EXCLI Journal 2011;10:69-84 – ISSN 1611-2156
Received: February 23, 2011, accepted: May 9, 2011, published: May 12, 2011

Review article:

DARK NIGHTS BEHIND THE WHITE CLOUDS – RISKS OF TOBACCO SMOKING ON HUMAN HEALTH BESIDES THE ORAL HEALTH AND MALIGNANCY

Zarin Zainul*****

Department of General Surgery, Chhatrapati Shahuji Maharaj Medical University, (Formerly KGMU) Chowk, Lucknow - 226 003, (U.P) INDIA
*Corresponding author: Telephone: 0522- 4103870; E-mail: zarin.csmmu@gmail.com

ABSTRACT

Tobacco smoking is the common practice in a large percentage of the population worldwide, and the incidence is continuously increasing. Tobacco smoking is the most preventable cause of lung cancer, and it also impairs oral health. People are aware of the carcinogenic effects of tobacco smoking on the lungs and oral cavity, but it is also a risk factor for many other harmful diseases. This review article covers most of the diseases that are associated with tobacco smoking, such as coronary artery disease (CAD), diabetes, chronic obstructive pulmonary disease (COPD), arthritis, impotency, infertility, tuberculosis, and Alzheimer's disease. The association of these diseases with tobacco smoking is discussed in detail in this review, along with their possible pathophysiology. This article focuses on the ongoing research of these diseases, and aims to raise awareness of the hazards of tobacco smoking, and to promote anti-smoking awareness programs.

Keywords: Tobacco smoking diseases, cardiovascular, COPD, diabetes, impotency, infertility, arthritis, Alzheimer's, tuberculosis

INTRODUCTION

The number of the cigarette smoker in the world is estimated at 1.3 billion, and this figure is expected to rise to 1.7 billion by 2025. Every second smoker will die of a tobacco-caused disease (WHO, 2003). Tobacco smoking causes lung cancer as well as it is an etiologic factor for several other cancers of the different organs and for the impaired oral health. It is a strong risk factor for many other diseases like cardiovascular diseases (CVD), coronary artery disease (CAD), diabetes, chronic obstructive pulmonary disease (COPD), arthritis, impotency, infertility, tuberculosis, Alzheimer's disease, etc. (Table 1). There are three major constituents of tobacco smoke like nicotine, Co, oxidants and harmful gases, which create a problem for human health. Tobacco smoking induced all diseases are discussed here along with their possible pathophysiologies.

Table 1: Tobacco smoking associated diseases

- **Cardiovascular Diseases (CVD)**
  Coronary artery diseases (CAD)
  Cerebrovascular diseases (Stroke)
  Abdominal Aortic Aneurysm (AAA)
  Peripheral Vascular disease (PVD)
  (Buerger's Disease)
- **Chronic Obstructive Pulmonary Disease (COPD)**
  Chronic Bronchitis
  Emphysema
- **Diabetes**
- **Tuberculosis**
- **Rheumatoid Arthritis (RA)**
- **Infertility**
- **Impotency**
- **Alzheimer's Disease (AD)**

EXCLI Journal 2011;10:69-84 – ISSN 1611-2156
Received: February 23, 2011, accepted: May 9, 2011, published: May 12, 2011

CARDIOVASCULAR DISEASES (CVD)

The association between smoking and cardiovascular disease (CVD) was first pointed out in 1950 (Hammond and Horn, 1958). CVD is a group of several diseases, such as coronary artery disease, cerebrovascular disease (stroke), abdominal aortic aneurysm (AAA), peripheral vascular disease, which are associated with the chronic tobacco smoking (Bišanović et al., 2011). Cigarette smoking is a major independent risk factor for CVD. While the association among chronic smoking and cardiovascular disease is well established, the pathophysiology is still not completely understood (Talukder et al., 2011).

- ***Coronary Artery Disease (CAD)***

Smoking predisposes individuals to atherosclerotic syndromes like coronary artery syndromes, myocardial infarction, stable angina and sudden death. The risks of coronary artery disease (CAD) are greatest in heavy smokers who have the longest duration of smoking (Burns, 2003). The relative rate of death from CAD in smokers is 70 % higher than non-smokers and deaths are even high, with 20 % in chronic and heavy smokers who have up to 15 cigarettes per/day (US Department of Health and Human Services, 1983).

Major components of tobacco smoke are: nicotine, CO, oxidants (per-oxides, nitrates, etc.) and harmful gases (Hammond et al., 1958; Benowitz, 2003) **[Figure 1]**. These components damage the endothelial cells, so the endothelial damage is the first step for the atherosclerotic development (Noronha et al., 1993; Lehr et al., 1993; Booyse et al., 1981; Boyle et al., 1997; Benowitz, 2003). Chemical oxidant toxicity disturbs the normal secretion of nitric oxide (NO), which is responsible for the vasodilatory functions of the endothelium from the endothelial cells (Boyle et al., 1997; Celermajer et al., 1996;Stafford et al., 1996; Higman et al., 1993; Kiowski et al., 1994). There is an important role played by the interaction between inflammatory cytokines and tobacco smoke constituents in the induction of endothelial dysfunction (Barbieri et al., 2011). It results in the impaired release of NO from the endothelium, causing the loss of coronary vasodilation (Leone, 2010). So, the regulatory functions of NO, like inflammation, leukocyte adhesion, platelet activation, thrombosis get impaired; these steps form an atheroma condition (Talukder et al., 2011; Pettiti and Kipp, 1986; Kool et al., 1993). A study suggests that the platelet activation is a link in the pathophysiology of diseases prone to thrombosis and inflammation. High mean platelet volume (MPV) is associated with a low grade inflammatory condition, leading to arterial and venous thromboses (Gasparyan et al., 2011). In contrast, smokers have higher levels of neutrophils and activated monocytes, resulting increased level of macrophages **(**Gasparyan et al., 2011). These also play an important role for the endothelial damage **(**Boyle et al., 1997), so the endothelium-derived nitric oxide (NO) plays a major role in the regulation of structure, function and endothelial dysfunction, which could be considered the first step in the pathogenesis of atherosclerosis (Grassi et al., 2010). Irregular inflammation leads to the disruption of the atherosclerotic plaques causing ruptured plaques and thrombosis (Lehr et al., 1993) **[Figure 2]**. Nicotine affects the hemodynamic parameter of the heart, increasing heart rate and smoking mediated blood pressure (Nicod et al., 1984). Atherosclerosis causes myocardial infarction and stroke. Nicotine mediates the release of adrenal catecholamine, which causes increased heart rate by lowering the coronary blood flow that increases myocardial contractibility, then the heart demands more oxygen, which may lead to myocardial ischemia. (Cryer et al., 1976; Laustiola et al., 1988). Adrenaline also causes high blood pressure, the most common risk factor for coronary heart disease. Nicotine induced catecholamine, promotes lypolysis and release of fatty acids that are converted into VLDL by the liver (Hellerstein et al., 1994) increasing serum LDL (bad choles-

EXCLI Journal 2011;10:69-84 – ISSN 1611-2156
Received: February 23, 2011, accepted: May 9, 2011, published: May 12, 2011

terol) and decreasing the levels of HDL (good cholesterol) (Fortman et al., 1986; Stone and Thorpe, 1985). Carbon monoxide (CO_2) has a strong affinity for hemoglobin (Hb) (Turner et al., 1986). Thus, the oxygen carrying capacity of the blood to the heart gets lowered. Due to an insufficient amount of O_2 to the heart, myocardial metabolism gets disturbed resulting in excessive heart work, leading to the MI (Garland et al., 1985), indicating that the angina pectoris is mostly precipitated by hemodynamic factors (Haerem et al., 1974).

