Republic of Iraq
Ministry of Higher Education
And Scientific Research
University of Baghdad
College of Dentistry

Oral adverse side effects of simvastatin in relation to serum and salivary trace element status

A Thesis

Submitted to the College of Dentistry University of Baghdad a Partial Fulfilment of the Requirements for the Degree of Master Science in Oral Medicine

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2018 A.D Baghdad -Iraq 1439 A.H

Dedication

To my family

My wife

My son and daughter

Eissa & Mariam

Who gave me the strength and support to complete this work

With love ……

Acknowledgement

First of all, Great thanks to Almighty God for inspiration me the strength and willingness to complete this study, and I pray that his blessing upon me continue throughout my life.

I want to express my great thanks with respect to ***Prof.Dr.Hussain F.Al-Howaizy***, Dean of the Collage of Dentistry, University of Baghdad for his support to the higher studies program.

I would like to extend my thanks to ***Prof.Dr.Nidhal H .Ghaib***, Assistant Dean of Scientific Affairs.

My deep appreciation and gratitude to ***prof. Dr. Jamal N. Ahmed***, Head Department Of Oral Diagnosis .Also to all seniors of this department for their efforts during my career in postgraduate study.

My sincere thanks and deep appreciation with all respects to my supervisor ***Prof. Dr. Taghreed F. Zaidan*** for her continuous support , scientific advices, inspiring discussion and great effort in the supervision of this study ,and to all professors and seniors in the department for their pleasant cooperation.

I would like to express my thanks to all staff and sub staff of Consulting Clinic of Department of Internal Medicine, Al-Hussain Teaching Hospital in Samawa City especially to ***Dr. Natiq M. Jabber*** and ***Dr. Youssef H. Kubba*** for their support and pleasant cooperation.

Deep gratitude and respect to ***Dr. Ali Yaqoob***, Head of Poisoning Centre in Ghazi Al-Hariri hospital and all staff and sub staff for their efforts and great aid in laboratory work.

My thanks also to all subjects who participated in this study.

A lot of thanks and gratitude to my family, my wife and my children Eissa and Mariam for their love, continuous support and encouragement.

Abstract

Background

Hyperlipidemia is an elevated fat (lipids), mostly cholesterol and triglycerides, in the blood**.** These lipids usually bind to proteins to remain circulated so called lipoprotein. Light density lipoprotein is of great risk to develop coronary heart diseases more than high density lipoprotein, the most complications of hyperlipidemia are myocardial infarction, angina, heart failure, ischemic stroke, peripheral arterial disease such as carotid stenosis or abdominal aneurysm of aorta, this disease can be categorized either primary or secondary.

Hyperlipidemia can be diagnosed by fasting lipoprotein profile such as total cholesterol, low density lipoprotein, high density lipoprotein, and triglycerides in blood sample. The possible treatments are dietary control of fat, plant sterol containing omega 3 fatty acids, lipid lowering agents such as simvastatin a member of statins family.

The aims of this study were to evaluate oral findings (oral manifestations, salivary flow rate, taste detection thresholds of the four basic tastes, and teeth mobility using Miller's mobility index) as an oral adverse side effects in patients on simvastatin treatment and to estimate trace elements (zinc and copper) in serum and saliva of those patients and compare it to control subjects.

Subjects, materials & methods

Eighty subjects were incorporated in this study; they were divided into two groups: forty patients on simvastatin treatment(20mg tablets/day) at least one year and over , their age range between (35-60) years, and forty

healthy control subjects of matched age and sex to patients ,with no signs and symptoms of any systemic diseases.

Each subject filled case sheet questionnaire .Informed consent and ethical approval was obtained. Intraoral examination was done to determine any oral alteration. Flow rate of saliva was estimated by collection of non - stimulated saliva and divide the volume obtained on 10 minutes. Teeth mobility was evaluated by Miller's mobility index .In this method the tooth is firmly held between 2 instruments to move back and front, mobility is scored on a scale of 0-3. 0: no detectable movement apart from physiologic tooth movement. 1: It indicates slight mobility with in less than 0.25 mm .2: slight mobility 0.25- 1mm in facial-lingual direction. 3: considerable mobility more than 1mm in all direction with vertical deformability is present. Taste detection threshold of the main four tastes (sweet, salt, sour and bitter) was estimated by using 15 different concentrations for each taste by using method of sip and spit with distilled water mouth wash in between interval of each test. Salivary and blood samples were collected to determine the level of salivary and serum zinc and copper trace elements by flame atomic absorption assay .

Results

The results showed that the mean and standard deviation of age was (47.65 ± 7.63) years. The only oral manifestations have been found in oral cavity of patients on simvastatin treatment were dry mouth and bitterness.

It has been shown that the mean of detection threshold of sweet in patients on simvastatin treatment was significantly higher ($p< 0.05$) than that in control subjects, also the detection threshold of sour and bitter tastes in those patients were significant ($p<0.001$) than that in the control subjects, while the detection threshold of salt taste in patients on

simvastatin treatment showed no significant difference ($p>0.05$). Salivary flow rate was highly significant decreased in those patients than in control subjects ($p < 0.001$). The mean of Miller's mobility score 0 was highly significantly higher in patients than in the control subjects ($p < 0.001$), while the Miller's mobility score 1 was highly significantly lower in patients than in the control subjects ($p < 0.001$). There were no patients on simvastatin with Miller's mobility score 2 and 3.

Serum and salivary zinc and copper were highly significantly decreased in patients on simvastatin treatment than that in control subjects ($p< 0.001$).

Conclusions

The only oral manifestations seen in the patients on simvastatin treatment were dry mouth and bitterness, with high taste detection threshold of sweet sour and bitterness, with the mobility of teeth were decreased. Salivary and serum zinc and copper were also decreased.

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List of Abbreviation

Abbreviations	Details
AE	Adverse Effects
ATP	Adenosine Tri Phosphate
ALA	Alpha Lipoic Acid
BDH	British Drug House
BMD	Bone mineral density
BMP-2	Bone morphogenetic protein-2
CHD	Coronary Heart Diseases
C7OH	Cholesterol 7-hydroxylase
Co	Cobalt
CPK	Creatine phosphokinase
Cr	Chromium
CT	Computerized tomography
Cu	Copper
Cu^{+}	Reduced form of copper
Cu^{+2}	Oxidized form of copper
CYP2C9	Cytochrome P450
CYP3A4	Cytochrome P450 3A4
CYP450	Cytochrome containing haem (haemoprotein)
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
FLP	Fasting lipoprotein profile
FPP	Farnesyl pyrophosphate
GC	Gustatory Centre
GGPP	Geranylgeranyl Pyrophosphate
GH	Growth Hormone
GI	Gastrointestinal
HDL	High density lipoprotein
HMG-CoA	3-hydroxy-3-methylglutaryl coenzyme A
IL	Interleukin
I	Iodine
IV	Intravenous
LDL	Light density lipoprotein
Ltd	Limited
MI	Myocardial infarction
MMPs	Matrix metalloproteinases
Mn	Manganese

Mo	Molybdenum
MR	Magnetic resonance
MT	Metallothionein
MTs	Metallothionein family
NCEP	National Cholesterol Education Program
OA	Osteoarthritis
25OHD	hydroxy vitamin D-25
PDL	Periodontal ligament
P-gp	P – glycoprotein
PONs	Paraoxonases
RA	Rheumatoid arthritis
Ras	Rheumatoid arthritis superfamily
RhoA	Rheumatoid homolog gene family member A
RNA	Ribonucleic acid
RTECS	Registry of toxic effects of chemical substances
Se	Selenium
SD	Standard deviation
sIgA	Specific secretary immunoglobulin A
SIM	Statins induced myopathies
TC	Total cholesterol
TCL	Therapeutic Life Style Change
TG	Triglyceride
T_{max}	Peak plasma concentration
VLDL	Very low density lipoprotein
Zn	Zinc

Introduction

Introduction

Hyperlipidemia is a member of groups of disorders which characterised by abnormal rising levels of blood lipid concentration. While fats play an important role in the metabolic processes of the body, high levels of blood fats increase the danger of developing coronary heart disease (CHD).These lipoproteins precipitate in the interstitial space of arteries emerging from aorta and compromising the heart muscle circulation. This famously known as atherosclerosis. More deposition of lipoproteins will completely block the blood supply to the heart, thus heart attack or what is called myocardial infarction (MI) occurs (Verma, 2017).

Statins is a 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase inhibitors, have revolution in the treatment of hypercholesterolemia. They are the most effective agents for lowering plasma cholesterol, and appreciable for their good tolerance. Studies by Angiograph technique have showed that statins decrease the propagation and the development of atherosclerosis. The action of statins was translated in noticeable reduction of morbidity and mortality of the cardiovascular events in many clinical observations (Vaughan *et al*., 2000).

All statins can interfere with the transforming of HMG-CoA to mevalonate (cholesterol precursor) by HMG-CoA reductase, a rate-limiting and early step in cholesterol synthesis. And competitively block HMG-CoA reductase by linking to the enzyme and strictly suppression binding to substrate. The amount of this inhibition offered by statin may vary according on the power of their enzymatic bonding (James, 2003).

Myotoxicity, the most acute and sever form represented in rhabdomyolysis, which happened with all statins, either in mono-therapy or in multiple therapy (Jamal *et al*., 2004).

The taste detection threshold is the minimal concentration which can be detected and clearly differentiated taste solution from the deionized water (Gomez *et al.*, 2004).

Zinc (Zn) is an essential nutrient for all forms of life and the importance of zinc lies in the fact that many body functions are linked to zinc containing enzymes (Fleet ,2000) .

Zinc as a trace element has indispensible role in human health and disease. It has been insufficiently recognised by a number of experts as an important public health issue in developing countries. It is the most numerous metal of the cell structure found in vesicles, cytosol, nucleus and organelles (King *et al*., 2003).

Copper is an essential element and micronutrient demanded by all aspects of life. Copper is a transition metal and shared in different biological pathways like mitochondrial respiration, embryonic development, hemoglobin levels regulation as well as liver and nervous system functions (Krupanidhi *et al.*, 2008).

AIMS OF THE STUDY

This study was aimed to:-

1- Evaluate oral findings (oral manifestations, salivary flow rate, taste detection thresholds of the four basic tastes) .

3-Miller’s mobility index) as an oral adverse side effects in hyperlipidemia patients on simvastatin treatment.

2- Estimate trace elements (zinc and copper) in serum and saliva of those patients and compare it to control subjects.

Chapter One

Review of Literature

Review of literatures

1.1 Hyperlipidemia

Hyperlipidemia is a condition of increased level of fat named lipids, mostly cholesterol and triglycerides, in the circulation. Hyperlipoproteinemia are so known because these fatty substances pass in the blood and bound to proteins. By this way the fatty substances can remain circulated (Harikumar *et al*., 2013).

