1.1. Introduction

Thyroid gland is one of the largest gland in endocrine system which do a variety of important metabolic functions, thyroid gland performs these functions through secretion of thyroid hormones; thyroxine (T4) tri-iodothyronine (T3) and calcitonin. Secretion of these hormones is regulated by other hormones from hypothalamus called thyroid releasing hormone (TRH) and thyroid stimulating hormone (TSH) from anterior pituitary gland (Nawaz, 2012)

Disturbance of these hormones may result in thyroid dysfunction refered to hyperthyroidism and hypothyroidism. Hyperthyroidism often refered to as an 'overactive thyroid', is a condition in which the thyroid gland produces and secretes excessive amounts of thyroid hormones, triiodothyronine (T3) and/or thyroxine (T4). This is the opposite of hypothyroidism ('sluggish thyroid'), which is the reduced production and secretion of T3 and/or T4 (Floyd, 2009)

Cigarette smoking has multiple, minor effects on thyroid function. Serum thyroxine (T4) levels are slightly elevated, while serum tri-idothyronine (T3) levels may be increased two to four time, Graves' disease, ophthalmopathy and thyroid hormone abnormalities have all been linked to smoking.

1.2 Literature review

2.1.1. Smoking

Smoking is the most common method of consuming tobacco, and tobacco is the most common substance smoked. The agricultural product is often mixed with other additives and then pyrolyzed. The resulting vapors are then inhaled and the active substances absorbed through the alveoli in the lungs. The active substances trigger chemical reactions in nerve endings which heighten heart rate, memory, alertness, and reaction time. Dopamine and later endorphins are released, which are often associated with pleasure. (Surgeon, 2001).

2.1.1.1. Epidemiology

2.1.1.2. Prevalence

1

In 2000, smoking was practiced by 1.22 billion people, predicted to rise to 1.45 billion people in 2010 and 1.5 to 1.9 billion by 2025. If prevalence had decreased by 2% a year since 2000 this figure would have been 1.3 billion in 2010 and 2025. (WHO, 2010).

As of 2002, about twenty percent of young teens (13–15) smoke worldwide, with 80,000 to 100,000 children taking up the habit every day—roughly half of whom live in Asia. Half of those who begin smoking in adolescent years are projected to go on to smoke for 15 to 20 years. The WHO states that "much of the disease burden and premature mortality attributable to tobacco use disproportionately affect the poor". Of the 1.22 billion smokers, 1 billion of them live in developing or transitional nations. Rates of smoking have leveled off or declined in the developed world. In the developing world, however, tobacco consumption is rising by 3.4% per year as of 2002. (WHO, 2010).

The WHO in 2004 projected 58.8 million deaths to occur globally, from which 5.4 million are tobacco-attributed, and 4.9 million as of 2007. As of 2002, 70% of the deaths are in developing countries. (WHO, 2010)

Table (1-1): Consumption

Smoking prevalence by gender (2000)		
	Percent smoking	
Region	**Men**	**Women**
Africa	29	4
United States	35	22
Eastern Mediterranean	35	4
Europe	46	26
Southeast Asia	44	4
Western Pacific	60	8

As of 2002, Approximately 5.5 trillion cigarettes are produced globally each year and are smoked by over 1.1 billion people or greater than one-sixth of the world population. While smoking rates have leveled off or declined in developed nations, they continue to rise in developing parts of the world. Smoking rates in the United

States have dropped by half from 1965 to 2006 falling from 42% to 20.8% of adults. In the developing world, tobacco consumption is rising by 3.4% per year. (WHO, 2010).

2.1.1.3 .Health effects of Cigarettes

Tobacco use leads most commonly to diseases affecting the heart and lungs, with smoking being a major risk factor for heart attacks, strokes, chronic obstructive pulmonary disease (COPD), emphysema, and cancer (particularly lung cancer, cancers of the larynx and mouth, and pancreatic cancer). It also causes peripheral vascular disease and hypertension, all developed due to the exposure time and the level of dosage of tobacco. Furthermore, the earlier and the higher level of tar content in the tobacco filled cigarettes causes the greater risk of these diseases. Cigarettes sold in developing nations tend to have higher tar content, and are less likely to be filtered, potentially increasing vulnerability to tobacco-related disease in these regions, The World Health Organization (WHO) estimates that tobacco caused 5.4 million deaths in 2004 and 100 million deaths over the course of the 20th century. Similarly, the United States Centers for Disease Control and Prevention describes tobacco use as "the single most important preventable risk to human health in developed countries and an important cause of premature death worldwide. (WHO, 2010).

 Smoke contains several carcinogenic pyrolytic products that bind to DNA and cause many genetic mutations. There are over 19 known chemical carcinogens in cigarette smoke. Tobacco also contains nicotine, which is a highly addictive psychoactive chemical. When tobacco is smoked, nicotine causes physical and psychological dependency. Tobacco use is a significant factor in miscarriages among pregnant smokers, it contributes to a number of other threats to the health of the fetus such as premature births and low birth weight and increases by 1.4 to 3 times the chance for Sudden Infant Death Syndrome (SIDS).(Paola Brancaccio, *et al*., 2008).The result of scientific studies done in neonatal rats seems to indicate

that exposure to cigarette smoke in the womb may reduce the fetal brain's ability to recognize hypoxic conditions, thus increasing the chance of accidental asphyxiation. Incidence of impotence is approximately 85 percent higher in male smokers compared to non-smokers and is a key factor causing erectile dysfunction (ED) (Peeters, 2005).

Plasma fibrinogen is an independent predictor of cardiovascular disease, including coronary heart disease (CHD), stroke and peripheral arterial disease. Its predictive value for CHD is similar to that of classical risk factors, such as smoking habit, blood pressure or serum cholesterol, and adds to risk prediction from these three variables. Plasma fibrinogen levels show a dose dependent increase in smokers; following smoking cessation, levels decrease towards similar values in those who have never smoked. In parallel with the fall in risk of CHD, an early rapid reduction is followed by a slower reduction over 10±15 years. Plasma fibrinogen levels may promote cardiovascular disease through several biological mechanisms, including atherogenesis, thrombogenesis and increased blood viscosity, which may reduce blood flow. It has been estimated that up to 50% of the increase in CHD risk associated with smoking could be attributed to the effects of smoking on fibrinogen. However, the causal significance of fibrinogen levels in cardiovascular disease remains to be established by large randomized trials of fibrinogen reduction. Increased fibrinogen synthesis in the liver, rather than decreased fibrinogen catabolism, has long been suspected, but there is a lack of published studies addressing this hypothesis. In the April issue of Clinical Science, (Hofedt F. D,*. et al.*, 1972). Report two studies of fibrinogen synthesis in male smokers. In the first study, current smokers had higher absolute fibrinogen synthesis rates than non-smokers, which were correlated with increased fibrinogen levels. In the second study, 2 weeks ' abstention from smoking in current smokers reduced both absolute synthesis rates and plasma fibrinogen levels. The authors conclude that increased

fibrinogen synthesis plays a primary role in the increased plasma fibrinogen level associated with smoking. This is an important step in elucidating the pathways through which smoking increases fibrinogen levels. (Hilary Mantel., 2001). Also discuss such pathways, including the possibility that the effects of smoking on fibrinogen synthesis are part of a generalized inflammatory reaction (e.g. to smoking-induced injury to the respiratory tract, blood vessels or other organs). Other measures of inflammation are also predictive of cardiovascular risk, including C-reactive protein, leukocyte counts and low serum albumin, as well as plasma viscosity and the erythrocyte sedimentation rate (which are determined by plasma levels of fibrinogen and other macromolecules). Similarly to fibrinogen, such measures also show a dose-dependent increase in smokers and decrease following smoking cessation. , cytokines, such as interleukin-6, are important mediators of these measures of the inflammatory response, including fibrinogen synthesis. Future studies of smoking, smoking cessation and plasma fibrinogen are required to define their relationship to other acute-phase markers and inflammatory cytokines. Fibrin degradation produces, such as D-dimer, may also play a role in fibrinogen synthesis and inflammatory reactions; D-dimer is also elevated in smokers and weakly related to plasma levels of fibrinogen and C-reactive protein. (Hunter, *et al.*, 2001) also discuss the possible role of catecholamine in smoking-induced hyperfibrinogenaemia.However, studies to date have shown variable effects of adrenergic-blocking drugs in reducing plasma fibrinogen levels.

2.1.2. Tobacco Use and Cardiovascular Disease

Cigarette smoking is a major cause of CVD, and past reports of the Surgeon General extensively reviewed the relevant evidence. Cigarette smoking has been responsible for approximately 140,000 premature deaths annually from CVD More, Than 1 in 10 deaths worldwide from CVD in 2000 were attributed to smoking Cigarette

smoking also influences other cardiovascular risk factors, such as glucose intolerance and low serum levels of high-density lipoprotein cholesterol (HDLc). (Ezzati, *et al*., 2005).

Beyond its status as an independent risk factor, smoking appears to have a multiplicative interaction with the other major risk factors for CHD—high serum levels of lipids, untreated hypertension, and diabetes mellitus. For instance, if the presence of smoking alone doubles the level of risk, the simultaneous presence of another major risk factor is estimated to quadruple the risk (2×2). The presence of two other risk factors with smoking results in approximately eight times the risk ($2 \times 2 \times 2$) of persons with no risk factors. Cigarette smoking also is a cause of peripheral arterial disease (PAD), aortic aneurysm, CHD, and cerebrovascular disease, but the relative risk (RR) of disease varies with the vascular bed. The highest RRs are observed for diseases of peripheral arteries in the lower extremities, and the lowest are for stroke; RRs are intermediate for CHD and aortic aneurysm, The general mechanisms by which smoking results in cardiovascular events include development of atherosclerotic changes with narrowing of the vascular lumen and induction of a hypercoagulable state, which create risk of acute thrombosis. The rapid decline in risk of a recurrent myocardial infarction (MI) after smoking cessation supports the role of smoking in thrombosis. In addition, abundant evidence demonstrates that smoking contributes to development of atherosclerotic plaque. (Ezzati, *et al*., 2005).

2.1.2.1. Coronary Heart Disease

2.1.3. Cigarettes Smoked per Day

Studies showed increased risk of having CHD at all levels of cigarette smoking, and increased risks were evident even for persons who smoked fewer than five cigarettes per day.(Bjartveit and Tverdal , 2005) Prospective mortality studies conducted in the 1960s and 1970s showed a clear increase in CHD mortality with an increase in the number of cigarettes smoked per day, regardless of

the actual number. Other studies suggested that risk increased up to at least 40 cigarettes per day. However, more recent data appeared to show an increase in CHD risk with more cigarettes smoked per day only up to about 25 cigarettes; the risk increased relatively little even with further increases in cigarette consumption. (Willett, *et al.*, 2003).