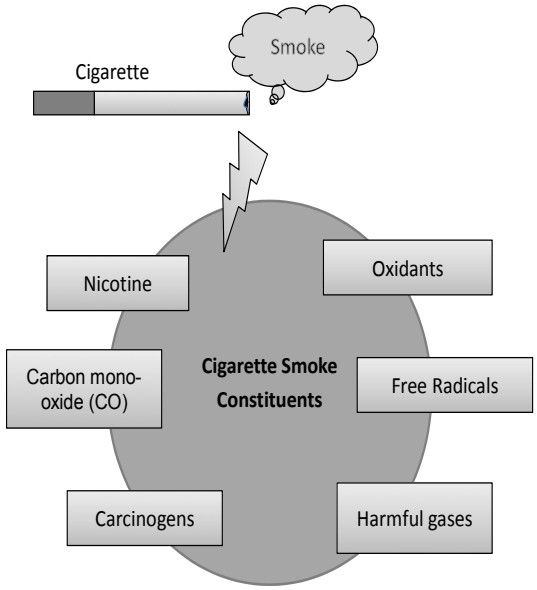

Figure 1: Tobacco smoke constituents

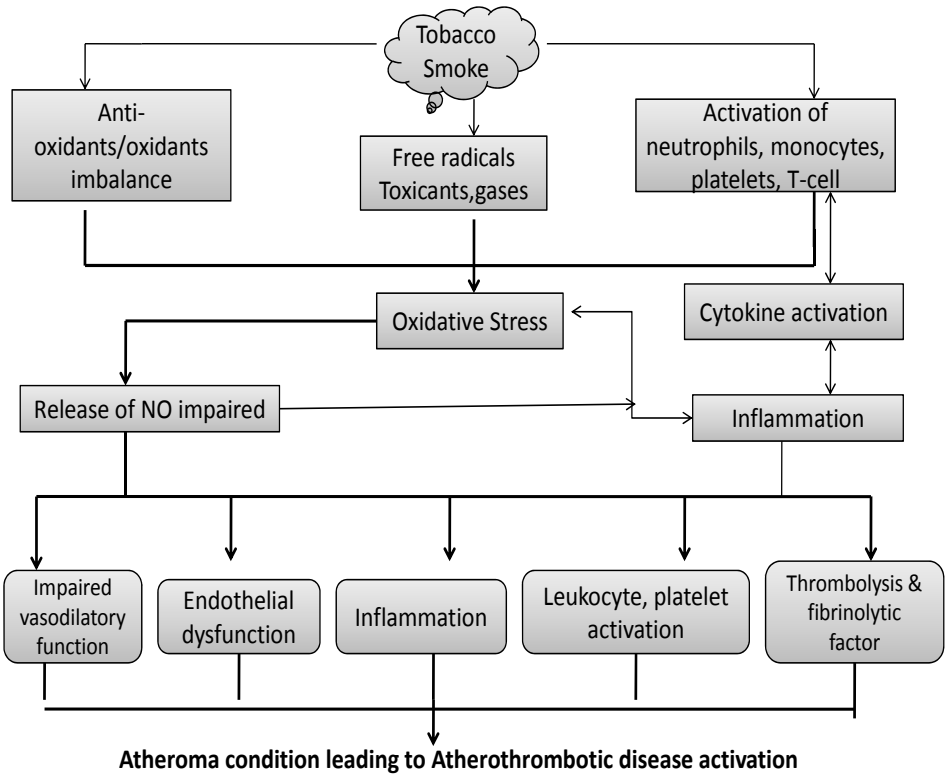

Figure 2: A possible pathophysiology of tobacco smoke induced cardiovascular disease (cardiovascular dysfunction)
Oxidants/anti-oxidants, radicals & other harmful contents of tobacco smoke activate the neutrophil, monocyte, platelets, T-cell induces cytokine activation leading to inflammation. Contents of tobacco smoke create oxidative stress which impairs the normal function of NO like (Impaired vasodilatory function, endothelial dysfunction, inflammation, leukocyte, platelet activation, thrombolysis & fibrolytic factor); all these events are affected leading to atheroma condition which further leads to atherothrombotic disease.

EXCLI Journal 2011;10:69-84 – ISSN 1611-2156
Received: February 23, 2011, accepted: May 9, 2011, published: May 12, 2011

- ***Cerebrovascular disease***

In the case of cerebrovascular disease, stroke mainly has been shown to be associated with the tobacco smoking (Nicotine) (Mazzone et al., 2010). In stroke a man loses his/her thinking ability/movement/ speech and the senses. Smokers have double risk of strokes than never smokers. Smoking associated risk of stroke may be associated with the atherogenic effects or high blood pressure (Mazzone et al., 2010). According to a recent study on the hippocampus, nicotine impairs estrogen receptor-mediated phosphorylation of a cyclic-AMP element binding protein, an event necessary for neuronal survival and also exacerbates ischemic damage (Raval et al., 2011).

- ***Abdominal Aortic Aneurysm (AAA)***

Tobacco **s**moking is the important risk factor for AAA (Nordon et al., 2011, Stolle et al., 2010). Atherosclerosis in the abdominal aortic region increases the risk of the aneurysm in the abdominal aortic region leading to AAA (Burns, 2003). Death rate is 2-3 times higher in those who quit smoking than a never smoker (Hajek et al., 2002). Atherosclerosis is the precursor for AAA. Aortic aneurysm in an animal model shows smooth muscle cell density decreased in medial layer with increased p53 (Holmes et al., 1996), smoking is also related to the inactivation of the alpha 1-anti trypsin leading to the theory that the inhibition of alpha 1-anti trypsin may lead to AAA (Starpetti et al., 1987). A recent study suggests that the formation and severity of the AAA in hypertensive apolipoprotein E [ApoE(-/-)] mice are accelerated by exposure to the mainstream smoke and the matrix metalloproteinases (MMP)-2, -3, -8, -9, and -12 in the abdominal aortas are highly expressed in angiotensin (Ang II) treated mice together with smoke exposure. And the proteolytic activity of MMP-2 and MMP-9 was also enhanced in Ang II-treated mice exposed to tobacco smoke (Nordon et al., 2011).

- ***Peripheral Vascular Disease (PVD)***

Tobacco smoking (nicotine) is a very important risk factor for PVD, mainly Buerger's disease or thromboangiitis obliterans (Highlander et al., 2011) in younger smokers and it becomes symptomatic through claudication, rest pain, ulcers and gangrene (Lawrence et al., 2008; Quintas and Albuquerque, 2008). This disease is an inflammatory occlusive disorder, which causes swelling of the small and medium-sized arteries (sometimes the veins) in the feet and legs (Highlander et al., 2011). It is more common in young smokers especially aged 20 to 40. It's a narrowing of arteries in the extremities caused by blocked arteries, which reduce blood circulation mainly occurs in leg and feet causing pain while walking and resting (Buerger's Disease) (Winstanley et al., 1995). Nine out of ten people with this disease are smokers. This disease is associated with atherosclerosis. In another word, atherosclerosis might be a primary consequence in the development of PVD (Constans et al., 2010). Moreover, the Buerger's disease and atherosclerosis may be associated with the endothelial dysfunction (Idei et al., 2011).