1.1.1 Significance:

In adults, light density lipoprotein (LDL) greatly has a higher risk and high density lipoprotein (HDL) at lower risk in relation of coronary heart disease (CHD) (Shamir and Fisher, 2000).

1.1.2 The risk factors for hyperlipidemia:

The obesity, no exercises, saturated fat and cholesterol rich food, poor diet in fruits, vegetables and fiber can lead to hyperlipidemia. In a combination to diet some other factors that can cause this abnormality. Hyperlipidemia can demonstrated as genetic disorder in families (Robert *et al*., 2012).

• Familial hypercholesterolemia – High LDL cholesterol levels.

• Familial hypertriglyceridemia – High Triglyceride levels.

• Familial combined hyperlipidemia – Low levels of LDL cholesterol, triglycerides, or both are high, and HDL. Hyperlipidemia can also be accompiend to disturbances in hormone function such as hypothyroidism, Cushing's syndrome and diabetes (Robert *et al*., 2012).

Related medications are (Joseph, 2005):

• Contraceptive pills.

• Hormonal therapy of dysmenorrhea.

• Some diuretics (water pills).

• Cardiovascular diseases treated with beta-blockers.

1.1.3 Diagnosis of hyperlipidemia

The National Cholesterol Education Program (NCEP) recommends that a fasting lipoprotein profile (FLP) such as total cholesterol, LDL, HDL, and triglycerides should be performed in at least once every 5 years for all adults 20 years of age and over (Barbara *et al.*, 2005).

1.1.4 Classification:

1.1.4.1 Familial (primary)

Fredrickson classified Familial hyperlipidemias depending mainly on the behavior of lipoproteins on electrophoresis or ultracentrifugation (Fredrickson and Lees, 1965). Primary hyperlipidemia may be caused by genetic problem (such as receptor protein mutation). And it does not recognized among the various genes in humans; the LDL receptor protein is encoded by the LDL-R gene on chromosome 19 that may be partially in charge for some of these disorders. (Kishore *et al.*, 2007)

1.1.4.2 Acquired (secondary)

Acquired hyperlipidemias (sometimes named secondary dyslipoproteinemias) as a result from another causative disorder such as diabetes that leads to changes in plasma lipid and lipoprotein metabolism often imitative primary type of hyperlipidemia and can have identical outcome. They may conduct in excess danger of coming early atherosclerosis or, when associate with hypertriglyceridemia, could progress to other complications such as pancreatitis and the chylomicronemia syndrome (Chait and Brunzell , 1990).

Diabetes Mellitus is the major cause of acquired hyperlipidemia in addition to use of drugs such as diuretics, beta blockers, and estrogens. Other conditions leading to acquired hyperlipidemia include renal failure,

nephrotic syndrome, alcohol consumption, hypothyroidism, some endocrine disorders and metabolic disorders (Harikumar *et al*., 2013).

1.1.5 Possible therapy:

The aims of therapy are lowering of low density lipoprotein (LDL) cholesterol levels and starting of Therapeutic Lifestyle Change (TLC) and suitable medical treatment. The main goal to create TLC and drug therapy is to lower the danger and repeated events like myocardial infarction (MI) , angina, peripheral arterial disease such as carotid stenosis or abdominal aneurysm of aorta ,heart failure, ischemic stroke, (Amit *et al.,* 2011).

Diet containing fish oil can be utilized to lower raised triglycerides, with the magnificent impact happening in patients with the massive severity (Mattar and Obeid, 2009).

There are some clues for advantage of sterol-containing plant that make Omega 3 (ω_3-fatty acids) that long chain Omega 3 fatty acids are effective for reducing triglyceride and cholesterol . At the pharmaceutical dose 3-4g /day can reduce plasma triglyceride about 25-50% after one month (Thompson *et al.*, 2002).

1.2 Statins:-

It is an agent used for its lipid-lowering activity that synthetically derived from fermentation end products of *Aspergillus terreus.* After oral administration, simvastatin, which is considered as an inactive lactone, is hydrolyzed to the end product β-hydroxyacid form. This is a blocker of 3-hydroxy-3-methylglutarylcoenzyme A reductase that catalysis the conversion of HMG-CoA to mevalonic acid, a necessary step in the biosynthesis of cholesterol (Tandon *et al*., 2005).

1.2.1 Types:-

The types of statins are as in table (1-1) (Bellosta *et al.*, 2008)

Table (1-1):- Types of statins

Statin	Brand name
Atorvastatin	Lipitor, Ator
Cerivastatin	Lipobay, Baycol (withdrawn from the market in August, 2001 due to risk of serious rhabdomyolysis)
Fluvastatin	Lescol, Lescol XL
Lovastatin	Mevacor, Altocor, Altoprev
Mevastatin	Compactin
Pitavastatin	Livalo, Livazo, Pitava
Pravastatin	Pravachol, Selektine, Lipostat
Rosuvastatin	Crestor
Simvastatin	Zocor, Lipex
Simvastatin + ezetimibe	Vytorin, Inegy
Lovastatin + niacin extended-release	Advicor, Mevacor
Atorvastatin + amlodipine	Caduet , Envacar
Simvastatin + niacin extended-r	Simcor

1.2.2 Pharmacological action:

The widespread known of statins pharmacological activity depends on the powerful blocking of the mevalonate endogenous pathway, which guides straightly to the cholesterol and isoprenoids biosynthesis (Gazzerro *et al*., 2012). Statins links to mammalian 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase at nano molar concentrations, procure to an efficient excommunication of the natural substrate HMG-CoA, which relate instate at micro molar concentrations (Moghadasian and Frohlich, 2001).

The interactions between HMG-CoA and statins reductase inhibit the opposing of HMG-CoA to L-mevalonate that end in the blocking of the circulating biosynthesis of cholesterol and various isoprenoids metabolites like geranylgeranyl pyrophosphate (GGPP) and farnesyl pyrophosphate (FPP) (Chow, 2008). These nondependent cholesterol belongings are declared as pleiotropic effects and involve, within the others, advancing of endothelial function, suppuration of inflammation of vessels and oxidation, and steadiness of atherosclerotic plaques (Gazzerro, 2012).

In fact, rosuvastatin also shows a polar interaction between the HMG-CoA reductase enzyme and methane sulfonamide group. These structural features submit this statin the most effective in expressions of dose capable to reduce HMG-CoA reductase performance by fifty percent (Davidson, 2002).

Among the statins aforesaid, simvastatin, lovastatin, fluvastatin and atorvastatin are lipophilic, while pravastatin and rosuvastatin are more hydrophilic. The lipophilic behaviors of the statins are escorted, an exception for pitavastatin, by minimal systemic bioavailability as a reason of an extreme first-pass impact at the hepatic level (García *et al.*, 2003).

The prospect effectiveness of statins as treatment medications has been estimated, statins varies in their hydrophobic/hydrophilic and solubility rates, which administer their biological and chemical functions at extra hepatic sites (Duncan *et al.*, 2004).

Simvastatin is a crystalline powder with white to off-white color, nonhygroscopic, freely soluble in organic solvents such as chloroform, methanol and ethanol and insoluble in water (Synthon Pharmaceuticals, 2007).

Simvastatin by mouth degradation tablets comprises 10 mg, 20 mg, 40 mg or 80 mg of simvastatin. The tablets start to dissolve within seconds in the mouth, permitting its active ingredients to be there after swallowing (Merck and Dohme, 1991).

Tablets also have the following inactive ingredients: iron oxide red (20 mg and 40 mg tablets only), crospovidone, glyceryl behenate, hydroxypropyl cellulose, iron oxide yellow (10 mg and 20 mg tablets only), mint menthol, povidone, silicified microcrystalline cellulose, and sucralose. Butylated hydroxyanisole is compiled as a preservative (Synthon Pharmaceuticals, 2007).

It lowers blood vessels inflammation, reduce myocardial events (Tandon *et al.*, 2005), decreases the extent of Alzheimer's disease and dementia (Fassbender *et al.*, 2001), terminates the development of inflammatory diseases (Christensen *et al.*, 2006), and cures chronic periodontitis (Pradeep and Thorat, 2015).

Statins are also recognized as HMG-CoA reductase inhibitors. They are group of drugs which is used to reduce high cholesterol. Their action by inhibition the enzyme HMG-CoA reductase, which have function in a main role in the production of cholesterol in the liver, and participate in

production about 70% of total body cholesterol (American Heart Association ,2016).

1.2.3 Pharmacokinetic properties of Statins:

The pharmacokinetic properties of the statins are coordinated by many factors, implicating their lactone active form, their lipophilic/hydrophilic rate, and their metabolism and absorption. Statins are given by mouth as active hydroxy acids, except for lovastatin and simvastatin, which are offered as lactone prodrugs and then transformed to hydroxy acid form by hydrolysis (Corsini *et al.,* 1995)**.**

The absorption percentage is about one-third and ninety-eight percent and the time to attain peak plasma concentration (T_{max}) is about 4 hours after ingestion. The absorption per day has various ranges according to the time of administration (Cilla *et al.*, 1996) and types of food in stomach; changes in lipid and apolipoprotein values were identical after day and night administration of atorvastatin (Garnett, 1995).

When consumpted with food, lovastatin is more likely effective to be absorbed (Garnett, 1995) and atorvastatin (Radanovich *et al.,* 2013), which have a lower absorption rate, while rosuvastatin (Davidson, 2002), simvastatin (Garnett, 1995), and cerivastatin, absorption are not interfere by food consumption (Muck *et al.,* 2004)**.**

The target organ of statins is liver; an effective first-step uptake could be more significant than high level of bioavailability to reach the statin effects. A spacious first-step extraction reveals a low systemic bioavailability (Muck *et al.,* 2004).

The solubility profile is an essential depicts that command the hepatoselectivity of the statins and their prohibition effect on HMG-CoA reductase. Lipophilic statins set inside the liver cells by passive diffusion, while hydrophilic statin uptake is carrier-mediated so lipophilic statins

display a dynamic activity at both extra hepatic and hepatic sites (Nezasa *et al.,* 2003).

1.2.4 Metabolism of the Statins in health and disease:-

Cytochrome P450-Mediated Metabolism of Statins:

In the liver, hydrolysis of statin lactones to their open acid forms enzymatically or chemically by paraoxonases or esterases (PONs) (Duggan and Vickers, 1990).

Lipophilic drugs are noticed to be liable in oxidative metabolism by the Cytochrome (CYP450) system (Schachter, 2001).

