REVIEW ARTICLE

RECORDS OF PHARMACEUTICAL AND BIOMEDICAL SCIENCES

A Review Article on the Investigation of Therapeutic Potential of Sildenafil in Experimentally-Induced Hind Limb Ischemia of Diabetic Model

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Abstract

Sildenafil citrate is a highly selective inhibitor of cyclic guanine monophosphate-specific phosphodiesterase type-5 (PDE-5), leads to smooth muscle relaxation, increases vascular perfusion and tissue blood flow. Clinical and experimental studies previously reported a protective effect of sildenafil in ischemic reperfusion settings in various models. Antioxidants have been reported to reduce ischemia reperfusion injury like vitamin E. Selenium (Se) is one of the most important antioxidants. Antioxidant enzymes such as thioredoxin reductase (TrxR) and glutathione peroxidase along with selenoprotein-P, are responsible for the transport and storage of Se. Nano-elemental Se (SeNPs) are more biocompatible with exhibiting a dramatic decrease in toxicity. Sildenafil and Nano selenium mediated therapeutic angiogenesis in diabetic hind limb ischemia. They improve blood supply, antioxidants delivery for cells and decrease necrosis in peripheral arterial disease (PAD). The induction of therapeutic angiogenesis by sildenafil and SeNPs achieved in this study along with resumed antioxidant defense gives hope of an alternative treatment.

Keywords: Sildenafil citrate; Nano-selenium; Hind limb ischemia.

1. Diabetes mellitus

1.1. Introduction

Aluminum (Diabetes mellitus is a bunch of heterogeneous conditions showing episodes of glucose intolerance and hyperglycemia. It happens due to deficiency of insulin, weakened insulin action, or both **(Karalliedde and Gnudi, 2014)**. These complications stand up as a result of imbalances in the mobilization of metabolic fuels and regulatory systems for storage, which involves the catabolism and anabolism of carbohydrates, proteins and lipids **(Siminialayi and Emem-Chioma, 2006; Mahomoodally et al., 2020)**.

Moreover, type 1 diabetes is happening in children at earlier ages, it is one of the most spread chronic diseases in childhood, although type 2 diabetes is also seen in older children, and is on the increase due to childhood overweight and obesity becoming more common **(Pulgaron and Delamater, 2014)**. Around 90% of all diabetes in rich and developing countries are of type 2. It has an association with improper utilization of insulin by target cells and tissues. It is currently a common health concern worldwide **(Narayan et al., 2006)**.

According to WHO (1994), this problem has been worse by rapid cultural and social dynamics, ageing populations, dietary changes, reduced physical activity and other unhealthy lifestyle and behavioral patterns. Diabetes mellitus and diminished glucose

tolerance, is existed in almost every population in the world and this trend is on the rise internationally **(World Health Organization, 1994)**.

1.2. History of diabetes mellitus

Though treatments of diabetes were identified since the Middle Ages, its pathogenesis elucidation arisen mainly in the 20th century. The role of the pancreas in diabetes was illustrated by Joseph Von Mering and Oskar Minkowski in 1889 **(Mering and Minkowski, 1890)**. In 1910, Sir Edward Albert Sharpey-Schafer implied that diabetics individuals lacked a single chemical which was normally produced by the pancreas and later this chemical was called as insulin **(Himsworth, 1936)**.

In 1921, insulin was extracted from bovine pancreases at the University of Toronto in Canada **(Tan and Merchant, 2017)**. Other findings in this field are: sulfonylureas identification in 1942, the radioimmunoassay for insulin discovered by Rosalyn Yallow and Solomon Berson, the metabolic syndrome discovery by Reaven in 1988 and understanding of thiazolidinediones in the 1990s in the handling of diabetes **(Patlak, 2002)**.

1.3. Prevalence of diabetes mellitus

Diabetes is one of the main global health burdens of this century. Each year more and more people becoming prone to this life-changing complication **(Sciberras et al., 2020)**. About 415 million adults are valued to have diabetes but many countries are still ignorant of the social and economic impact of this disease **(Bommer et al., 2018)**. This lack of understanding is the biggest barrier to effective prevention strategies of diabetes **(Adu et al., 2019)**.

Most regions over the globe are facing a continuous increase in diabetics. The Western Pacific Region has 153 million adults with diabetes whereas the North America and Caribbean Region has one out of eight adults with the disease **(Pedersen, 2019)**. Europe has approximately 140,000 number of type 1 diabetes children. In the South-East Asia Region, 24.2% of all live births face high blood glucose during pregnancy. In the Middle East and North Africa Region, two out of five adults with diabetes remain undiagnosed **(Saeedi et al., 2019)**.

1.4. Classification of diabetes mellitus

1.4.1. Type 1 diabetes

Auto immune response: It is stated as a series of autoimmune disease where the beta cells of pancreas are slowly destroyed by the body's own immune system which decreases insulin production. Genetic factors: Investigators have selected at least 18 genetic positions as IDDM1-IDDM18 (Insulin dependent diabetes mellitus), which are linked to type 1 diabetes **(Xu et al., 2019)**.

The IDDM1 (Insulin dependent diabetes mellitus) region endorses the HLA (Human leukocyte antigen) genes that encode proteins called major histocompatibility complex. In this location immune responses are affected by these genes **(Morran et al., 2015)**. Environmental factors: Due to unexpected stress like an infection where the β-cells of pancreas reduced below 5-10%. Coxsackie viruses are a family of intestinal viruses which attack the intestinal tract causing destruction of insulin producing pancreatic β cells (Table 1) **(Murea et al., 2012)**.

Treatment:

Insulins are the best choice to treat type 1 diabetes & they can be administered by injections and insulin pump. Insulins are of three type's rapid acting long acting and intermediate acting Some insulins like regular insulin (HUMULIN 70/30, NOVOLIN 70/30), Insulin isophane (HUMULIN N, NOVOLIN N), and insulin glulisine (APIDRA), insulin lispro (HUMALOG), insulin aspart (NOVOLOG) **(Donner and Sarkar, 2000)**.

Some long-acting insulins are detemir (LEVEMIR) and glargine (LANTUS). Pramlintide (SYMLIN) inj. is a artificial version of a chemical free hormone which is amylin produced by β cells and some angiotensin receptor blockers; ACE inhibitors, aspirin and cholesterol lowering drugs are used **(Poon and King, 2010)**.

Islet grafting was been discovered as a therapy for type 1 diabetes in selected patients with inadequate glucose control despite insulin therapy. Artificial pancreas is a closed loop insulin delivery. It is connected to a continuous monitor of glucose to insulin pump. The device which distributes correct amount of insulin automatically when the monitor specifies the need for the pump **(Latres et al., 2019)**.

1.4.2. Type 2 diabetes

Type 2 Diabetes ranges from Insulin Resistance with Relative Insulin Deficiency to Predominantly an Insulin Secretory Defect with Insulin Resistance. This form of diabetes accounts for 90-95% of diabetes. It was previously referred to as non-insulin dependent diabetes. It encompasses individuals with insulin resistance and relative (rather than absolute) insulin deficiency (table 6) **(American Diabetes, 2013)**.

Most patients are reported obese and this obesity itself produces some degree of insulin resistance. Ketoacidosis often occurs spontaneously in this diabetes **(Chiasson et al., 2003)**. Type 2 diabetes frequently remains undiagnosed because of gradual onset of hyperglycemia and at earlier stages the patient shows none of the classic symptoms of diabetes **(American Diabetes, 2009)**.

Treatment:

Oral hypoglycemic agents are valuable in the treatment of type 2 DM and insulin also includes in it and those agents include Sulphonylureas, Alpha glucosidase inhibitors, Biguanides and Thiazolidinediones **(Ganesan et al., 2021)**. The main purpose is to correct metabolic disorder like resistance to insulin and insufficient insulin secretion. They are given in combination with a suitable diet and changes in lifestyle. They show loss of weight, increase glycemic control decrease the risk of cardiac problems (Table1) **(Roberts et al., 2013)**.

