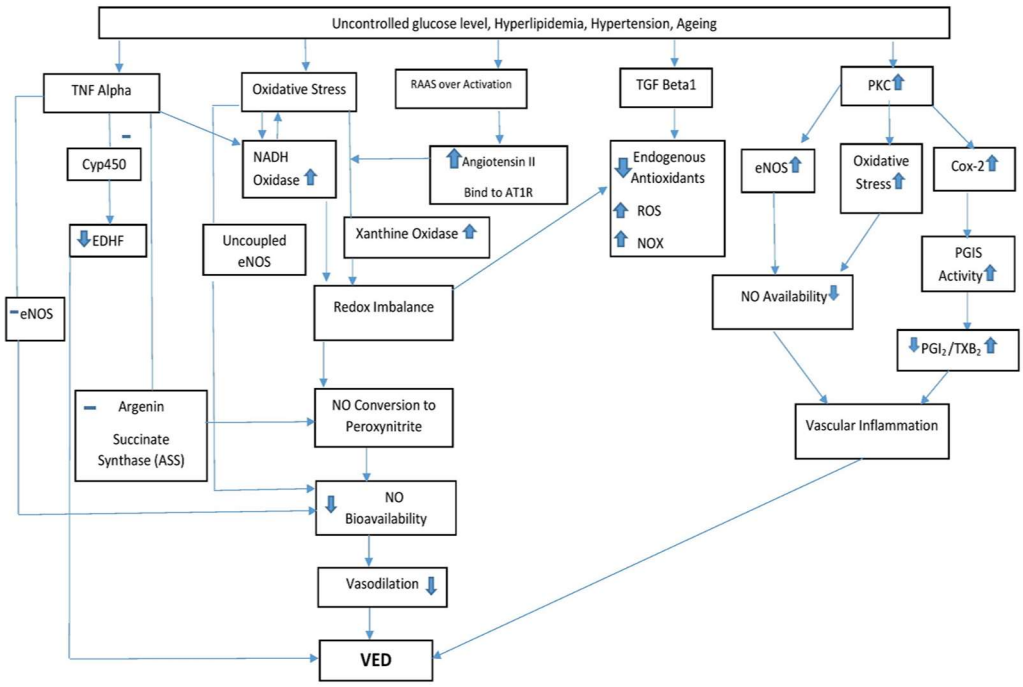

Figure 1: Correlation of TGF beta, TNF alpha, RAAS, Oxidative stress and Protein kinase C in Vascular endothelial dysfunction pathogenesis

Oxidative stress:

ROS is generated via multiple cellular processes, majorly the imbalance between the generation of ROS and the intrinsic antioxidant defense system which is responsible for the increasing level of ROS with in the body. In addition to this the abnormality in the elimination of these free radicals is also another factor. Generally the production of ROS and elimination are dependent on enzymatic and non-enzymatic pathways. (Pennathur, S. and Heinecke, J.W., 2007) Enzymatic pathway includes numerous enzymes including NADPH oxidase (NOX), xanthine oxidase (XO) and uncoupled NOS myeloperoxidase, COX lipoxygenase (LOX), and different numerous amine oxidases are involved in vascular ROS. Among these enzymes, elevated level of NADPH oxidase is majorly involved in ROS generation in vascular generation. NADPH oxidase belongs to a multimolecular enzyme which consist of numerous family members from NOX1, NOX2, NOX4 and NOX5 (Warnholtz, A et al., 1999). Interestingly all the factors such as (Diabetes Mellitus, Hyperlipidemia, Nicotine, Arsenic etc.) involved in the pathogenesis of VED are associated with increased expression of NOX. Therefore targeting NOX is rational for the halt of ROS generation (Porasuphatana, S et al., 2003). Also there are multiple Non-enzymatic source involved such as Cu/Zn-SOD cytosol, Mn-SOD mitochondria, GSH peroxidase, GSH-S-transferase, GSSG reductase and catalase. Also mitochondrial respiration generally leads to free radicals production. (Valko, M et al., 2007).