Tobacco smoking and chronic obstructive pulmonary disease (COPD)

Smoking is the major cause of COPD. Approx. 80-90 % of COPD is caused due to smoking (Sethi et al., 2000). Tobacco smoke increases the risk of dying from COPD by ten times (Kim et al., 2011, Streck et al., 2010). About 50 % of COPD patients are active cigarette smokers (van Dijk et al., 2010). Several destructive processes are involved in the pathobiology of COPD, including: inflammation, extracellular matrix destruction (protease and anti-protease imbalance) and oxidative stress (oxidant and anti-oxidant imbalance). Tobacco smoking is strongly associated with COPD. In the case of COPD lung compartments mainly involve diseases relating to airway (chronic bronchitis) and parenchymatous destruction (emphysema) (Ferrara, 2011; Sethi and Rochester, 2000).

EXCLI Journal 2011;10:69-84 – ISSN 1611-2156
Received: February 23, 2011, accepted: May 9, 2011, published: May 12, 2011

Cigarette smoke contains approximately $(10)^{17}$ oxidant molecules (per-oxides, NO) per puff (Pryor et al., 1993). Chronic oxidative stress caused by cigarette smoking, induces mucus secretion and inhibits cystic fibrosis transmembrane conductance regulator function. The increased mucus viscosity renders the airways susceptible to bacterial infections, a hallmark of chronic bronchitis (Cantin, 2010). Due to oxidative stress alveolar macrophages get activated and release neutrophil chemotactic factors (Praticò et al., 1998) such as LTB4, IL-8 (Keatings et al., 1996; Zakrzewski et al., 1987). Then these inflammatory cells release proteases (MMPs, neutrophil elastase) (Shapiro, 1994). By stimulating CD+8Th cells, it releases chemokines (IFN-γ, IL-4, IL-13) and perforins (Barnes, 1996). Neutrophil elastase proteolyses the alveolar elastin, leading to alveolar wall destruction causing emphysema and mucus hypersecretion, which is a prominent feature of COPD (Finkelstein et al., 1995). Neutrophil elastase and MMPs accounts for most of the protease and anti-protease imbalances in COPD. α -1 anti-trypsin is the inhibitor of neutrophil elastase, but individuals are most susceptible to emphysema if they have a congenital deficiency of α-1 anti-trypsin **[Figure 3]** (Stoller and Aboussouan, 2005). Several genomic studies regarding smoking associated COPD are under investigation. According to (Sood et al., 2010) there is a link between wood smoke exposure and aberrant promoter methylation of the p16, or GATA4 genes, which synergistically increase the risk for reduced lung function in cigarette smokers. Another study by Ishii et al. (2011) proposes that a serotonin transporter gene, SLC6A4, is thought to be related to nicotine dependence and depression, which is one of the comorbidity of chronic obstructive pulmonary disease (COPD).

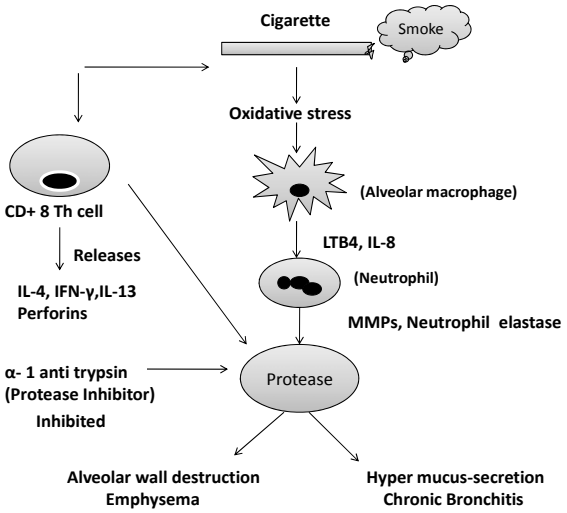

Figure 3: A possible mechanism of tobacco smoke induced Chronic Obstructive Pulmonary Disease (COPD): Oxidants of tobacco smoke activate the alveolar macrophages that activate neutrophils and also release neutrophil chemotactic factors like IL-8, LTB4, then the neutrophils release protease that breaks down the tissues in the lung causing emphysema leading to chronic mucus hypersecretion (chronic bronchitis). Activity of protease inhibitor (α-1 anti-trypsin) gets impaired. CD+8 cells may also be involved in this cascade.

Tobacco smoking and diabetes

Cigarette smoking is an independent modifiable risk factor for development of diabetes (Zhang et al., 2011; Jee et al., 2010; XIE et al., 2009). 50 % of smokers are more likely to develop diabetes compared to non-smokers (American Council on Science and Health, 2007). Smoking has been identified as a risk factor for insulin resistance, which can lead to diabetes type-2 (insulin-independent). In a type-2 diabetes the body does not produce enough insulin or insulin produced by the body does not work properly hence called insulin resistance. Cigarette smoke damages blood vessels, which impair insulin sensitivity by reducing the blood flow in muscle tissue (Reaven and Tsao, 2003; Targher et al., 1997). Diabetes is associated with several other further clinical problems like retinopathy, gangrene, kidney failure and blindness. Tobacco smoking can make all these problems worse (Targher, 2005; Utah Department of Health, 26 September 2007),

although the exact mechanism is still not fully understood.

Tobacco smoking and tuberculosis (TB)

Association between tobacco smoking and tuberculosis was first observed in 1918 (Webb, 1918; WHO, 2003). Active smoking is significantly associated with TB infection and disease (Leung et al., 2010) (Wen et al., 2010) while second hand smoking is associated with tuberculosis infections in children and younger people (Leung et al., 2010). Up to one in five deaths from TB could be avoided if patients were not smokers (Tobacco & Tuberculosis Fact sheet 07). Tobacco smoking is the solid etiological factor for the accelerated decline in the lung function (Ross et al., 2010). Pathophysiology of tobacco smoking associated TB may be related to the several possible mechanisms, such as impairment in the immune response, CD4 lymphopenia (Altet et al., 1996), hormonal imbalances, disruption of cilia function (Buskin et al., 1994), morphological and functional changes in alveolar macrophages (Davies et al., 2006), so it may be a causal factor for an individual to be easily infected with mycobacterium tuberculosis leading to pulmonary tuberculosis. However, the exact pathophysiology of smoking associated tuberculosis is still not well understood.

Tobacco smoking and arthritis (RA)