Table 1: Pharmacological therapy of type-2 DM

Type of drug	Drug generic	Brand name
Sulphonylureas	Glimepiride	AMARYL
	Glipizide	DIABETA
	Glyburide	GLYNASE GLUCOTROL
Biguanides	Metformin	GLUCOPHAGE
Thiazolidinediones	Pioglitazone	ACTOS, AVANDIA
Alphaglucosidase inhibitors	Acarbose	PRECOSE, GLYSET
Meglitinides	Nateglinide	PRANDIN, STARLIX

1.5. *In-vivo* studies models on Diabetes

1.5.1. Chemical induction of diabetes mellitus

The majority of studies issued in the field of ethno pharmacology between 1996 and 2006 employed this model. Streptozotocin are by far the most frequently used drugs and this model has been useful for the study of multiple aspects of the disease. Both drugs employ their diabetogenic action when they are taken parenterally (intravenously, intraperitoneally or subcutaneously). The dose of these agents essential for inducing diabetes depends on the animal species, route of administration and nutritional status (Figure 1) **(Federiuk et al., 2004)**.

1.5.1.1. Streptozotocin model of diabetes mellitus

Streptozotocin is an antibiotic derived from Streptomyces achromogenes and structurally is glucosamine derivative of nitrosourea. Rakieten and his associates first demonstrated the diabetogenic property of STZ in dogs and rats in 1963. Streptozotocin stops DNA synthesis in mammalian and bacterial cells. In the bacterial cells, it initiates special reaction with cytocine groups, causing degeneration and destruction of DNA. Additionally, STZ increases activation of poly adenosine diphosphate ribosylation and nitric oxide release. As a result of STZ action, pancreatic -cells are demolished by necrosis **(Zhou et al., 2001)**. In adult rats, 60 mg/kg is the most common dose of STZ to induce insulin dependent diabetes **(Patel et al., 2006)**.

STZ is also efficacious after intraperitoneal administration of a similar or higher dose, but single doses below 40 mg/kg in adult mice, STZ given in multiple lowdoses (40 mg/kg, i.v. for 5 days) **(Rees and Alcolado, 2005)** induces an insulin dependent diabetes that is quite similar to the autoimmune forms (islet inflammation and cell death) of Type 1 diabetes. On the other hand, a single dose between 60 and 100 mg/kg of STZ **(Lei et al., 2005)**, administered systemically can also cause insulin may be ineffective dependent diabetes, but it absences the autoimmune profile (Figure 2) **(Yu et al., 2000)**

1.5.1.2. Alloxan model of diabetes mellitus

Alloxan is the also used chemical for induction of diabetes mellitus. It is a well- known diabetogenic agent widely used to induce Type 1 diabetes in animals **(Viana et al., 2004)**. Alloxan is a urea derivative which causes selective necrosis of the pancreatic islet β-cells. It is used to produce experimental diabetes in animals such as rabbits, rats, mice and dogs. A solution of 2% alloxan (40mg/kg) diluted in 0.9% normal saline was administered to the animals through the iliac vein. The animals were allowed to resume feeding and drinking 30 minutes after the drug administration. In order to evaluate the effect of alloxan and to chemically launch the diabetic condition, an incision was made in any of the four veins in the tail of the rat after induction a blood glucose level was determined by using a portable glucose analyzer. (Figure 3) **(Al-Awar et al., 2016)**.

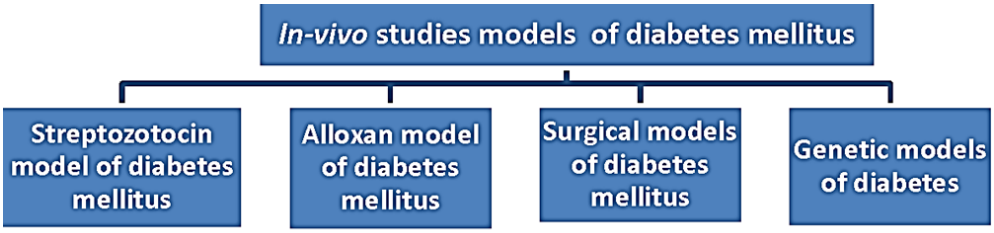

Figure 1: In-vivo study models of diabetes

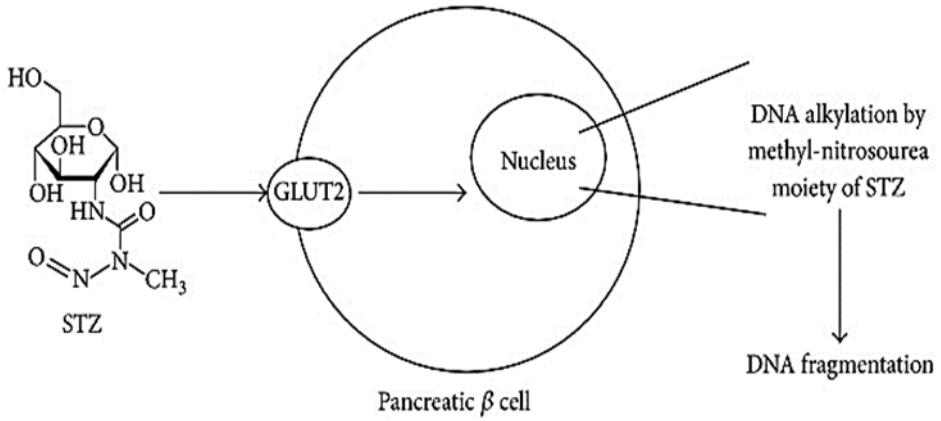

Figure2: The mechanism of action of streptozotocin (STZ) in β cells (Al-Awar et al., 2016)

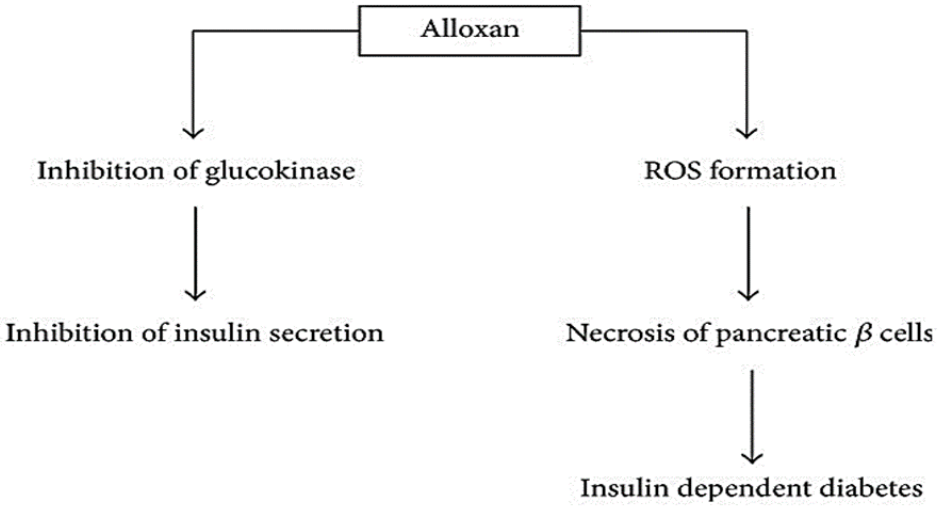

Figure 3: The main pathological effects of alloxan (Al-Awar et al., 2016).

1.5.2. Surgical models of diabetes mellitus

The complete removal of the pancreas was done to induce diabetes. Few researchers have used this model in the last years to explore effects of natural products with animal species such as rats, pigs, dogs and primates **(Choi et al., 2004; Lei et al., 2005; Rees and Alcolado, 2005)**.
More recently, partial pancreatectomy has been used, but large resection (more than 80% in rats) is needed to induce mild to moderate hyperglycemia. In this case, small additional resection can yield in significant hypoinsulinemia **(Masiello, 2006)**

1.5.3. Genetic models of diabetes

Spontaneously develop diabetic rat - These models allow the evaluation of the effect of a natural product in an animal without the interference of side effects induced by chemical drugs like alloxan and STZ reported above. Example is the spontaneously diabetic Goto-Kakizaki rat which is an inherited lean model of type 11 diabetes originating from selective breeding over many generations of glucose-intolerant nondiabetic Wister rats **(Chen and Wang, 2005)**.
Regarding type-1 diabetes models, the mouse represents hyperglycemia between 12 and 30 weeks of age, whereas in rats it occurs around 12 weeks of age. One great advantage of these models is that they can be rolled as model of atherosclerosis which represents the long-term complication of diabetes mellitus and tested against several natural products **(Wu and Huan, 2007)**.