2.1.3.1 Duration of Smoking

Researchers have not always demonstrated a significant relationship between duration of cigarette smoking and CHD risk when adjustment was made for other risk factors and the number of cigarettes smoked perday, Variation in the number of cigarettes smoked per day and in the products smoked during the lifetime of a smoker is often substantial, but this variable is not well captured in epidemiologic studies. (Burns, *et al.*, 2008).

Age is colinear with duration of smoking, because the two variables grow in tandem after a person starts to smoke and the RRs for smoking and CHD decline with advancing age. Furthermore, most smokers begin to smoke during adolescence, which promotes the colinearity. These realities make it difficult to estimate the independent contributions of age and duration of smoking to risk of CHD in multivariate models. However, the two studies of the American Cancer Society are a good source of data, because each study consists of more than 1 million men and women. Analyses of these data stratified by age and the number of cigarettes smoked per day showed steady increases in CHD mortality rates with increasing duration of smoking for persons younger than age 70 years. Using data from CPS-I, investigators calculated the risk of developing CHD by age and duration of smoking; For almost all age groups younger than age 70 years, RRs increased with increasing duration of smoking. Data from CPS-II on men also demonstrated a pattern of increasing RR with age-specific mortality due to CHD and increasing duration of smoking for each level of cigarettes smoked per day. Even though data in these analyses were not adjusted for

potential differences in other cardiovascular risk factors, the findings presented a convincing picture of increasing risk of CHD with longer duration of smoking. (Baskin , 1999).

2.1.3.2. Smoking Cessation

The risks of MI and death from CHD are lower among former smokers than among continuing smokers in many studies, including those with data adjusted for levels of other risk factors , The risk fell rapidly, decreasing about one-half in one year , Risks appear to remain slightly elevated for more than a decade after persons stopped smoking, but in some studies this increased risk was not statistically significant Among smokers who had MI or angiographically documented CHD, persons who stopped smoking had a substantially lower rate of reinfarction than did those who continued to smoke. Reduction in risk was evident within the first year after MI. Risk continued to be lower among former smokers than among continuing smokers for prolonged periods after the first MI .Studies also demonstrated rapid reduction in risk after persons stopped smoking among populations at high risk for CHD and among women. (Kamath, *et al*., 2000).

Patients with angiographically documented CHD who stopped smoking at the diagnosis of CHD or before diagnosis– had lower death rates from MI or CHD than did continuing smokers. In addition, the benefit of stopping smoking did not decline with advancing age. (Vanderpump, *et al*., 1995).

In the 16-year follow-up of the multiple risk factor intervention trial research group, mortality from CHD was 11.4 percent lower in the "special intervention" group than in the "usual care" group. This result may illustrate the benefit of stopping smoking, because one of the interventions targeted smoking cessation . (Simon., 2001). reported that in addition to benefits for CHD, stopping smoking also reduces morbidity and mortality in patients with left ventricular dysfunction. In this study, the benefits of stopping smoking on mortality and recurrent congestive heart failure requiring

hospitalization were similar to the benefits from treatments with angiotensin-converting-enzyme (ACE) inhibiting drugs, β-blockers, or spironolactone, which are mainstays for the treatment of heart failure.(Suskin , *et al.*, 2001).

2.1.3.3 Race and Ethnicity

In 2004, heart disease mortality was higher among African Americans than among Whites. From 1999 through 2004, the prevalence of acute MI was higher for African Americans than for Whites aged 35 through 54 years; however, for ages 55 years and older, the prevalence of acute MI was higher among Whites. (Sexton PT; Walsh J and Jamrozik K, . 1997)

2.1.3.4 Sudden Death

Most sudden death is due to CVD. In many epidemiologic studies, RRs for sudden cardiac death were higher than RRs for CHD or MI among persons who smoked. The RRs for sudden death among current smokers, compared with lifetime nonsmokers, often exceeded 3.0 . in multivariate analysis of the combined data from the Framingham Heart Study and the Albany Study, which examined sudden cardiac death in men aged 45 through 64 years, cigarette smoking was the risk factor with the highest statistical significance , in a study of data from the 1986 National Mortality Followback Survey among persons with no history of CHD, cigarette smoking was the only modifiable risk factor associated with sudden coronary death and it was one factor associated with increased risk of sudden coronary death among persons with known CHD.(Sexton ,*et al* ., 1997).

(Peeters and colleges,. 2003). found an association between smoking cessation and reduction in death from cardiac arrhythmia for patients with left ventricular dysfunction after MI. Finally, the risk of recurrent cardiac arrest among smokers surviving out-of-hospital cardiac arrest was lower among persons who then stopped smoking than among those who continued to smoke. (Hallstrom , *et al* .,1986).

2.1.3.4.1. Stroke

After adjustment of data for other risk factors, cigarette smokers have higher risk of stroke and higher mortality from cerebrovascular disease than do lifetime nonsmokers, and a dose-response relationship is evident (Djoussé, *et al*., 2002). In addition, in the 20-year follow-up of a prospective study of mortality that controlled for other cardiovascular risk factors, cigarette smoking increased the risk of death from stroke and mortality rates grew the number of cigarettes smoked increased .

(Sela , *et al* ., 2002).

In a meta-analysis of data from 32 studies, the overall RR for stroke associated with cigarette smoking was 1.5 (95 percent confidence interval [CI], 1.4–1.6) (Shinton and Beevers. , 1989) . The RRs varied with the stroke subtypes: 1.9 for cerebral infarction, 0.7 for cerebral hemorrhage, and 2.9 for subarachnoid hemorrhage. The researchers reported a dose-response relationship between the number of cigarettes smoked per day and the RR. The data suggested a sustained higher risk of stroke among former smokers younger than age 75 years than the risk for nonsmokers in the same age group. For all ages combined, RR for former smokers was 1.2. (Wolf, *et al.*, 1988).

During the 26-year follow-up of the cohort in the Framingham Heart Study, cigarette smoking was a significant risk factor for stroke. The risk declined, however, among smokers who had stopped smoking for two years and was similar to that of lifetime nonsmokers after five years of abstinence from smoking. In the 12-year follow-up of the Nurses' Health Study, RR for stroke among current smokers was 2.58 compared with nonsmokers, but it was 1.34 among former smokers compared with nonsmokers. Once those who stopped smoking had abstained for two to four years, their risk for stroke could not be distinguished from that of lifetime nonsmokers. In addition, the pattern of decline in total risk for stroke after stopping smoking remained the same after adjustments for other risk factors. (Wolf, *et al.*, 1988).

2.1.3.4.2 Aortic Aneurysm

Mortality studies consistently demonstrated higher risk of death from abdominal aortic aneurysm among cigarette smokers than among nonsmokers, In addition, the risk rose with an increasing number of cigarettes smoked per day.(Vardulaki , *et al* ., 2002).

Studies have demonstrated an association of cigarette smoking with prevalence of aortic aneurysm or aortic dilation, as determined by ultrasonography in cohorts of men and women, even after adjustment for a large number of known risk factors. Cigarette smoking has been associated with increased growth of abdominal aortic aneurysms. This finding suggests that more frequent monitoring of smokers for this condition is necessary. With increasing duration of abstinence from smoking, the risk of developing an abdominal aneurysm appears to slowly decline. (Wilmink, *et al.*, 1993).

2.1.3.4.3. Peripheral Arterial Disease

Cigarette smoking and diabetes are well established as the major risk factors for PAD, and a strong dose-response relationship for smoking was observed even after adjustment for other CVD risk factor. Data from the Framingham Heart Study demonstrated increased risk of PAD among both young and older male and female cigarette smokers after adjustment for other cardiovascular risk factors. In addition, this risk increased with the increase in the number of cigarettes smoked per day, and this result was statistically significant. The Framingham Offspring Study reported a similar finding. Finally; researchers have observed a significantly higher rate of late arterial occlusion in patients who continued to smoke after peripheral vascular surgery than in those who stopped smoking. Among smokers with claudication, progression to critical limb ischemia is reduced in those who stopped smoking. (Jonason and Bergström, 1987).

2.1.4. Pathophysiology

This section on pathophysiology focuses primarily on mechanisms by which cigarette smoking may increase risk of CVD.

2.1.4.1 Cigarette Smoke Constituents and Cardiovascular Disease

Three constituents of cigarette smoke have received the greatest attention as potential contributors to CVD: nicotine, carbon monoxide (CO), and oxidant gases. Some research also investigated the contributions of polycyclic aromatic hydrocarbons (PAHs), particulate matter, and other constituents of tobacco smoke to the pathophysiology of CVD including atherogenesis. (Bhatnagar, 2006). Nicotine, which is absorbed rapidly from cigarette smoke, was found in arterial blood levels of 40 to 100 ng/mL after each cigarette was smoked, The typical dose of nicotine systematically absorbed from each cigarette is 1 to 2 milligrams (mg). Although plasma nicotine levels peaked sharply after each cigarette, trough values also rose during the first six to eight hours of regular smoking during the day. This accumulation pattern was consistent with an elimination half-life for nicotine of two hours. (Benowitz, *et al.*, 1982).

Nicotine is a symathomimetic drug that releases catecholamines both locally from neurons and systemically from the adrenal gland. In studies of the pharmacodynamics of nicotine, the intensity of its maximal effect was greater with more rapid delivery Pharmacodynamic studies also indicated that although tolerance to the effects of nicotine developed rapidly, tolerance was incomplete. (Jabbar, *et al.*, 2008).

In one study, a constant intravenous infusion of nicotine increased the heart rate even though nicotine levels in the blood were relatively low. As the infusion continued, the heart rate reached a plateau despite a progressive rise in blood levels of nicotine. The same phenomenon was observed in comparisons of acceleration of heart rate with level of blood nicotine during regular cigarette smoking throughout the day. (Benowitz., 2003).

In another study, heart rate measured by ambulatory monitoring was higher throughout the day when persons were smoking than when they were not smoking. The extent of elevation was independent of the blood level of nicotine absorbed from the cigarettes. The researchers concluded that the elevated heart rate reflected persistent stimulation of the sympathetic nervous system, a possible contributing factor to CVD. Nicotine may also contribute to endothelial dysfunction, lipid abnormalities, and insulin resistance, CO is a major constituent of cigarette smoke. In regular smokers, carboxyhemoglobin levels average about 5 percent, compared with 10 percent or higher in heavy smokers. These values compare with levels of 0.5 to 2 percent in nonsmokers, depending on exposure to automobile exhaust. Like nicotine levels, elevated carboxyhemoglobin levels persist for 24 hours a day in smokers. (DeBias, *et al.*, 1976).

