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

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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 pathophysiology.

Table 1: Tobacco smoking associated diseases

| Disease Category | Disease/Sub-disease |
|------------------|---------------------|
| 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) | |
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; Celniker 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; Petitti 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-
terol) and decreasing the levels of HDL (good cholesterol) (Fortman et al., 1986; Stone and Thorpe, 1985). Carbon monoxide (CO₂) 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 O₂ 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 & fibrinolytic factor); all these events are affected leading to atheroma condition which further leads to atherothrombotic disease.
• **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 Anerysm (AAA)**

Tobacco smoking 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).
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 aromatized 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 IL-1α, IL-1β, IL-6, IL-8 and CCR20. IL-1 and IL-6 induces differentiation of Th17 cells, which finally releases IL-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).
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., 2010). 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.

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