Acyl glucuronide and acyl CoA derivatives both may resumption to statin acids through hydrolysis. In addition, statin open acids are irreversibly clarified by oxidation and glucuronidation processes, statins as lactone forms rapidly undergo oxidation via the microsomal cytochrome P450 (P450) family of enzymes (Bottorff and Hansten, 2000).

The Cytochrome (CYP3A4) isoenzyme is the master of microsomal enzyme that metabolizes a lot of statins, involving lovastatin, atorvastatin, and cerivastatin, simvastatin into active derivates accountable for HMG-CoA reductase inhibition (Lennerna, 2003).

In fact, the prime effective metabolites of simvastatin are the hydroxy acid and its 6-hydroxy, 6-hydroxymethyl, and the 6-exomethylene derivatives (Prueksaritanont *et al.,* 2003), while for atorvastatin, 2-hydroxy- and 4-hydroxy- atorvastatin acid are reported (Jacobsen *et al.,* 2000).

1.2.5 Statins excretion

The predominant way of removal of plurality of statins by the liver through the bile after metabolism (Knopp, 1999).

Rosuvastatin is also cleared, largely with no change, by both the liver and kidney (Martin *et al*., 2003). Canalicular outflow carriers P-

glycoprotein (P-gp) and multidrug impedance linked to the protein 2 are two of the main ATP-dependent out flow pumps for excretion of statin (Kitamura *et al.,* 2008). Furthermore, the excretion of statins through urine, excluding for pravastatin, is very low. A diver to other statins, up to sixty percent of pravastatin that intravenously administered is passing through in the human's urine (Hatanaka, 2000).

1.2.6 Factors That May Affect Statins Metabolism.

a. Ethnicity or race.

No clinical clues connect interethnic varieties in cerivastatin pharmacokinetics with black, white, and Japanese persons after oral treatment (Muck *et al*., 2004). But Yasuda *et al*., (2009) showed that factors that accompiend with existence could affect the metabolism of statin. Ethnicity or race, food intake, sex and age, and concomitant diseases are factors may affect the pharmacokinetic and pharmacodynamics profile of the statins.

b. **Food intake.**

Taking statins with food together may change their pharmacokinetic and pharmacodynamics behavior. It was announced that utilization of oat bran soluble fiber and pectin combined with lovastatin decreases its absorption (Metzger *et al.,* 2009).

Mediterranean people, who utilized olive oil in their diet, can promote cholesterol lowering effect of simvastatin matched with sunflower oil. On other side, the consumption of polyunsaturated rich oils, via the activation of cytochrome P450, could decline some of statins half-life and subsequent their effects on lowering cholesterol (Vaquero *et al.,* 2010).

c. **Sex and Age.**

The effects of variation in sex and age on pharmacokinetic behavior of statins were fully documented. The offering of discrete dosage regimens of simvastatin and lovastatin in hypercholesterolemic patients with flare up the plasma concentrations of total and active statins only in old aged women and persons (aged 70–78 years). However, these sex and age related variations do not need adjustment of dosage regimens, because plasma concentrations of statin are not necessarily attached to their effectiveness and the therapeutic window of simvastatin and lovastatin is extremely wide (Cheng *et al.,* 1992).

In precise, individuals who have HMG-CoA reductase single nucleotide polymorphisms, know-how to decrease sensitivity of statin and minimal reductions in cholesterol, apolipoprotein B, and triglyceride (Medina *et al.*, 2008).

d. Concomitant diseases.

Like patients suffered hepatic and renal diseases, statin treatment is required (Yoshida *et al.,* 2009). In pathological situation like critical renal dysfunction, the removal kinetic of statins appears to be changed. Of course, total and active lovastatin plasma levels are boosted in their affects in comparison with healthy subjects (Que´rin *et al.,* 1991).

In contrast, chronic renal failure and hyperlipidemic patients, persons on hemodialysis, have no proves of rise assemblages of atorvastatin or its main active metabolite over various dosing, in compare with healthy volunteers (Lin *et al.,* 2010).

1.2.7 Adverse effects (AE) of simvastatin:

Statins are usually well sustained. The farthest recurrent side effects are modest form such as gastrointestinal disturbances or urine discoloration.

The obvious clinical problem is the hepatotoxicity accompiend with statin therapy can be described by an elevation of hepatic aminotransferases, autoimmune-type responses, hepatocellular and cholestatic injury, and fulminant hepatic failure (Liu *et al.*, 2013).

In addition, (myalgia, myopathy) sign of myotoxicity happen in about ten percent of patients on statin, and it could be extended to rhabdomyolysis, usually recognized by huge necrosis of muscle, myoglobinuria, and acute renal failure (Williams and Feely, 2002).

Rhabdomyolysis is the extreme serious adverse effect (AE) of statin therapy, but also the less continual. Creatine phosphokinase (CPK) increasing to 10 times higher than normal, has been reported (Silva *et al*., 2006).

Less dangerous AE, such as myalgia and increased hepatic transaminases levels consisting about two thirds of AE, but these symptoms retreated after ceasing the treatment (Silva *et al*., 2006). Statins were proposed as a prospective cause of oral ulcerations (Yuan and Woo, 2015).

There have been shown that, a high percentage of oral Symptoms (Dry mouth, itchiness in tongue, lips and throat, bitterness, cough) in patients have been taking statins that have been cleared the AE vanished in a high percentage of patients after cessation of the treatment, and amelioration was noticed as soon as the third day after interruption. Nearly 94 % of patients with insomnia notify superior rest after interruption of the treatment (Pascual-Cruz *et al*., 2008).

1.2.8 Pharmacological treatment:

Inhibition of cholesterol synthesis in both the liver and extra hepatic tissue is the main mechanism of action of statins, leading to lowering total cholesterol (TC) and low density lipoprotein (LDL) (Lago,2005).

Their pharmacological effect is dose-dependent, that is meaning, reaching a plateau at high doses. Statins are usually prescribed one dose/ day, at night, because cholesterol synthesis maximally occurs at morning. Ultimately, this is the treatment of a good option in the treatment of hypercholesterolemia (Pascual-Cruz *et al*., 2008).

1.2.9 Effects of simvastatin on organs:

1.2.9.1 Bone:

Statins in proposed studies, which are proven lipid-lowering drugs, impact turnover of bone by encouraging formation of bone .The suggested mechanism that statins enhances bone geneses include an provoking expression of bone morphogenetic protein 2 synthesis (BMP-2) (Ada *et al.*, 2003).

Meta-analysis of clinical studies since 2007 by Uzzan represent that statins have a positive effect on the bone mineral density (BMD) in deferent sites of the body (Uzzan *et al*., 2007).

Statins restrain bone resorption and stimulate formation of bone, having a paired action on bone metabolism (Chuengsamarn *et al*., 2010).

Increased amassed statin use corresponded to a later sequal decrease in the risk of fracture (Rejnmark *et al*., 2006).

Supposedly after time , medications that can interpose in this pathophysiological and biochemical cascade, like statins, in a diversity of doses, make them applied for the management of disorders of bone as ectopic ossification syndromes (Tsartsalis *et al* .,2012).

1.2.9.2 Induction of osteogenic differentiation:

The mechanism at molecular level of statin-enhance osteogenesis is obscure, may be activation of rheumatoid arthritis superfamily (Ras) or homolog gene family member A (RhoA) coding raise cytoskeletal tension, which functions an important role in the mesenchymal stem cells osteogenic differentiation (Chun *et al.*, 2015). Simvastatin also accretion the osteogenic proteins expression, actin filament thickness, and the number of focal adhesions (Chun *et al.*, 2015).

Other studies have pointed out that statins spend bone anabolic effects through the promotion of osteoblastic differentiation, suggesting that it could be used for the treatment of common metabolic bone diseases such as osteoporosis (Maeda *et al.*, 2001; Martez *et al*., 2001).

Users were found to have a decreased hazard of fracture compared to users of non-statin lipid-lowering drugs (Rejnmark *et al*., 2006).

1.2.9.3 Simvastatin and chondrocyte development:

Statin, by blocking of 3-hydroxy-3-methylglutarylcoenzyme A (HMG-CoA) reductase, preventing production of Matrix metalloproteinases (MMPs) by cultured chondrocytes (Lazzerini *et al*., 2004).

These findings proposed a likely additional mechanism for statin in revers action of osteoarthritis (OA) involving cartilage degeneration. More studies are needed to explain the definite effect of statin on the pathogenesis of OA (Kazuo and Rie ,2010).

Forthright effects on chondrocytes have also been elucidated, with the MMPs suggested as a probable statin target (Wu *et al.*, 2007*).* Statins may also reduce chondrocyte senescence (Yudoh and Karasawa, 2010).

1.2.9.4 Simvastatin and facial muscles (masticatory and expression)

Most ordinarily muscle pain is the experienced statin medication side-effect. Statin persuades myopathy with a series of myopathic disorders varies from mild myalgia to deadly Rhabdomyolysis (Robert *et al*., 2010).

Many mechanisms of statin induced myopathy have been proposed. The most suggested theories are alteration of respiration in mitochondrion and cellular membranes derangement, the depletion of isoprenoids which control myocyte apoptosis (Haper and Jacobson, 2007).

Statins elevate tyrosine phosphorylation that result in rising in cytosolic calcium leading to apoptosis is only the solitary theory (Dirks and Jones, 2006).

1.2.9.5 Simvastatin and temporomandibular joint problems

Curation of arthritis in temporomandibular join (TMJs) induced experimentally with intra-articular simvastatin kept normal growth of condylar bone (Callista *et al*., 2015) 3.and reports of amendment of rheumatoid arthritis (RA) patients (McCarey et *al.* , 2004).

Statins were revealed to apply a cytotoxic effect on human T, B and myeloma cells by accelerating their apoptosis (Cafforio *et al.* , 2005), and also alter apoptosis of smooth muscle and endothelial cells leading to change vascular function and neovascularization (Muck *et al*. , 2004).

1.2.9.6 Simvastatin and salivary glands

Accumulation of abnormal fat in the parotid (major) salivary glands may be disclosed by using Short Time Inversion Recovery and fat-

saturation magnetic resonance (MR) sequences and computerized tomography (CT) values (Ioanna *et al* .,2015).

Keep an eye on fat sedimentation might be of multi benefit weapon in diagnosis any parotid glands disorders. Simvastatin therapy resulted in a considerable decline of serum lipid profile but to a measly lower weight of parotid gland (Pijpe *et al*. , 2006).

Statins repair parotid glands alteration caused by hyperlipidemia, resulting at last to gland remodeling (Ferreira *et al.*, 2007).