2. Peripheral arterial disease

2.1. Definition

Peripheral artery disease (PAD) is an irregular narrowing of arteries other than those that provide the heart **(Marco et al., 2020)**. When narrowing occurs in the heart, it is called coronary artery disease, and in the STZ, it is called cerebrovascular disease **(Schurch et al., 2018)**. Peripheral artery disease most commonly affects the legs, but other arteries may also be involved such as those of the arms, neck, or kidneys (Schurch et al., 2018). The classic symptom is leg pain when walking which resolves with rest, known as intermittent claudication (Figure. 4) **(Violi et al., 2012).** Other symptoms include skin ulcers, bluish skin, cold skin, or abnormal nail and hair growth in the affected leg **(Hooi et al., 2002)**. Complications may include an infection or tissue death which may require amputation; coronary artery disease, or stroke (**Schurch et al., 2018**). Up to 50% of people with PAD do not have symptoms **(Violi et al., 2012**)

2.2. Background and epidemiology

Peripheral arterial disease (PAD) of the lower extremities affects approximately 8.5 million people in the U.S., remaining the commonest cause of death in England and Wales and more than 200 million people worldwide **(Gerhard-Herman et al., 2017)**, while its incidence is expected to rise **(Kim et al., 2019)**. PAD is an independent risk factor for cardiovascular morbidity, including coronary artery disease (CAD) and cerebrovascular accidents (CVA) **(Golomb et al., 2006)**. Consistent with this, patients with PAD are at almost six-fold higher risk for acute myocardial infarction (MI), ischemic stroke and/or death compared to general population **(American Diabetes, 2003; Mahmood et al., 2014)**.
The incidence of PAD differs in the population from 15–20% in people older than 70 years 3 to 10%, in people younger than 70 years to **(Selvin and Erlinger, 2004)**. However, ~40% of PAD patients are without symptoms **(Hiatt, 2001; Schirmang et al., 2009)**. One third of PAD patients will experience a complete obstruction of a main artery to the leg at first presentation **(Fowkes et al., 1991; Norgren et al., 2007)**. Uncommon among younger people, the incidence of PAD upsurges abruptly with age and affects a substantial proportion of the elderly population. Allison et al appraised the ethnic-specific prevalence in the U.S. combining data from 7 community-based studies. These studies included representation from 5 ethnic groups: Native Americans, non-Hispanic whites (NHW), Hispanics African Americans (AA) and Asian Americans **(Allison et al., 2007)**.
Global data on trends in PAD prevalence between the years 2000 and 2010 were recently published **(Fowkes et al., 2013)**. Over that period, the number of individuals with PAD increased by 28.7% in low-income and middle-income countries and by 13.1% in high-income countries. Therefore, studies examining the frequency of PAD among high-risk groups and recognizing risk factors for PAD are crucial in order to optimize the treatment strategies for those patients and improve PAD prognosis. It should be also taken into account that as the U.S. population is highly diverse, specific data on PAD course among several ethnic groups are of

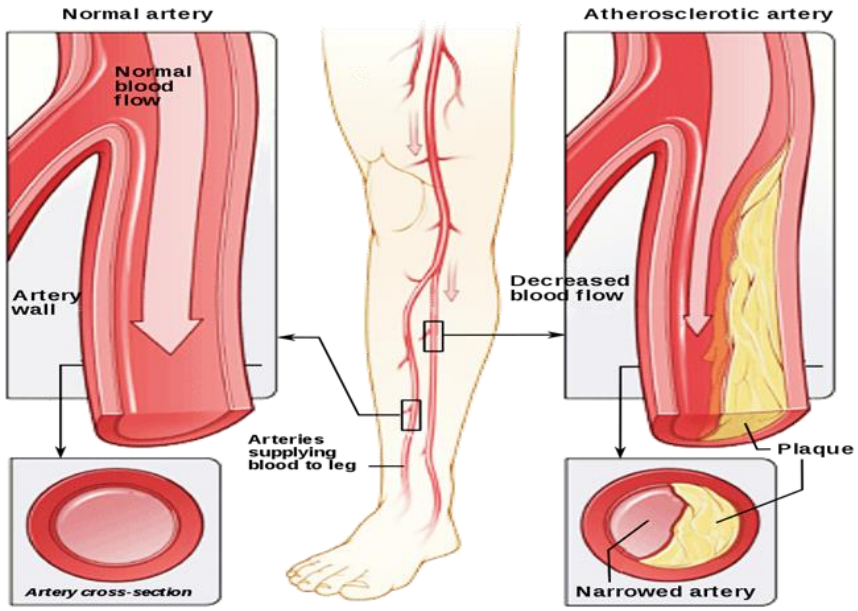

Figure 4: (A) shows a normal artery with normal blood flow. The inset image shows a cross-section of the normal artery. (B) shows an artery with plaque buildup that is partially blocking blood flow.

significant importance **(Perez and Hirschman, 2009)**.

2.3. Pathophysiology and risk factors

PAD outcomes from any disease-causing stenosis or occlusion of the lower limb arteries **(Flu et al., 2010)** with atherosclerosis disease being the most mutual etiology. Atherosclerosis includes endothelial dysfunction, lipid disturbances, thrombosis, platelet activation, oxidative stress, vascular smooth muscle activation, re-modelling and genetic factors **(Faxon et al., 2004)**.

Also, the role of inflammation has been documented in all stages of atherosclerosis development **(Libby et al., 2002)**. It usually affects arterial bifurcations due to the effect of flow disturbance leading to diminished endogenous athero-protective mechanisms. Whilst this has allowed the identification of multiple potential circulating biomarkers **(Ridker et al., 2001)**, the complex and interwoven pathophysiology of plaque formation has limited the success of pharmaco-modulating agents.

Risk factors for atherosclerosis include race; male gender; increasing age; smoking; diabetes mellitus; hypertension; dyslipidemia; hypercoagulable and hyperviscous states; hyperhomocysteinaemia; systemic inflammatory conditions and chronic renal insufficiency **(Fowkes et al., 1991).**

Overall, PAD increases with smoking, African-American ethnicity, renal insufficiency, diabetes mellitus and hypercholesterolemia **(Selvin and Erlinger, 2004)**, while it has been documented that developing critical limb ischemia (CLI) is more likely with ankle–brachial index (ABI) ,0.7, age over 65 years, smoking, and hypercholesterolemia **(Hirsch et al., 2006)**

Non-atherosclerotic causes of PAD are beyond the scope of this study but are listed in table 2.

2.4. Morbidity and mortality

Only ~25% of patients with IC will significantly worsen, most commonly (7% to 9%) in the first year after diagnosis compared with 2–3% per year thereafter **(Norgren et al., 2007)**. The reported rate of CLI is around 200–400 new cases every year per million population **(Rothwell et al., 2004)** and ~1 out of every 100 patients with IC will suffer from CLI per year **(Ubbink, 2004)**. Although major amputation is a rare outcome of claudication, with only 1–3% of claudicants needing it over a 5-year period **(Norgren et al., 2007)**, limbs with ulceration due to arterial insufficiency treated without revascularization will have a 19% risk of amputation at 6 months and 23% risk at 1 year **(Marston et al., 2006)**.

Cardiovascular risk varies with the severity of PAD and is closely correlated with both reduced and increased ankle brachial pressure index. The relationship between ABI and mortality over a

Table 2: Non-atherosclerotic causes of PAD.

Peripheral emboli
Aneurysm thrombosis or thromboembolism (aortic, popliteal)
Arteritis • Takayasu's disease • Thromboangiitis obliterans (Buerger's disease) • Giant cell arteritis • Polyarteritis nodosa
Fibromuscular dysplasia
Pseudoxanthoma elasticum
Prior trauma or irradiation injury
Aortic coarctation
Endofibrosis of the external iliac artery (iliac artery syndrome in cyclists)
Primary vascular tumors
Young patients • Adventitial cyst of the popliteal artery • Popliteal entrapment • Persistent sciatic artery

period of 10 years in the Strong Heart Study at 5, 10 and 15 years is 30, 50 and 70%, respectively, and similar rates are found in asymptomatic patients. Twenty-five percent of CLI patients will die within a year of diagnosis **(Norgren et al., 2007)**.