Cigarette smoking is a solid risk factor for rheumatoid arthritis (RA) (Källberg et al., 2011; Okamoto et al., 2011; Sugiyama et al., 2010). Cigarette smoke produces several oxidants (super-oxides, hydroxyl ion, etc.), which create oxidant and anti-oxidant imbalance that may activate redox sensitive transcription factor such as NF-kB, which in turn reduces the glutathione level (Nguyen et al., 2003). Glutathione (GSH), an anti-oxidant helps protect cells from ROS such as free radicals and peroxides (Pompella et al., 2003). Nicotine alters macrophage function (pinocytosis, endocytosis, microbial killing and reducing TNF-α secretion induced by LPS) (Green and Carolin, 1967). Synovial cells possess aromated hydrocarbon receptors for polycyclic aromatic hydrocarbons (PAHs) released from tobacco smoking, after the binding of PAHs to AhRs on synovial fibroblast-like cells; these cells release several pro-inflammatory cytokines and chemokines in excess like 1L-1α, IL-1β, IL-6, IL-8 and CCR20. IL-1 and IL-6 induces differentiation of Th17 cells, which finally releases 1L-17, then induces IL-1, IL-6 and TNF-α release from macrophages (Onozaki, 2009). Tobacco smoking decreases the levels of anti-inflammatory cytokines, such as IL-10 (Arnson et al., 2010). This acute inflammatory reaction leads to chronic inflammation under the influence of genetic factors, hormones leading to RA**.** (Itoh et al., 2007a, b) **[Figure 4].** According to a study, high-grade inflammatory diseases associate with active rheumatoid arthritis (Gasparyan et al., 2011). PAD2 and PAD4, genes encoding (Peptidyl Arginine Deiminase) are expressed in the synovium of RA patients (Foulquier et al., 2007; Dong et al., 2007) whereas PAD4 is highly expressed in the synovium and found to be associated with the development of RA. PAD4 is an estrogen dependent (Buchan et al., 1988) while smoking has anti-estrogenic effects through the formation of inactive 2-hydroxy catechu estrogens (Baron et al., 1990), which would counteract PADs. Tobacco smoke increases the risk of citrullination that is catalyzed by PAD enzyme. These citrullinated antigens may be helpful for exploring the pathogenic mechanisms. Antibodies to the citrullinated proteins are present in HLA ‘shared epitope’ alleles (SE) positive patients (Goeldner et al., 2011; Wegner et al., 2010). It was observed that without any treatment smokers are affected by osteoarthritis (OA) leukocytosis (biomarker of cardiovascular risk) (Bartolone et al., 2010).

EXCLI Journal 2011;10:69-84 – ISSN 1611-2156
Received: February 23, 2011, accepted: May 9, 2011, published: May 12, 2011

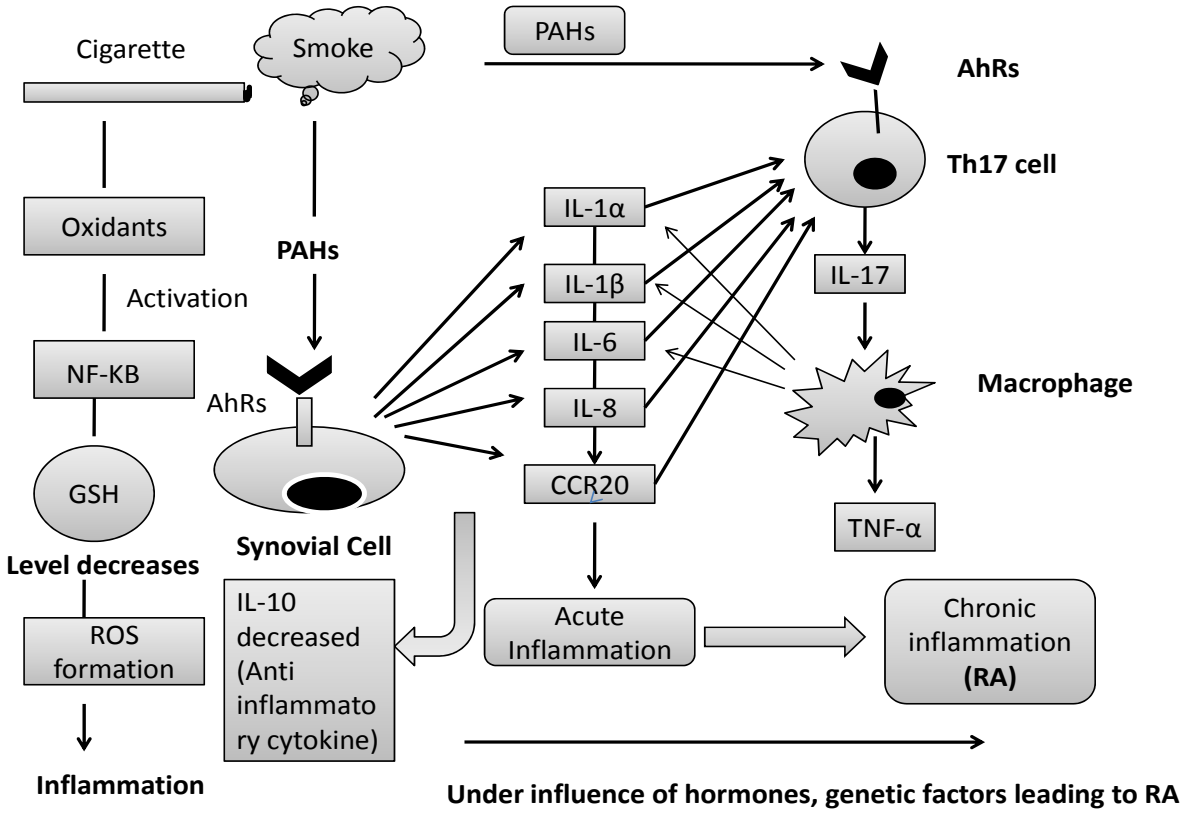

Figure 4: A possible pathophysiology of tobacco smoke induced rheumatoid arthritis (RA). Oxidants from tobacco smoke activate the transcription factor NF-κB which decreases the level of glutathione, then reactive oxygen species (ROS) level increases leading to Inflammation. **In detail** tobacco smoke activates pro-inflammatory cytokines and chemokines mediated by the binding of polycyclic aromatic hydrocarbon (PAHs) to the aromatic hydrocarbon receptors on synovial cells, then these cytokines and chemokines induce T-helper 17 cells (Th17) Th17 cells induces IL-17, then the IL-17 induces IL-1, IL-6, and TNF-α production from macrophage. Now the acute inflammation process leads to chronic inflammation under the effects of several factors like hormones, genetic factors.

Tobacco smoking and impotency

Tobacco smoking impairs the erection of the penis, causing erectile dysfunction ED, which leads to impotency (Chan et al., 2010). It has been noticed that penile blood flow in smokers is lower than non-smokers, which is the main cause of impotency (Rosen et al., 1991; Condra et al., 1986,). Use of tobacco smoke may increase the likelihood of moderate or complete ED by at least two-fold and heavy smokers are more likely to be impotent (Mirone et al., 2002; McVary et al., 2001). Smoking predisposes smokers to arterial risk factors causing atherosclerosis by damaging the vessels (Enevoldsen et al., 2011; Jiang et al., 2010). Atherosclerotic changes increase the susceptibility of impotency to the smokers (Odriozola et al., 2010). However, the exact pathophysiology of smoking associated impotency is still unclear (McVary et al., 2001).

Tobacco smoking and male infertility

Smoking is associated with men's infertility by affecting the sperm production, motility, morphology and spermatogenesis (Monoski et al., 2002). Smoke-induced toxins primarily hamper sperm motility and seminal fluid quality causing asthenozoospermia (Gaur et al., 2010). Tobacco smoking impairs the sperm DNA integrity and

nuclear maturation (Niu et al., 2010). CO, nicotine, polycyclic aromatic hydrocarbons and other oxidants cause oxidative damage, which further damage DNA in spermatozoa (Shen et al., 1997). Tobacco smoking also affects seminal plasma leucocytes then; it generates excess free oxygen radicals, which may cause sperm DNA fragmentation (Koskimies et al., 2010). Nicotine content in tobacco smoke also seems to be a potent factor that can alter the fertility potential of man by inducing the membrane impairments, altering the GSH metabolism cycle, changing the sperm morphology and motility, and also by inducing the DNA fragmentation (Arabi and Shareghi, 2005). The extent of oxidative damage among smokers was associated with the decrease in anti-oxidants defenses in the sperm of infertile males (Pasqualotto et al., 2008). Oxidative stress by cigarette smoking may have significant inverse effect on the protamine 1 (P1) and 2 (P2), a nuclear protein necessary for proper sperm chromatin condensation and subsequent male fertility (Hammadeh et al., 2010). The oxidants of tobacco smoke lower the zinc level that is required for the sperm chromatin stability in the semen of smokers (Liu et al., 2010). Serum estradiol (E2) and prolactins are increased in smokers as compared to non-smokers (Attia et al., 1989). Estradiol impairs spermatogenesis, E2 level increases catecholamine level, which produces ischemia of seminiferous tubules (Klaiber and Broverman, 1988). A dose response relationship is found between smoking and testosterone. Luteinizing hormone (LH) and the LH free testosterone ratios were observed (Ramlau-Hansen et al., 2007). According to Kapoor and Jones (2005) smoking adversely affects the testosterone level due to changes in plasma-binding capacity than the direct effect of nicotine on androgens.