An approaching connection between parotid gland enlargement and high plasma lipid levels may be complemented. This enlargement may be sign of changes in parotid gland's microstructural, and it may demonstrate its notice, by other researchers, weakness in function and salivary flow rates in these patients. It is clear that statins, decrease the serum lipid profile, may act a conservative role in organs' damages caused by hyperlipidemia by renovation the existed changes (Ioanna *et al*., 2015).

1.2.9.7 Effects of simvastatin on taste function:

The majority of the studies on taste abilities have concentrated on three main parameters: taste intensity, taste quality, and pleasantness/unpleasantness. In taste tests, the uses of pure compounds in solution permit to focus on the gustatory part of the taste sensation (Bruno *et al.*, 2011).

The chemosensory systems of the body (like taste) play roles in maintaining normal metabolic body functions. Pathology of taste may result in two major functional abnormalities: loss of acuity, which can be either diminished (hypogausia) or a total loss of the ability to taste (ageusia), or the distortion of taste (parageusia) (Seymour *et al.,* 1998).

1.3 Trace elements:

Essential trace elements of the human body that found in small amount in the body tissue include copper (Cu), zinc (Zn), selenium (Se), cobalt (Co), iodine (I), chromium (Cr), molybdenum (Mo) and manganese (Mn), In spite of these elements calculated for only 0.02% of the total body weight, they play important function, e.g., as trace bioactive substances or active centers of enzymes (Osamu, 2004).

1.3.1 Zinc:

The zinc metabolic functions are depending broadly on its existence more than 300 metalloenzymes embraced in feasible all kinds of metabolism. Significance of zinc including, in humans, enzymes implicates alkaline phosphatase, carbonic anhydrase, thymedine kinase, RNA and DNA polymerases, carboxypeptidases, and alcohol dehydrogenase. Zinc also take place in a great role of protein synthesis and has a paramount role in gene expression both structural and enzymatic roles (Milne, 2000).

1.3.1.1 Metabolism:

Zinc is the trace element second to iron as the most plenteous in the body. About 20-30 % of consumed food, zinc is absorbed largely in duodenum and jejunum. The embalmment of zinc homeostasis manifests to be principally gastrointestinal, with increasing intake, loss of zinc in feaces increases when urinary excretion is stable (AL-Omary, 2008).

Zinc is carried out in blood plasma particularly by (60-70%) albumin and alpha – (30-40%) macroglobulin, with a few amounts linked with transferrin and frees amino acid. Feces are the major excretion for zinc and

urinary losses of zinc approximately 0.6 mg /day. Sweat losses are the same to those in urine (AL-Omary, 2008).

1.3.1.2 Biological function: Zinc affects numerous body system and functions, such as bone formation, growth, reproduction, brain development fetal development, membrane stability sensory functions (like taste and smell), immune mechanisms, and wound healing (Berg and Shi, 1996).

Zinc is also a co-factor of over 300 metalloenzymes like, dehydrogenase, peptidase, carbonic anhydrase, RNA and DNA polymerase, Superoxide dismutase, alkaline phosphatase, the activity of these enzymes may serves as an indicator of zinc deficiency (AL-Omary, 2008).

1.3.1.3 Zinc deficiency:

Zinc deficiency might cause growth retardation**,** male hypogonadism**,** skin changes **,**mental lethargy **,**delay wound healing **,**impaired immune response **,**susceptibility to infection , poor appetite **,**abnormal neurosensory changes **,**taste disturbances (Henry *et al*., 1993).

Zinc is familiar to render as the active heart of about 300 enzymes, and is a basic human's trace element. It had known that the amount of zinc has been taken each day perhaps inadequate in relation to the par day demand in some sets of subjects (young women on weight-reducing diet regimen, children, elderly people, and others). These people may develop almost shortage or true lack of zinc (Ynagisawa, 2002).

The gain of zinc deficiency is usually caused by drastic deficiency of nutrient ions involve zinc, or very off-balanced diets (inadequate intake of animal proteins opulent in zinc). The vast continual causes of zinc

deficiency are long term parenteral therapy of high-calorie and enteral nutrition. Prolonged parenteral therapy with high-calorie unavoidable enhances zinc shortage. To prevent its appearance, intravenous (IV) infusion additives with five trace elements (iron, zinc, copper, manganese, and iodine) (Ynagisawa, 2002).

Zinc reduction can promote if the amount of dietary zinc is not enough in proportion to the demand, or if the patients suffer from, diarrhea, malabsorption or intestinal fistula. Moreover, zinc deficiency can be encouraged by continued consumption of refined foods with low mineral, foods with additives with chelating activity (sodium polyphosphate) (Sato *et al.,* 2009).

1.3.1.4 Factors affecting zinc level in body fluids:

1- Dietary intake:

Border line of suboptimal zinc and status zinc deficiency has been observed in many groups of the people in both industrialized and less developed countries. Although the cause in some cases may be insufficient zinc in diet, blockers of zinc absorption are probably the most common causative factor. Phytate, which is found in essential foods like rice, cereals, and corn, has a powerful negative effect on zinc absorption from composite meals (Lönnerdal, 2000).

2-Protein quantity and quality:

Dietary protein studies on absorption of Zn have also produced conflicting results. Protein digestion products and dietary protein such as casein phosphopeptides have been observed to enhance Zn absorption (Leland *et al.,* 2013).

These backup the other theories that protein recovers Zn absorption by promoting Zn availability for carrier binding. With protein, and factors like sources, animal or plant, having a great effect (Lönnerdal, 2000).

3-Calcium:

It appears, out of the way, that calcium has a negative effect on zinc absorption (Lönnerdal , 2000).

The studies prompted the hypothesize that the elevated calcium in the intestine was combining with Phytate, thus turning it unavailable site to bind Zn. This is the pathway that have been suggested and performed in study models. Calcium enhanced zinc absorption, but the end result was not important when they planned for dietary zinc and Phytate. In opposite, this promoting effect of calcium to be more declared at low Phytate levels (Hunt and Beiseigel, 2009).

4- Iron:

Supplementations of iron are commonly supported as a prophylactic treatment and are mostly taken with meals to decrease side effects, but absorption of zinc can conflict with iron (Harvey *et al*., 2007).

Oral therapy of iron may spoil zinc absorption so zinc status in a dose-independent fashion and iron supplements may ruin zinc status, especially in populations with insufficient intakes of dietary micronutrient (Freddy *et al*., 2003).

5-Copper:

No predatory influence on zinc absorption was noticed, submitting that little rise intakes of copper has no interpose with zinc absorption if zinc intake is contentment (Lönnerdal , 2000).

Malavolta *et al*., (2015) stated that there are mechanisms are established to lower concentration of Zn in serum and to elevate serum concentration of copper in the existence of inflammatory conditions.

6-Cadmium:

The cadmium-induced alteration in zinc homeostasis outcome in an elevated retention of zinc in the liver and/or kidney (Brzóska and Monisuska, 2001), because of accumulation of cadmium and induction of metallothionein in these organs (Brzóska *et al*., 2000).

Oishi *et al.*, (2000) stated that many studies clarified that cadmium could interpose with the metabolism and transport of many essential metals.

7-Low-molecular-weight ligands and chelators:

When zinc brew a congregation between complex and low-molecular-weight ligand or chelator that can be easily absorbed, it is possibly that the total impact on zinc absorption will be affirmative, due to the high solubility of zinc., organic acids (e.g., citrate) ,amino acids (e.g., histidine, methionine) and Ligands/chelators (e.g., EDTA) have thence been utilized in endeavor to stimulate bioavailability of zinc (Lönnerdal, 2000).

1.3.2 Copper:

1.3.2.1 Biological functions:

Copper has a serious function in metabolism of human body, in general due to it makes many definitive enzymes to be functioned perfectly (Harris, 2001).

Copper can play role in both pro-oxidant and antioxidant. natural occurring of free radicals in the body and can cause harm cell walls, the interaction with genetic material, and participate to cause health troubles and diseases .The antioxidant, scavenging or free radicals neutralization by

copper may decrease or aid in preventing part of these damages (Davis ,2003; Araya ,2006).

Copper is an important dietary nutrient and periodic intake of copper is necessary for healthy life. Copper is needed for important enzymes and metabolic systems for proper functioning (Olivares *et al.,* 2000).

Gastric and duodenum absorption of dietary copper is rapidly taken up from the liver portal venous circulation, the principal organ involved in copper homeostasis and regulation. Biliary excretion is the solely mechanism for copper removal, and the amount of copper passed in the bile is depended directly on the size of the hepatic copper pool (Gitlin, 2002).

1.3.2.2 Toxicity:

Acquired type of toxicity of copper can occur from intake or absorbing overflowing copper (e.g., from ingesting an acidic food or drinks that has had extended contact with a copper container). Diarrhea ,Nausea, vomiting, and self-limited gastroenteritis may happen more extreme toxicity results from swallowing (suicide tendency) of gram quantities of a copper salt (e.g., copper sulfate) or via skin absorption of considerable amounts of copper (e.g., if copper salt are applied to large areas of burned skin with compresses saturated solution). Anuria and hemolytic anemia may be life threatening (Larry, 2008).

Copper intake per day is about 1-3 mg/day. Diversity in water, food and vitamin supplement utilization can rise or decline demand of copper but this amount is enough for body needs (Svetlana *et al.,* 2007).

1.3.2.3 Metabolism of copper:

Copper is a metal with redox-active that is always utilized by organisms living in environments rich with oxygen and that fluctuates between the reduced (Cu+) states and oxidized (Cu^{2+}) state (Ridge *et al*. ,2008).

Sensitive step occurs in the genes encoding proteins function identification in copper homeostasis (copper uptake, intracellular allocation, and efflux and in the controlling) (Prohaska and Gybina, 2004).

The recognition of genes encoding copper homeostasis proteins has a significant progress in basic features of their function, frameworks, and mechanisms of action in copper equilibrium (Kim *et al.,* 2007). Pain, diarrhea, inky urine in appearance, severe headache and difficult breathing , jaundice, bluish brown fluid consistency of discolored stool, allergies, alopecia, anemia, loss of appetite , restlessness, cognitive disorder, asthma, autism, candida infection , arthritis ,depression, infertility of men, dysmenorrhea, fibromyalgia, chronic infections, prostatitis, loss of memory, migraine headaches, cold perspiration indicates circulatory failure , convulsion , coma and death are usually connected to copper toxicity (Badiye *et al*, 2013).

According to Doris, (1997) the Registry of Toxic Effects of Chemical Substances (RTECS) the minimal issued oral deadly dose of hydrated form of copper sulphate was 1088 mg/kg body weight /day, while the minimal oral toxic dose was 272 mg/kg body weight /day. For anhydrous form copper sulphate, fatal oral doses have been documented as 50 and 857 mg/kg body weight /day. In children the lowest toxic oral dose has been reported to be 150 mg/kg body weight /day, but oral intake of copper in high doses is unusual due to its unsatisfying taste when concentration is high(Olivares *et al* . , 2000).