2.5. Screening and Diagnosis

2.5.1. Clinical examination

The American Diabetes Association (ADA) endorses (Table3) an initial screening for LEAD based on an in-depth interview and a clinical examination including a history of reduced walking speed, leg fatigue, claudication, and the palpation of the pedal pulses **(American Diabetes, 2018)**. Diabetic neuropathy may hide symptoms of LEAD, and should be systematically screened as well. Distal diabetic neuropathy is also embedded in medial arterial calcification that leads to incompressible arteries **(Lehto et al., 1996; Jeffcoate et al., 2009)**.

The clinical presentation of LEAD can be evaluated according to Lerich and Fontaine or Rutherford classification (Table 4). IC and rest pain are the most important signs to be evaluated, though they can be lacking or difficult to attribute exclusively to LEAD **(American Diabetes, 2018)**.

2.5.2. Ankle–brachial index testing

Ankle–brachial index has known as the relatively simple, non-invasive, and inexpensive tool for LEAD diagnosis **(Weiss et al., 2018)**. The ADA endorses the assessment of ABI as a first line non-invasive test in patients with symptoms or signs of LEAD **(American Diabetes, 2018)**. It is computed as a ratio of systolic blood pressure at the ankle to the systolic blood pressure in the upper arm (Figure5) **(Li et al., 2013)** .

The performance of ABI for LEAD screening is particularly unreliable in people with diabetes **(Potier et al., 2011; Guirguis-Blake et al., 2018)**. A comprehensive systematic review reported a variable performance: the sensitivity of ABI < 0.9 ranged from 29 to 95% (median at 63%), and its specificity diverse between 58 and 97% (median 93%). The addition of ABI > 1.3 did not improve the discrimination. The measurement of ABI is also dependent on operator skills **(Davies et al., 2014)**.

2.5.3. Ultrasound and other imaging methods

Doppler ultrasound exam (Figure 6) is an imaging method with a good LEAD diagnosis performance (sensitivity 93% and specificity 97%) **(Polak, 1995)**. It is a non-invasive, simple, and an affordable method permitting anatomical and hemodynamic vascular assessments, regardless of medial arterial calcifications, but it is still dependent on the operator practice. The Doppler waveform analysis delivers further information; a triphasic waveform mirrors a normal hemodynamic state and then the absence of LEAD. The presence of monophasic or biphasic waveforms has a good

negative predictive value but her positive predictive value remains less consistent depending on the presence of peripheral neuropathy **(Brownrigg et al., 2016)**. Interestingly, a previous study has exposed that a semi-quantitative score built on the ultrasonographic features of the lower limb arteries may benefit in the assessment of LEAD across different stages, as well as the assessment of its related to cardiovascular risk **(Santoro et al., 2016)**. A recent finding recommended that this score could be better than ABI to screen LEAD **(Santoro et al., 2018)**.

The magnetic resonance angiography, computed tomography angiography and angiography permit a precise topographic diagnosis and are often performed in the pre-operative work-up when large arterial vessels are involved. The topography of LEAD is usually characterized as proximal (from the common iliac to the superficial femoral artery) and distal lesions (from the popliteal to the dorsal pedis artery). The distal localization has been revealed to be more common than the proximal one in patients with diabetes (Figure 14) **(Aboyans et al., 2010)**.

2.6. Co-relation between PAD and Angiogenesis

2.7.

The development of vascular tissues may be considered in several different contexts. Three different processes may involve in the growth of new blood vessels i.e., neovascularization: vasculogenesis, angiogenesis and arteriogenesis **(Persson and Buschmann, 2011)**.

This is illustrated in Table 5 **(Freedman and Isner, 2002)**. Vasculogenesis is stated as the in-situ formation of blood vessels from endothelial progenitor cells (EPCs) or angioblasts **(Peters, 2018)**. It begins with the formation of cell clusters or blood islands in the embryonic process. Growth and fusion of multiple blood islands in the embryo ultimately give rise to the capillary network structure **(Udan et al., 2013)**. After the onset of blood circulation, this network differentiates into an arteriovenous vascular system. EPCs are positioned at the periphery of the blood islands, while hematopoietic stem cells (HSCs) are set in the center of the blood islands during the early embryonic stages. EPCs give rise to endothelial cells, whereas HSCs develop into mature blood cells after blood island fusion **(Chopra et al., 2018)**.Vasculogenesis has been considered to be limited to the embryo **(Risau et al., 1988)** while neovascular formation in adults was thought to be the consequence of angiogenesis **(Murohara, 2003)**.

Angiogenesis defines as the sprouting, growth of small vessels, the branching of existing capillaries by the assembly of endothelial cells from preexisting vessels **(Ribatti and Crivellato, 2012)**. Angiogenesis happens in the healthy body for healing wounds and for returning blood flow to tissues after injury or insult. In females, angiogenesis also occurs during the monthly reproductive cycle and during pregnancy **(Chau et al., 2017)**.

Physiology of angiogenesis

The healthy body regulates angiogenesis through a series of "on" and "off" switches. The main "on" switches are referred as angiogenesis-stimulating growth factors, while the main "off switches" are known as angiogenesis inhibitors **(Sullivan and Brekken, 2010)**. When angiogenic growth factors are formed in excess of angiogenesis inhibitors, the balance is sloped in favor of blood vessel growth. On the contrary, when inhibitors are existing in excess of stimulators, angiogenesis is stopped. The normal, healthy body preserves a perfect balance of angiogenesis modulators and, in general, angiogenesis is "turned off" by the production of more inhibitors than stimulators **(Bisht et al., 2010)**.

The principal growth factors driving angiogenesis are vascular endothelial growth factor (VEGF) and fibroblast growth factor-2 (FGF2) **(Murakami and Simons, 2008)**. VEGF is a mitogen protein highly specific for EC. FGF-1 and FGF-2 are mitogenic proteins for a wider variety of cell types than VEGF, i.e. their receptors are expressed on fibroblasts, smooth muscle and endothelial cells **(Ucuzian et al., 2010)**. There are other positive regulators as hepatocyte growth factor and angiopoietin-1 **(Li et al., 2005)**.

Table 3: Publications of the major international guidelines in screening, diagnosis, and treatment of lower-extremity

Society	Guidance	Journal	Year	References
American Diabetes Association	Microvascular complications and foot care: standards of medical care in diabetes	Diabetes Care	2018	**(American Diabetes, 2018)**
US Preventive Services Task Force	Screening for peripheral artery disease and cardiovascular disease risk assessment with the ankle–brachial index	JAMA	2018	**(Curry et al., 2018)**
American Heart Association & American College of Cardiology	Management of patients with lower extremity peripheral artery disease	Circulation	2017	**(Gerhard-Herman et al., 2017)**
European Society of cardiology & European Society for Vascular Surgery	Diagnosis and treatment of peripheral arterial diseases	Eur Heart J	2018	**(Aboyans et al., 2018)**

Table 4: Classifications of peripheral arterial disease by clinical symptoms

Fontaine classification		Rutherford classification		
Stage	Clinical symptoms	Stage	Category	Clinical symptoms
I	Asymptomatic	0	0	Asymptomatic
IIa	Mild claudication	I	1	Mild claudication
IIb	Moderate to severe claudication	I	2	Moderate claudication
III	Ischemic rest pain	I	3	Severe claudication
IV	Ulceration or gangrene	II	4	Ischemic rest pain
		III	5	Minor tissue loss
		IV	6	Major tissue loss

