2. Literature Review

2.1 Smoking

2.1.1 Definition

Tobacco smoking is the practice of burning tobacco and inhaling the smoke (consisting of particle and gaseous phases). (A more broad definition may include simply taking tobacco smoke into the mouth, and then releasing it, as is done by some with tobacco pipes and cigars). The practice may have begun as early as 5000-3000 BC (Gately*et al*., 2004).

Smoking is the inhalation of the smoke of burning tobacco encased in cigarettes, pipes, and cigars. Casual smoking is the act of smoking only occasionally, usually in a social situation or to relieve stress. A smoking habit is a physical addiction to tobacco products. Many health experts now regard habitual smoking as a psychological addiction, too, and one with serious health consequences (Berrettini and Batra*et al.,* 2003).

2.1.2 Tobacco in the world

Tobacco in the world about 550 million kegs of tobacco is grown in 4.2 lakh hectares of land and 250 million kg of tobacco is released for local consumption. In India 337 million people above 10 years of age consume tobacco. Every year 1 million people die prematurely due to tobacco smoking related diseases (devaranavadgi et al, 2012).

The mechanism by which smoking increase the cardiovascular diseases are unclear. Recently it has been suggested that smoking adversely affects the concentration of plasma lipids and lipoprotein levels. However studies to date have revealed incomplete, inconclusive or conflicting results about the association of smoking on the plasma lipids and lipoproteins. It has been estimated that 1% increase in plasma concentration is associated with a 2.7% increase in risk, as tobacco is grow more in northern Karnataka and also due to paucity of work done in this part the present study was undertaken. The present study provides a detailed profile of the plasma lipid and lipoprotein levels depending on the duration and intensity of smoking (Devaranavadgi al, 2012)

2.1.3 Epidemiology

The detailed mortality and morbidity statistics on smoking tend to conceal the overall impact of the habit on health. About 3 million people die each year from smoking in economically developed countries, half of them before the age of 70. Cancers of eight sites are recognized as being caused by smoking lung cancer almost entirely and the others (upper respiratory, bladder, pancreas, esophagus, stomach, kidney, leukemia) to a substantial extent. Six other potentially fatal diseases are also judged to be caused by smoking: respiratory heart disease, chronic obstructive lung disease, stroke, pneumonia, aortic aneurysm and ischemic heart disease, the most common cause of death in economically developed countries. Non-fatal diseases, such as peripheral vascular disease, cataracts, hip fracture, and periodontal disease, which cause appreciable disability, cost and inconvenience; are also caused by smoking. In pregnancy, smoking increases the risk of limb reduction defects, spontaneous abortion, ectopic pregnancy, and low birth weight. While there are some diseases for which smoking shows a protective effect, the 'benefits' of these are negligible in relation to the illness and premature mortality caused by smoking. About 20% of all deaths in developed countries are caused by smoking; an enormous human cost which can be completely avoided. (Doll *et al*., 1994).

2.1.4 Social context of tobacco cigarette smoking

Definition: The social environment, social context, sociocultural context, or milieu, refers to the immediate physical and social setting in which people live or in which something happens or develops (Yang *et.al,* 2010). The effectiveness of tobacco-related public health messages may be diluted by the unintentional stigmatization of smoking behaviors. As observed, smoking is more prevalent in low-income groups and the danger is that stigmatizing smokers will exacerbate existing health-related inequalities by limiting their

(and perhaps their children's) access to health services. Some have argued that smoke-free legislation may have contributed to feelings of stigma when smoking in public yet there is little evidence to suggest that such legislation has contributed to increased smoking in the home. However due to the clustering of socio-economic groups in particular geographical areas, some researchers have argued that stigmatizing smokers could lead to 'smoking islands' which may reinforce rather than discourage smoking (Chapman and Freeman *et,al.* 2008).

There is some evidence that different socio-economic groups understand, respond to and reflect on smoking bans in public places differently. For example it has been hypothesized that the lower uptake of smoking cessation among lower income groups may be due in part to a disparity between the 'middle-class' professionals delivering tobacco control initiatives and the 'marginalized' low income smoker. One solution might be to include the targeted groups in the delivery of interventions, which may help raise the participation of low-income smokers (Graham *et.al*, 2012).