1.3.2.4 Copper deficiency:

-causes:

1. Surgery:

Famous cause of copper insufficiency is Bariatric surgery , such as gastric bypass surgery (Klevay, 2006).

2. Toxicity of zinc: excess utilization of zinc leads to copper shortage (Kumar, 2006).

3. Hereditary Disorders of copper:

Menkes disease representing symptoms of the scattered, steel colored "kinky hair" and paleness. Menkes disease is an inherited fault that leads to a copper deficiency (Olivares *et al*., 2000).

4. Other causes of copper disorders:

It is seldom suggestion that over dose supplementation of iron results in myelopathy related copper deficiency. Coeliac disease is a rare cause of copper deficiency, perhaps due to intestinal malabsorption. Still, a great percentage, about less quarter of cases has obscure causes (Jaiser & Winston, 2010).

1.3.2.5 Signs and symptoms:

1. Blood symptoms

Microcytic, normocytic or macrocytic anemia and neutropenia (Klevay, 2006). Within six weeks of copper surrogate neutropenia and anemia ideally resolved (Fong *et al*., 2007).

2. Neurological symptoms:

Copper insufficiency can lead to a broad set of neurological problems involving, myelopathy (Schleper and Stuerenburg, 2001). Peripheral neuropathy (Pineles *et al*., 2010), and optic neuropathy (Kumar, 2006).

1.4 Taste

1.4.1 Taste sensation:

Taste has been largely considered as a minor sense. It offers data about only a restricted number of stimulus kinds (sweet, salty, sour, bitter,

umami, and a few others possibly fat), and has conducted much less clinical and medical investigation awareness than smell due to in details below, it is relatively immune to important changes (Cowart , 2010).

However, taste stability and simplicity may be observed as speaking to its strict role as body gatekeeper, safeguard animals and humans from ingestion hazardous materials and support consumption of nutritious ones (Cowart *et al.,* 2007).

Chemical particles received by taste receptor cells in the oropharyngeal epithelia are understood in the primary gustatory cortex in the brain (Buck, 2000).

Taste cells stimulated by taste substances convey chemical data to peripheral sensory neurons named gustatory neurons; their cell bodies are situated in the VIIth, IXth, and Xth cranial sensory ganglia (Buck, 2000).

Taste buds dispensed in the oral cavity at anterior region are innervated by greater superficial petrosal nerves and chorda tympani from geniculate ganglia, while posterior region are innervated by glossopharyngeal nerves from petrosal ganglia (Lundy and Norgren., 2004).

Gustatory center neurons interact with milliseconds, and these interactions are taste specific and inform special but composing neural structures that respond to the type of each tastant by subjecting paired changes in firing rate are used to differentiate between tastants (Katz and Simon, 2002).

1.4.2 Taste function

Taste assists to maintain nutrition and distinguish toxins . There are five basic tastes are set apart today: salty, sweet, bitter and sour, umami. Salty

and sour taste sensations are both revealed via ion channels , sweet, bitter, and umami tastes, in such away, are recognized through gustatory (G) protein-coupled taste receptors (Bachmakov *et al.*, 2008).

1.4.3 Taste map:-

It is a famous misconception that various portions of the tongue are exclusively in charge of different essential tastes. It is cleared with a schematic map of the tongue (figure 1-1); with specific parts of the tongue assorted for each taste (Wanjek, 2006). This was scientifically demolished by later research; all taste sensations bring from all regions of the tongue, although assorted parts are more sensitive to proven tastes (O'Connor, 2008).

Some parts of the tongue may be capable to detect a taste first than others do, all parts are evenly good at transporting the senses of all tastes. Threshold sensitivity may be various across the tongue, but not intense (Purves *et al.*, 2011).

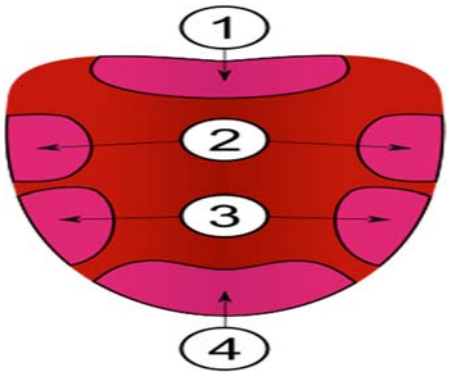

Figure (1-1) :- Tongue map Area no.1 taste bitter ,area no.2 taste sour ,area no. 3 taste saltiness , area no. 4 taste sweet (Wanjek, 2006).

1.4.4 Taste buds:-

They include the taste receptor cells, also named as gustatory cells. These structures composed from the five parts of taste perception salty, sour, bitter, sweet and umami; in which the collection of these elements which specify these divers tastes to various regions of the tongue, in fact these tastes can be find out by any portion of the tongue (Jung *et al*., 2004).

Taste pores are tiny openings in the tongue epithelium; parts of the food melted in saliva bring to contact with the taste receptors where the gustatory cells are situated (Shier *et al*., 2016). About 2,000–8,000 taste buds in the human tongue (Elizabeth and Reginald, 2009).

Taste buds are so small chemical sensors that occupy the initial portion of the elementary tract, the oral cavity. These outward taste organs respond to a vast variety of chemical substances, ranged from protons to proteins (Stephen, 2013).

1.4.5 Gustatory pathway:-

The gustatory system is congregated structure. It contains reception, transduction, propagation, and perception of a chemical tasting. Every one of these processes requires a specific and effective procedure of plentiful mechanisms (Ksouda *et al.*, 2011).

The structures of high center of taste are; thalamus, insular cortex, caudate nucleus, anterior cingulated gyrus, parahippocampal gyrus, lingual gyrus, and temporal gyri (Mattes *et al.,* 1990).

Taste perception is situated at the taste buds level, in which the taste receptors are located, and at different points of the oral cavity (Felix *et al*., 2009).

The vagal and glossopharyngeal nerves also convey overall sensory nerve fibers for the upper digestive and oral mucosa, as does the trigeminal (V) cranial nerve (Matsumoto *et al*., 2001; Grundy, 2006).

The process to differentiate taste types (e.g., sweet, bitter) is remain dialectical. One set of experiments reveal that gustatory cortical neurons respond to numerous qualities of taste in a prompt timescale (Stapleton *et al*., 2006).

Cells of taste receptor are reactive to the quantity and type of chemicals melted in saliva and permit for the recognition of the five basic taste: salt, sweet, bitter, sour (acidic) and umami (savory taste of amino acids) (Spector and Travers, 2005).

1.4.6 Role of zinc in taste sensation:-

Zinc is widely spread in the food supply and is related with the sense of taste, but the actual mechanism has not been fully understood. The absorption of zinc may be affected by the existence of other food ingredients (Aliani, 2013).

The presence of phytic acid in plant foods and entire grains substantially decrease the biological availability of zinc in the gastrointestinal tract and therefore its absorption (Couzy *et al*., 1998).

Zinc acts an important role in taste conception, and zinc deficiency is in charge for taste sense abnormalities in healthy persons (Ueda *et al*., 2006).

Zinc acts as a cofactor of alkaline phosphatase activity which is the most profuse enzyme in the membrane of taste bud (Fukasawa *et al.*, 2008).

The major effects of zinc deficiency are the alterations in the number and size of taste buds and structural variations in the cells of taste buds as well as decline in related sensitivity of nerve (Chou *et al* ., 2001).

Zinc supplementation has been exhibited to be effective in the management of taste abnormalities noticed among patients with taste disorders (Sakagami *et al*., 2009). In healthy persons, the recognition threshold for salty taste can be elevated by zinc supplementation (Tupe and Chiplonkar, 2009).

In cases of patient with cancer, Zinc utilization get better the symptoms of dysgeusia caused by radiation (Imai *et al.,* 2013).

1.4.7 Role of copper in taste sensation:-

The perception process of copper at the cellular level has not been clearly distinguished (Plattig, 1988).

Copper appears to affect the sucrose taste threshold at low or high copper concentrations (John and Borello, 1976).

Knudsen and Weismann, 1978 showed that the changes in the taste intensity for sweet, salt, sour, and bitter importantly paralleled the divergence in urinary copper before and during therapy with penicillamine. For that, the patients who exhibit the most obvious loss of taste had a lower urinary copper output than those whose taste acuteness was less defected.

1.4.8 Taste disturbance:

Signals pass through three main areas: the Nucleus Tractus Solitary situated in the medulla oblongata, the Ventral Posteromedial nucleus of the thalamus, and the Central trigeminal Tract at the level of the pons or midbrain (Tsivgoulis *et al.*, 2011).

Psychological factors can alter thresholds of the four basic tastes. The presence of neurotransmitters from various mood states can influence taste sensitivity (Hummel *et al.,* 2007).

It has been notified that when normal serotonin and noradrenaline levels are hold up, as they typically are in patients complaining from depression and anxiety, they have a taste disorders. Patients with depression often have a low sensitivity to all tastes and those with panic disorders have a low sensitivity to bitter tastants (Heath *et al*., 2014).

Chemosensory dysfunctions have multiple causes, psychogenic, systemic, oral, and neurological pathologies, though, pharmaceuticals are the wide spread cause of taste disturbances (Ksouda *et al.,* 2011).

In fact, taste sensitivity is declined with age (Naik and Claussen, 2010). Causes have been related to saliva in many cases because of the components in saliva that can provoke receptors of taste and alter taste susceptibility by chemical interaction (Sasano *et al*., 2010).

Some causes of taste disorders can include tumors, viral infections, and lesions interrupting the pathways of taste, head injury, epilepsy, radiation therapy, hypothyroidism and psychiatric disorders. Again, some drugs have unwanted effects that directly affect taste sensitivity or cause

hyposalivation, thus the outcome is dropping of sensitivity of taste (Sasano *et al.*, 2010).

1.4.8.1 Types of taste disorders:

1- Hypogeusia:

Hypogeusia is a category of taste disorders with patient who complains symptoms of a decreased potency to taste difference in foods (Naik and Claussen, 2010).

2- Ageusia:

Alexandra (2014) stated that ageusia is a group of taste disorder in which those who have symptoms of loss of taste at all. Causes of ageusia are not fully understood but look like to be related to injury of the cortex and central pathways and drug use and can be elucidated in some situations, though, as a sequence to harm the cortex and central pathways that are accountable for taste (Ribas and Duffau, 2012).

3- Dysgeusia:

Dysgeusia is a category of taste disorder that describes the presence of a metallic, foul, or malodorous taste in their mouth with no physiological causes (Naik and Claussen, 2010). As well, many patients with dysgeusia inform an impulsive bitter taste when eating sweet material (Hsiao and Li, 2007).