Tobacco smoking and Alzheimer's disease (AD)

Tobacco smoking is a modifiable risk factor for Alzheimer's disease (Rusanen et al., 2011). Heavy smoking almost doubled the risk of AD (Ott et al., 1998). Alzheimer's disease is a brain neurodegenerative disorder causing dementia, memory loss, disability, impairment of intellectual function (Fratiglioni and Wang, 2000). Vascular risk factor of an individual, such as hypertension, high blood pressure, atherosclerosis, arterial fibrillation, stroke at a time of current AD impacts on the rate of progression of AD (Mielke et al., 2007). However, the risk of CVD is a major risk factor for AD (Lightwood et al., 2001). Tobacco smoking induces oxidant and anti-oxidant imbalance creating oxidative stress leading to inflammation causing tissue injury (Isik et al., 2007; Burke and Fitzgerald, 2003). ROS (Reactive oxygen species) generations cause neurodegeneration within the brain tissues because the brain is the more susceptible to oxygen free radical damage (Polidori et al., 2007). Midlife smoking is associated with an increased risk of dementia and AD later in life only among those individuals carrying the apolipoprotein (APOE ε4 allele) (Rusanen et al., 2010), although the pathophysiology of smoking related AD remains to be elucidated.

CONCLUSION

Tobacco smoking is pandemic. Besides, the impaired oral health and malignancy, it is the cause of several chronic and harmful diseases. Long term cigarette exposure, whether active or passive also makes a person more susceptible to easily get developed various diseases like cardiovascular diseases, diabetes, tuberculosis, chronic obstructive pulmonary disease (COPD), impotency, infertility, Alzheimer's disease, arthritis, etc. Tobacco smoking induced atherosclerotic syndromes are the precursor for cardiovascular diseases like coronary artery syndromes (myocardial infarction, stable angina, and sudden death), cerebrovascular disease, abdominal aortic aneurysm, and peripheral vascular disease, diabetes and impotency. There is a major role of smoking induced oxidants and anti-oxidants imbalance in causing the COPD, arthritis and tuberculosis. In case of COPD, MMPs, neu-

trophil elastase, and α-1 anti-trypsin should be mainly focused to reveal the exact pathophysiology of smoking induced COPD. Tobacco smoking is the solid etiological factor for the accelerated decline in the lung function, so it may be a causal factor for an individual to be infected with mycobacterium tuberculosis leading to pulmonary tuberculosis. It might be a possible hypothesis for the smoking induced tuberculosis. However, there is a conflict in case of smoking associated Alzheimer's disease, most of the studies are in favor of smoking induced AD, but some are not. To overcome with this problem, a long term follow-up study should be done. Nicotine replacement therapy should be encouraged for smoking cessation. Smoker awareness programmes regarding all these diseases should be conducted as well as the anti-smoking advertisement must be made and promoted worldwide. Participants in our scientific research trial should be rewarded; it will be helpful to motivate the smokers to be included in our research.

REFERENCES

Altet MN, Alcaide J, Plans P, et al. Passive smoking and risk of pulmonary tuberculosis in children immediately following infection. A case control study. Tubercle Lung Dis 1996;77:537–44.

American Council on Science and Health, 26 September 2007. The scoop on smoking. "Diabetes".

Arabi M, Shareghi B. Anti-fertility effect of nicotine. Zhonghua Nan Ke Xue 2005;11: 323-30.

Arnson Y, Shoenfeld Y, Amital H. Effects of tobacco smoke on immunity, inflammation and autoimmunity. J Autoimmun 2010; 34:258-65.

Attia AM, El-Dakhly MR, Halawa FA, Ragab NF, Mossa MM. Cigarette smoking and male reproduction. Arch Androl 1989;23: 45-9.

Barbieri SS, Zacchi E, Amadio P, Gianellini S, Mussoni L, Weksler BB, Tremoli E. Cytokines present in smoker's serum interact with smoke components to enhance endothelial dysfunction. Cardiovasc Res 2011 Mar 1. [Epub ahead of print].

Barnes PJ. Mechanism of action of glucocorticoids in asthma. Am J Respir Crit Care Med 1996;154:S21–S27.

Baron JA, La Vecchia C, Levi F. The antiestrogenic effect of cigarette smoking in women. Am J Obstet Gynecol 1990;162**:** 502-14.

Bartolone S, Calzavara E, Russo GA, Carnì A, Mannucci C, Pieratti A, Caputi AP, Calapai G. White cells count in smokers affected by rheumatic diseases. Rheumatol Int 2010 Jul 30. [Epub ahead of print].

Benowitz NL. Cigarette smoking and cardiovascular disease: pathophysiology and implications for treatment. Progr Cardiovasc Dis 2003;46:91–111.

Bišanović S, Mehić B, Sivić S. Status of lipids and the frequency diseases of cardiovascular origin in smokers according to the length period of smoking and a number of cigarettes smoked daily. Bosn J Basic Med Sci 2011;11:46-51.

Booyse FM, Osikowicz G, Quarfoot AJ. Effect of chronic oral consumption of nicotine on the rabbit aortic endothelium. Am J Pathol 1981;102:229-38.

Boyle EM, Lille ST, Allaire E, Clowes AW, Verrier ED. Endothelial cell injury in the cardiovascular surgery: Atherosclerosis. Ann Thoracic Surg 1997;63:885-94.

Buchan G, Barrett K, Turner M, Chantry D, Maini R, Feldmann M. Interleukin-1 and tumour necrosis factor mRNA expression in rheumatoid arthritis: prolonged production of IL-1 alpha. Clin Exp Immunol 1988;73: 449-55.

Burke A, Fitzgerald GA. Oxidative stress and smoking-induced vascular injury. Progr Cardiovasc Dis 2003;46:79–90.

Burns DM. Epidemiology of smoking-induced disease. Progr Cardiovasc Dis 2003;46:11–29.

Buskin SE, Gale JL, Weiss NS, Nolan CM. Tuberculosis risk factors in adults in King County, Washington, 1988 through 1990. Am J Pub Health 1994;84:1750–6.

Cantin AM. Cellular response to cigarette smoke and oxidants: adapting to survive. Proc Am Thorac Soc 2010;7:368-75.

Celermajer DS, Adams MR, Clarkson P et al. Passive smoking and impaired endothelium-dependent arterial dilatation in healthy young adults. New Engl J Med 1996;334: 150-4.

Chan SS, Leung DY, Abdullah AS, Lo SS, Yip AW, Kok WM, Ho SY, Lam TH. Smoking-cessation and adherence intervention among Chinese patients with erectile dysfunction. Am J Prev Med 2010;39:251-8.