In the context of smoke-free homes, interventions some have argued that such strategies may have unintentional outcomes for socially disadvantaged mothers. Socially disadvantaged women have higher levels of stress and quitting cigarettes may be more difficult to manage among this group (Graham *et.al*, 2012).

Interventions that aim to reduce smoking in the home could focus on 'parents' and not single out mothers who smoke. Moreover, second-hand smoke messages should focus on the health concerns of second-hand smoke exposure and promote social inclusion, optimism and hope.

It is important that already marginalized groups better understand stigma and smoking in order that initiatives that aim to reduce children's exposure to second hand smoke can

build on smokers' sense of self-efficacy and control rather than contribute to further perceptions of stigma (Farrimond*et.al,* and Joffe*et.al,* 2006).

2.1.5 Effect of cigarette smoking

2.1.5.1 Smoking and cardiovascular risk

Cigarette smoking is associated with increased CHD morbidity and mortality. The use of filters was proven ineffective to mitigate the health hazards of smoking. Acute active and passive smoking can increase arterial stiffness; data for chronic smoking is contradictory. As expected, smoke-free policies, when implemented, may lead to a reduced incidence of acute coronary events. Furthermore, in a meta-analysis quitting smoking was shown to significantly reduce CHD mortality. This protective effect was greater than that achieved by other treatments such as the use of thrombolysis, aspirin and beta-blockers, as reported in a previous meta-analysis.

Cochrane systematic Review found that smoking cessation was associated with a significant reduction in the risk of all-cause mortality in CHD patients, a result that was regarded 'substantial compared with other secondary preventive therapies such as cholesterol lowering' (Mackay *et al* 2010).Cigarette smoking has been also related to an increased risk of non-fatal and fatal stroke which rapidly decreases after quitting smoking especially in lighter smokers. Of note, this link between cigarette smoking and stroke is characterized by a strong dose response relationship (Shah *et al.*, 2010).

2.1.5.2 Smoking and Pulmonary diseases

Chronic obstructive pulmonary disease (COPD), a disease causally linked to smoking in the 1964 report. Mortality from (COPD) continues to rise, and smoking remains responsible for the majority of cases. For asthma, another obstructive lung disease, the evidence was found to be sufficient to infer that smoking is a cause of incident asthma in

adolescents. Increase neurogenic inflammation in the bronchial airway (Bessac*et al.*, 2008).

The mechanisms by which active smoking could contribute to the causation of asthma include chronic airways inflammation, impaired muco-ciliary clearance, impaired growth of the lungs during childhood, and increased bronchial hyper responsiveness (Simon and Liedtke*et al.*, 2008).

2.1.5.3 Cigarette Smoking effect on total antioxidant status

The substantially higher additive genetic effect on residual total antioxidant status (TAS) phenotypic variance in smokers is not expected. Cigarette smoking is a known environmental factor with a rich source of free radicals, which can reduce antioxidant capacity (Whitehead *et al.*, 2001).

Cigarette smoking would be expected to have a strong effect on total antioxidant status (TAS), which might disguise rather than enhance genetic contributions. However, because plasma antioxidants are directly stressed by cigarette smoke–derived free radicals, cigarette smoking could have triggered biological antioxidant responses that are largely under genetic control. It could also be possible that cigarette smoking has created a more homogeneous environment so that the genetic contribution becomes more readily detectable by the statistical model. Indeed, the relationships between DNA sequence polymorphisms and some phenotypic changes, such as hemostatic proteins, were strengthened in smokers (Humphries *et al.*, 1999).

2.1.5.4 Smoking and cancer

Considerable epidemiologic evidence, including data from studies in which measures have been taken to address potential confounding, indicates that smokers are at an increased risk for liver cancer specially hepatocellular carcinoma (IARC *et al.*, 2004 and *Marshall et al.*, 2011).

In the latter systematic review, Botteri and colleagues searched the literature through May 2008 and evaluated data from six studies that compared the association of smoking and colon cancer separately from smoking and rectal cancer mortality. The RRs of ever smokers and current smokers were significantly higher for rectal cancer mortality than for colon cancer (Botteri et al. 2008a).