Fundamentally the disparity among the antioxidant defence and the engendering of (ROS) results in Oxidative stress including redox signalling and control disruption. (Apel, K. and Hirt, H., 2004). Also the various biochemical reactions in our body (deduction of molecular oxygen in aerobic respiration which yields superoxide and hydroxyl radicals, and its spin off electrons, conversion of oxygen to superoxide, hypochlorous acid production) leads to the free radicals generation. (Santilli, F et al., 2015) Free radicals can also be generated in retaliation to outsourced electromagnetic radiation, like gamma ray and generally the production of ROS and elimination are dependent on enzymatic and non-enzymatic pathways. (Pennathur, S. and Heinecke, J.W., 2007)

Oxidative stress is identified as significant contributor in the pathogenesis of vascular endothelial Dysfunctioning. So, oxidative stress is considered as the central mediator in the progression of vascular endothelial dysfunction (Ishikawa, T. and Seki, K., 2018). ***As induction of reactive oxygen species and nitrogen reactive species are associated with oxidative stress, also in the activation pathways involved in the induction and progression of vascular endothelial dysfunction (VED).*** Oxidative stress is considered as central player on the pathogenesis of vascular endothelial dysfunction. it is suggested from recent studies that antioxidant rich diet, vegetables, fruits, olive oil, herbal teas and chemically nitrates, calcium channel blockers, increasing bioavailability of NO, (Sena CM et al., 2018) increasing the blood flow, reducing the chest pain, widening and relaxing the vessels and repairing of endothelium are helpful.

TGF Beta 1:

In human body, there are various factors, which control and run the body in a balanced manner. Numerous growth regulators, and growth suppressors, plays vital role in maintaining homeostasis and running the human body in better way. In mammals three isomers of transforming growth factor β are present as β1, β2 and β3, which plays important role in development and regulating growth. Few activities perform by TGF β are extracellular matrix formation, hampering proliferation of most cells simultaneously promoting mesenchymal cell growth and possess immunosuppressive functions (Lawrence, D.A., 1996). Growth factor of other peptides are synchronized by TGF β, also direct positive and negative effects (Sporn, M.B et al., 1986). Transforming growth factor β is one of the vital growth factors which results in formation of new blood vessels and repairing the damaged blood vessels upon any external stress, such as mechanical injury to the blood vessels (Lebrin, F et al., 2005). TGF β is important growth factor which plays multiple role in our body. Regarding endothelium, it helps in the growth of the endothelial cells along with various mediators, and also helps in balanced functioning of vascular endothelium system. Upon disruption of this vital growth factor, the homeostasis in the vasculature gets disrupts and leads to various pathological events, such as endothelium dysfunction. And as described above, disruption of endothelium system results in various diseases such cardiovascular diseases, stroke, diabetes, insulin resistance, and many more. The importance of mentioning TGF β in endothelium dysfunction is for reason as it can be drug target for the scientists who would like to develop proper treatment for endothelium dysfunction. Here, we can see that if we introduce a molecule in body which helps in disruption of proliferation and development of TGF β in the body, it can help in proper treatment of endothelium dysfunction and treatment of its effects such as cardiovascular diseases, diabetes, stroke, insulin resistance to name a few. TGF β plays vital role in whole vasculature system and its importance for the same has been widely studied and understood. Hence, relevance of transforming growth factor β with relevance to endothelium dysfunction is an important part of our study (Michiels C., 2003). TGF β strongly inhibits of the growth of many cells (epithelial cells, hematopoietic cells, endothelial cells and immune cells) and also possess pro apoptotic effect and induction of epithelial cells differentiation. Hence these action helps in tumor suppression in the context of cancer. Also TGF β1 messenger RNA level increases in stroke and exerts neuro protective effects when TGF β signilling is blocked ischemia damage increases. TGF β1 perform a crucial role in the Diabetic nephropathy which causes development of glomerulosclerosis and intestinal fibrosis, whereas TGF β2 causes cardiac fibrosis by (TGF β receptor type II can promote cardio myocytes apoptosis and cardiac hypertrophy). The challenge is to maintain the homeostasis of TGF β in body, as complication are encountered with altered level of TGF β depending upon its expression on different body organs. To control the expression of TGF β is tedious because is has both positive and negative effects in different body parts as TGF β has biphasic action during tumerogenesis (suppress the tumor in early stage but promoting tumor progression in later phase). Furthermore the response to the TGF β blockage are complex in nature and have genetic variations in individuals.