CO exposure can aggravate ischemia and worsen symptoms in persons with vascular disease, although it is not clear that CO contributes directly to atherosclerosis. CO binds avidly to hemoglobin, reducing the amount of hemoglobin available to carry oxygen and impeding release of oxygen by hemoglobin. In some studies, inhalation of CO at levels comparable to those in cigarette smokers reduced exercise tolerance in patients with angina pectoris, intermittent claudication, or COPD . Another study reported that CO exposure in persons with obstructive coronary disease resulted in a greater degree of exercise-induced ventricular dysfunction and an increase in the number and complexity of ventricular arrhythmias during exercise (Sheps, *et al.*, 1990). Inhaling CO reduced the threshold for ventricular fibrillation in animals. (DeBias, *et al.*, 1976). Long-term CO exposure in smokers resulted in greater red blood cell mass and reduced the oxygen- carrying capacity of red blood cells, resulting in relative hypoxemia. In response to hypoxemia, red blood cell masses increased to maintain the amount of oxygen needed by organs in the body. The increase in red blood cell mass increased

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blood viscosity and may contribute to hypercoagulation in smokers, Cigarette smoke delivers a high level of oxidizing chemicals to smokers, including oxides of nitrogen and many free radicals from both the gas and tar phases of cigarette smoke. Exposure to oxidant chemicals in smoke was associated with depletion of endogenous levels of antioxidants, manifested as lower blood levels of vitamin C in smokers than in nonsmokers, Cigarette smoking also was reported to increase levels of lipid peroxidation products in the plasma and urine of smokers. Study results also indicated that oxidant stress contributes to several potential mechanisms of CVD, including inflammation, endothelial dysfunction, lipid abnormalities such as oxidation of low-density lipoprotein (LDL), and platelet activation. (Burke, *et al.*, 2003).

Acrolein, a reactive aldehyde produced by endogenous lipid peroxidation, is present at high levels in cigarette smoke. Acrolein binds covalently to form protein adducts, and acrolein-induced modification of proteins has been implicated in atherogenesis. Acrolein modifies apolipoprotein A-I (APO A-I), the major protein in HDL.

 HDL protects against atherosclerosis. Acrolein-protein adducts co-localize with APO A-I in macrophages in the intima of human atheromatous blood vessels. (Sapolsky, *et al.*, 1986).

Acrolein also oxidized thioredoxins 1 and 2 in endothelial cells. Thioredoxins are prominent antioxidant proteins that regulate the oxidation-reduction balance critical for normal cell function. These results suggest that oxidation of thioredoxins can result in dysfunction and death of endothelial cells, contributing to atherosclerosis. In addition, acrolein induces production of the enzyme cyclooxygenase-2 (COX-2) in human endothelial cells *in vitro*. (Park, *et al.*, 2007)This finding is relevant because COX-2 is expressed in atherosclerotic lesions and may participate in atherogenesis. Acrolein may contribute to thrombogenicity in smokers by inhibiting antithrombin activity. Finally, acrolein induces

hypercontraction in isolated human arteries and could contribute to smoking-induced coronary vasospasm. (Chakera, *et al.*, 2012).

Cigarette smoke contains a number of metals, including aluminum, cadmium, copper, lead, mercury, nickel, and zinc. Metals in cigarette smoke catalyze the oxidation of cellular proteins (Bernard, *et al.*, 2006). This reaction may lead to structural damage, endothelial dysfunction, and detachment of endothelial cells from the walls of blood vessels. Mixtures of metals and oxidants may be particularly damaging to endothelial cells. Cadmium levels are higher in serum of smokers, and cadmium accumulates in the aortic walls of smokers. Epidemiologic evidence indicates an association between serum levels of cadmium and lead and CVD, including hypertension and MI. (Abu-Hayyeh, *et al.*, 2001).

PAHs found in the tar fraction of cigarette smoke reportedly accelerated atherosclerosis in experimental animals. Weekly injections of benzo[a]pyrene and 7,12-dimethylbenz[a]anthracene, at doses below those that produce tumors, increased development of atherosclerotic plaque in the aortas of cockerels. Similarly, inhaled butadiene, a component of the vapor phase of cigarette smoke, increased the amount of atherosclerotic plaque in the same animal model; the researchers speculated that one mechanism of atherogenesis is a mutation, followed by hyperproliferation of smooth muscle or other cells that may contribute to growth of atherosclerotic plaque (Penn and Snyder, 1996).

2.1.4.2. Mechanisms

Cigarette smoking produces acute myocardial ischemia by adversely affecting the balance of demand for myocardial oxygen and nutrients with myocardial blood supply (Figure1-1). The increase in demand for oxygen in the myocardium is a consequence of nicotine stimulation of the sympathetic nervous system and the heart, Cigarette smoking acutely increases levels of plasma norepinephrine and epinephrine and enhanced 24-hour urinary

excretion of these catecholamine's, Regular smoking increases the heart rate both in the short term (up to 20 beats per minute) and throughout the day (average increase, 7 beats per minute), as measured during ambulatory monitoring. Nicotine also increases heart rate, blood pressure, and myocardial contractility. These hemodynamic changes result in increases in myocardial work that in turn require increased myocardial blood flow (Abdullatif, *et al.*, 2006).
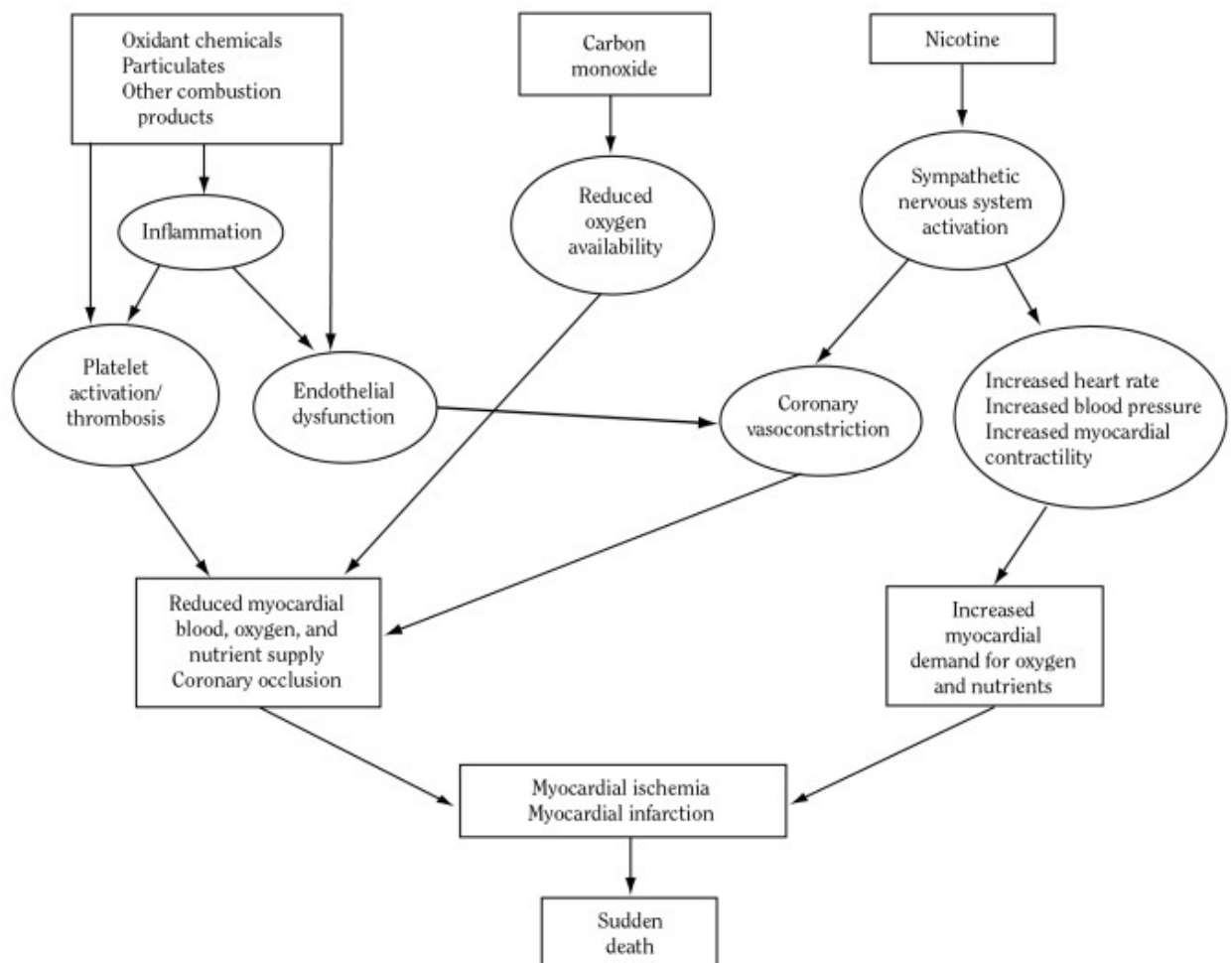

Figure (1-1) Overview of mechanisms by which cigarette smoking causes an acute cardiovascular event

In healthy persons, cigarette smoking increases coronary blood flow in response to increases in myocardial work. In smokers, the

response in coronary blood flow to increased myocardial demand was impaired (i.e., reduced coronary vasodilatory reserve) (Czernin and Waldherr., 2003). Cigarette smoking played a direct role by constricting coronary arteries through nicotine-mediated action on α-adrenergic receptors and by induction of endothelial dysfunction by nicotine and oxidizing chemicals (Puranik and Celermajer., 2003). In addition, oxidant chemicals contribute to platelet activation and thrombogenesis. (Burke and FitzGerald., 2003).

Exposure to CO may also contribute to the adverse hemodynamic effects of cigarette smoking. By producing functional anemia, CO increases the need for coronary blood flow, especially during physical exertion. An in-adequate vasodilatory flow reserve produced by cigarette smoking, in the face of need for increased coronary blood flow mediated by carbon dioxide, could contribute to myocardial ischemia with exercise in smokers,In addition to the mechanisms described in Figure 6.5, cigarette smoking has effects on inflammation, insulin sensitivity, and lipid abnormalities that most likely contribute to smoking-induced CVD. (Burke and FitzGerald, 2003).