2.1.5.5 Cigarette smoking generalized effects

The evidence is sufficient to infer that cigarette smoking increases risk for all-cause mortality in men and women. The evidence is sufficient to infer that the relative risk of dying from cigarette smoking has increased over the last 50 years in men and women in the United States. The evidence is sufficient to infer a causal relationship between smoking and diminished overall health. Manifestations of diminished overall health among smokers include self-reported poor health, increased absenteeism from work, and increased health care utilization and cost (Thun*et al.*, 2013).

2.1.5.6 Cigarette smoking affecting fetal growth and death

The effects of maternal smoking during pregnancy on birth weight have been recognized. Studies of tobacco use and birth weight must necessarily include consideration of the concurrent effects on gestational age. Maternal smoking is associated with a 27% increase in the risk of preterm delivery compared with nonsmokers. Several studies have also found an increased risk of preterm delivery among smokeless tobacco users compared with tobacco nonusers (Baba *et al.*, 2012; England et *al.*, 2013; Gupta and Sreevidya*et al.*,2004).

In studies of human infants, prenatal tobacco exposure affects recovery from hypoxia in preterm infants. Infants also display impaired arousal patterns that correspond to cotinine levels. These changes in autonomic function and/or arousal could increase the risk of

sudden infant death syndrome (SIDS), although a causal pathway has not been established (Richardson *et al.*, 2009).

Nicotinic acetylchonine receptors (nAChRs) are receptors that are ordinarily activated by endogenous acetylcholine, but that also can be stimulated by nicotine, resulting in disruption of normal cholinergic signaling (Albuquerque *et al.*, 2009). nAChRs are expressed early in fetal development in the central, peripheral, and enteric nervous systems, and transient, regional patterns of increased nAChR expression occur throughout perinatal and postnatal development. nAChRs are involved in neurogenesis, migration, differentiation, and synaptogenesis, in regulating the growth of developing neurites, guiding path finding of these projections, and mediating pruning of hippocampal and cortical neurons through effects on apoptosis. Depending on the subunit composition, and the dose and duration of exposure, exogenous nicotine can activate or inactivate a given receptor, potentially altering fetal development. Stillbirth (fetal death after 28 weeks gestation) and neonatal death (death within 28 days of birth) are directly affected and may occur (Dwyer *et al.*, 2008).

2.1.6 Environmental tobacco smoking

Environmental tobacco smoke that is inhaled involuntarily or passively by someone who is not smoking. Environmental tobacco smoke is generated from the sidestream (the burning end) of a cigarette, pipe or cigar or from the exhaled mainstream (the smoke puffed out by smokers) of cigarettes, pipes, and cigars. Environmental tobacco smoke was classified as a "known human carcinogen" in 2000, based on the causal relationship observed between passive exposure to tobacco smoke and human lung cancer and based also on studies that have conclusively shown an increased risk of lung cancer in nonsmoking women living with smoking husbands or working with smoking co-workers. Environmental tobacco smoke is abbreviated ETS. Inhaling environmental tobacco

smoke is called involuntary or passive smoking. Leading to different forms of cancer (lung cancer and breast cancer) with an increased rates of brain tumor, in addition to elevated risks of asthma and other lung complications, cardiac disorders, ear, nose and throat infections and many problems during pregnancy leading futuristic problems (Samet*et al.,* 2008).

2.1.7 Cigarette smoking and trace elements

Tobacco smoke contains many oxidants and free radicals that can cause damage to lipids, proteins, DNA, carbohydrates and other bio-molecules. In-vivo antioxidant nutrients which include vitamin C, Se, Zn and Cu play a crucial role in defending against oxidant damage (Al-Numair*et al.,* 2006).

Each puff of a tobacco contains 104 oxidants in the tar phase and 105 in the gas phase. It has been demonstrated that one of the prominent risk factors for increased lipid peroxidation is smoking (Kocyigit*et al.,* 2001).

In some studies, it has been shown that tobacco smoking can alter trace elements metabolism (Dubick*et al.,* 1991).

Since trace elements are required in small quantities as an essential component of antioxidative enzymes (cytoplasmic Cu-Zn- superoxide dismutase contains copper and zinc metals as cofactors), tobacco smoking can affect its activities, thereby indirectly damaging trace elemental metabolism (Zahraie*et al.,* 2005).

The search for its etiology has led to some theories that dietary intake of minerals and in particular, trace elements may have a role in the progress of atherosclerosis. The present study was conducted to obtain data on the effects of cigarette smoking to trace elements, total cholesterol and triglycerides in leading to the risk of CAD (Singh *et al.,* 1998).

