

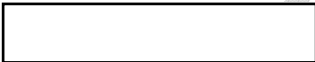
1 **Genetic and Environmental Attributes of Chronic Pancreatitis**

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32 **Abstract**

33 Chronic pancreatitis (CP) is a chronic progressive inflammatory disease of the pancreas.
34 Tropical chronic pancreatitis is a severe form of chronic pancreatitis with multifactorial
35 aetiology. In addition to the growing evidence of attributes of genetic factors, the
36 environmental factors may also play crucial roles in the progression and pathogenesis of
37 chronic pancreatitis as these factors may interact with the genetic components of individuals.
38 Oxidative stress related genes may modify the effects of ambient tobacco smoking and
39 alcohol on chronic pancreatitis. In this review, an endeavour has been made to present an
40 updated account of the contribution of gene environment-interaction on the onset and
41 progression of chronic pancreatitis.

42 **Keywords:** Environmental factors, chronic pancreatitis, Oxidative stress, Smoking, Alcohol

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44 **Running Title:** Environmental factors influence chronic pancreatitis

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53 **Introduction**

54 Chronic pancreatitis (CP) is a progressive inflammatory disorder ultimately leading to
55 irreversible structural changes resulting in functional impairment of exocrine and/or
56 endocrine physiology (1, 2). The existing reports indicate that despite the involvement of
57 some genetic factors, the environmental factors also influence the onset as well as
58 progression of the disease. Alcohol is recognised as the major cause of chronic pancreatitis.
59 In developed countries, 60–70% of patients with CP have a long history of heavy alcohol
60 consumption whereas smoking has been described as an additional risk factor (3-4). Since
61 1982 (5) smoking has been recognized as one of the major risk factors for CP, particularly in
62 alcohol-related CP compared to CP arising from other causes (6). Alcohol is used by a far
63 greater number of people than those who actually go on to develop CP, indicating variable
64 genetic susceptibility.

65 Environmental factors such as cigarette smoking, alcohol, high-fat diets, fossil fuel products
66 and high temperature cooked meat sources may expose the human pancreas to toxins released
67 by these factors (7,8). Induction of phase I xenobiotics metabolising enzymes in the pancreas,
68 principally cytochrome monooxygenases in response to a number of these agents, have been
69 reported to produce cytotoxic lipophilic intermediates that can potentially overcome their
70 abilities to detoxify such products (9). Initially in 1994, Cavallini et al first described the
71 effect of tobacco and alcohol on pancreatic lithogenesis during the course of chronic
72 pancreatitis. They found that medium to heavy smokers had a significantly increased risk of
73 developing calcifications in pancreas but found no effects in those using alcohol (10).

74 The results of recent studies suggest that chronic pancreatitis has a strong genetic basis. The
75 increasing knowledge of gene-environment interaction has provided new insight in the
76 pathogenesis of chronic pancreatitis (11). Tobacco smokings are known to contain free

radicals and to induce their direct formation at the tissue level causing damage of cell membranes, proteins, DNA, chronic tissue inflammation and their remodelling in the long run (12,13). Upon exposure, different protein systems including those scavenging reactive oxygen species (ROS) are up-regulated, and the level of response is influenced by variation in expressions of underlying genes. Likewise, polymorphisms in oxidative stress related candidate genes like glutathione s-transferases (GSTs), microsomal epoxide hydroxylase (EPHX) or heme-oxygenase 1 (HMOX-1), have been associated with decline in CP function. The environmental factors such as ethanol, smoking and other putative etiologic factors may contribute to chronic pancreatic injury.