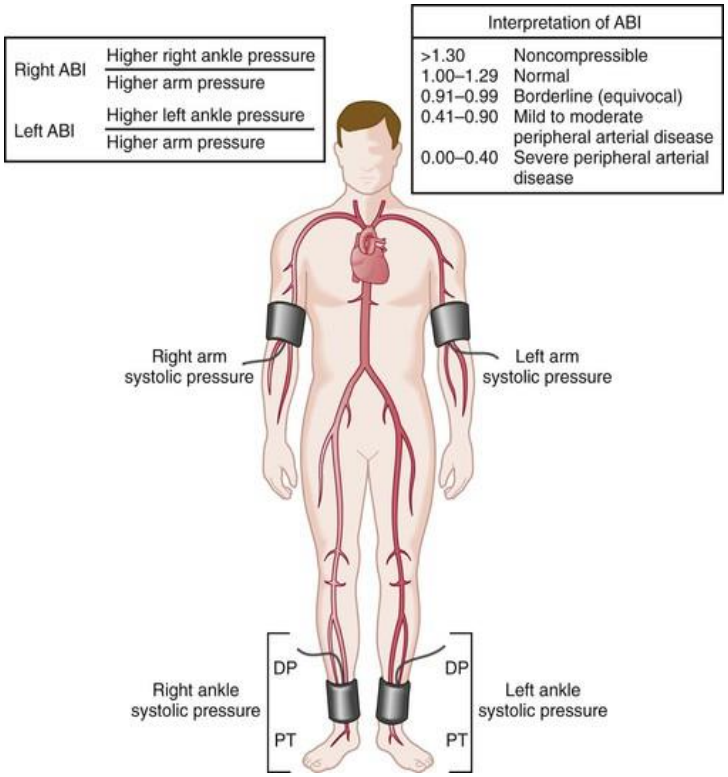

Figure 5: Measurement of the ankle-brachial index (ABI). DP indicates dorsalis pedis artery; PT, posterior tibial artery (Li et al., 2013).

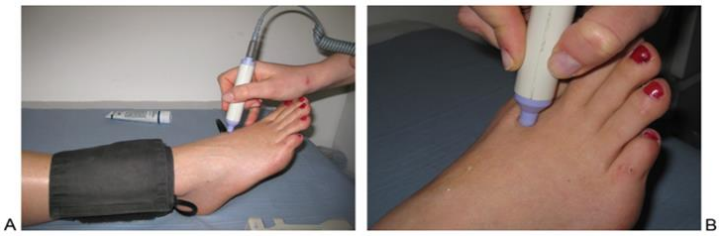

Figure 6: (A) Doppler assessment of the dorsalis pedis pulse in a healthy foot. (B) Positioning for assessment of pedal arch patency.

Table 5: Types of neovascularization

	Vasculogenesis	**Angiogenesis**	**Arteriogenesis**
Primary stimuli	Growth& development	Ischemia or hypoxia, inflammation	Shear stress, inflammation
Cell types involved	Endothelial stem cells	Endothelial cells, smooth muscle cells & pericytes	Endothelial cells
Resulting vessels	De novo blood vessels	Capillaries	Arterioles
Contribution to adult tissues	Not clear	Yes	Yes

Table 6: Pro-angiogenic and Anti-angiogenic Factors.

Pro-angiogenic Factors*	**Anti-angiogenic Factors**
Angiogenin Angiopoetin-1 Del-1 Fibroblast growth factor, acidic(aFGF) Fibroblast growth factor, basic (bFGF) Follistatin Granulocyte colony-stimulating factor (G-CSF) Hepatocyte growth factor (HGF)† Interleukin-8 (IL-8) Leptin Midkine Placental growth factor (PiGF)) Platelet-derived endothelial cell growth factor (PD-ECGF) Platelet-derived growth factor-BB (PDGF-BB) Pleiotrophin (PTN) Proliferin Transforming growth factor-alpha (TGFalpha) Transforming growth factor-beta (TGF-beta) Tumor necrosis factor-alpha (TNF-□) Vascular endothelial growth factor (VEGF)‡ * Factors known to activate endothelial cell growth and movement. † Also known as scatter factor (SF). ‡ Also known as vascular permeability factor.	Angiostatin (plasminogen fragment) Antiangiogenic antithrombin III Cartilage-derived inhibitor (CDI) CD59 complement fragment Endostatin (collagenXVIII fragment) Fibronectin fragment Gro-beta Heparinases Heparinhexasaccharide fragment Human chorionic gonadotropin (hCG) Interferon alpha, beta, gamma Interferon inducible protein (IP-10 Interleukin-12 (IL-12) Kringle 5 (plasminogen fragment) Tissue inhibitors of metalloproteinases (TIMPs) 2-methoxystriadol Placental ribonuclease inhibitor Plasminogen activator inhibitor Platelet factor 4 (PF4) Prolactin 16kD fragment Retinoids Tetrahydrocortisol-S Thrombospondin-1 (TSP-1) Transforming growth factor beta (TGF-□) Vasculostatin Vasostatin (calreticulin fragment)

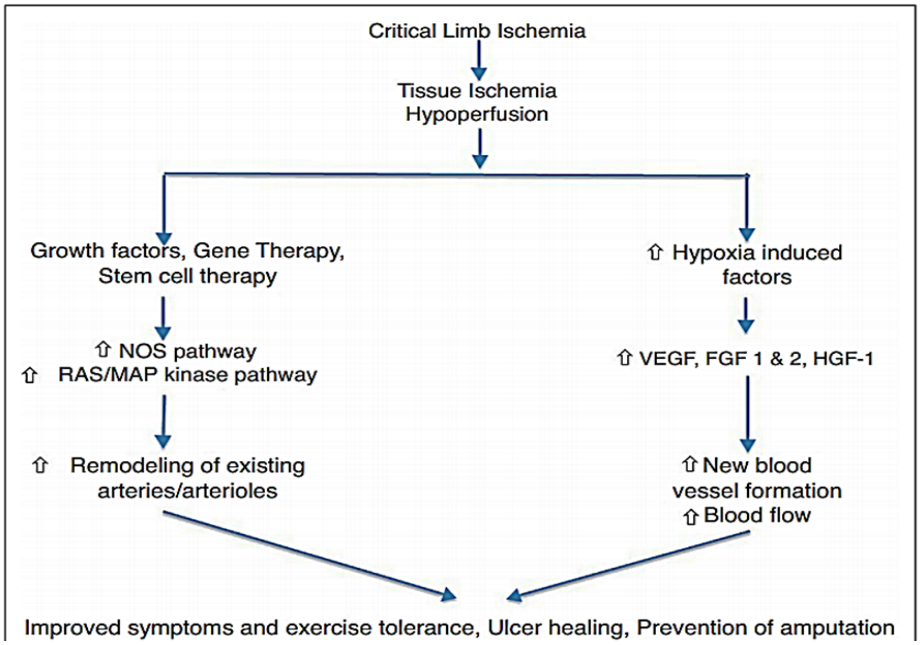

Figure 7: Therapeutic angiogenesis in critical limb ischemia: mechanisms and outcomes (Inampudi et al., 2018).

Angiogenesis is physiologically suppressed by one or more of the known endogenous inhibitors, including angiopoietin-2, angiostatin, endostatin, interferon-alfa **(Krock et al., 2011)**. Tumor necrosis factor-alpha (TNF-alpha), transforming growth factor-beta (TGF-beta), interleukin4 (IL-4) and IL-6 are bifunctional modulators. These molecules are either stimulators or inhibitors depending on the amount, the site, the microenvironment, the presence of other cytokines, etc. (Table 6) **(Aung et al., 2000)**.

The major driver to stimulate angiogenesis is local tissue ischemia or hypoxia (Figure 7). The oxygen tension drops results in a rapidly increased expression of hypoxia inducible factor-1 (HIF-1). HIF-1 is a transcription factor that adjusts a master genetic program that controls many forms of energy homeostasis at cellular and systemic levels. HIF-1 is composed of two subunits, HIF-1α and HIF-1β. **(Zhu and Bunn, 2001)**. The increased expression of HIF-1α leads to increased transcription of a number of genes involved in angiogenesis, including VEGF and VEGF receptor-2, angiopoietin-2 and Tie-2 **(Lekas et al., 2006; Vincent and Kelly, 2007)**.

Together with hypoxia, inflammation is an essential stimulus of neovascularization. Inflammation may promote angiogenesis in a number of ways. Macrophages and T-lymphocytes are often present in myocardial ischemia and ischemic injury **(Sullivan et al., 2000)**. These blood-born inflammatory cells are a source of VEGF **(Arras et al., 1998; Couffinhal et al., 1999)** and a host of other angiogenic and arteriogenic factors including bFGF, IL-2, TNF-α and metalloproteinases **(de Muinck and Simons, 2004)**.