2.2 Copper

Copper (Cu) is a relatively soft yet tough metal with excellent electrical and heat conducting properties. Copper is widely distributed in nature both in its elemental form and in compounds. Copper forms alloys with zinc (brass), tin (bronze), and nickel (cupronickel, widely used in coins) (Bishop *et al.,* 2010).

2.2.1 Health effects

The copper content in the normal human adult is 50–120mg. Copper is distributed through the body with the highest concentrations found in liver, brain, heart, and kidneys. Hepatic copper accounts for about 10% of the total copper in the body.46 Copper is also found in cornea, spleen, intestine, and lung(Sakar*et al., 1994).*

Copper is a component of several metalloenzymes, including ceruloplasmin, cytochrome C oxidase, superoxide dismutase, tyrosinase, metallothionein, dopamine hydroxylase, lysyl oxidase, clotting factor V, and an unknown enzyme that cross-links keratin in hair. Ceruloplasmin is the best known yet the least understood copper protein. It is a 2-globulin, and each 132,000-molecular-weight molecule contains six atoms of copper.Ceruloplasmin levels are influenced by hormones (Sakar*et al., 1994).*

2.2.2 Absorption, transport, and excretion

An average day's diet may contain 10 mg or more of copper (Sakar*et al., 1994).*The amount of copper absorbed from the intestine is 50%–80% of ingested copper (Milne *et al.,* 1996).

About half of dietary copper is excreted in feces. The exact mechanisms by which copper is absorbed and transported by the intestine are unknown. Copper absorption is impaired in severe diffuse diseases of small bowel, lymph sarcoma, and scleroderma (Sakar*et al., 1994).*

Copper losses in the urine and sweat are approximately 3% of dietary intake. Menstrual losses of copper are minor (Milne *et al.,* 1996).

2.2.3 Deficiency

Copper deficiency is observed in premature infants. Copper deficiency is related to malnutrition, malabsorption, chronic diarrhea, hyperalimentation, and prolonged feeding with low-copper, total-milk diets. Signs of copper deficiency include:

(1) Neutropenia and hypochromic anemia in the early stages.

(2) Osteoporosis and various bone and joint abnormalities that reflect deficient copper-dependent cross-linking of bone collagen and connective tissue.

(3) decreased pigmentation of the skin and general pallor.

(4), in the later stages, possible neurologic abnormalities (hypotonia, apnea, psychomotor retardation) (Milne *et al.,* 1996).

Subclinical copper depletion contributes to an increased risk of coronary heart disease. An extreme form of copper deficiency is seen in Menkes disease. This invariably fatal, progressive brain disease is characterized by peculiar hair, called kinky or steely, and retardation of growth. Clinical forms include progressive mental deterioration, coarse feces, and disturbance of muscle tone, seizures, and episodes of severe hypothermia. Symptoms of Menkes disease usually appear at the age of 3 months and death usually occurs in 5-year-olds (Milne *et al.,* 1996).

2.2.4 Toxicity

Wilson's disease is a genetically determined copper accumulation disease that usually presents between the ages of 6 and 40 years. Its manifestations include neurologic disorders, liver dysfunction, and Kayser-Fleischer rings (green-brown discoloration) in the cornea caused by copper deposition. Early diagnosis of Wilson's disease is important because complications can be effectively prevented and in some cases the disease can be halted with use of zinc acetate or chelation therapy(Milne *et al.,* 1996).

2.2.5 Laboratory evaluation of copper status

Copper is measured by flame AAS, ICP-MS, ICP-AES, and ASV. Serum copper and urine copper are used to monitor the nutritional adequacy and to screen for Wilson's disease, copper toxicity in premature children, and in children with Indian childhood cirrhosis (ICC), which is not limited to Indian children (Bishop *et al.*, 2010).

2.3Magnesium

Magnesium (Mg^{2+}) is the fourth most abundant cation in the body and second most abundant intracellular ion (Bishop *et al.*, 2010).