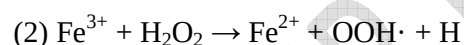
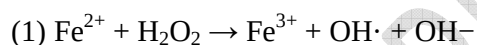
Alcohol consumption may adversely affect the digestive system and cause pancreatitis:

Alcohol abuse was proposed as a causative agent of pancreatitis in 1878 by Freidrich (Friedrich 1878). In 1970s Sarles proposed that alcohol causes pancreatitis via precipitation of the secreted proteins (protein plug formation) within small pancreatic ducts leading to acinar atrophy and fibrosis (14,15,16). Some animal experiments have shown that chronic alcohol administration produces changes in the acinar cells. It has been shown that the pancreatic content of the digestive enzymes such as trypsinogen, chymotrypsinogen, lipase and the lysosomal enzyme such as cathepsin B is increased in alcohol fed rats (17). The risk for developing pancreatic disease occurs when there is a daily consumption of greater than 100 g of ethanol for men and 80 g for women for more than five years. Therefore, there is variability in the disease progression.

Smoking induced generation of free radicals and oxidative stress during chronic

pancreatitis: Smoking has been proved to be independently associated with chronic pancreatitis (18). The pancreatic disease is a complex disorder resulting from multiple defects, which, when combined, lead to failure of control systems and metabolic homeostasis.

The developmental factors like protein, genes and other pathways that govern interaction between environmental factors and their impacts on the cellular level lead to make the pathogenesis more complicated. The central role of free radicals in tobacco smoke mediated carcinogenesis and oxidative stress has been established by a series of studies (19-20). An important finding by Pryor and co-workers was that cigarette tar has high concentrations of stable free radicals, identified as a semiquinone (QH•) and carbon-centered radicals (-C•) as detected by EPR (21). The most interesting is a quinone/semiquinone/hydroquinone (Q/QH•/QH₂) system in the tar polymeric matrix (22). The stable free radicals were identified as o- and p-benzosemiquinone radicals and their role in the DNA damage through the formation of HO• were detected by EPR spin-trapping (23). The following mechanisms have been identified: the QH• radicals reduce O₂ into O₂•⁻, which can dismutate to form H₂O₂ and then with Fe²⁺ (cigarette tar itself contains high concentrations of iron) can generate highly oxidizing hydroxyl radicals through the Fenton reaction shown as following:



Free radicals adversely influence multiple factors in pancreatic cells: The reactions of free radicals especially OH• with these membranes constituents lead to lipid peroxidation within the membranes followed by disintegration of the cells and ultimately to cell death. ROS can also disrupt mitochondrial membrane potential (øm), leading to release of cytochrome c and subsequent DNA fragmentation due to H₂O₂-induced mitochondrial damage (24). In other pathways, switching on proinflammatory cascades not only exerts direct effects on the pancreatic cells, but also initiates the migration, adhesion, and infiltration of inflammatory cells into the exocrine pancreas. Genes to be involved in migration and adhesion process are chemokines. The intercellular adhesion molecules (ICAMs) are under

the regulation of the redox-sensitive kinases or transcription factors such as MAPKs, NF- κ B, and activator protein-1 AP-1(25, 26, 27) .So the mechanism by which smoking contributes to pancreatic injury or by which smoking accelerates the pancreatic inflammatory process, is associated to the activation of multiple signal transduction pathways due to nicotine exposure explained in figure.1. This event results in high levels of intracellular calcium release and may be responsible for cell cytotoxicity and cell injury (28).

Smoking and development of acute and chronic pancreatitis: The large effects of tobacco smoking were caused by long-term cumulative exposure in current smokers as well as the remaining effects in former smokers, especially in men. So the recent advances in basic research have revealed that stimulus or upstream signals regulating the ROS/RNS-generating enzymes might also play a role in the pathogenesis of pancreatic inflammations, thus opening a possible new therapeutic avenue against these diseases (29). Oxidative stress plays a critical role in both acute and chronic pancreatic inflammation. Generation of ROS/RNS from numerous enzymatic systems, including xanthine oxidase, nitric oxide synthase, CYP2E1, and NADPH oxidase, not only directly oxidizes a wide range of biomolecules, but also switches on several stress-activated pathways like MAPK, NF- κ B, cytokines and other pro-inflammatory pathways(30,31). Apart from the epidemiologic evidence of an association between smoking and development of acute and chronic pancreatitis, a biological effect of smoking seems plausible because both animal studies and human studies have demonstrated changes into the pancreas and in pancreatic functioning after exposure to tobacco smoke.