Condra M, Morales A, Owen JA, Surridge DH, Fenemore J. Prevalence and significance of tobacco smoking in impotence. Urology 1986;27:495–8.

Constans J, Solanilla A, Boulon C, Conri C. Peripheral occlusive arterial disease in the young patient. Presse Med 2010;39:11-6.

Cryer PE, Haymond MW, Santiago JV, Shah SD. Norepinephrine and epinephrine release and adrenergic mediation of smoking associated hemodynamic and metabolic events. N Engl J Med 1976;295:573-7.

Davies PD, Yew WW, Ganguly D, Davidow AL, Reichman LB, Dheda K, Rook GA. Smoking and tuberculosis: the epidemiological association and immunopathogenesis. Trans R Soc Trom Med Hyg 2006;100:291-8.

Dong S, Zhang Z, Takahara H. Estrogen-enhanced peptidylarginine deiminase type IV gene (PADI4) expression in MCF-7 cells is mediated by estrogen receptor-alpha-promoted transfactors activator protein-1, nuclear factor-Y, and Sp1. Mol Endocrinol 2007;21:1617-29.

Enevoldsen MS, Henneberg KA, Jensen JA, Lönn L, Humphrey JD. New interpretation of arterial stiffening due to cigarette smoking using a structurally motivated constitutive model. J Biomech 2011;44:1209-11.

Ferrara A. Chronic obstructive pulmonary disease. Radiol Technol 2011;82:245-63.

Finkelstein R, Fraser RS, Ghezzo H, et al. Alveolar inflammation and its relation to emphysema in smokers. Am J Respir Crit Care Med 1995;152:1666–72.

Fortman SP, Haskel SL, William PT. Changes in plasma high density lipoprotein cholesterol after changes in cigarette use. Am J Epidemiol 1986;124:706-10.

Foulquier C, Sebbag M, Clavel C, Chapuy-Regaud S, Al Badine R, Méchin MC, Vincent C, Nachat R, Yamada M, Takahara H, Simon M, Guerrin M, Serre G: Peptidyl arginine deiminase type 2 (PAD-2) and PAD-4 but not PAD-1, PAD-3, and PAD-6 are expressed in rheumatoid arthritis synovium in close association with tissue inflammation. Arthritis Rheum 2007;56:3541-53.

Fratiglioni L, Wang HX. Smoking and Parkinson's and Alzheimer's disease: review of the epidemiological studies. Behav Brain Res 2000;113:117-20.

Garland C, Barrett-Connor E, Saurez L, Criqui MH, Wingard DL. Effect of passive smoking on ischemic heart disease mortality of non-smokers. Am J Epidemiol 1985;121:645-50.

Gasparyan AY, Ayvazyan L, Mikhailidis DP, Kitas GD. Mean platelet volume: A link between thrombosis and inflammation? Curr Pharm Des 2011;17:47-58.

Gaur DS, Talekar MS, Pathak VP. Alcohol intake and cigarette smoking: impact of two major lifestyle factors on male fertility. Indian J Pathol Microbiol 2010;53:35-40.

Goeldner I, Skare TL, de Messias Reason IT, Nisihara RM, Silva MB, da Rosa Utiyama SR. Association of anticyclic citrullinated peptide antibodies with extra-articular manifestations, gender, and tabagism in rheumatoid arthritis patients from southern Brazil. Clin Rheumatol 2011 Feb 22. [Epub ahead of print].

Grassi D, Desideri G, Ferri L, Aggio A, Tiberti S, Ferri C. Oxidative stress and endothelial dysfunction: say no to cigarette smoking! Curr Pharm Des 2010;16:2539-50.

Green GM, Carolin D: The depressant effect of cigarette smoke on the in vitro antibacterial activity of alveolar macrophages. N Engl J Med 1967;276**:**421-7.

Haerem JW. Platelet aggregates and mural microthrombin in early stages of acute, fatal coronary diseases. Thromb Res 1974;5:243-9.

Hajek P, Taylor TZ, Mills P. Brief intervention during hospital admission to help patients to give up smoking after myocardial infarction and bypass surgery: randomized controlled trial. BMJ 2002;324:87–9.

Hammadeh ME, Hamad MF, Montenarh M, Fischer-Hammadeh C. Protamine contents and P1/P2 ratio in human spermatozoa from smokers and non-smokers. Hum Reprod 2010;25:2708-20.

Hammond EC, Horn D. Smoking and death rates- report on forty-four months of follow up of 187,783 men. 2: Death rates by cause. J Am Med Assoc 1958;166:1294–1308.

Hellerstein MK, Benowitz NL, Neese RA. Effects of cigarette smoking and its cessation on lipid metabolism and energy expenditure in heavy smokers J Clin Invest 1994; 93:256-72.

Highlander P, Southerland CC, Von Herbulis E, Gonzalez A. Buerger disease (thromboangiitis obliterans): a clinical diagnosis. Adv Skin Wound Care 2011;24:15-7.

Higman DJ, Greenhalgh RM, Powell JT. Smoking impairs endothelium-dependent relaxation of sephenous vein. Brit J Surg 1993;80:1242-5.

Holmes DR, López-Candales A, Liao S, Thompson RW. Smooth muscle apoptosis and p53 expression in human abdominal aortic aneurysm. Ann NY Acad Sci 1996; 800:286-7.

Idei N, Nishioka K, Soga J, Hidaka T, Hata T, Fujii Y, Fujimura N, Maruhashi T, Mikami S, Teragawa H, Kihara Y, Noma K, Chayama K, Higashi Y. Vascular function and circulating progenitor cells in thromboangitis obliterans (Buerger's disease) and atherosclerosis obliterans. Hypertension 2011;57:70-8.

Ishii T, Wakabayashi R, Kurosaki H, Gemma A, Kida K. Association of serotonin transporter gene variation with smoking, chronic obstructive pulmonary disease, and its depressive symptoms. J Hum Genet 2011;56:41-6.

Isik B, Ceylan A, Isik R. Oxidative stress in smokers and non-smokers. Inhal Toxicol 2007;19:767-9.

Itoh Y, Hayashi H, Miyazawa K, Kojima S, Akahoshi T, Onozaki K. 17beta-estradiol induces IL-1alpha gene expression in rheumatoid fibroblast-like synovial cells through estrogen receptor alpha (ERalpha) and augmentation of transcriptional activity of Sp1 by dissociating histone deacetylase 2 from ERalpha. J Immunol 2007a;178:3059-66.

Itoh Y, Hayashi H, Xu J, Takii T, Miyazawa K, Ariga H, Akahoshi T, Waguri-Nagaya Y, Otsuka T, Okamoto T, Onozaki K. Dihydrotestosterone inhibits tumor necrosis factor alpha induced interleukin-1alpha mRNA expression in rheumatoid fibroblast-like synovial cells. Biol Pharm Bull 2007b;30:1140-3.

Jee SH, Foong AW, Hur NW, Samet JM. Smoking and risk for diabetes incidence and mortality in Korean men and women. Diabetes Care 2010;33:2567-72.

Jiang CQ, Xu L, Lam TH, Lin JM, Cheng KK, Thomas GN. Smoking cessation and carotid atherosclerosis: the Guangzhou Biobank Cohort Study—CVD. J Epidemiol Community Health 2010;64:1004-9.

Källberg H, Ding B, Padyukov L, Bengtsson C, Rönnelid J, Klareskog L, Alfredsson L; EIRA Study Group. Smoking is a major preventable risk factor for rheumatoid arthritis: estimations of risks after various exposures to cigarette smoke. Ann Rheum Dis 2011;70:508-11.