2.3.1 Magnesium physiology

Magnesium (Mg^{2+}) is the fourth most abundant cation in the body and second most abundant intracellular ion. The average human body (70 kg) contains 1 mole (24 g) of $Mg2^{+}$. Approximately 53% of Mg^{2+} in the body is found in bone, 46% in muscle and other organs and soft tissue, and less than 1% is present in serum and red blood cells.15 Of the $Mg2^{+}$ present in serum, about one third is bound to protein, primarily albumin. Of the remaining two thirds, 61% exists in the free or ionized state and about 5% is complexed with other ions, such as PO_4^{-} and citrate. Similar to Ca^{2+}, its free ion is physiologically active in the body (Whang*et al.*, 1997).

The role of Mg^{2+} in the body is widespread. It is an essential cofactor of more than 300 enzymes, including those important in glycolysis, transcellular ion transport, neuromuscular transmission, synthesis of carbohydrates, proteins, lipids, and nucleic acids, and release of and response to certain hormones. The clinical usefulness of serum Mg^{2+} levels has greatly increased in the past 10 years as more information about the analyte has been discovered. The most significant findings are the relationship between abnormal serum Mg^{2+} levels and cardiovascular, metabolic, and neuromuscular disorders. Although serum levels may not reflect

total body stores of Mg^{2+}, serum levels are useful in determining acute changes in the ion (Bishop *et al.*, 2010).

2.3.2 Regulation

Rich sources of Mg^{2+} in the diet include raw nuts, dry cereal, and "hard" drinking water; other sources include vegetables, meats, fish, and fruit (Elin*et al., 1994*).

Processed foods, an ever-increasing part of the average U.S. diet, have low levels of Mg^{2+} that may cause an inadequate intake. This in turn may increase the likelihood of Mg^{2+} deficiency (Elin*et al., 1994*).

The small intestine may absorb 20%–65% of the dietary Mg^{2+}, depending on the need and intake (Elin*et al., 1994*).

The overall regulation of body Mg^{2+} is controlled largely by the kidney, which can reabsorb Mg^{2+} in deficiency states or readily excrete excess Mg^{2+} in overload states. Of the nonprotein-bound Mg^{2+} that gets filtered by the glomerulus, 25%–30% is reabsorbed by the proximal convoluted tubule (PCT), unlike Na^{+}, in which 60%–75% is absorbed in the PCT. Henle's loop is the major renal regulatory site, where 50%–60% of filtered Mg^{2+} is reabsorbed in the ascending limb. In addition, 2%–5% is reabsorbed in the distal convoluted tubule (Polancic*et al.*, 1991).

The renal threshold for Mg^{2+} is approximately 0.60–0.85 mmol/L (1.46–2.07 mg/dL). Because this is close to normal serum concentration, slight excesses of Mg^{2+} in serum are rapidly excreted by the kidneys. Normally, only about 6% of filtered Mg^{2+} is excreted in the urine per day(Elin*et al., 1994*).

Mg^{2+} regulation appears to be related to that of Ca^{2+} and Na^{+}. Parathyroid hormone (PTH) increases the renal reabsorption of Mg^{2+} and enhances the absorption of Mg^{2+} in the intestine. However, changes in ionized Mg^{2+} have a far greater effect on PTH secretion. Aldosterone and thyroxine apparently have the opposite effect of PTH in the kidney, increasing the renal excretion of Mg^{2+} (Polancic*et al.*, 1991).

2.3.3 Clinical applications

2.3.3.1 Hypomagnesaemia

Hypomagnesaemia is most frequently observed in hospitalized individuals in intensive care units or those receiving diuretic therapy or digitalis therapy. These patients most likely have an overall tissue depletion of Mg^{2+} as a result of severe illness or loss, which leads to low serum levels. Hypomagnesaemia is rare in non-hospitalized individuals (Polancic*et al.*, 1991).

There are many causes of hypomagnesemia; reduced intake is least likely to cause severe deficiencies in the United States. An Mg^{2+} deficient diet as a result of starvation, chronic alcoholism, or Mg^{2+} deficient IV therapy can cause a loss of the ion. Various GI disorders may cause decreased absorption by the intestine, which can result in an excess loss of Mg^{2+} via the feces. Malabsorption syndromes; intestinal resection or bypass surgery; nasogastric suction; pancreatitis; and prolonged vomiting, diarrhea, or laxative use may lead to an Mg^{2+} deficiency. Neonatal hypomagnesemia has been reported as a result of various surgical procedures. A primary deficiency has also been reported in infants as a result of a selective malabsorption of the ion (Polancic*et al.*, 1991).