2.1.4.3. Nitric Oxide

Cigarette smoking has injurious effects on the vascular endothelium .abnormalities in the release of chemical mediators occur as a consequence of endothelial dysfunction and are likely to contribute to the prothrombotic condition of smokers. Examples include decreases in NO-mediated inhibition of interactions between platelets and the blood vessel wall, in platelet-induced NO, and in inhibition of platelet activation. Blood vessel tone is more sensitive to low NO levels than is platelet function. The importance of NO deficiency mediated by oxidative stress in thrombosis is suggested by familial childhood stroke resulting from deficiency in glutathione peroxidase. This condition decreases NO levels in association with both increased expression of P-selectin in platelets and platelet aggregation and activation. (Kenet, *et al.*, 1999).

2.1.4.3.1. Inflammation

Studies demonstrate that cigarette smoking results in a chronic inflammatory state, evidenced by increased counts of circulating leukocytes, [CRP](), and acute-phase reactants such as fibrinogen. Cigarette smoking also activates monocytes and enhances recruitment and adhesion of leukocytes to blood vessel walls, an integral step in vascular inflammation. Research indicates that inflammation contributes to atherogenesis, because high leukocyte counts and high levels of CRP and fibrinogen are all powerful predictors of future cardiovascular events. (Lemaire., 2002).

2.1.5. Thyroid gland

The thyroid gland is one of the larger endocrine glands, weighing 2-3 grams in neonates and 18-60 grams in adults, and is increased in pregnancy. With a butterfly-shaped organ it composes of two cone-like lobes or wings, lobus dexter (right lobe) and lobus sinister (left lobe), connected via the isthmus (Nawaz, 2012). The thyroid isthmus is variable in presence and size, can change shape and size, and can encompass a cranially extending pyramid lobe (lobus pyramidalis or processus pyramidalis), remnant of the thyroglossal duct (Igbal, 2012). Thyroid gland is situated on the anterior side of the neck, lying against and around the larynx and trachea, reaching posteriorly the oesophagus and carotid sheath. it starts cranially at the oblique line on the thyroid cartilage (just below the laryngeal prominence, or 'Adam's Apple'), and extends inferiorly to approximately the fifth or sixth tracheal ring. it is difficult to demarcate the gland's upper and lower border with vertebral levels because it moves position in relation to these during swallowing(Aggrawal, 2011) .it covered by a thin fibrous sheath, the capsula glandulae thyroidea, composed of an internal and external layer. The external layer is anteriorly continuous with the lamina pretrachealis fasciae cervicalis and posteriorolaterally continuous with the carotid sheath. The gland is covered anteriorly

with infrahyoid muscles and laterally with the sternocleidomastoid muscle also known as sternomastoid muscle. On the posterior side, the gland is fixed to the cricoid and tracheal cartilage and cricopharyngeus muscle by a thickening of the fascia to form the posterior suspensory ligament of Berry (Yalcin, *et al* ., 2005).The thyroid glands firm attachment to the underlying trachea is the reason behind its movement with swallowing (Kamath, 2010). The thyroid is supplied with arterial blood from the superior thyroid artery, a branch of the external carotid artery, and the inferior thyroid artery, a branch of the thyrocervical trunk, and sometimes by the thyroid ima artery, branching directly from the subclavian artery.The venous blood is drained via superior thyroid veins, draining in the internal jugular vein, and via inferior thyroid veins, draining via the plexus thyroideus impar in the left brachiocephalic vein (Marreez, 2013).

2.1.5.1. Thyroid physiology

The primary function of the thyroid is production of the hormones triiodothyronine (T3), thyroxine (T4), and calcitonin. Up to 80% of the T4 is converted to T3 by peripheral organs such as the liver, kidney and spleen. T3 is several times more powerful than T4, which is largely aprohormone. (Stephen, 2001).
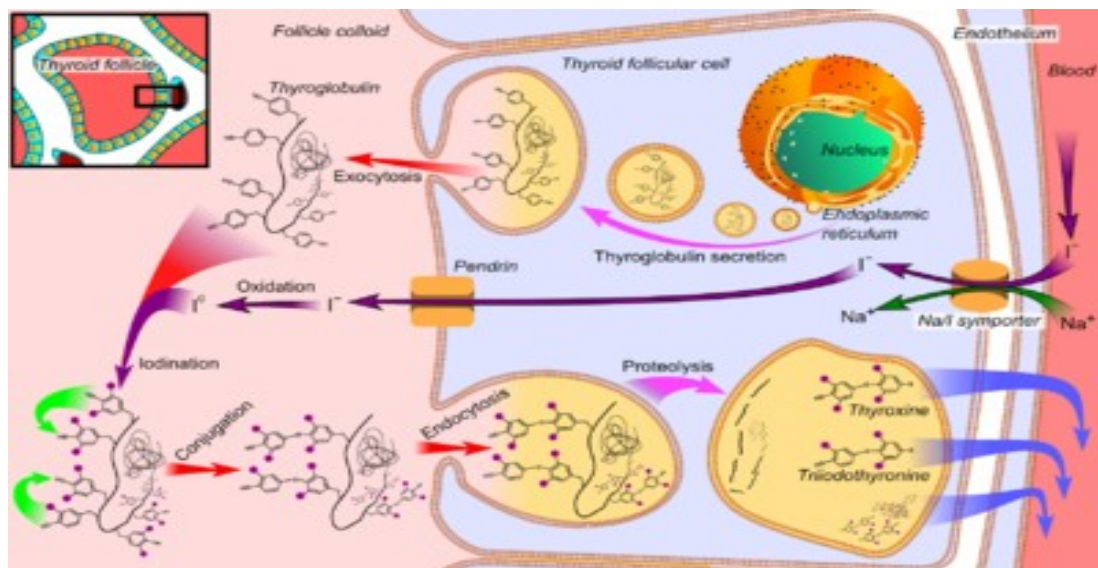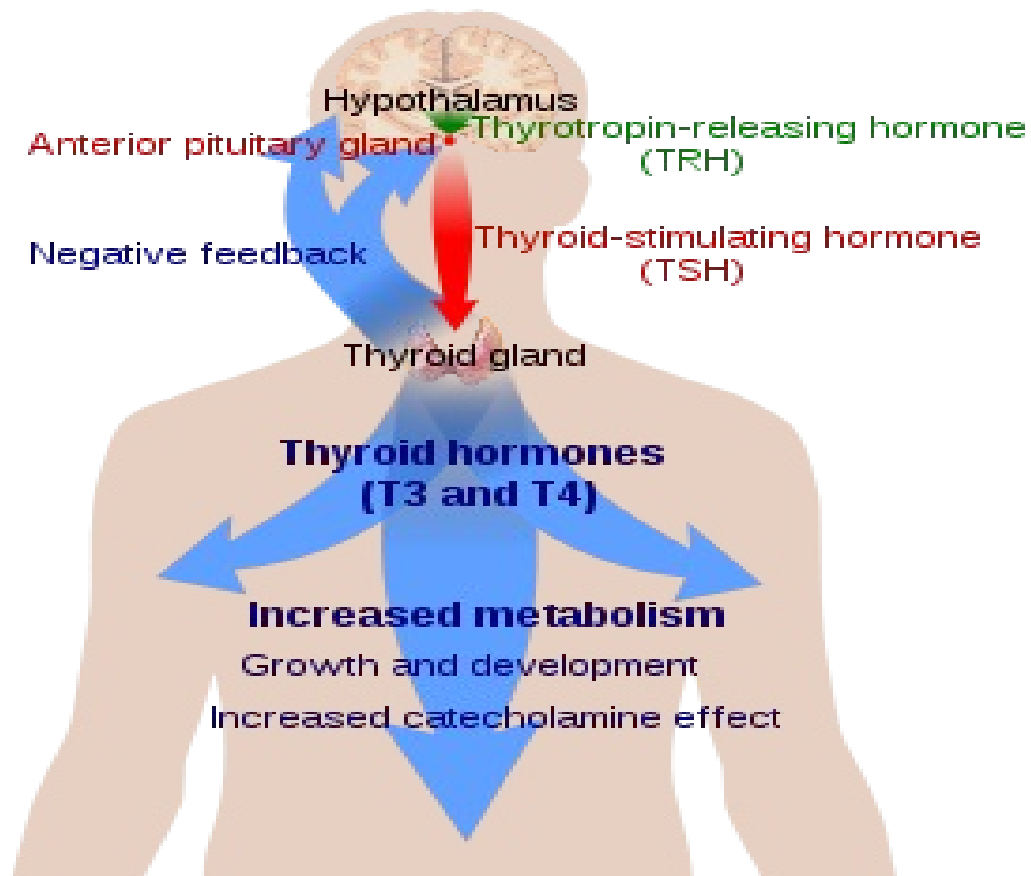
Thyroid system

Figure 1.3 Synthesis of the <u>thyroid hormones</u>, as seen on an individual <u>thyroid follicularcell</u> (Boron , 2003) .

2.1.5.2. T_3 and T_4 production and action

- Thyroglobulins are protiens synthesized in the rough endoplasmic reticulum and follows the secretory pathway to enter the colloid in the lumen of the thyroid follicle by exocytosis

- Meanwhile, a sodium-iodide (NaI) symporter pumps iodide (I^-) actively into the cell, which previously has crossed the endothelium by largely unknown mechanisms.

- This iodide enters the follicular lumen from the cytoplasm by the transporter pendrin, in a purportedly passive manner (Bernard, 2007)

- In the colloid, iodide (I^-) is oxidized to iodine (I^0) by an enzyme called thyroid peroxidase.(TPO)

- Iodine (I^0) is very reactive and iodinates the thyroglobulin at tyrosyl residues in its protein chain (in total containing approximately 120 tyrosyl residues).

- In conjugation, adjacent tyrosyl residues are paired together.

- The entire complex re-enters the follicular cell by endocytosis.

- Proteolysis by various proteases liberates thyroxine and triiodothyronine molecules, which enters the blood by largely unknown mechanisms.