It is evaluated that overall 50-75 % of cancer patients can have dysgeusia. The average of dysgeusia is significantly correlated with the gathering of radiation therapy sessions (Mosel *et al.*, 2011).

1.4.8.2 Management of taste disorders:

1- Artificial saliva and pilocarpine:

Patients are able to minimize the result of xerostomia with Sugarless gum, mouth freshener mints, or lozenges, or physicians can enhance salivary flow with salivary substitute or by pilocarpine (Giudice, 2006).

Saliva substitutions imitate the natural saliva characteristics by lubricating and defend the mouth but without digestive or enzymatic advantages (Preetha and Banerjee, 2005).

Pilocarpine is a cholinergic drug analogue to the acetylcholine neurotransmitter . Acetylcholine has a role in producing saliva by stimulating the salivary glands (Mervyn *et al.*, 2004).

The elevation in saliva flow is beneficial in progressing the movement of tastants to the taste buds (Giudice, 2006).

2- Zinc supplementation:

The regular oral dose of 25–100 mg /day reveals an efficient treatment for dysfunction of taste offer zinc at low levels in the blood serum. There are no enough amounts of proofs to mark if supplementation of zinc is able to cure dysgeusia when minimum concentrations of zinc are not confined in the blood (Heyneman, 1996).

3- Altering drug therapy:

The impact of dysgeusia related to drug that it can sometime be inverted by cessation the patient's regimen of medication that changes taste (Bromley and Steven, 2000).

It became clear that drug-induced dysgeusia can be changed to another drug from the same class or lowering the drug's dose (Giudice, 2006).

4- Alpha lipoic acid:

Alpha Lipoic Acid (ALA) is an antioxidant that is synthesized in nature by human cells (University of Maryland Medical Center, 2009).

The ALA used for burning mouth syndrome inducing investigations in its prospect to cure dysgeusia (Femiano *et al*., 2002).

5- Managing Dysgeusia:

These involve the use of non-metallic silverware, away from foods with metallic or bitter taste, encouraging the utilization of high protein foods, relishing foods with condiment and spices, offering foods cold in order that reduce any odor or odious taste, over and over brushing teeth and using mouthwash, or using sialogogues like sour-tasting drops or chewing sugar-free gum that enhance the production of saliva (Hong *et al* .,2009).

6- Psychological impact:

Since the old ages are usually polypharmacy, they are at danger for taste alterations; increase the likelihood to developing depression, anorexia , and intemperate loss of weight (Padala *et al*., 2006).

1.5 Saliva

Saliva is one of the body fluids, mainly produced by three major pairs of salivary glands (parotid, submandibular and sublingual) and by plenty of minor salivary glands (Fabian *et al*., 2012).

1.5.1 Functions of saliva:

1.5.1.1 Protection and lubrication:

Saliva makes a seromucosal encasing that lubricates and save the oral tissues against vexing substances (Nagler, 2004). This takes place because

of mucins (high proteins and carbohydrate content) in charge of preserve against dehydration, lubrication, and servicing the viscoelasticity of saliva. They also adjust the microorganism's adhesion to the tissue surfaces of oral cavity, which give a share in the control of fungal and bacterial colonization. Plus, they conserve against proteolytic offense by microorganisms to the tissues. Lubricant effects of these proteins are assessing Mastication, speech, and deglutition (Amerongen and Veerman, 2002).

Antimicrobial behavior through Specific Secretary Immunoglobulin A e.g. non-specific (e.g. Lysozyme, Lactoferrin and Myeloperoxidase) and sIgA. Anti-microbial mechanisms aid to oversight the micro flora of mouth (Whelton, 2012).

1.5.1.2 Buffering capacity

Buffer system of saliva acts to defend the mouth as follows:

1. It restrains potent pathogenic microorganism's colonization (Nagler, 2004).

2. Saliva buffers (neutralizes) and immaculate the production of acids by acidogenic microorganisms, so, protecting from demineralization of enamel (Ten, 1998).

Urea is a buffer substance found in entire salivary fluid which is the end product of protein catabolism and amino acid that causes a fast elevation in biofilm pH by elaborating carbon dioxide and ammonia when hydrolyzed by bacterial ureases (Ertugrul, 2003).

1.5.1.3 Dilution and cleaning:

Free sugars forms are found in whole unstimulated and stimulated saliva at an average concentration of 0.5 to 1 mg/100mL (Edgar *et al*., 2004).

Its fluid uniformity offers mechanical cleaning of the left overs found in the oral cavity like cellular and food debris, non-adherent bacteria. Stop-flow effects head for to remove surplus carbohydrates, for that reason, limiting the availability of sugars to the biofilm microorganisms (Negler, 2004).

1.5.1.4 Tooth Enamel Integrity:

Saliva has important function in keeping the integrity of physical-chemical of tooth enamel by amending demineralization and remineralization. The basic factors that control the constantly of enamel hydroxyapatite are the active intensification of phosphate, free calcium, fluoride in solution and the pH of saliva (Axelsson, 2000; Maria *et al.*, 2005).

Remineralization of a decayed tooth before cavitation can be contingent, at most due to the calcium and phosphate ions availability in saliva (Stack and Papas, 2001).

1.5.1.5 Digestion:

Saliva is in question of the primary digestion of starch, favoring the food bolus formation (Karthikeyan, 2014).

This activity happens fundamentally through existence of the digestive enzyme α-amylase (ptyalin) in the structure of the saliva. Its biological function is dividing the starch into maltotriose, maltose, and dextrins. This

enzyme is believed to be an important of good functioning salivary glands (Enberg *et al*., 2001).

1.5.1.6 Excretion and Water balance:

Technically the oral cavity is located outside the body; materials which are secreted in saliva are excreted. This is a highly incomplete excretory route as reabsorption may take place in the intestinal tract (Edgar *et al.*, 2004).

Glycoproteins in the saliva like mucins help in preserving water in the saliva. Due to the numerous of negatively charged carbohydrate side chains including groups such as sialic acid, mucins are hydrophilic. Their hydrophilicity support holding water in saliva and thus combat dehydration in the oral cavity. (Fejerskov and Kidd, 2008). When dehydration happens, there is declining in extracellular matrix fluid due to the lack of fluid, hence Hyposalivation occurs. In intense dehydration, the quantity of serous saliva will be rebated leading to the sensation of thirst. Water balance can be restored by drinking fluids (Silverthorne, 2004).

1.5.1.7 Saliva and taste perception:

Saliva takes part in preserving the taste buds structures and taste-sensing cells (Morris *et al*., 2000).

The saliva hypotonicity (minimum levels of chloride, glucose, sodium, and urea) and its ability to offer the degradation of materials permit the gustatory buds to understand assorted flavors. Salivary protein, Gustin, manifested to be indispensable for the buds growth and ripeness (Humphrey and Williamson, 2001; Berkovitz *et al*., 2002)

It is probably that the salivary flow rate can adjust the tastants concentration and various soluble taste perception-related mediators due to a dilution effect (Lugaz *et al*., 2005; Heinzerling *et al*., 2011).

The saliva buffering ability may also play a distinct duty in the sensation of sour taste which is intensely related (even if not mandatory commensurate) (De Simone and Lyall, 2006).

Coupled with the pH value .Though, it has to be proved that higher salivary buffer capacity and/or higher flow rate does not guide to weaken capacity of taste sensation (Lugaz *et al*., 2005).

Elevated concentration of proven proteins of saliva like salivary alpha-amylase, Salivary Immunoglobulin-A (sIgA) and salivary albumin also appear to be connected with ameliorate taste perception called in rapport to the sensation of bitter taste (Dsamou *et al.,* 2012).

1.6 Teeth mobility:

The proposition that stated, statins have beneficial effects for periodontal hard tissue regeneration (Kim *et al*., 2011).

Optimal concentrations of simvastatin solutions could be collected with bone grafts to reinforce their regenerative potential (Kinra *et al.,* 2010).

The leverage long-term secure profile and low cost of this compound make it a convenient agent in periodontal treatment (Guthrie, 2006).

Bone loss prevention with simvastatin treatment in patients with chronic periodontitis and documented that have useful effects on tooth mobility and alveolar bone loss with periodontaly involved patients (Fajardo *et al.,* 2010).

Chapter Two

Subjects, Materials & Methods

Subjects, Materials and Methods

2.1 Subjects:

The study samples consisted of 80 subjects; the subjects were divided into two groups:

Group 1: Forty patients on simvastatin treatment (20mg tablets/day), age between (35-60) years.

Group 2: Forty healthy control subjects with no signs and symptoms of any systemic diseases, they were gender and age matched to that of patients.

Patients were collected from Al-Samawa teaching hospital in Al-Samawa city .The laboratory works were done in the Poisoning consultation center, Ghazi Al-Hariry hospital. This study was carried out during the period between 20/12/2016 to 20/5/2017.

2.1.1 Inclusion criteria:

All patients on simvastatin treatment (20mg tablets/day) at least one year and over and others were healthy subjects.

2.1.2 Exclusion criteria:

Any subject demonstrated the following conditions were not included in the study: - diabetics, thyroid and parathyroid disease, autoimmune disease, chemotherapy, smoking, alcoholics, neoplastic diseases.

Informed consent and ethical approval was obtained from each subject (appendix I I). Each subject fills a case sheet questionnaire (appendix I).

2.2 Materials:

1- Taste solutions

Sweet: 15 solutions of sucrose from (1.5 -15 mmol /L) in 1mmol increment.

Sour: 15 solutions of citric acid from (48- 720 µmol /L) in 48 µmol increment.

Salty: 15 solutions of sodium chloride from (1-78 mmol /L) in 5.5 mmol increment.

Bitter: 15 solutions of urea from (89- 117 mmol /L) in 2 mmol increment Figure (2- 1)

Figure (2-1) Taste testing solutions for subjects

Deionized water: was used as solvent. Taste solutions were prepared freshly in regular intervals (Gomez *et al.*, 2004). Figure (2-2)

Figure (2-2) Deionized water

2- Zinc assay :standard solution zinc nitrate BDH Chemicals Ltd Poole England .

3- Copper assay: standard solution cupric nitrate BDH Chemicals Ltd Poole England.

Figure (2-3) Cupric nitrate standard solution for atomic absorption assay

4- Glasses: graduated pipette, volumetric flask, graduated beakers, glass rod, screw-cap bottles.

5- Plastics: disposable syringes with stainless steel needles, disposable cups, sterilized disposable plane tubes.