TNF Alpha:

TNF-α is pro-inhibitory cytokine which has been studied widely responsible for the pathogenesis of Endothelium Dysfunction. It has been observed that TNF-α receptor 1 and TNF-α receptor 2, where majorly TNF-α receptor 1 is responsible for major expression of TNF-α induced Endothelium Dysfunction. TNF-α causes Endothelium dysfunction by decreasing the levels of Nitric oxide in the vascular system along with increased degradation of Nitric oxide with inducing oxidative stress in the whole body (Picchi et al. 2006). It has been observed and widely studied that TNF-α is mainly responsible for increasing Free radicle generation in the body and also increasing the inflammatory responses across the whole vascular infrastructure of the body. Various research's have been carried out where it has been observed and tested the role of TNF-α in increasing the pathophysiological reason for Endothelium Dysfunction. And by now stated that in endothelium dysfunction there is predominantly imbalance of vasodilation and vasoconstriction in the vascular structure of the body and TNF-α here leads to elevate the risk factors associated with the Endothelium Dysfunction also increase the other pathophysiological events responsible for the over expression of stress, oxidative stress, inflammatory responses, damage to the anticoagulation and coagulation balance in the body and damage to the increased expression of Nitric oxide in the body. It has been observed and widely tested that TNF-α leads to increased vasoconstrictive autacoids expression in the body leading to over expression of Endothelium Dysfunction along with its associated pharmacological as well as pathophysiological events in the whole vascular infrastructure of the body. Not only this it has been also widely studied and observed that TNF-α leads to increased neurodegenerative processes in the body, also increasing the risks of causing cancer in the whole body (*Iwasima, T, et al.,2019*). Ever since the importance of TNF-α has been discovered in the pathophysiology of wide variety of diseases, it has been widely studied and its correlation has been understood in correspondence to not only Endothelium Dysfunction, but also Neuro-Degenerative diseases, Nervous system disorder, Obesity, Diabetes, Insulin resistance, Inflammatory responses across the body and increased expression of cancer at various sites in and around the whole body (Gao, X. et al., 2007). TNF-α is mainly involved in the homeostasis of various systems in the body. And on its over expression due to mechanical stress or internal and external factors it leads to imbalance cascade of reactions across the body. This is mainly responsible for the expression of wide variety of diseases in various systems of the body and leading to plethora of diseases to the human body. There it has been selected for the purpose of study, as TNF-α is very important cytokine to be studied and its role in the pathogenesis of various diseases. TNF-α increases the risks factors associated with factors responsible for the occurrence of Endothelium Dysfunction in the body, as it leads to high rate of vasoconstriction by increasing the oxidative stress, and decreasing the expression of Nitric oxide in the vascular infrastructure of the body. Thus it has been observed that TNF-α plays a degenerative role in the pathophysiology of Endothelium Dysfunction (Gao, X. et al., 2008).

Renin Angiotensin Aldosterone System:

Elevated RAAS circulation in the body elevates the angiotensin II activities directly acting on AT1 receptors expressing detrimental effects on endothelium. The renin–angiotensin–aldosterone