Thyroxine (T_4) is synthesised by the follicular cells from free tyrosine and on the tyrosine residues of the protein called thyroglobulin (Tg). Iodine is captured with the "iodine trap" by the hydrogen peroxide generated by the enzyme thyroid peroxidase (TPO) (Ekholm, 1997) and linked to the 3' and 5' sites of the benzene ring of the tyrosine residues on Tg, and on free tyrosine. Upon stimulation by the thyroid-stimulating hormone (TSH), the follicular cells reabsorb Tg and cleave the iodinated tyrosines from Tg in lysosomes, forming T_4 and T_3 (in T_3, one iodine atom is absent compared to T_4), and releasing them into the blood. Deiodinase enzymes convert T_4 to T_3 (Bianco, 2002) Thyroid hormone secreted from the gland is about 80-90% T_4 and about 10-20% T_3 (endocrineweb, 2009 and Stephen,

2001). Cells of the developing brain are a major target for the thyroid hormones T_3 and T_4. Thyroid hormones play a particularly crucial role in brain maturation during fetal development (Kester, 2004)

A transport protein that seems to be important for T_4 transport across [blood–brain barrier](#) organic anion transporting polypeptide 1C1(OATP1C1) has been identified.

a second transport protein is monocarboxylate transporter 8 (MCT8) is important for T_3 transport across brain cell membranes (Jansen, 2005).

Non-genomic actions of T_4 are those that are not initiated by liganding of the hormone to intranuclear thyroid receptor. These may begin at the plasma membrane or within cytoplasm. Plasma membrane-initiated actions begin at a receptor on the integrin alphaV beta3 that activates ERK1/2. This binding culminates in local membrane actions on ion transport systems such as the $Na^{(+)}/H^{(+)}$ exchanger or complex cellular events including cell proliferation. These integrins are concentrated on cells of the vasculature and on some types of tumor cells, which in part explains the proangiogenic effects of iodothyronines and proliferative actions of thyroid hormone on some cancers including gliomas. T_4 also acts on the mitochondrial genome via imported isoforms of nuclear thyroid receptors to affect several mitochondrial transcription factors. Regulation of actin polymerization by T_4 is critical to cell migration in neurons and glial cells and is important to brain development T_3 can activate phosphatidylinositol 3-kinase by a mechanism that may be cytoplasmic in origin or may begin at integrin alpha V beta3 (Kester , 2004).

In the blood, T_4 and T_3 are partially bound to thyroxine-binding globulin (TBG), transthyretin, and albumin. Only a very small fraction of the circulating hormone is free (unbound) - T_4 0.03% and T_3 0.3%. Only the free fraction has hormonal activity. As with the steroid hormones and retinoic acid, thyroid hormones cross the cell

membrane and bind to intracellular receptors (α_1, α_2, β_1 and β_2), which act alone, in pairs or together with the retinoid X-receptor as transcription factors to modulate DNA transcription (Stephen , 2001).

2.1.5.3. T_4 and T_3 regulation

The production of thyroxine (T4) and triiodothyronine (T3) is regulated by thyroid-stimulating hormone (TSH), released by the anterior pituitary. The thyroid and thyrotropes form a negative feedback loop: TSH production is suppressed when the T_4 levels are high (Johannes , 2002) . The TSH production itself is modulated by thyrotropin-releasing hormone (TRH), which is produced by the hypothalamus and secreted at an increased rate in situations such as cold exposure (to stimulate thermogenesis). TSH production is blunted by somatostatin also called somatotropin releasing-inhibiting hormone (SRIH), rising levels of glucocorticoids and sex hormones (estrogen and testosterone), and excessively high blood iodide concentration (Jack , 2002).

2.1.5.4. Calcitonin

Calcitonin is additional hormone produced by the thyroid contributes for the regulation of blood calcium levels . Parafollicular cells produce calcitonin in response to hypercalcemia. Calcitonin stimulates movement of calcium into bone, in opposition to the effects of parathyroid hormone (PTH). However; calcitonin seems far less essential than PTH, as calcium metabolism remains clinically normal after removal of the thyroid (thyroidectomy), but not the parathyroid . (chainika. , 2011).

2.2. Thyroid disorders

2.2.1 Hyperthyroidism

Often refered to as an 'overactive thyroid', is a condition in which the thyroid gland produces and secretes excessive amounts of the free (not protein bound, and circulating in the blood (Dario., 2008) thyroid hormones, (T3) &/or (T4). This is the opposite of hypothyroidism ('sluggish thyroid'), which is the reduced production and secretion of T3 and/or T4 (Floyd., 2009). Hyperthyroidism is a type of thyrotoxicosis, a hypermetabolic clinical syndrome which occurs when there are elevated serum levels of T3 and/or T4 (Kittisupa mongkol, 2009). Graves' disease is the most common cause of hyperthyroidism (Walter, 2003).While, hyperthyroidism may cause thyrotoxicosis they are not synonymous medical conditions; some patients may develop thyrotoxicosis as a result of inflammation of the thyroid gland (thyroditis), which may cause the release of excessive thyroid hormone already stored in the gland but does not cause accelerated hormone production. Thyrotoxicosis may also occur by the ingestion of excessive amounts of exogenous thyroid hormone in the form of thyroid hormone supplements such as the most widely used supplement level of thyroxine; it is also known by other terms such as exogenous thyrotoxicosis, alimentary thyrotoxicosis, or occult factitial thyrotoxicosis (Floyd , 2009).Disease management and therapy differ for thyrotoxicosis caused by hyperthyroidism and thyrotoxicosis caused by other conditions. Thyroid imaging and radiotracer thyroid uptake measurements, combined with serologic data, enable specific diagnosis and appropriate patient treatment (Floyd, 2009).

2.2.2. Symptoms and signs of hyperthyroidism

Hyperthyroidism may be asymptomatic, but when it is not, symptoms are due to an excess of thyroid hormone. Thyroid hormone is important at a cellular level, affecting nearly every type of tissue in the body. Thyroid hormone functions as a controller of the pace of all of the processes in the body. This pace is called the metabolic rate (Janet, 2013).

If there is too much thyroid hormone, every function of the body tends to speed up. Therefore, some of the symptoms of hyperthyroidism may be nervousness, irritability, increased perspiration, heart racing, hand tremors, anxiety, difficulty sleeping, thinning of the skin, fine brittle hair, and muscular weakness especially in the upper arms and thighs. More frequent bowel movements may occur, but diarrhea is uncommon. Weight loss, sometimes significant, may occur despite a good appetite (though 10% of people with a hyperactive thyroid experience weight gain) vomiting may occur, and, for women, menstrual flow may lighten and menstrual periods may occurless often (Janet, 2013).

Thyroid hormone is critical to normal function of cells. In excess, it both overstimulates metabolism and exacerbates the effect of the sympathetic nervous system, causing "speeding up" of various body systems and symptoms resembling an overdose of epinephrine (adrenaline). These include fast heart beat and symptoms of palpitations, nervous system tremor such as of the hands and anxiety symptoms, digestive system hypermotility, unintended weight loss, and (in "lipid panel" blood tests) a lower and sometimes unusually low serum cholesterol (Janet, 2013).

Major clinical signs include weight loss (often accompanied by an increased appetite), anxiety, intolerance to heat, hair loss, muscle aches, weakness, fatigue, hyperactivity, irritability, hypoglycemia , apathy, polyuria, polydipsia, delirium, tremor, pretibial myxedema, and sweating. In addition, patients may present with a variety of symptoms such as palpitations and arrhythmias (the notable ones being atrial fibrillation), shortness of breath (dyspnea), loss of libido, amenorrhoea, nausea, vomiting, diarrhea, gynaecomastia and feminization. Long term untreated hyperthyroidism can lead to osteoporosis. These classical symptoms may not be present often in the elderly (Chan, 1999).

Neurological manifestations can include tremors, chorea, myopathy, and in some susceptible individuals (in particular of Asian descent)

periodic paralysis. An association between thyroid disease and myasthenia gravis has been recognized. The thyroid disease, in this condition, is autoimmune in nature and approximately 5% of patients with myasthenia gravis also have hyperthyroidism. Myasthenia gravis rarely improves after thyroid treatment and the relationship between the two entities is not well understood (Klecha, 2008).

In graves' disease, which is the most common form or cause of hyperthyroidism, the eyes may look enlarged because the eye muscles swell and push the eye forward. This can only be resolved surgically by orbital decompression. Sometimes, one or both eyes may bulge. Some patients have swelling of the front of the neck from an enlarged thyroid gland (a goitre). Because hyperthyroidism, especially Graves' disease, may run in families, examinations of the members of a family may reveal other individuals with thyroid problems (Chan, 2011).

Minor ocular (eye) signs, which may be present in any type of hyperthyroidism, are eyelid retraction ("stare"), extra-ocular muscle weakness, and lid-lag. In hyperthyroid stare (Dalrymple sign) the eyelids are retracted upward more than normal (the normal position is at the superior corneoscleral limbus, where the "white" of the eye begins at the upper border of the iris). Extra-ocular muscle weakness may present with double vision. In lid-lag (von Graefe's sign), when the patient tracks an object downward with their eyes, the eyelid fails to follow the downward moving iris, and the same type of upper globe exposure which is seen with lid retraction occurs, temporarily. These signs disappear with treatment of the hyperthyroidism.Neither of these ocular signs should be confused with exophthalmos (protrusion of the eyeball), which occurs specifically and uniquely in hyperthyroidism caused by Graves' disease (note that not all exophthalmos is caused by Graves' disease, but when present with hyperthyroidism is diagnostic of graves' disease). This forward protrusion of the eyes is due to

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immune-mediated inflammation in the retro-orbital (eye socket) fat. Exophthalmos, when present, may exacerbate hyperthyroid lid-lag and stare

(Klecha, 2012).

2.2.3. Thyroid storm

Thyrotoxic crisis (or thyroid storm) is a rare but severe complication of hyperthyroidism, which may occur when a thyrotoxic patient becomes very sick or physically stressed. Its symptoms can include: an increase in body temperature to over 40 degrees Celsius (104 degrees Fahrenheit), tachycardia, arrhythmia, vomiting, diarrhea, dehydration, coma, and death. Thyroid storm requires prompt treatment and hospitalization (Mary, 2012).

2.2.4. Hypothyroidism

 Is a state in which the thyroid gland does not make enough thyroid hormone.Iodine deficiency is often cited as the most common cause of hypothyroidism worldwide but it can be caused by many other factors. It can result from the lack of a thyroid gland or from iodine-131 treatment, and can also be associated with increased stress. Severe hypothyroidism in infants can result in cretinism (Falls, 2003).

2.2.4.1. Classification of hypothyroidism

Hypothyroidism is often classified by association with the indicated organ dysfunction (Simon, 2006)

2.2.4.2. Primary hypothyroidism

 It occurs due to defect in the thyroid gland itself, the most common causes include Hashimoto's thyroiditis (an autoimmune disease) and radioiodine therapy for hyperthyroidism also may developed as aresult of prevoiusly thyroid gland surgery (Falls, 2003).