6- Instruments: Diagnostic instruments (disposable mirrors and probes)

Figure (2-4) Examination tools

7- Equipments: microplate reader, shaker and incubator, refrigerator, centrifuge, micropipette, flame atomic absorption assay device. Figure (2-5).

Figure (2-5) Nov AA 300 Atomic Absorption Device

2.3 Methods:-

2.3.1 Intraoral examination

Oral examination begins with the lips proceeding to the right buccal mucosa, including the upper and the lower sulcus, retro molar area, upper and lower labial mucosa, the left buccal mucosa, palatal mucosa and the surface, the margins of the tongue with the inferior surface of the tongue and the floor of the mouth were examined (World Health Organization, 2013). Figure (2-6)

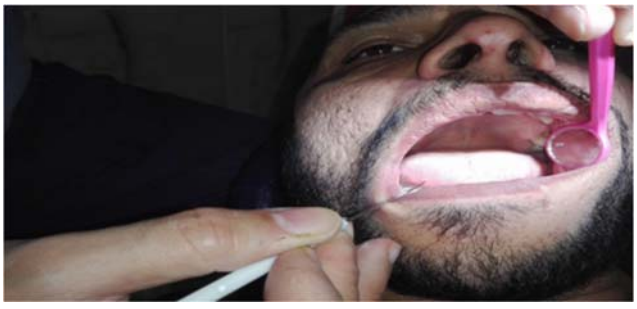

Figure (2-6) Intraoral examination

All clinically evidences of mucosal alteration (redness, swelling, ulcer, etc.) were determined and recorded, to find any oral manifestations.

2.3.2 Salivary flow rate:

Salivary flow rate was calculated as volume in ml of saliva sample collected within 10 minutes divided by time in minutes required for collection (Salivary flow rate =salivary volume /time = ml/min) **(**Laine *et al* .,1988).

2.3.3 Assessing of taste detection threshold:-

Each taste gradient consisted of 15 solutions , from 1.5 to 15.5 mmol (in 1 mmol increments) for sucrose , from 1 – 78 mmol (in5.5 mmol increments) for sodium chloride , from 48 – 720 µmol (in 48 µmol increments) for citric acid , and from 89 -117 mmol (in 2 mmol increments) for urea (Amerine and Pangborn ,1965).

Preparation of taste solutions by calculation the amount of taste substance in grams dissolved in deionised water for recommended concentration according to weight (g)= molecular weight(g/mole) x concentration(M) x volume(ml)/1000 (Koenig *et al.* , 2000).

A volume of 10 ml of each taste gradient solution , previously brought to room temperature (22-25 C^0) , was offered to the participants in disposable cups coded in random numbers, ordered progressively higher concentration starting from deionized water as blank (Gomez *et al* ., 2004). The concentrations of solutions used are shown in table (2-1).

The sip and spit method was used, the taste solution were swirled around in the mouth briefly and expectorated into an empty cup (Mojet *et al*., 2003) figure (2-7).

(1)

(2)

(3)

(4)

(5)

(6)

Figure (2-7) Taste Detection Threshold (sip and spit) (Mojet *et al.*, 2003).

Table (2-1):- The concentrations of taste solutions used (Amerine and Pangborn ,1965)

Sucrose mmol/L	**Sodium chloride mmol/L**	**Citric acid µmol/L**	**Urea mmol /L**
1.5	1	48	89
2.5	6.5	96	91
3.5	12	144	93
4.5	17.5	192	95
5.5	23	240	97
6.5	28.5	288	99
7.5	34	336	101
8.5	39.5	384	103
9.5	45	432	105
10.5	50.5	480	107
11.5	56	528	109
12.5	61.5	567	111
13.5	67	624	113
14.5	72.5	672	115
15.5	78	720	117

2.3.4 Teeth mobility assessment:-

By modified Miller's mobility index of horizontal tooth mobility, Miller's classification is the most commonly used clinical methods for determining tooth mobility (Laster *et al*., 1975). In his method the tooth is firmly held between 2 instruments to move back and front, mobility is scored on a scale of 0-3 as follow:-

0: no detectable movement apart from physiologic tooth movement.

1: It indicates slight mobility with in less than 0.25 mm

2: slight mobility 0.25- 1mm in facial-lingual direction

3: considerable mobility more than 1mm in all direction with vertical deformability is presented (Purkait *et al.*, 2016) (Appendix III).

Teeth are selected according to Ramfjord teeth: - upper right central incisor and first molar left second bicuspid lower right second bicuspid, lower left central incisor and first molar (Ramfjord ,1967) . So the score was calculated by summation of the scores of the 6 teeth in such a way that how many zeros no. 1, no. 2 and no. 3 of each subject. Figure (2-8).

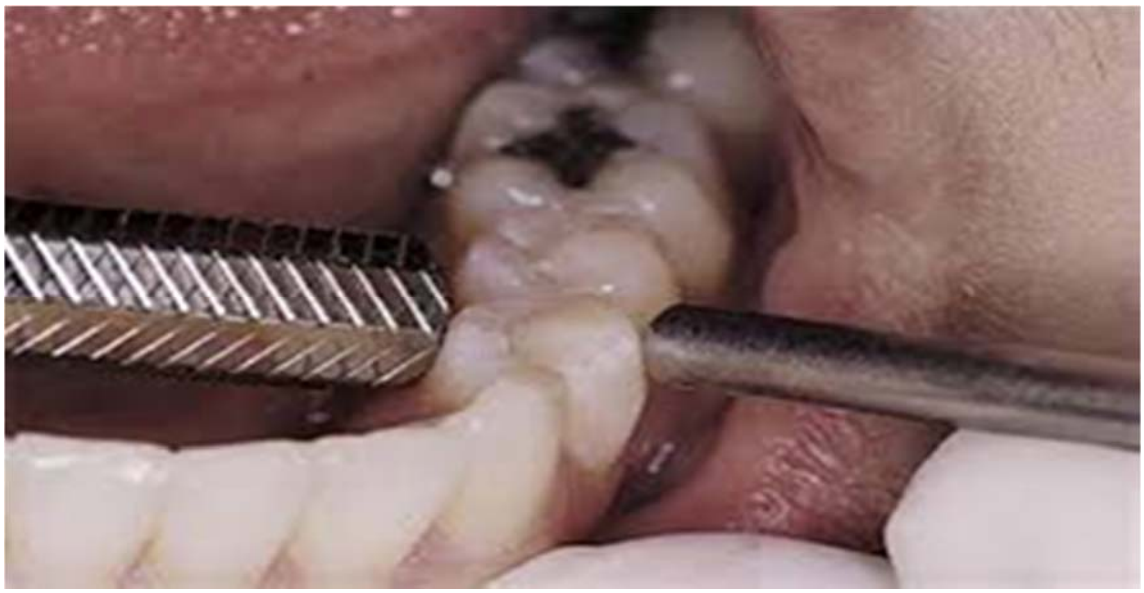

Figure (2-8) Teeth mobility assessment by modified Miller's mobility index

2.3.5 Collection of samples:-

2.3.5.1 Blood sample:

Venous blood sample (5ml) was drawn from all subjects (fasting 12 hours) using disposable syringe with 21 gauge stainless steel needle in sitting position .The fresh blood sample was placed in plain disposable tube .

The blood was allowed to clot at 37 C^0 for 15-20 minutes then centrifuged at 3000 rpm for 15 minutes, the serum was obtained ,they were divided in parts in sterile micro centrifuge tubes and was stored at -20 C^0 in deep freezer until analysis .The tubes was labelled subject's name by water resistant marker . Figure (2-9)

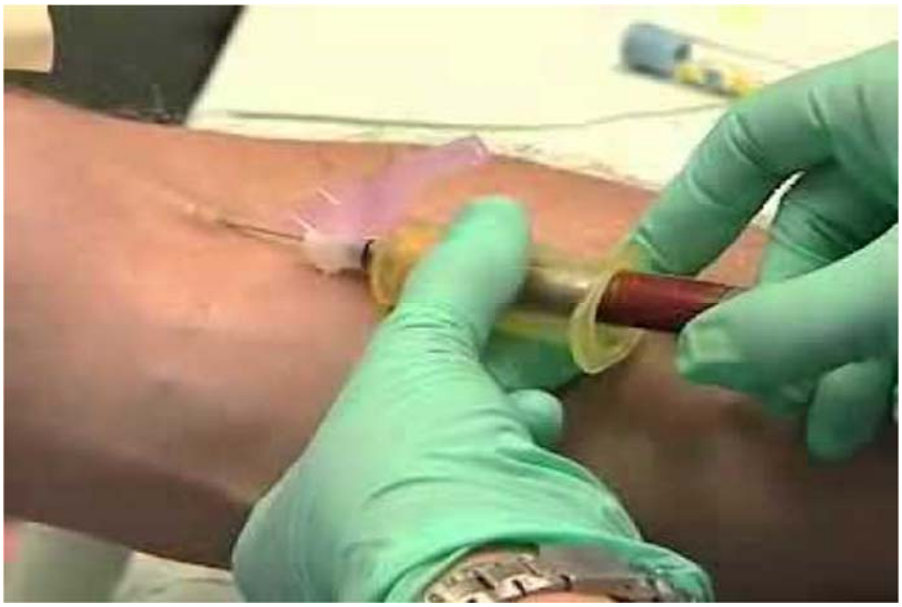

Figure (2-9) Venous blood collection

2.3.5.2 Saliva sample

Unstimulated whole saliva was collected under standardized condition by using spitting method (Dittmer, 1991). Collection is done at the morning from (9-11 a.m.), the subjects were fasting 12 hours. before collection and asked to rinse their mouths well to remove debris, spitting into graduated tubes for about 10 minutes.

The subjects were asked to sit on a chair so their heads bent forward to prevent stimulation by tongue movement and prevent swallowing of saliva .Then stop watch was used. The saliva was collected into graduated tube, closed immediately by plastic stopper. Figure (2-10)

Figure (2-10) Saliva sample collection

The collected saliva was centrifuged at 3000 rpm for 10 minutes; the clear supernatant is separated, divides in parts and was stored at -20 C^0 in deep freeze until analysis.

2.3.6 Analytical method:

Zinc in saliva and serum were determined by using the flame atomic absorption assay technique with standard working curve is directly proportional to the zinc concentration in the sample (Figure 2-11).

Copper in serum and saliva were determined by using the flame atomic absorption assay technique with standard working curve (Figure 2-12).