A chronic congenital hypomagnesemia with secondary hypocalcemia (autosomal recessive disorder) has also been reported; molecular studies have revealed a specific transport protein defect in the intestine(Schlingman*et al.*, 2002).

Mg^{2+} loss due to increased excretion by way of the urine can occur as a result of various renal and endocrine disorders or the effects of certain drugs on the kidneys. Renal tubular disorders and other select renal disorders may result in excess amounts of Mg^{2+} being lost through the urine because of decreased tubular reabsorption (Bishop *et al.*, 2010).

Several endocrine disorders can cause a loss of Mg^{2+}. Hyperparathyroidism and hypercalcemia may cause increased renal excretion of Mg^{2+} as a result of excess

Mg^{2+} ions. Excess serum Na^{+} levels caused by hyperaldosteronism may also cause increased renal excretion of Mg^{2+}. A pseudohypomagnesemia may also be the result of hyperaldosteronism caused by increased water reabsorption. Hyperthyroidism may result in an increased renal excretion of Mg^{2+} and may also cause an intracellular shift of the ion. In persons with diabetes, excess urinary loss of Mg^{2+} is associated with glycosuria (Sims and Whang*et al.,* 2000).

Hypomagnesaemia can aggravate the neuromuscular and vascular complications commonly found in this disease. Some studies have shown a relationship between Mg^{2+} deficiency and insulin resistance; however, Mg^{2+} is not thought to play a role in the pathophysiology of diabetes mellitus (Sims and Whang*et al.,* 2000).

The American Diabetes Association has issued a statement regarding dietary intake of Mg^{2+} and measurement of serum Mg^{2+} in patients with diabetes (Sims and Whang*et al.,* 2000).

Several drugs, including diuretics, gentamicin, cisplatin, and cyclosporine, increase renal loss of Mg^{2+} and frequently result in hypomagnesemia. The loop diuretics, such as furosemide, are especially effective in increasing renal loss of Mg^{2+}. Thiazide diuretics require a longer period of use to cause hypomagnesemia. Cisplatin has a nephrotoxic effect that inhibits the ability of the renal tubule to conserve Mg^{2+}. Cyclosporine, an immunosuppressant, severely inhibits the renal tubular reabsorption of Mg^{2+} and has many adverse effects, including nephrotoxicity, hypertension, hepatotoxicity, and neurologic symptoms such as seizures and tremors. Cardiac glycosides, such as digoxin and digitalis, can interfere with Mg^{2+} reabsorption. The resulting hypomagnesemia is a significant finding because the decreased level of Mg^{2+} can amplify the symptoms of digitalis toxicity (Polancic*et al.,* 1991).

Excess lactation has been associated with hypomagnesemia as a result of increased use and loss through milk production. Mild deficiencies have been

reported in pregnancy, which may cause a hyper-excitable uterus, anxiety, and insomnia (Bishop *et al.*, 2010).

2.3.3.1.1 Symptoms of hypomagnesemia

A patient who is hypomagnesaemia may be asymptomatic until serum levels fall below 0.5 mmol/L. (Polancic*et al.*, 1991).

Varieties of symptoms can occur. The most frequent involve cardiovascular, neuromuscular, psychiatric, and metabolic abnormalities (Polancic*et al.*, 1991).

The cardiovascular and neuromuscular symptoms result primarily from the ATPase enzyme's requirement for Mg^{2+}. Mg^{2+} loss leads to decreased intracellular K^+ levels because of a faulty Na^+ - K^+ pump (ATPase). This change in cellular RMP causes increased excitability that may lead to cardiac arrhythmias. This condition may also lead to digitalis toxicity (Bishop *et al.*, 2010).

Muscle contraction also requires Mg^{2+} and ATPase for normal Mg^{2+} uptake following contraction. Normal nerve and muscle cell stimulation requires Mg^{2+} to assist with the regulation of acetylcholine, a potent neurotransmitter.

Hypomagnesaemia can cause a variety of symptoms from weakness to tremors, tetany, paralysis, or coma. The CNS can also be affected, resulting in psychiatric disorders that range from subtle changes to depression or psychosis. Metabolic disorders are associated with hypomagnesemia (Whang*et al.*, 1997).