2.2.4.3. Secondary hypothyroidism

Occurs if the pituitary gland does not create enough thyroid-stimulating hormone (TSH) to induce the thyroid gland to produce enough thyroxine and triiodothyronine.

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Although not every case of secondary hypothyroidism has a clear-cut cause, it is usually caused by damage to the pituitary gland, as by a tumor, radiation, or surgery (Falls, 2003). Secondary hypothyroidism accounts for less than 5% (Agabegi, 2008) or 10% of hypothyroidism cases (Burness, 2008)

2.2.4.4. Tertiary hypothyroidism

Results when the hypothalamus fails to produce sufficient thyrotropin-releasing hormone (TRH). TRH prompts the pituitary gland to produce thyroid-stimulating hormone (TSH). Hence may also be termed hypothalamic-pituitary-axis hypothyroidism. It accounts for less than 5% of hypothyroidism cases (Agabegi, 2008).

2.2.4.5. Signs and symptoms of hypothyroidism

Early hypothyroidism is often asymptomatic and can have very mild symptoms. Subclinical hypothyroidism is a state of normal thyroid hormone levels, thyroxine (T4) and triiodothyronine (T3), with mild elevation of thyrotropin, thyroid-stimulating hormone (TSH). With higher tsh levels and low Free T4 levels, symptoms become more readily apparent in clinical (or overt) hypothyroidism (Hilary, 2003)

Giving up the Ghost, which describes amongst other things the effects on her of thyroid failure, which was treated by permanent medication once belatedly diagnosed (Hilary, 2003)

2.2.4.6. Early and late signs and symptoms of hypothyroidism

• Cold intolerance, increased sensitivity to cold
• Constipation
• Weight gain and water retention (Yeum, 2002)
• Bradycardia (low heart rate – fewer than sixty beats per minute)
• Fatigue
• Decreased sweating
• Muscle cramps and joint pain
• Dry, itchy skin

- Thin, brittle fingernails

- Rapid thoughts

- Depression

- Poor muscle tone (muscle hypotonia)

- Female infertility; any kind of problems with menstrual cycles

- Hyperprolactinemia and galactorrhea

- Elevated serum cholesterol(Yeum, 2002)

- Goiter (enlarged thyroid gland)

- Slow speech and a hoarse, breaking voice – deepening of the voice can also be noticed, caused by Reinke's Edema.

- Dry puffy skin, especially on the face

- Thinning of the outer third of the eyebrows (sign of Hertoghe)

- Abnormal menstrual cycles

- Low basal body temperature

- Thyroid-related depression

- Infertility in both men and women

- Mood swings

- Acute fatigue syndrome

- Stress

- Decreased libido in men

- hypertension; Hypothyroidism increased peripheral vascular resistance, increase diastolic pressure, increased mean arterial pressure (Rubin, *et al.*, 2009)

2.2.4.7. Uncommon signs and symptoms of hypothyrodism

- Impaired memory (Samuels, 2008)

- Impaired cognitive function (brain fog) and inattentiveness (Rubin ,*et al.,* 2009)

- Pradycardia.

- Reactive (or post-prandial) hypoglycemia (Hofeldt, 1972)

- Sluggish reflexes.

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- Hair loss.
- Anemia caused by impaired haemoglobin synthesis (decreased erythropoietin levels), impaired intestinal iron and folate absorption or B_{12} deficiency from pernicious anemia. (Jabbar , 2008)
- Difficulty swallowing
- Shortness of breath with a shallow and slow respiratory pattern
- Increased need for sleep
- Irritability and mood instability
- Yellowing of the skin due to impaired conversion of beta-carotene (Lavelle, 2010) to vitamin A (carotoderma).
- Impaired renal function with decreased glomerular filtration rate.
- Acute psychosis (myxedema madness) (a rare presentation of hypothyroidism).
- Decreased libido in men (Velázquez, 1997) due to impairment of testicular testosterone synthesis.
- Decreased sense of taste and smell (anosmia)
- Puffy face, hands and feet (late, less common symptoms)
- Gynecomastia
- [Deafness (Velázquez, 1997)](#)
- Enlarged tongue (Lavelle, 2013)

2.2.4.8. Subclinical hypothyroidism

Subclinical hypothyroidism occurs when thyrotropin (TSH) levels are elevated but thyroxine (T_4) and triiodothyronine (T_3) levels are normal (Jack, 2002). In primary hypothyroidism, TSH levels are high and T_4 and T_3 levels are low. TSH usually increases when T_4 and T_3 levels drop. TSH prompts the thyroid gland to make more hormones. In subclinical hypothyroidism, TSH is elevated but below the limit representing overt hypothyroidism. The levels of the active hormones will be within the laboratory reference ranges (Jack, 2002).

2.2.4.9. Causes of subclinical hypothyroidism

Iodine deficiency is the most common cause of hypothyroidism worldwide, in iodine-replete individuals hypothyroidism is frequently caused by Hashimoto's thyroiditis (Chakera, 2012 and Gaberscek, 2011) or otherwise as a result of either an absent thyroid gland or a deficiency in stimulating hormones from the hypothalamus or pituitary (Chakera, 2012).

Exposure to iodine-131 from nuclear fallout, which is chemically indistinguishable from non-radioactive isotopes and taken up by the thyroid gland with them, destroys thyroid cells and increases the risk of hypothyroidism (Lazarus,2002).congenital hypothyroidism is very rare, accounting for approximately 0.2% of cases, and can have several causes such as thyroid aplasia or defects in the hormone metabolism. Thyroid hormone insensitivity (most often T3 receptor defect) also falls into this category, although in this condition levels of thyroid hormones may be normal or even markedly elevated (Lazarus, 2002).

Hypothyroidism can result from postpartum thyroiditis up to 9 months after giving birth, characterized by transient hyperthyroidism followed by transient hypothyroidism. The syndrome is seen in 5 to 9% of women. The first phase is typically hyperthyroidism; the thyroid then either returns to normal, or a woman develops hypothyroidism. Of those women who experience hypothyroidism associated with postpartum thyroiditis, 25 to 30% will develop permanent hypothyroidism requiring lifelong thyroxine replacement therapy (Lazarus, 2002). Hypothyroidism can result from de Quervain's thyroiditis, which, in turn, is often caused by having bad case of flu that infects and destroys part, or all, of the thyroid.Hypothyroidism can also result from sporadic inheritance, sometimes autosomal recessive . (Offermanns, 2008).

Temporary hypothyroidism can be due to the Wolff-Chaikoff effect. A very high intake of iodine can be used to temporarily treat hyperthyroidism, especially in an emergency situation. Although iodide is a substrate for thyroid hormones, high levels reduce iodide

organification in the thyroid gland, decreasing hormone production. The antiarrhythmic agent amiodarone can cause hyper- or hypothyroidism due to its high iodine content (Offermanns, 2008). Hypothyroidism can be caused by lithium-based mood stabilizers, usually used to treat bipolar disorder (previously known as manic depression). infact, lithium has occasionally been used to treat hyperthyroidism; other drugs that may produce hypothyroidism include interferon alpha, interleukin-2, and thalidomide (Offermanns, 2008)

2.2.4.10. Stress and hypothyroidism

Stress is known to be a significant contributor to thyroid dysfunction; this can be environmental stress as well as lesser-considered homeostatic stress such as fluctuating blood sugar levels and immune problems. Stress's effect on thyroid function can be indirect, through its effects on blood sugar levels (dysglycemia), (Rettori, 1987), but it can also have more direct effects. Stress may cause hypothyroidism or reduced thyroid functioning by disrupting the hypothalamic pituitary-adrenal (HPA) axis which down-regulates thyroid function,(Sapolsky, 1986) reducing the conversion of T4 to T3, (Ongphiphadhanakul, 1994), weakening the immune system thus promoting autoimmunity (Guhad, 1996), causing thyroid hormone resistance (Kimura,2007), and resulting in hormonal imbalances. Indeed; excess estrogen in the blood caused by chronic cortisol elevations can result in hypothyroid symptoms by decreasing levels of active T3 (Steingold, 1991). Stress also affects thyroid functioning through the sympathetic nervous system (Klecha, 2008). A 1994 study of refugees from East Germany who experienced chronic stress found them to have a very high rate of hypothyroidism or subclinical hypothyroidism, although not all refugees displayed clinical or behavioral symptoms associated with this reduced thyroid functioning (Bauer, 1994). TSH levels correlate positively with physiological stress (Peeters, 2005 and Stouthard,

1994). Adrenal insufficiency can also result in hypothyroid symptoms without affecting the thyroid itself (Abdullatif , 2006).

2.3.1. Diagnosis of thyroid disorders
2.3.2. Thyroid tests are crucial

The signs and symptoms associated with thyroid disease, both hypo- and hyperthyroidism, are nonspecific; thus, laboratory tests play crucial roles in the diagnosis and management of disease, including monitoring response to therapy. (Beers, 2006; Landenson, 2010 & Perros, 2009) In papillary and follicular thyroid cancers, thyroglobulin is crucial for evaluating treatment response, and in medullary thyroid cancer, calcitonin plays a critical role in diagnosis and monitoring treatment response (Abalovich, 2007; Stragnaro, 2011& Kloos, 2009).

2.3.3. Diagnosis of Hyperthyroidism

Hyperthyroidism is characterized by excess thyroid hormones. Hyperthyroidism can occur due to problems in the thyroid itself (primary disease), pituitary (secondary disease), or hypothalamus (tertiary disease). Among the several types of hyperthyroidism, the most common are Graves' disease (diffuse toxic goiter), toxic multinodular goiter, and iatrogenic disease (excess supplementation during replacement therapy). The typical profile for primary hyperthyroidism is low TSH and a high Free T4 level. In some cases of hyperthyroidism, the profile is low TSH, normal Free T4, and high Free T3 levels. A sensitive TSH test is the recommended screening test in patients at risk for hyperthyroidism (Kloos, 2009; Landenson, 2010 & perros, 2010). The TSH test should be done in conjunction with a free T4 test and, in select cases, followed by a FT3 test. In secondary disease, TSH levels may be high or normal with elevated free T4 levels and/or free T3 levels. In addition, the presence of thyroid stimulating antibodies (TSA) is indicative of Graves' disease. The specific presence of thyroid-stimulating antibodies is the key differentiating factor between Graves' disease and other

hyperthyroid conditions.thyroid peroxidase antibodies (TPO) may also be present in Graves' disease. If there are thyroid nodules present, then additional studies such as thyroid scans and/or ultrasound may be needed. Patients who have been treated for hyperthyroidism are also at risk for hypothyroidism (Beers, 2006; Landenson, 2010 & Perros, 2009).