Kapoor D, Jones TH. Smoking and hormones in health and endocrine disorders. Eur J Endocrinol 2005;152:491–9.

Keatings VM, Collins PD, Scott DM, Barnes PJ. Differences in interleukin-8 and tumor necrosis factor-a induced sputum from patients with chronic obstructive pulmonary disease or asthma. Am J Respir Crit Care Med 1996;153:530-4.

Kim DK, Hersh CP, Washko GR, Hokanson JE, Lynch DA, Newell JD, Murphy JR, Crapo JD, Silverman EK; COPD Gene Investigators. Epidemiology, radiology, and genetics of nicotine dependence in COPD. Respir Res 2011;12:9.

Kiowski W, Linder L, Stoschitzky K, Pfisterer M, Burckhardt D, Burkart F, Bühler FR. Diminished vascular response to inhibition of endothelium -derived nitric oxide and enhanced vasoconstriction to exogenously administered andothelin-1 in clinically healthy smokers. Circulation 1994;90: 27-34.

Klaiber EL, Broverman DM. Dynamics of estradiol and testosterone and seminal fluid indexes in smokers and nonsmokers. Fertil Steril 1988;50:630-4.

Kool MJ, Hoeks AP, Struijker Boudier HA, Reneman RS, Van Bortel LM. Short- and long-term effects of smoking on arterial wall properties in habitual smokers. J Am Coll Cardiol 1993;22:1881-6.

Koskimies AI, Savander M, Ann-Marie N, Kurunmäki H. Sperm DNA damage and male infertility. Duodecim 2010;126:2837-42.

Laustiola KE, Lassila R, Kaprio J, Koskenvuo M. Decreased β-adrenergic receptor density and catecholamine response in male cigarette smokers – A study of monozygotic twin pair disordant for smoking. Circulation 1988;78:1234-40.

Lawrence PF, Lund OI, Jimenez JC, Muttalib R. Substitution of smokeless tobacco for cigarettes in Buerger's disease does not prevent limb loss. J Vasc Surg 2008;48:210-2.

Lehr HA, Kröber M, Hübner C, Vajkoczy P, Menger MD, Nolte D, Kohlschütter A, Messmer K. Stimulation of leukocyte/vascular endothelium interaction by oxidized low-density lipoproteins hairless mice. Involvement of CD11b/CD 18 adhesion receptors complex. Lab Invest 1993;68:388-95.

Leone A. Smoking and hypertension: Independent or additive effects to determining vascular damage? Curr Vasc Pharmacol 2010 Dec 14. [Epub ahead of print]

Leung CC, Lam TH, Ho KS, Yew WW, Tam CM, Chan WM, Law WS, Chan CK, Chang KC, Au KF. Passive smoking and tuberculosis. Arch Intern Med 2010;170: 287-92.

Lightwood J, Fleischmann KE, Glantz SA. Smoking cessation in heart failure: it is never too late. J Am Coll Cardiol 2001; 37:1683–4.

Liu RZ, Gao JC, Zhang HG, Wang RX, Zhang ZH, Liu XY. Seminal plasma zinc level may be associated with the effect of cigarette smoking on sperm parameters. J Int Med Res 2010;38:923-8.

Mazzone P, Tierney W, Hossain M, Puvenna V, Janigro D, Cucullo L. Pathophysiological impact of cigarette smoke exposure on the cerebrovascular system with a focus on the blood-brain barrier: expanding the awareness of smoking toxicity in an underappreciated area. Int J Environ Res Public Health 2010;7:4111-26.

McVary KT, Carrier S, Wessells H; Subcommittee on Smoking and Erectile Dysfunction Socioeconomic Committee, Sexual Medicine Society of North America. Smoking and erectile dysfunction: evidence based analysis. J Urol 2001;166:1624-32.

Mielke MM, Rosenberg PB, Tschanz J, Cook L, Corcoran C, Hayden KM, Norton M, Rabins PV, Green RC, Welsh-Bohmer KA, Breitner JC, Munger R, Lyketsos CG. Vascular factors predict rate of progression in Alzheimer disease. Neurology 2007;69: 1850-8.

Mirone V, Imbimbo C, Bortolotti A, Di Cintio E, Colli E, Landoni M, Lavezzari M, Parazzini F. Cigarette smoking as risk factor for erectile dysfunction: results from an Italian epidemiological study. Eur Urol 2002;41:294-7.

Monoski M, Nudell DM , Lipshultz LI. Effects of medical therapy, alcohol, and smoking on male fertility. Contemp Urol 2002;June:57-63.

Nguyen C, Teo JL, Matsuda A, Eguchi M, Chi EY, Henderson WR Jr, Kahn M. Chemogenomic identification of Ref-1/AP-1 as a therapeutic target for asthma. Proc Natl Acad Sci U S A 2003;100:1169-73.

Nicod P, Rehr R, Winniford MD, Campbell WB, Firth BG, Hillis LD. Acute systemic and coronary hemodynamic and serologic responses to cigarette smoking in long-term smokers with atherosclerotic coronary artery disease. J Am Coll Cardiol 1984;4: 964–71.

Niu ZH, Liu JB, Shi TY, Yuan Y, Shi HJ. Impact of cigarette smoking on human sperm DNA integrity. Zhonghua Nan Ke Xue 2010;16:300-4.

Nordon IM, Hinchliffe RJ, Loftus IM, Thompson MM. Pathophysiology and epidemiology of abdominal aortic aneurysms. Nat Rev Cardiol 2011;8:92-102.

Noronha-Dutra AA, Epperlein MM, and Woolf N. Effect of cigarette smoking on cultured human endothelial cells. Cardiovasc Res 1993;27:774-8.

Odriozola AA, Quintanilla MG, Arias JG, Tamayo AL, González GI. Vascular erectile dysfunction. Arch Esp Urol 2010;63:611-20.

Okamoto S, Adachi M, Chujo S, Yamada K, Akita K, Itoh S, Takii T, Hayakawa K, Onozaki K. Etiological role of cigarette smoking in rheumatoid arthritis: Nasal exposure to cigarette smoke condensate extracts augments the development of collagen-induced arthritis in mice. Biochem Biophys Res Commun 2011;404:1088-92.

Onozaki K. Etiological and biological aspects of cigarette smoking in rheumatoid arthritis. Inflamm Allergy Drug Targets 2009;8:364-8.

Ott A, Slooter AJ, Hofman A, van Harskamp F, Witteman JC, Van Broeckhoven C, van Duijn CM, Breteler MM. Smoking and risk of dementia and Alzheimer's disease in a population based cohort study: the Rotterdam Study. Lancet 1998;351(9119): 1840-3.

Pasqualotto FF, Umezu FM, Salvador M, Borges E Jr, Sobreiro BP, Pasqualotto EB. Effect of cigarette smoking on anti-oxidant level and presence of leukoctospermia in infertile men: A prospective study. Fertil Steril 2008;90:278-83.

Pettiti DB, Kipp H. The leukocyte count: Association with intensity of smoking and persistence of effect after quitting. Am J Epidemiol 1986;123:89-95.

Polidori MC, Griffiths HR, Mariani E, Mecocci P. Hallmarks of protein oxidative damage in neurodegenerative diseases: focus on Alzheimer's disease. Amino Acids 2007;32:553–9.