3. Phosphodiesterase inhibitors

The phosphodiesterase (PDE) super family is numerous, multipart and represents 11 gene families (PDE-1 through PDE-11). Each of the PDE families (Table 7) contains one to four genes, and many genes generate multiple isoforms. All the members of the PDE superfamily diverge in various aspects such as localization or tissue distribution, mode of regulation and inhibitor specificity **(Cheng and Grande, 2007)**.

The PDEs are found in the cytosol, plasma membranes, endoplasmic reticulum, nuclear membranes and the cytoskeleton **(Houslay et al., 1998; Nyby et al., 2003)**. Phosphodiesterases are controlled by intracellular phosphorylation, cyclic nucleotide concentrations, interaction with regulatory proteins, subcellular compartmentalization, and binding of Ca_2þ/calmodulin, as well as by variations in gene expression **(Cheng and Grande, 2007)**.

PDE-3, PDE-4, and PDE-7 and PDE-8 hydrolyze only Cyclic adenosine monophosphate (cAMP) (cAMP-PDE). PDE-5, PDE-6 and PDE-9 hydrolyze only cGMP (cGMP-PDE), and isozymes PDE-1 and PDE-2 accept both nucleotides as a substrate **(Dousa, 1999; Cheng and Grande, 2007).**

3.1. Role of phosphodiesterases

Mammalian cyclic nucleotide PDEs are regionally spread in the human body, relating to their intervention in mediating intracellular signal through interaction with cell surface receptor. These metallophosphohydrolases are categorized in eleven different isoenzymes, depending upon relative sequence, subcellular localization, substrate and inhibitor specificity, among which PDE-4 is the most abundant one in the human body **(Rutten et al., 2007)**.

Recently, PDE-2 has appeared as promising key to CNS disorders. Among various candidates of PDE family members (PDE-1 to PDE-11), few are specific to cGMP hydrolysis, others to cAMP, and some hydrolyze both **(Beavo and Brunton, 2002).** The presence of a variation of cAMP-hydrolyzing PDEs, conservation of PDEs among different species as well as with evolution, points out towards the critical importance of PDE family **(Halpin, 2008)**.

Phosphodiesterase plays a vital part in regulating the level of cAMP and cGMP through the hydrolysis of these nucleotides by PDEs to 5′-nucleotide monophosphates which leads to elimination of the signals of these second messengers from neurons and glial cells **(Manganiello et al., 1988)**.

3.2. Phosphodiesterases-5 classification

The PDE-5 member of PDEs is also named as cGMP-PDE, cGMP-binding phosphodiesterase, or PDE V. In human, bovine, and rat vascular smooth muscle, PDE5 was purified and characterized as a cytosolic PDE isozyme that specifically hydrolyzes cGMP without being activated by Ca/calmodulin **(Rybalkin et al., 2003a)**. The PDE-5 enzymes are derived mainly from single gene in the human corpus cavernosum PDE-5A and have two 5` splice variants PDE-5A1 and PDE-5A2 **(Corbin and Francis, 1999)**.

Localization and distribution

Phosphodiesterase-5 mRNA was reported to be expressed in aortic smooth muscle cells, heart, placenta, skeletal muscle, pancreas, and, to a much lesser extent, in the liver, and lung **(Nagayama et al., 2008)**.

Table 7: Phosphodiesterases superfamily (Cheng and Grande, 2007, Lugnier, 2006)

Family	Substrate	Regulations	Inhibitors	Clinical applications
PDE-1	cAMP/cGMP	Ca_2þ/calmodulin activated	Vinpocetine Nicardipine Nimodipine	-Dementia, memory loss
PDE-2	cAMP/cGMP	Stimulated/ activated by cGMP	Oxindole (2)	-Acute respiratory distress syndrome -Memory loss
PDE-3	cAMP/cGMP	cGMP-inhibited	Lixazinone Cilostamide Milrinone Cilostazol Dihydro-pyridazinone	-Glomerulonephritis -Congestive heart failure -Intermittent claudication -Thrombosis -Pulmonary hypertension
PDE-4	cAMP	cGMP-insensitive. Phosphorylated by PKA Phosphorylated by ERK	Rolipram Denbufylline Cilomilast Roflumilast	-Glomerulonephritis -Asthma, COPD a -Bipolar depression -Autoimmune encephalomyelitis -Organ transplantation
PDE-5	cGMP	PKA/PKGphosphorylated Binds cGMP	Sildenafil (Viagra) Zaprinast Dipyridamole Ariflo Vardenafil Tadalafil	-Chronic renal failure -Salt retention in nephritic syndrome -Pulmonary hypertension -Erectile dysfunction -Organ transplantation
PDE-6	cGMP	Transducin-activated	Zaprinast Dipyridamole Vardenafil Tadalafil	-Selective PDE-6 -Inhibitors have little applications due to adverse effects on vission.
PDE-7	cAMP	Rolipram-insensitive	Dipyridamole Thiadiazole	Airway and immunological diseases.
PDE-8	cAMP	Rolipram-insensitive isobuty-1-methylxanthine-insensitive	Dipyridamole	Immunological applications.
PDE-9	cGMP	IBMX-insensitive	Zaprinast	Possible hypoglycemic effects
PDE-10	cAMP/cGMP	Unknown	Dipyridamole Papaverine	Treatment of Schizophrenia and psychiatric disorders.
PDE-11	cAMP/cGMP	Unknown	Tadalafil Dipyridamole	Anticipated improvement of human testicular functions.

3.3. Phosphodiesterases-5 inhibitors

Zaprinast is the first characterized selective PDE-5 inhibitor. Later, more PDE-5 inhibitors were updated and these were mainly indicated for erectile dysfunction. Presently, three PDE-5 inhibitors have been permitted by the U.S. food and drug administration (FDA) for use in the United States: sildenafil citrate, tadalafil, and vardenafil hydrochloride trihydrate **(Gratz et al., 2009)**.

3.3.1. Tadalafil

Tadalafil is an orally administered drug to treat male erectile dysfunction (impotence) under the brand name Cialis. Tadalafil is permitted for the treatment of pulmonary arterial hypertension. Tadalafil has more recently stated a potential anti-inflammatory effect in vitro on the inflammatory response of endothelial cells increased by myeloperoxidase-modified low-density lipoprotein or tumor necrosis factor alpha **(Roumeguere et al., 2010)**.

3.3.2. Vardenafil

Vardenafil is closely involved in both function and marketing to sildenafil and tadalafil. Structurally, the vardenafil molecule differs from sildenafil by only a methyl group and the position of one nitrogen atom in its structure. It has a relatively short effective time as compared to sildenafil **(Rybalkin et al., 2003b)**. Sildenafil and vardenafil also improve early memory consolidation of object information **(Prickaerts et al., 2004)**. Some studies showed that vardenafil and tadalafil, PDE-5/6 inhibitors, are able to induce caspase-dependent apoptosis in B-chronic lymphocytic leukemia cells **(Liu et al., 2008)**.