2.3.4. Diagnosis of Hypothyroidism

Hypothyroidism, characterized by insufficient amounts of thyroid hormones, can occur due to problems in the thyroid itself (primary disease), pituitary (secondary disease), or hypothalamus (tertiary disease). The recommended screening test for hypothyroidism is a sensitive TSH test; it can be accompanied by or followed by a Free T4 test, and possibly a Free T3 test (Vanderpump, 1995; Chakera, 2012; Sapolsky, 1986 & Steingold, 1991) .The typical profile for primary hypothyroidism is high TSH and low Free T4 levels; Free T3 levels may be normal or low. One of the most common types of primary hypothyroidism is Hashimoto's disease. It is an autoimmune disease in which the thyroid gland is gradually destroyed by cellular and autoimmune-mediated immune processes. Hashimoto's is characterized by the presence of anti-TPO antibodies and chronic inflammation of the thyroid gland·Secondary hypothyroidism is typically characterized by low free T4 levels and low or normal levels of TSH (Vanderpump, 1995; Sapolsky 1986 & Steingold,

Table1.2. Thyroid test description and utility (Perros, 2010; Baskin, 2002; Glafore, 2009).

Test	Utility
TSH	Measures thyroid-stimulating hormone, also known as thyrotropin (TSH); it is the primary screening test for thyroid dysfunction (hyperthyroidism and hypothyroidism).

Third-generation TSH	A highly sensitive TSH assay, which is especially helpful in diagnosing and monitoring hyperthyroidism. A third-generation TSH test is defined as having functional sensitivity (20% CV) at a level less than 0.02 µIU/mL.
Free T4	Measures free T4; used to evaluate thyroid function; elevations associated with hyperthyroidism, low levels associated with hypothyroidism. Free T4 is the portion of T4 not bound to protein and is metabolically active.
Total T4	Measures all of T4 hormone, protein bound and free.
Free T3	Measures free T3; used to evaluate thyroid function; elevations associated with hyperthyroidism, low levels associated with hypothyroidism. It is the unbound portion of T3 and is metabolically active.
Total T3	Measures all of T3 hormone, protein bound and free.
T uptake	Estimates the amount of protein-binding sites for thyroid hormones.
TPOAb/ATPO	Measures antibodies to thyroid peroxidase (TPOAb/ATPO). TPO converts iodide to organic iodine, an important step in thyroid hormone synthesis. It is useful in differentiating Hashimoto's thyroiditis from other hypothyroid conditions.
Thyroglobulin/ Tg	Measures thyroglobulin; used in differentiated thyroid cancer to monitor treatment response.

TgAb/aTg (antithyroglobulin antibody)	Measures antibodies to thyroglobulin (TgAb/aTg); useful for evaluating for possible interference in thyroglobulin assays; also useful in both hyper- and hypothyroidism and differentiated thyroid cancer
TRAb	Measures TSH receptor antibodies, both inhibitory and stimulating immunoglobulins. Used to confirm Graves' disease.
TSI/TSIAb	Measures thyroid-stimulating antibodies (TSI/TSIAb), a subset of thyroid receptor antibodies that are specific to Graves' disease; therefore, a choice assay to confirm Graves' disease
Thyroxine-binding globulin/TBG	Measures TBG, the major thyroid hormone-binding protein.
Calcitonin	Measures calcitonin, which is produced by the C cells of the thyroid and by medullary thyroid cancer cells; useful as an aid in the diagnosis and management of medullary thyroid cancer.

Table 1.3 Diagnostic indicators of thyroid diseases (Windy, 2009)

T_3	FT_4	Total T_4	TSH	Disease
Increased	Increased	Increased	Decreased	Primary hyperthyroidism
Increased	Increased	Increased	Increased	Secondary hyperthyroidism
Decreased	Decreased	Decreased	Increased	Primary hypothyroidism
Decreased	Decreased	Decreased	Decreased	Secondary hypothyroidism

Table 1.4 Normal ranges of thyroid function tests

Test	Abbreviation	Normal ranges
Serum thyrotropin/thyroid-stimulating hormone	TSH	0.3–3.0 µU/ml
Free thyroxine	FT_4	7–18 ng/l = 0.7–1.8 ng/dl
Serum triiodothyronine	T_3	0.8–1.8 µg/l = 80–180 ng/dl
Radioactive iodine-123 uptake	RAIU	10–30%
Radioiodine scan (gamma camera)	N/A	N/A - thyroid contrasted images
Free thyroxine fraction	FT4F	0.03–0.005%
Serum thyroxine	T_4	46–120 µg/l = 4.6–12.0 µg/dl
Thyroid hormone binding ratio	THBR	0.9–1.1
Free thyroxine index	FT4I	4–11
Free triiodothyronine l	FT_3	230–619 pg/day
Free T3 Index	FT3I	80–180
Thyroxine-binding globulin	TBG	12–20 ug/dl T4 +1.8 µg
TRH stimulation test	Peak TSH	9–30 µIU/ml at 20–30 min.
Serum thyroglobulin l	Tg	0-30 ng/m
Thyroid microsomal antibody titer	TMAb	Varies with method
Thyroglobulin antibody titer	TgAb	Varies with method

- µU/ml = mU/l, microunit per milliliter

- ng/dl, nanograms per deciliter

- µg, micrograms

- pg/day, picograms per day

- µIU/ml = mIU/l, micro-international unit per milliliter

- See [2] for more information on medical units of measure

2.4. Background Study

Cigarette smoking has multiple, effects on thyroid function. Serum thyroxine (T4) levels elevated or are slightly elevated, while serum tri-idothyronine (T3) levels may be increased two to four time. (Sepkovic, *et al.*, 1986) found increased serum T3 and T4 levels in heavy smokers. Of course, terms like increase or decrease do not necessarily indicate abnormal levels.

The abnormalities described include small goiters , thyrotropin-independent increases in thyroid function, most often slight increases in serum tri-iodothyronine and thyroglobulin concentrations.

These findings suggest that smoking in some way directly affected thyroid growth and function, but how it might do so itis not known. Nicotine causes sympathetic activation, which can increase thyroid secretion. Alternatively, nicotine or some other component of tobacco smoke might have direct thyroid-stimulating actions. Despite the association with goiter and small increases in thyroid secretion, in several case-control studies smoking was not a risk factor for either non-toxic or toxic multinodular goiter, indicating that its overall contribution to these disorders must be small.

Cigarette smoking has been linked to thyroid disease, although studies of this problem have not shown consistent affects , with some studies linking smoking to increased thyroid hormone, and others to decreased thyroid hormone levels.

They found that current smokers have higher thyroxine levels and lower thyroid stimulating hormone levels than never smokers and formers smokers. The higher thyroxine levels that detected in smokers , compared to non- smokers diminished when controlled to thyroxine- binding globulin and testosterone. (Shine, et al., 2011).

One related to higher levels of thyroxine – binding globulin and testosterone among smokers compared to non-smokers , and another related to higher levels of thyrotoxins in tobacco smoke in heavy smokers compared to light and moderate smokers.

(Hegedus, et al., 1983) Found acorrelation between thyroid volume and thyroid hormone levels with smoking . asignificant correlation in a randomly selected groups of 219 subjects , they found that increase in thyroid volume, thyroxine , tri-iodothyronine and iodide deficiency and decrease in thyroid stimulating hormone by inhalationof thiocyanate.

In regard to thyroglobulin (Tg) levels,(*Christensen, et al., 2007).* found that smokers had significantly higher levels of serum Tg in comparison to non-smokers or ex-smokers.

(Hegedus, et al., 2009). found the same results among smokers who were compared with individuals who had never smoked. They also found that Tg was positively correlated to the volume of the thyroid gland, with a higher correlation in smokers. However, even if the goitrous subjects in this study serum Tg levels remained higher among smokers, indicating that smoking has an independent thyroid stimulating effect.

Similar results were found in two other case-control studies. The prevalence of smokers was 56% and 41% respectively in patients with Graves' disease and 41% and 30% in the control groups. The relative risk (RR) - odds ratio - was 1.9 and 1.4 respectively. Another study showed a prevalence of smokers of about 50% among hyperthyroid patients.

(Shine, et al., 2011). on the other hand, failed to confirm an increased prevalence of smokers among those with Graves' hyperthyroidism without relevant ophthalmopathy.

1.4. Objectives

1.4.1. General objective

Assess serum thyroid hormones and thyroid stimulating hormone among Sudanese smokers in Khartoum State in comparison with healthy none smokers volunteers.

1.4.2. Specific objectives

1. To estimate serum thyroid hormones and thyroid stimulating hormones levels among Sudanese smokers and non- smokers.

2. To study the correlation between age and duration of smoking on thyroid hormones and thyroid stimulating hormone among smkers.

1.3. Rationale

The incidence of thyroid dysfunction was increase in the last years which may affect other organs causing abnormalities including cardiac and skeletal muscle problems, many people may die from the heart attack and/ or become unable to do work. Most of these complications may arrive from the thyroid dysfunction.

Cigarette smoking has multiple effects on the thyroid gland. It has both stimulatory as well as inhibitory actions on thyroid function and is also a powerful risk factor for development of thyroid disease. Graves' disease, Graves' ophthalmopathy and thyroid hormone abnormalities have all been linked to smoking.

To the best of our knowledge there has been no previous study established to assess the association between smoking and thyroid dysfunction in sudan. Therefore, the present study was conducted mainley to assess the effect of Cigarette smoking on thyroid hormones.

2. Materials and methods

2.1. Study approach

This study utilized the quantitive approach in which the thyroid hormones and thyroid stimulating hormone are investigated in Sudanese smokers in Khartoum state .

2.2. Study design

The study is descriptive and design is case control community base study

2.3. Study area and duration

This study was conducted in Khartoum state from April to October 2013

2.4. Study population

Eighty plasma samples were collected from adult Sudanese individuals smokers with different sex and age, in addition to fifty health volunteers match in age and sex with tests group as a control .

2.5. Selection criteria

i. Exclusion criteria

Tests and control subjects on thyroid treatment, hypertension and/or diabetes mellitus were excluded

ii. Inclusion criteria

Sudanese people with different sex, age group range from (20- 65) years and apparently healthy individuals as control group.

For cigarette smokers study group is heavy smoker which is according to the recommendations of the world health organization (who) smokers with daily cigarettes consumption of more than towenty pieces per day.