Pompella A, Visvikis A, Paolicchi A, De Tata V, Casini AF. The changing faces of glutathione, a cellular protagonist. Biochem Pharmacol 2003;66:1499–503.

Praticò D, Basili S, Vieri M, Cordova C, Violi F, Fitzgerald GA. Chronic obstructive pulmonary disease is associated with an increase in urinary levels of isoprostane F2a-111, an index of oxidant stress. Am J Respir Crit Care Med 1998;158:1709–14.

Pryor WA, Stone K. Oxidants in cigarette smoke. Radicals, hydrogen peroxide, peroxynitrate, and peroxynitrite**.** Ann N Y Acad Sci 1993;686:12-27; discussion 27-8.

Quintas A, Albuquerque R. Buerger's disease: current concepts. Rev Port Cir Cardiotorac Vasc 2008;15:33-40.

Ramlau-Hansen CH, Thulsturp AM, Aggerholm AS, Jensen MS, Toft G, Bonde JP. Is smoking a risk factor for decreased semen quality? A cross-sectional analysis Hum Reprod 2007;22:188-96.

Raval AP, Hirsch N, Dave KR, Yavagal DR, Bramlett H, Saul I. Nicotine and estrogen synergistically exacerbate cerebral ischemic injury. Neuroscience 2011;181: 216-25.

Reaven G, Tsao PS. Insulin resistance and compensatory hyperinsulinemia. The key player between cigarette smoking and cardiovascular disease? J Am Coll Cardiol 2003;41:1044-7.

Rosen MP, Greenfield AJ, Walker TG, Grant P, Dubrow J, Bettmann MA, Fried LE, Goldstein I. Cigarette smoking: an independent risk factor for atherosclerosis in the hypogastric-cavernous arterial bed of men with arteriogenic impotence. J Urol 1991;145:759–63.

Ross J, Ehrlich RI, Hnizdo E, White N, Churchyard GJ. Excess lung function decline in gold miners following pulmonary tuberculosis. Thorax 2010;65:1010-5.

Rusanen M, Kivipelto M, Quesenberry CP Jr, Zhou J, Whitmer RA. Heavy smoking in midlife and long-term risk of Alzheimer disease and vascular dementia. Arch Intern Med 2011;171:333-9.

Sethi JM, Rochester CL. Smoking and chronic obstructive pulmonary disease. Clin Chest Med 2000;21:67–86.

Shapiro SD. Elastolytic metalloproteinases produced by human mononuclear phagocytes: potential roles in destructive lung disease. Am J Respir Crit Care Med 1994;150(Suppl):S160–S164.

Shen HM, China CE, Ni ZY, New AL, Lee BL, Ong CN. Detection of oxidative DNA damage in human sperm and the association with the cigarette smoking. Reprod Toxicol 1997;11:675-80.

Sood A, Petersen H, Blanchette CM, Meek P, Picchi MA, Belinsky SA, Tesfaigzi Y. Wood smoke exposure and gene promoter methylation are associated with increased risk for COPD in smokers. Am J Respir Crit Care Med 2010;182:1098-104.

Stafford RS, Becker CG. Cigarette smoking and atherosclerosis. In: Fuster V, Ross R, Topol EJ (eds). Atherosclerosis and coronary artery disease (pp 303-25). Philadelphia, PA: Lippincott-Raven, 1996.

Starpetti AV, Schultz RD, Feldhause RJ, Cheng SE, Peetz DJ. Factors influencing the enlargement rate of small abdominal aneurysm. J Surg Res 1987;43:211-9.

Stolle K, Berges A, Lietz M, Lebrun S, Wallerath T. Cigarette smoke enhances abdominal aortic aneurysm formation in angiotensin II-treated apolipoprotein E-deficient mice. Toxicol Lett 2010;199:403-9.

Stoller JK, Aboussouan LS**.** Alpha1-antitrypsin deficiency**.** Lancet 2005;365: 2225–36.

Stone MC, Thorpe JM, Plasma fibrinogen - A major coronary risk factor. J R Coll Gen Pract 1985;35:565-9.

Streck E, Jörres RA, Huber RM, Bergner A. Effects of cigarette smoke extract and nicotine on bronchial tone and acetylcholine-induced airway contraction in mouse lung slices. J Investig Allergol Clin Immunol 2010;20:324-30.

Sugiyama D, Nishimura K, Tamaki K, Tsuji G, Nakazawa T, Morinobu A, Kumagai S. Impact of smoking as a risk factor for developing rheumatoid arthritis: a meta-analysis of observational studies. Ann Rheum Dis 2010; 69:70-81.

Talukder MA, Johnson WM, Varadharaj S, Lian J, Kearns PN, El-Mahdy MA, Liu X, Zweier JL. Chronic cigarette smoking causes hypertension, increased oxidative stress, impaired NO bioavailability, endothelial dysfunction, and cardiac remodeling in mice. Am J Physiol Heart Circ Physiol 2011;300:H388-96.

Targher G. How does smoking affect insulin sensitivity? Diabetes Voice, June 2005 Vol 50, Special Issue.

Targher G, Alberiche M, Zenere MB, Bonadonna RC, Muggeo M, Bonora E. Cigarette smoking and insulin resistance in patients with noninsulin-dependent diabetes mellitus. J Clin Endocrinol Metab 1997;82: 3619-24.

Tobacco & Tuberculosis Fact sheet 07. http://www.tobaccofreeunion.org/content/en/8/

Turner JA, Mc Nichol MW, Sillet RW. Distribution of carboxyhemoglobin concentration in smokers and in non-smokers. Thorax 1986;41:25-7.

US Department of Health and Human Services. The health consequences of smoking: cardiovascular disease; a report of the surgeon general. Atlanta, GA. 84-50204, 1983.

Utah Department of Health, 26 September 2007. Tobacco prevention and control program “Tobacco and Diabetes.”

van Dijk WD, Heijdra Y, Scheepers PT, Lenders JW, van Weel C, Schermer TR. Interaction in COPD experiment (ICE): a hazardous combination of cigarette smoking and bronchodilation in chronic obstructive pulmonary disease. Med Hypotheses 2010;74:277 80.

Webb GB. The effect of the inhalation of cigarette smoke on the lungs. A clinical study. Am Rev Tuberc 1918;1:25–7.

Wegner N, Lundberg K, Kinloch A, Fisher B, Malmström V, Feldmann M, Venables PJ. Autoimmunity to specific citrullinated proteins gives the first clues to the etiology of rheumatoid arthritis. Immunol Rev 2010;233:34-54.

Wen CP, Chan TC, Chan HT, Tsai MK, Cheng TY, Tsai SP. Ther reduction of tuberculosis risks by smoking cessation. BMC Infect Dis 2010;10:156.

Winstanley M, Woodward S, Walker N. Tobacco in Australia: Facts and issues 1995. Victoria: Victorian smoking and Health Program, 1995.

World Health Organization. The World health report 2003: Shaping the future. Geneva: WHO, 2003. www.who.int/whr/2003/en/

Xie XT, Liu Q, Wu J, Wakui M. Impact of cigarette smoking in type 2 diabetes development. Acta Pharmacol Sin 2009;30: 784–7.

Zakrzewski JT, Barnes NC, Costello JF, et al. Lipid mediators in cystic fibrosis and chronic obstructive pulmonary disease. Am Rev Respir Dis 1987;136:779–82.

Zhang L, Curhan GC, Hu FB, Rimm EB, Forman JP. Association between passive and active smoking and incident type 2 diabetes in women. Diabetes Care 2011;34: 892-7.