3.3.3. Sildenafil

Sildenafil was initially researched for the use in hypertension (high blood pressure) and angina pectoris (a symptom of ischemic heart disease). Phase I clinical trials under the direction of Ian. Osterloh proposed that the drug had little effect on angina, but it could induce marked penile erections **(Terrett NK, 1996; Vardi and Nini, 2007)**

3.3.3.1. Mechanism of action

Sildenafil is a potent and selective inhibitor of cGMP-specific PDE-5 that protects cGMP from degradation in the corpus cavernosum. Nitric oxide leads to increased levels of cGMP and smooth muscle relaxation (vasodilation) of the intimal cushions of the helicine arteries. This smooth muscle relaxation leads to vasodilation and increased inflow of blood (Figure 8) **(Webb et al., 1999)**

3.3.3.2. Pharmacokinetics

Sildenafil is broken down in the liver by hepatic metabolism using cytochrome enzymes, mainly cytochrome P450 and cytochrome P450 2C9 hepatic isoenzymes. The major product of metabolization by these enzymes is N-demethylated sildenafil, which is further metabolized. Sildenafil metabolites are excreted in feces (80%) and urine (13%). It reaches the maximum plasma concentration within one hour **(Moore et al., 2002)**. It is rapidly absorbed through the gut, with a bioavailability of 40%. The maximum serum concentrations of sildenafil are reached 0.5–1.5 hours after an oral dose administration **(Mondaini et al., 2003)**. The half-life of sildenafil is approximately 4 hours and hence the drug is effective in a 6–8 hourly after dosing **(Eloi-Stiven et al., 2007).**

3.3.3.3. ***Side effects***

Mild hypotension has been reported (especially in combination with nitrates in adults), and in patients with liver dysfunction, sildenafil has to be administered with care. It is also worthwhile that children being placed on sildenafil should get periodic ophthalmologic examinations as there have been some reports of visual deficits in adults on sildenafil, in children are not severe and often are masked by the underlying hemodynamics **(Agostino et al., 2007; Floryk and Thompson, 2008).**
In clinical trials, the most common adverse effects of sildenafil use included headache, flushing, indigestion, nasal congestion, and impaired vision, including photophobia and blurred vision. Some sildenafil users have put a complain of seeing everything tinted blue (cyanopsia) **(O'Malley, 2006).** Some complained of blurriness and loss of visions and a number of studies have linked sildenafil use with non arteritic anterior ischemic optic neuropathy **(Laties, 2009)**.

3.3.3.4. *Interactions and contraindications*

Protease inhibitors inhibit the metabolism of sildenafil, hereby, effectively multiplying the plasma levels of sildenafil, increasing the incidence and severity of side effects **(Dadey, 2015)**. Erythromycin and cimetidine, both of which can also lead to prolonged plasma half-life levels. The use of sildenafil and an alpha blocker at the same time may lead to low blood pressure **(Kloner, 2005)**. Sildenafil is contraindicated in NO donors, organic nitrites and nitrates, severe hepatic or renal impairment, hypotension, recent stroke or heart attack and hereditary degenerative retinal disorders **(Cheitlin et al., 1999)**.

4. Antioxidants

Reactive oxygen species (ROS) and reactive nitrogen species (RNS) are the terms jointly defining free radicals and other non-radical reactive derivatives also called oxidants. Biological free radicals are extremely unstable molecules which are products of normal cellular metabolism. They have electrons available to react with various organic substrates such as lipids, proteins and deoxyribonucleic acid (DNA). Free radicals are well documented for playing a dual part as both deleterious and beneficial species, since they can be either harmful or beneficial to living systems **(Valko et al., 2007)**.

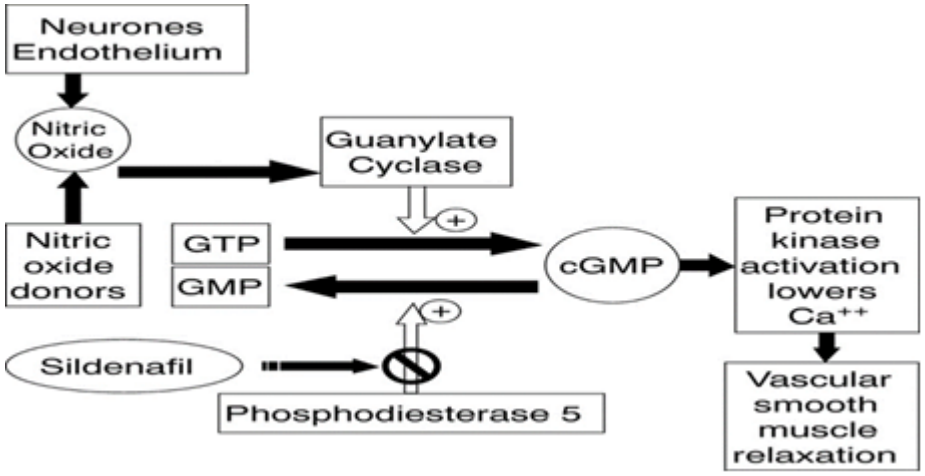

Figure 8: Mechanism of action of Sildenafil (Sung, et al., 2003)

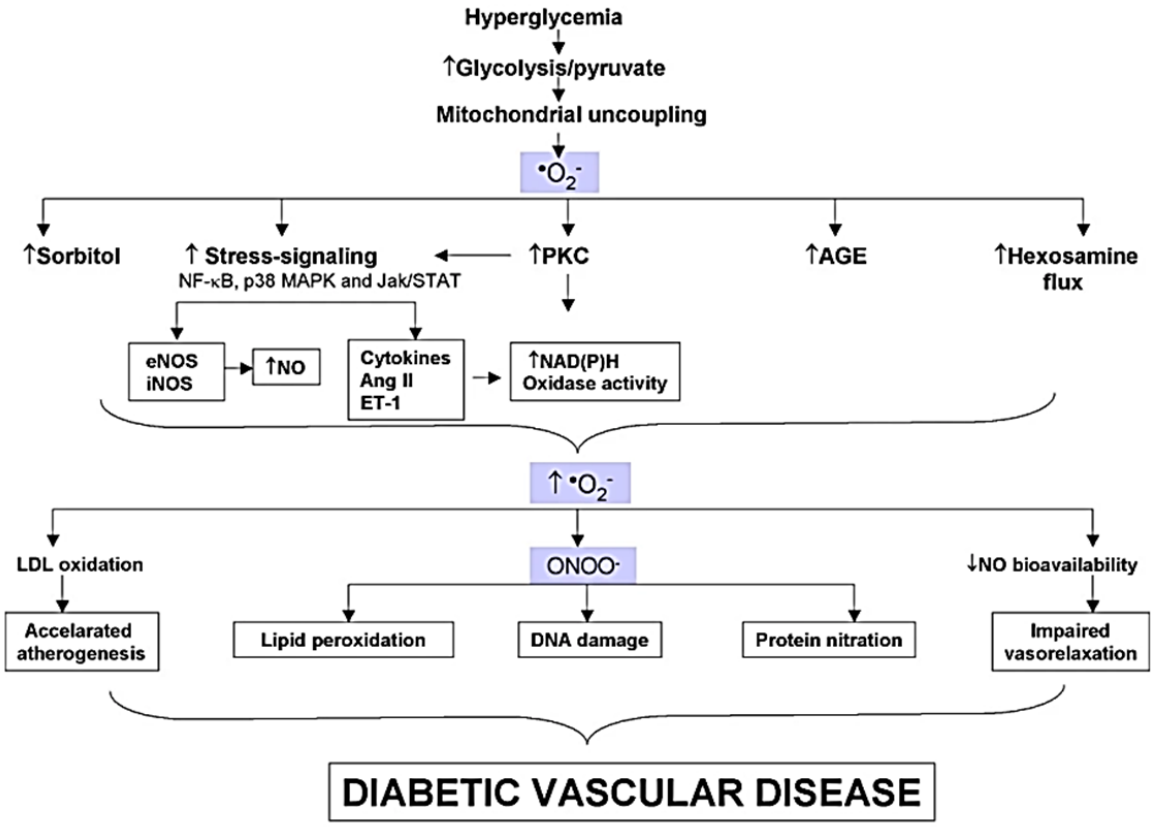

Figure 9: generation of reactive species and downstream targets in diabetes (Johansen et al., 2005).

Free radicals produced under physiological conditions are maintained at steady state levels by endogenous or exogenous antioxidants (externally supplied through foods or supplements) which act as free radical scavengers. However, oxidative stress ensues when the production of free radicals overwhelms the detoxification capacity of cellular antioxidant system causing biological damage **(Abdollahi et al., 2004; Ridnour et al., 2004; Halliwell, 2011)**.

4.1. Pathways of free radical generation in diabetes mellitus

In diabetes, ROS is thought to be generated through amplified polyol pathway **(Chung et al., 2003)**, increased formation of advanced-glycation end products (AGEs) **(Baynes and Thorpe, 1999)** and protein kinase C (PKC) activation **(Inoguchi et al., 2003)**.