2.6. Study variable

Both quantitative and qualitative variables were included.

2.7. Sample size

Sample size was calculated according to the following formula

N = s* z/d

N = sample size

Z = confidence level

S = standard deviation

D = desiredmaginal error

Due to short time and the financial problem and reagent limitation, the sample size was restricted to 130 subjects

2.8. Tools of data collection

Structural interviewing questionnaire was designed to collect and maintain all valuable information case examined.

2.9. Sample processing

Three ml of venous blood samples were collected from both test and control subject, by standard procedure. Then samples were drawing in heparinized containers and mixed then centrifuged at 3600 rpm for 5 mints and the plasma was separated immediately, and stored at 2-8°C until analyzed.

2.10. Materials

Enzyme –immunoassay (EIA) for quantitative determination of Thyroid stimulating hormone (TSH) and Thyroxine (T4), pathozyme TSH reagent, Pathozyme T4 reagent and pathozyme (T3) reagent. kits were provided from Marina company.

2.11. Method

2.11.1Thyroid stimulating hormones measurement

i.Principle

Specific anti-TSH antibodies are coated onto microtitration wells. Test sera are applied. Then goat anti- TSH labeled with Horseradish peroxidase enzyme (conjugate) is added .if human TSH is present in the sample it will combine with the antibody on the well and the enzyme conjugate, resulting in the TSH molecule being sandwiched between the solid phase and the enzyme linked antibodies.After incubation, the wells are washed to remove unbound labeled antibodies. On addition of the substrate (TMB), a colour will develop only in those wells in which the enzyme conjugate is present, indicating the presence of TSH. The enzyme reaction is stopped by the addition of dilute hydrochloric acid and the absorbance is then measured at

 450 nm.

ii. procedures

see appendixes page 54

iii. Calculation

Using a software package choose a quadratic regression curve fit.

2.11.2. Thyroxine measurement

i. principle

Specific anti- T4 antibodies are coated onto microtitration wells. Test sera are applied .T4 with Horseradish peroxide enzyme (conjugate) is added which competes with the released serum T4 for available binding sites on the solid phase.

After incubation, the wells are washed with water to remove any unbound T4 or T4 enzyme conjugate. On addition of the substrate (TMB), a colour develops only in those wells in which enzyme are present, indicating a lack of serum T4. The reaction is stopped by

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the addition of dilute Hydrochloric acid and the absorbance in then measured at 450nm filter.

ii. procedures

see appendixes page 54

iii. Calculation

Using a software package choose a polygon with data extrapolation curve fit

2.11.3 Tri-iodothyronine measurement

i. principle

Specific anti- T3 antibodies are coated onto microtitration wells. Test sera are applied .T3 with Horseradish peroxide enzyme (conjugate) is added which competes with the released serum T3 for avialable binding sites on the solid phase.

After incubation, the wells are washed with water to remove any unbound T4 or T4 enzyme conjugate . on addition of the substrate (TMB), a colour develops only in those wells in which enzyme is present , indicating a lack of serum T4. The reaction is stopped bythe addition od dilute Hydrochloric acid and the absorbance in then measured at 450nm filter.

ii. procedures

see appendixes page 54

iii. Calculation

Using a software package choose a polygon with data extrapolation curve fit.

2.12 Quality control

The precision and accuracy of all method in this study were checked each time a patch was analyzed by including commercially prepared control done by using normal and pathological human sera for

thyroid hormone. Result ±2SD of the target value of the control sera were accepted.

2.13 Data analysis

The data were analyzed using statistical package social science (SPSS) computer system. Mean, standard deviations were obtained. T test was used to compare between means, P value was considered significant ≥ 0.05, correlation (R) between thyroid hormones with both age and duration of smoking is considered to be statistically significant at (P $\leq$ 0.05)

3. Results

The study populaion comprised of 80 healthy haevy Sudaneses smoker. At mean age of 35.2± 2.25 years, and range from 20 - 23 of cigarette smoking were agreed to be study group. In addition to 50 healthy volunteers with age and sex matched served as control group .

As illustrated in table 1 , 2 and 3 there is significant decrease in thyroid stimulating hormone in healthy haevy smoker respectively when compare with control groups.

(1.68 ± 1.11 versus 2.21 ± .99 μIu/ml , respectively) , (p ≤ 0.05) Where as there is significant increase in Thyroxine and Tri-iodothyronine in healthy haevy smoker 146.8 ± 39 versus 96.7 ± 25.4 μIu/ml , 2.36 ± .76 versus 1.96 ± .59 μIu/ml respectively) (p ≤ 0.05) .

As presented in table (4) there is significant correlation between smoking and both age and the duration of smoking in healthy haevy sudanese smoker (p ≥ 0.05).

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Table 4 .3

Comparison of Thyroid stimulating hormone (TSH) in healthy Sudanese smokers compared with that of the control group.

Groups	Mean (μlu/ml)	Std . deviation	Range	P . value
Tests 80	1.68	1.11	1.0 – 4.1	
Control 50	2.21	0.99	1.0 - 3.5	0.000

 * The mean difference is significant at $P \leq 0.05$

 ** The mean difference is significant at $P \leq 0.01$

*** The mean difference is significant at $P \leq 0.001$

Table 4.4: Comparison of Thyroxine (T4) in healthy Sudanese smokers compared with that of the control group.

Groups	No	Mean (μlu/ml)	Std.deviation	Range	P.value
Test	80	146.8	39	67 - 230	0.000
Control	50	96.7	25.4	48 - 148	

*The mean difference is significant at $P \leq 0.05$

** The mean difference is significant at $P \leq 0.01$

*** The mean difference is significant $P \leq 0.001$

Table 4.5: Comparison of Tri- iodothyronine (T3) in healthy Sudanese smokers with their control

Group	No	Mean (nM/ml)	Std. deviation	Range	P. value
Test	80	2.36	.76	0.8 - 3.9	0.001
Control	50	1.96	0.59	1.7 - 3.0	

 * The mean difference is significant at P ≤ 0.005

** The mean difference is significant at P ≤ 0.01

*** The mean difference is significant at P ≤ 0.001

Table 4.6: Correlation of Thyroid hormones in healthy Sudanese smokers with age and duration of smoking.

Variable		Age	duration
TSH	Pearson (r) correlation	0.129	0.229
	Sig. (2 – tailed) (p)	0.14	0.01
T4	Pearson correlation	0.189	0.043
	Sig. (2- tailed	0.032	0.026
T3	Pearson correlation	0.245	0.068
	Sig. (2 – tailed)	0.005	0.439

* Correlation is significant at the 0.01 level (2 – tailed)

** Correlation is significant at the 0.05 level (2 – tailed)

5.1 Discussion

In this community based case control study which carried out during the period of April – October 2013 in Khartoum State to determine Thyroid hormones and thyroid stimulating hormone levels in Sudanese Cigarette Smokers. {all males; 80 Cigarette smokers and 50 non-smokers} were investigated.

  The current study showed significant increase in Thyroxine level in healthy smokers concentration (ng/ml) mean in Cigarette smokers were 146.8 ng/ml

  (P-Value=.000)   and for non-smokers were 96.7 ng/ml, which indicate that smokers have higher Thyroxine level than non-smokers.

  Tri-iodothyronine in Cigarette smokers were 2.36 (P-Value=.001) and for non-smokers were 1.96 our result were apparently agreed with previous studies of

 (Miller., 2010) and disagree with the study of (Benowitz., 2003).

Thyroid stimulating hormone were 1.68 (P-Value=.000) and for non-smokers were 2.21 Our result were apparently agree with previous studies of (Miller., 1997 Benowitz., 1996 ; and Jefferis., 2001 and their colleagues) were apparently agree with previous studies of (Miller., 2010 ; Benowitz., 2011 ; Jefferis., 2012 and their colleagues).

These findings suggested that smoking in some way directly affected thyroid growth and function, but how it might do so it is not known. Nicotine causes sympathetic activation, which can increase

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thyroid secretion. Alternatively, nicotine or some other component of tobacco smoke might have direct thyroid-stimulating actions. Despite the association with goiter and small increases in thyroid secretion, in several case-control studies smoking was not a risk factor for either non-toxic or toxic multinodular goiter, indicating that its overall contribution to these disorders must be small. (Miller., 2010) .

This study also showed that there is weak correlation between h smoking and thyroid stimulating hormone level (TSH) with age and duration of smoking This note is similar to those reported by(Paola *et al.*, 2007 ; Neal *et al* 2009 & Gledhill *et al* ., 1988). who cited within each ethnic group, young adult have normal serum levels of Thyroid stimulating hormones , which decline slightly with age and duration of smoking during the geriatric period.

The present study show strong correlation between smokers with thyroxine (T4) and tri-iodothyronine (T3). These findings might be due to defect in thyroid stimulating hormone receptors on the thyroid gland and thus T3 & T4 were found to be increase whereas, TSH level is decreased. Also negative correlation might be due excessive utilitilization of TSH in a group with hyperthyroidism so the T3 & T4 were found to be high whereas, TSH level is low. These findings were similar as those obtained by

 (Rashmi *et al.*, 2003) who reported. These findings suggest that smoking in some way directly affected thyroid growth and function, but how it might do so itis not known. Nicotine causes sympathetic activation, which can increase thyroid secretion. Alternatively, nicotine or some other component of tobacco smoke might have direct thyroid-stimulating actions. Despite the association with goiter and small increases in thyroid secretion, in several case-control studies smoking was not a risk factor for either non-toxic or toxic multinodular goiter, indicating that its overall contribution to these disorders must be small.

5.2. Conclusion

study shows that there is increase plasma Thyroxine level, in Sudanese smokers in compare to control of non-smokers individuals, slight increase in Tri-iodothyronine activity and decrease in Thyroid stimulating hormone activity.

There is significant increase of smoking duration on plasma Thyroxine level according to our statistical study.

There is significant decrease of smoking duration on Thyroid stimulating hormones activity according to our statistical study.

There is significant increase of smoking duration on Tri-iodothyronine according to our statistical study.

Also the study found that smoking had weak correlation with thyroid stimulating hormone (TSH) and stronge correlation with thyroxine (T4) and tri-iodothyronine (T3).

5.3. Recommendation

1-Thyroid function test must be assessed and screened for healthy heavy smokers.

2-Physicians should use caution when interpreting Thyroid hormones levels specialy among smokers.

3-Larger sample size with controlled condition should be focus to establish the effect of smoking on Thyroid hormones level.

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