Conclusion:

Among the numerous environmental factors reported so far playing crucial role in influencing the health of humans, consumption of alcohol and smoking has been found not only to generate toxic free radicals but also adversely influence the oxidative pathway and transcription processes into pancreatic cells resulting into further aggravation of chronic pancreatitis. These factors may exert synergistic effect with those of genetic factors making the disease conditions even worse as they interact with the genetic components of individuals. In this review, an endeavour has been made to present an updated account of the contribution of gene environment-interaction on the onset and progression of chronic pancreatitis.

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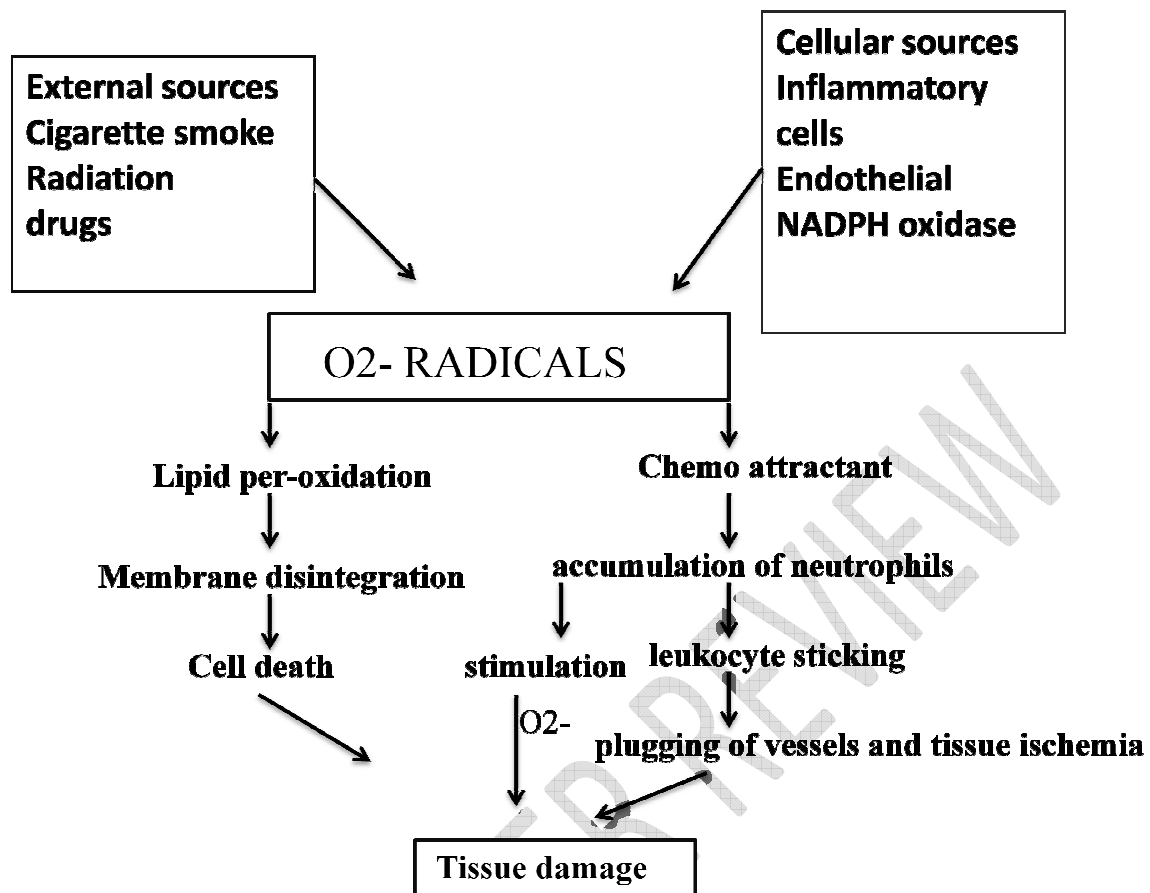


Fig.1. Direct and indirect effects of oxygen free radicals