Studies have indicated that approximately 40% of hospitalized patients with hypokalemia are also hypomagnesaemia. In addition, 20%–30% of patients with hyponatremia, hypocalcemia, or hypophosphatemia are also hypomagnesaemia (Whang*et al.*, 1997).

Mg^{2+} a deficiencies can impair PTH release and target tissue response, resulting in hypocalcaemia. Replenishing any of these deficient ions alone, often does not remedy the disorder unless Mg^{2+} therapy is provided. Mg^{2+} therapy alone may

restore both ion levels to normal; serum levels of the ions must be monitored during treatment (Whang*et al.*, 1997).

2.3.3.1.2 Treatment of hypomagnesaemia

The preferred form of treatment is by oral intake using magnesium lactate, magnesium oxide, or magnesium chloride or an antacid that contains Mg^{2+}.

In severely ill patients, an $MgSO_4$ solution is given parentally. Before initiation of therapy, renal function must be evaluated to avoid inducing hypomagnesaemia during treatment (Whang*et al.*, 1997).

2.3.3.2 Hypermagnesaemia

It is observed less frequently than hypomagnesemia. The most common cause for elevated serum Mg^{2+} is renal failure (GFR, < 30 mL/min). The most severe elevationsare usually a result of the combine effects of decreased renal function and increased intake of commonly prescribed Mg^{2+}-containing medications, such as antacids, enemas, or cathartics. Nursing home patients are at greatest risk for this occurrence (Polancic*et al.*, 1997).

Hypermagnesemia has been associated with several endocrine disorders. Thyroxine and growth hormone cause a decrease in tubular reabsorption of Mg^{2+}, and a deficiency of either hormone may cause a moderate elevation in serum Mg^{2+}. Adrenal insufficiency may cause a mild elevation as a result of decreased renal excretion of Mg^{2+} (Polancic*et al.*, 1997).

$MgSO_4$ may be used therapeutically with preeclampsia, cardiac arrhythmia, or myocardial infarction. Mg^{2+} is a vasodilator, and can decrease uterine hyperactivity in eclampsic states and increase uterine blood flow. This therapy can lead to maternal hypermagnesemia, as well as neonatal hypermagnesemia due to the immature kidney of the newborn. Premature infants are at greater risk to develop actual symptoms (Polancic*et al.*, 1997).

Studies have shown that IV Mg^{2+} therapy in myocardial infarction patients may reduce early mortality (Elin*et al.*, 1994).

2.3.3.2.1 Symptoms of hypermagnesaemia

Symptoms of hypermagnesemia typically do not occur until the serum level exceeds 1.5 Mmol/L (Polancic*et al.*, 1997).

The most frequent symptoms involve cardiovascular, dermatologic, GI, neurologic, neuromuscular, metabolic, and hemostatic abnormalities

Mild to moderate symptoms, such as hypotension, bradycardia, skin flushing, increased skin temperature, nausea, vomiting, and lethargy may occur when serum levels are 1.5–2.5 Mmol/L (Polancic*et al.*, 1997).

Life-threatening symptoms, such as electrocardiogram changes, heart block, asystole, sedation, coma, respiratory depression or arrest, and paralysis, can occur when serum levels reach 5.0 Mmol/L.16 Elevated Mg^{2+} levels may inhibit PTH release and target tissue response. This may lead to hypocalcemia and hypercalcuria (Polancic*et al.*, 1997).

Normal hemostasis is a magnesium dependent process that may be inhibited as a result of competition between increased levels of Mg^{2+} and Ca^{2+} ions. Thrombin generation and platelet adhesion are two processes in which interference may occur (Polancic*et al.*, 1997).

2.3.3.2.2 Treatment of hypermagnesaemia

Treatment of Mg^{2+} excess associated with increased intake is to discontinue the source of Mg^{2+}. Severe symptomatic Hypermagnesaemia requires immediate supportive therapy for cardiac, neuromuscular, respiratory, or neurologic abnormalities. Patients with renal failure require hemodialysis. Patients with normal renal function may be treated with a diuretic and IV fluid (Bishop *et al.*, 2010).

2.4 ZINC

Zinc (Zn) is a bluish white, lustrous metal. Zinc is stable in dry air and becomes covered with a white coating when exposed to moisture. Zinc is the fourth most used metal (after iron, aluminum, and copper). Zinc and its compounds are used in a production of alloys, especially brass (with copper), in galvanizing steel, in die casting, in paints, in skin lotions, in treatment of Wilson's disease, and in many over-the-counter medications (Bishop *et al.*, 2010).