system (RAAS) is a expository index of systemic vascular resistance along with blood volume regulation. While as reflex of baroreceptor response with decreased arterial pressure, the RAAS is whole sole accountable for more chronic modifications. RAAS is associated with Rennin, Angiotensin II and Aldosterone through beta agonism, reduced salt transport to DCT of nephron, or by reduced renal blood flow RAAS eventually land up with uplifted arterial pressure. (John H. Fountain 1 and S. L. L., 2017) Angiotensin II is the foremost effector peptide in Renin angiotensin aldosterone system (RAAS) with two receptors that are Angiotensin 1 receptor (AT 1 R) and another is angiotensin 2 receptor (AT 2 R) which has contradictory effect on activation. The Anti-inflammatory, contractile behavior and mitogenicity of the wall of vessel is regulated by endothelium. Endothelium produces molecule which possessing biological activities due to Nitric oxide. Either decreased endothelial production of Nitric oxide or decreased nitric oxide bioavailability promotes vasoconstriction, lumen prothrombosis, inflammation and proliferation of smooth muscles cells (Ignarro, L.J. and Napoli, C., 2004.) Angiotensin II manage Nitric oxide expression as Angiotensin 1 receptor down regulates Nitric oxide production. (Yan, C et al., 2003) Endothelium function is hampered by increased level of Ang II, as Its elevated level oxidative stress and inflammation. The endothelium maintain the homeostasis of vascular tone by synthesis of Nittic oxide and Angiotensin II, as nitric oxide provides Vasodilatation, anticoagulation and by smooth muscle proliferation inhibition on the contrary Angiotensin II possesses vasoconstrictive, fibrotic and inflammatory physiological actions through AT1 receptor The endothelium maintain the homeostasis of vascular tone by synthesis of Nitric oxide and Angiotensin II, as nitric oxide provides Vasodilatation, anticoagulation and by smooth muscle proliferation inhibition, on the contrary Angiotensin II possesses vasoconstrictive, fibrotic and inflammatory physiological actions through AT1 receptor. (Schulman, I.H., Zhou, M.S. and Raij, L., 2005). Angiotensin II manage Nitric oxide expression as Angiotensin 1 receptor down regulates Nitric oxide production. (Yan, C et al., 2003). Endothelium function is hampered by increased level of Ang II, as its elevated level oxidative stress and inflammation. ROS at low concentration perform in physiological activity of endothelium to maintain the vascular contractility (Touyz, R.M., 2004) whereas elevation in ROS due to pathological reasons upshot with damaging the vessel wall. (Lassegue, B. and Clempus, R.E., 2003)

Due to RAAS signalling pathways complexity than previously thought, half-century later, new RAAS inhibitors are still being developed. Indeed, numerous experimental and clinical evidences indicate that pharmacological inhibition of RAAS with angiotensin-converting enzyme inhibitors (ACEIs), angiotensin receptor blockers (ARBs), direct rennin inhibitors (DRIs), and mineralocorticoid receptor antagonists (MRAs) is effective in treating hypertension and diabetic renal injury, and the results show a reduction in CVD and heart-related events worldwide. (Pacurari *et al.*, 2014)

Protein Kinase C:

Protein kinase C was discovered by a Japanese scholar in 1977, from rat's neuron cytoplasm, it shares its roots with serine/threonine kinase and 12 subtypes of PKC have been reported. PKC partake in cell signal transduction pathways. PKC isoforms are classified according to whether they contain domains that bind Ca2 þ or DAG, both of which positively regulate the kinase activity. Conventional PKC (a, b1, b2, and g) ties with both Ca2 þ and DAG, the novel PKC (d, e, Z, y, m) ties to DAG, however not Ca2 þ, and abnormal PKC (z, l) ties not one or the other. The actuation of regular and novel PKC isoforms requires the right phosphorylation of the isoforms and the presence of cofactors like Ca2 þ and DAG. When appropriately phosphorylated, expansions in Ca2 þ or DAG quickly or constantly will actuate its movement to the membranous compartments of the cells to evoke natural activities. Quick and momentary increments of DAG and Ca2 þ levels are generally instigated by cytokines by means of the initiation of phospholipase C. Persistent enactment of PKCs require supported heights of DAG, which includes the initiation of phospholipase D/C or the all over again amalgamation of DAG. In hyperglycaemic and diabetic express, these pathways presumably add to the enactment of DAG-PKC overflow (Noh H. and King GL., 2007).