4.1.1. Aldose reductase pathway and ROS generation

Aldose reductase is the rate limiting enzyme of the polyol pathway. The nicotinamide adenine dinucleotide phosphate (NADPH)-requiring aldose reductase, catalyzes the reduction of glucose to sorbitol followed by the oxidation of sorbitol to fructose by NAD+ dependent sorbitol dehydrogenase. At normal blood glucose concentration (5.5 mM), aldose reductase catalyzed reaction signifies less than 3% of total glucose utilization **(Morrison et al., 1970)**. However, hyperglycemia results in saturation of hexokinase and more than 30% of glucose is shifted into the polyol pathway **(Gonzalez et al., 1984)**.

The polyol pathway also outcomes in reduction in the bioavailability of NAD(P)H. Reduction of NAD(P)H also declines the synthesis of nitric oxide (NO), a vasculo-protective agent. NAD(P)H serves as a cofactor for nitric oxide synthase (NOS) which manufactures NO from L-arginine. If endothelial nitric oxide synthase (eNOS) lack its substrate, L-arginine or one of its co-factor, it may yield superoxide radical ($\cdot O_2^-$) instead of NO and this is referred to as ‘‘uncoupled state of nitric oxide’’ **(Vasquez-Vivar et al., 1998)**.

4.1.2. Advanced glycation end product (AGEs) formation and ROS generation

Advanced glycation end products constitute a heterogeneous group of molecules formed by non-enzymatic reactions of reducing sugars, ascorbate and other carbohydrates with amino acids, lipids and nucleic acids [98, 99]. Glycation end products adducts such as N- Carboxy- methyl lysine (CML) pyraline and pentosidine are found to be elevated in diabetic tissues **(Stitt, 2001; Wautier and Guillausseau, 2001; Stitt et al., 2005)**.

Once formed, AGEs can cause tissue damage by two main pathways which are: (1) formation of cross links that alter protein structure and function and, (2) interaction of AGE with AGE-cell surface receptors on the surfaces of various cells such as endothelial cells, macrophages, neurons, and smooth-muscle cells resulting in activation of cell signaling and gene expression that induces oxidative stress and inflammation **(Nishikawa et al., 2000; Vlassara and Palace, 2002; Peppa et al., 2004; Sourris and Forbes, 2009; Giacco and Brownlee, 2010)**.

4.1.3. Protein kinase C (PKC) activation and ROS generation

PKC activation (Figure 9) is related to vasoconstriction, proliferation and overgrowth of smooth muscle cells as well as accelerated synthesis of extracellular matrix proteins, and thus plays significant roles in the onset and progression of vascular cell dysfunction in diabetes mellitus **(Koya and King, 1998; Meier and King, 2000; Way et al., 2001)**. Two major pathways have been involved in the activation of PKC in hyperglycemia. Persistent and excessive activation of several PKC isoforms occur primarily from enhanced de novo synthesis of diacylglycerol (DAG) from glucose via surge in triose phosphate availability **(Inoguchi et al., 1992; Shiba et al., 1993; Du et al., 2003; Giacco and Brownlee, 2010; Tessari et al., 2010)**. There is also evidence that the interaction between AGE’s and their cell-surface receptors can result in enhanced activity of PKC isoforms **(Derubertis and Craven, 1994; Thallas-Bonke et al., 2008)**.

4.2. Anti-oxidative agents in the management of diabetes mellitus

Due to the implication of hyperglycemia-induced oxidative stress in diabetes, these patients should in theory benefit from antioxidant supplementation. The beneficial effect of antioxidants has been reported in animal models of diabetes and in diabetic patients **(Maritim et al., 2003; Liu et al., 2006)**.

4.2.1. Vitamins

Vitamin E is a fat-soluble vitamin. It has been shown that plasma α-tocopherol concentrations are minor in diabetics compared to controls **(Nourooz-Zadeh et al., 1997)** and appear to be even lower in diabetics with complications such as microangiopathy than in diabetics without difficulties **(Martin-Gallan et al., 2003)**. Administration of Vitamin E has confirmed to be beneficial in avoiding cellular damage by inhibition of lipid peroxidation, protein oxidation, protein glycations and platelet aggregation **(Rhee et al., 2005; Devaraj et al., 2008; Minamiyama et al., 2008)**. Vitamin E supplementation for two weeks (600 mg/day) dropped urinary F2-isoprostanes (a marker of lipid oxidation) in type 2 diabetics **(Davi et al., 1999)**. It was shown in a study that a decrease in plasma F2-isoprostanes was seen in type 2 diabetic patients afterward six weeks supplementation with Vitamin E **(Wu et al., 2007)**.

4.2.2. Flavonoids

Flavonoids (bioflavonoids) are a diverse group of polyphenols (phenyl benzopyrans) which function as phytochemicals **(Corradini et al., 2011)**. Flavonoids are recognized for their multi-directional biological activities including anti-diabetic efficacy. Experimental evidence has shown that flavonoids exhibit anti-inflammatory **(Middleton et al., 2000)**, anticarcinogenic **(Batra and Sharma, 2013)**, antiviral **(Selway, 1986)** and antiallergic properties. These effects are generally associated with free radical scavenging activity of flavonoids. The antioxidant effects of flavonoids are boosted by the number and position of hydroxyl groups in the molecule. The catechol structure, presence of unsaturation and 4-oxo function in the C-ring also involves to their radical scavenging activity **(Rice-Evans et al., 1996; Heim et al., 2002)**. Flavonoids may be capable of binding the transition metal ions, which play a role in glycoxidation, thus stopping metal-catalysed formation of hydroxyl radicals or related species from H_2O_2 **(de Groot and Rauen, 1998)**.

4.2.3. *Selenium*

Selenium was discovered as a by-product of sulfuric acid **(Berzelius, 1818)**. Fittingly, selenium was also spotted in the moon dust brought back by the 1969 Apollo mission **(Flohé et al., 2000)**. Although, it was largely unnoticed as a therapeutic agent for over 100 years due to its toxicity, recent decades have established its importance for mammalian life, with the recognition that selenium manages the functioning of certain proteins, designated as selenoproteins **(Rayman, 2000; Kryukov and Gladyshev, 2002)**.
The naturally occurring element selenium (Se) plays a major role in a wide variety of biological processes in mammals **(Arbogast and Ferreiro, 2010)**. Se administration increases the antioxidant ability of several intracellular systems. In addition, Se showed hepatoprotective effect against malathion-induced liver injury and diabetic rats **(Aboul-Soud et al., 2011; Zou et al., 2016)**.

- **Nano-Selenium**

Various sizes of Nano-Se can be attained by changing the concentration of bovine serum albumin (BSA). Generally, the smaller sized nanoparticles are more effective than those of larger size **(Oberdorster et al., 2005)**. For example, smaller sized regular nanoparticles employ a stronger cytotoxic effect on endothelial cells than those of larger size **(Deng et al., 2001)**.
Few studies proved that Nano-selenium intake could improve the antioxidant activity of the animals **(Zhu et al., 2010)**, while Nasirpour et al. concluded that nano-selenium supplementation amends the negative effects of oxidative stress **(Nasirpour et al., 2017)** due to the interaction between the nanoparticles and $–NH_2$, C=O, ^-COO, and –C–N– groups of proteins **(Zhang et al., 2004)**. However, as Se has an very narrow threshold range between beneficial biological dosage and toxicity limit, a pharmacological level of SeNPs may also have potential toxicity and ill effects **(Husbeck et al., 2006; Nilsonne et al., 2006; Aillon et al., 2009; Nasirpour et al., 2017)**. Besides, oxidation promotion is stated to be the main disadvantage for nanoparticles, and it grows increasing attention, which has been the bottleneck for SeNP application **(Nel et al., 2006)**.
It has been described that Nano-Se has a size effect on redox reactivity **(Mishra et al., 2005)**, and Nano-Se in the range of 5–200 nm has a size dependent effect in scavenging various free radicals in vitro, such as 1,1-diphenyl-2- picryhydrazyl (DPPH) and the superoxide anion **(Huang et al., 2003)**. Therefore, when cells are in a Se deficient state, the avidity of Se uptake mechanisms may be enlarged to maintain the biosynthesis of selenoenzymes. Under the circumstance of Se deficiency, cells may uprise one or more effective pathways for Se uptake, leading to the disappearance of the size effect of Nano-Se on selenoenzyme synthesis **(Peng et al., 2007)**.

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