2.4.1 Health effects

Zinc is second only to iron in importance as an essential trace element. The main biochemical role of zinc is its influence on the activity of more than 300 enzymes (from the classes of oxireductases, transferases, hydrolases, lyases, isomerases, and ligases). Zinc can be essential for the structure, regulation, and catalytic action of an enzyme. Zinc occurs in enzymes that realize the synthesis and metabolism of DNA and RNA. Zinc influences the synthesis and metabolism of proteins, participates in glycolysis and cholesterol metabolism, maintains membrane structures, effects functions of insulin, and affects growth factor (Thunus*et al.*, 1994).

Chronic oral zinc supplementation interferes with copper absorption and may cause copper deficiency. This ability to interfere with copper absorption is also the basis for using zinc to treat Wilson's disease. Copper status should be monitored in patients on long-term zinc therapy (Jacobs *et al.,* 1996 and Bales *et al.,* 1986).

2.4.2 Absorption, transport, and excretion

The body content in a normal individual is about 2.5 g zinc, which is mainly in muscles (60%) and skeleton (30%). The remaining 10% is distributed in all tissues with highest concentrations in eyes, prostate, and hair. All tissue levels depend on age (Thunus*et al.,* 1994).Zinc absorption mainly occurs in the small intestine and especially in the jejunum (Thunus*et al.*, 1994).

In blood, the absorbed zinc is distributed between RBCs (80%), plasma (17%), and white blood cells (3%) (Fisher *et al.,* 1975)

Different factors modify the absorption of zinc. The factors increasing zinc absorption include: presence of animal proteins and amino acids in a meal intake of calcium and unsaturated fatty acids (Cunnane*et al.,* 1982 and andSandström*et al.,* 1980 and Solomons *et al.,* 1982).

The factors decreasing zinc absorption include intake of iron,taking zinc on empty stomach,presence of copper at high levels, and age. In normal dietary circumstances, about 90% of zinc is excreted in feces (Hambridge *et al.,* 1986 and Lönnerdal *et al.,* 1996).

2.4.3 Deficiency

Nutritional zinc deficiency is widespread all over the world. Zinc deficiency causes growth retardation, slows skeletal maturation, causes testicular atrophy, and reduces taste perception. Old age, pregnancy, lactation, and alcoholism are also associated with poor zinc nutrition (Milne *et al.,* 1996)

Infants with acrodermatatisenteropathica (zinc malabsorption) usually first develop characteristic facial and diaper rash. Untreated, symptoms progress and include growth retardation, diarrhea, impaired T-cell immunity, insufficient wound healing, infections, delayed testicular development in adolescence, and early death. Zn deficiency in adolescents is manifested by slow growth or weight loss, altered taste, delayed puberty, dwarfism, impaired dark adaptation, alopecia, emotional instability, and tremors. In severe cases, lymphopenia may occur; death follows an overwhelming infection (Hambridge *et al.,* 1986).

2.4.4. Toxicity

Zinc is relatively nontoxic. Nevertheless, high doses (1g) or repetitive doses of 100 mg/day for several months may lead to disorders, especially gastrointestinal tract symptoms, decrease in heme synthesis due to an induced copper deficiency,

and hyperglycemia. Exposure to ZnO fumes and dust may cause “zinc fume fever.” The symptoms include chemically induced pneumonia, severe pulmonary inflammation, fever hyperpnea, coughing, pains in legs and chest, and vomiting (Thunus*et al.*, 1994).

2.4.5 Laboratory Evaluation of Zinc Status

Zinc is measured by flame AAS, ICP-AES, and ICP-MS. Low urine zinc levels in presence of low serum zinc levels, usually confirms zinc deficiency (Fisher *et al.*, 1975).

Low serum zinc in an apparently healthy (nonstressednonseptic) patientcwho has normal serum albumin levels can be used as evidence of zinc deficiency, especially if urine zinc levels are also low. Normal serum zinc cannot be interpreted as evidence of normal zinc stores (Milne *et al.*, 1996).

Zinc concentration in red blood cells is approximately 10 times that in serum (Milne *et al.*, 1996).