Protein kinase C (PKC) is very familiar being developed of vascular insulin obstruction and vascular dysfunction. Ruboxistaurin (RBX), a PKC inhibitor, has been broadly used to concentrate on vascular capability in creature models connected with metabolic disorder and in clinical research (Lu X, et al., 2011). PKC isoforms have assorted impacts in various vascular cell types, with noticeable consequences for VSM. The job of each PKC isoform in specific vascular reactions has been upheld by estimating PKC quality articulation, protein levels and PKC action, and by deciding the impacts of pharmacological isoform-explicit PKC inhibitors as well as knockout mice and transgenic rodents (Ringvold HC and Khalil RA., 2017).

PKC activation can directly increase the permeability of albumin and other macromolecules through barriers formed by endothelial cells, probably by phosphorylating cytoskeletal proteins forming the intracellular junctions. As well, PKC activation could also regulate vascular permeability and neovascularization via the expression of growth factors such as VEGF, which has been demonstrated as a key factor in the pathogenesis of diabetic retinopathy (Noh H. and King GL., 2007).

Protein kinase C Another glucose-induced alteration in cellular metabolism that may account for endothelial dysfunction is activation of protein kinase C. Hyperglycaemia causes de novo synthesis of diacylglycerol, leading to activation of protein kinase C -preferentially the b-isoform, a pathway now demonstrated in all vascular tissues involved in diabetic complications. The consequences of protein kinase C activation are multiple, since it is involved in a variety of cellular functions. Of relevance to impaired responses to endothelium dependent agonists are the activation of phospholipase A2 with increased production of arachidonic acid metabolites, and the inhibition of Na+-K+-ATPase. Antioxidants have been reported to prevent diacylglycerol-protein kinase C-mediated vascular dysfunction in diabetes, indicating a link between oxidative stress and the

protein kinase C pathway which eventually leads to the downturn of Nitric oxide bioavailability (DE Vriese AS, et al., 2000)

CONCLUSION

Above stated risk factors associated with dysfunction are promptly involved in enhancing the intensity and pathway of oxidative stress accompanied by decrease bioavailability of nitric oxide. So, oxidative stress can be conceived as the central mediator in the pathogenesis and progression of vascular endothelial dysfunction. However various antioxidants have shown promising result in protection in relation to vascular endothelial dysfunction. As the consequences of long term administration of oxidative stress on cardiac activity has to be identified before any clinical implication. As the focus is on oxidative stress, it has been demonstrated that cardiovascular diseases, diabetes mellitus, hyperlipidaemia, kidney failure, inflammatory disorders are effected by the free radical generations which is a major concern, amalgamating all above cardiovascular risks are utmost common disorders in recent scenario, so by targeting the oxidative stress pathway there could be ray of curing the disorders and reduction in the mortality rate. And ministering free radical generation along with the cardiovascular diseases could relief and improve the quality of treatments. (Nishi et al., 2010). Additionally there has been enormous studies encountered for cardiovascular diseases perhaps there is less prominent treatments evident in current and previous times. However introducing antioxidants treatment has been quite promising in current time and since different signalling or identification of novel targets site is required for the management of cardiovascular diseases. It is suggested from recent studies that antioxidant rich diet, vegetables, fruits, olive oil, herbal teas and chemically nitrates, calcium channel blockers and, increasing bioavailability of NO, (Sena CM et al., 2018) increasing the blood flow, reducing the chest pain, widening and relaxing the vessels and repairing of endothelium. Hence by targeting paramount risk factors oxidative stress levels, TNF alpha, TGF beta, RAAS, Protein kinase C could reach out for the improved treatments, which would be difficult for researchers to target all the risk factors simultaneously. ***Therefore the motive of this compilation is to provide insight about the role of above mentioned factors as central player in the pathogenesis of vascular endothelial dysfunction (VED) which could be manage by any therapeutic intervention accommodating ant diabetic, hypolipidemic, antioxidant and anti-inflammation action which can block all the possible pathways for the progression of vascular endothelial dysfunction and ameliorate quality of treatment and life.***

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