The wave length of copper measurement was 324.7 nm, while for Zn was 213.9 nm

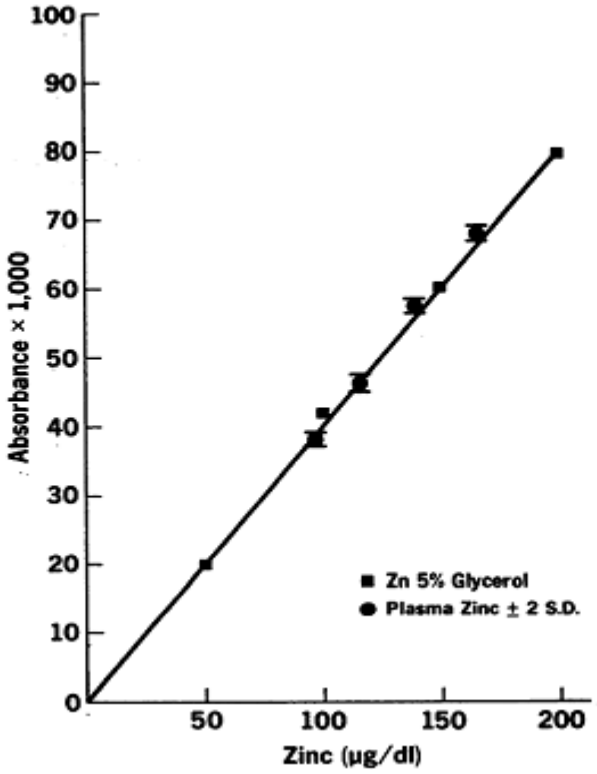

Figure (2-11): The standard working curve of zinc

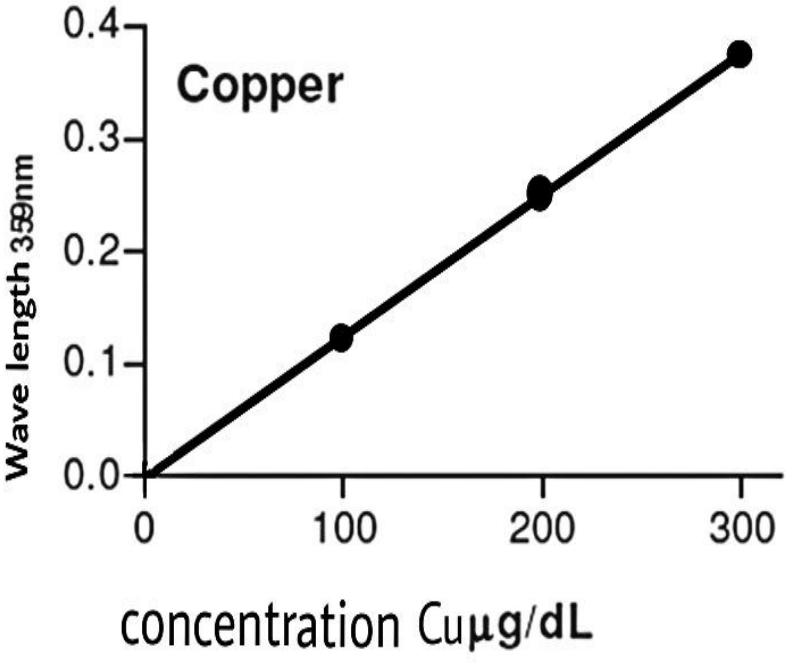

Figure (2-12): The standard working curve of copper

2.3.7 Statistical analysis:-

A computerized program, the statistical package for the social sciences (SPSS) was used for data analysis.

Both descriptive and inferential statistics was used.

1-descriptive statistics

Statistical figures and tables, Mean and Standard deviation (SD), Range.

2-inferential statistics

Student t-test (unpaired), Pearson correlation, multiple regression analysis

The results were considered significant, when the level of significance is 0.05 or less.

Chapter Three

Results

Results

3.1 Clinical findings:-

The total samples of this study consisted of 80 subjects, they were divided in to two groups:-

1- Forty patients on simvastatin treatment

2- Forty healthy control subjects. :

3.1.1 Age:

This study showed that the age range of patients on simvastatin treatment was (35-60 years) with a mean age and standard deviation of 47.65 ± 7.63 years. For the control subjects the age range was also (35-60 years) with mean and standard deviation 48.12±7.20 years.

Statistical analysis using t-test showed no significant differences between the mean age of patients on simvastatin treatment and ages of controls subjects ($p > 0.05$) (Table 3-1).

Table (3-1):- The range and mean ages of patients on simvastatin treatment and control subjects.

Groups	No.	Age range (years)	Mean (years)	SD	p-value
Patients on simvastatin	40	35-60	47.65	7.63	0.88 (NS)*
Control subjects	40	35-60	48.12	7.2	

*NS:- None significant

3.1.2 Gender:-

The results showed that the number of male patients was 23 (57.5%) and the number of female patients was 17(42.5%). Also for the control subjects the number of male subjects was 23 (57.5%) and the number of female subjects was 17(42.5%) The results showed that the percentage of male patients on simvastatin treatment was higher than the percentage of female patients.

3.1.3 Duration of simvastatin treatment:-

The results showed that the range of duration of treatment was(1-6) years, the mean and standard deviation was 2.36±1.36 year , the number and percentage of patients on simvastatin treatment of (1-3) years duration was 25 (62.5%), from (3-5) years were 11 (27.5%), and patients on simvastatin treatment ≥ 5 years were 4 (10%) (Table 3-2).

Table (3-2):- The number and percentage of patients on simvastatin according to the duration of treatment.

Duration of treatment		**No. of patients**	**%**
Range 1-6 years	**Mean ±SD**		
1-3	2.36±1.36	25	62.5
4-5		11	27.5
≥ 5		4	10

3.2 Oral Findings:-

3.2.1 Oral manifestations

The results of this study showed that no oral lesions or other oral manifestations were found in the oral cavity of patients on simvastatin treatment, but those patients were complaining of dry mouth 16(40%) and bitterness 24(60%) patients .

3.2.2 Taste detection threshold:-

This study showed that the mean and standard deviation of the taste detection threshold of sucrose (sweetness) of patients on simvastatin treatment was 14.90 ±0.63 mmol/l ,and for the control subjects was 9.40 ±0.74 mmol/l .

The mean and standard deviation of the detection threshold of salty taste for patients on simvastatin treatment was 17.63 ± 5.21 mmol/l, in control subjects was 16.55 ±4.88 mmol/l. For the sour taste, the results showed that the mean and standard deviation of the detection threshold for citric acid of patients was 330.40 ±44.75 µmol/l , while in control subjects the detection threshold for citric acid (sourness) was 172.80±30.35 µmol/l.

For the bitter taste, it has been shown that the mean and standard deviation of urea (bitterness) in patients was 104.15±1.72 mmol/l, while for control subjects was 97.1±1.75mmol/l (Table 3-3).

It has been shown that the detection threshold of sweet in patients on simvastatin treatment was significantly higher ($p < 0.05$) than that in the control subjects, also the detection threshold of sour and bitter tastes in

those patients were highly significantly increase (p<0.001) than that in the control subjects , while the detection threshold of salt taste in patients on simvastatin treatment showed no significant differences than that in the control subjects ,although it was higher in the patients (p>0.05) (Table 3-3) (Figure 3-1).

Table (3-3):- The mean and standard deviations of the detection threshold of the four tastes of patients on simvastatin treatment and control subjects.

Group	Sweet		Salt		Sour		Bitter	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Patients on simvastatin	14.90	.63	17.63	5.21	330.40	44.75	104.15	1.72
Control	9.40	.74	16.55	4.88	172.80	30.35	97.10	1.75
p- values	*P< 0.05		p> 0.05 NS		P< 0.001**		**P< 0.001	

All units in mmol/L except for sourness in µmol/l
** **Highly significant p<0.001**
* **Significant p< 0.05** **NS: - None significant**

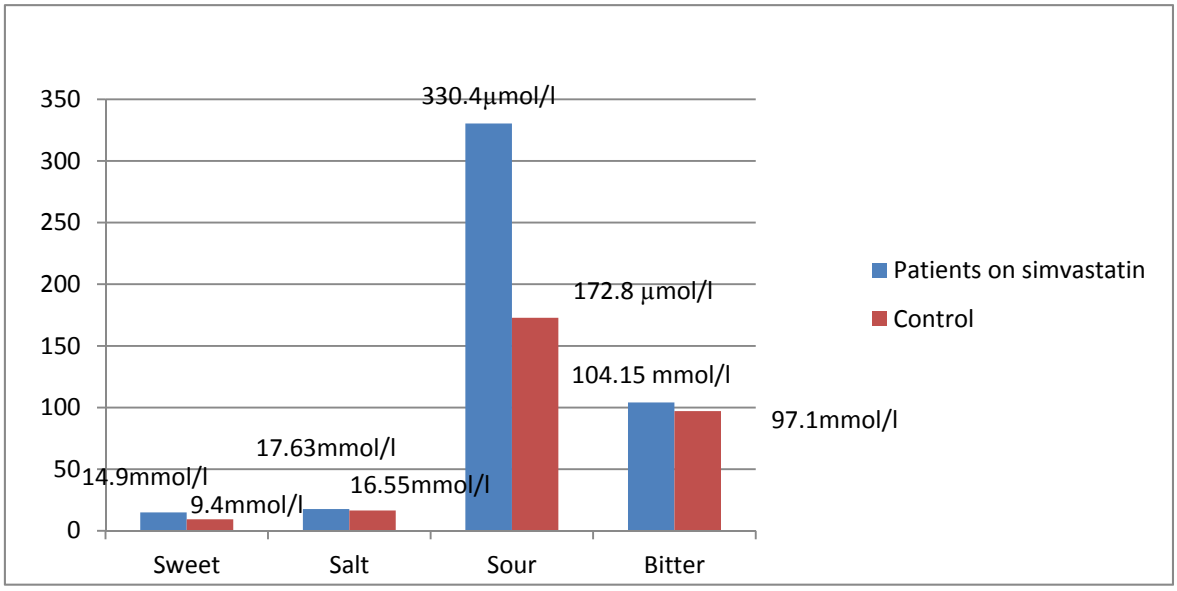

Figure (3-1): The mean of the taste detection thresholds of the study groups.

3.2.3 Salivary flow rate:-

This study showed that the mean and standard deviation of salivary flow rate of patients on simvastatin was 0.33±0.08 ml/min, while for the control subjects was 0.59± 0.04 ml/min.

Statistical analysis showed that salivary flow rate was highly significantly decreased in patients on simvastatin treatment than that in control subjects ($p < 0.001$) (Table 3-4) (Figure 3-2).

Table (3-4):- The mean and standard deviations of salivary flow rate of patients on simvastatin and control subjects.

	Patients on simvastatin treatment (mean ± SD)	Control (mean ±SD)	P -value
Salivary flow rate(ml/min)	0.33±0.08	0.59± 0.04	**0.0001

** **P<0.001: high significant**

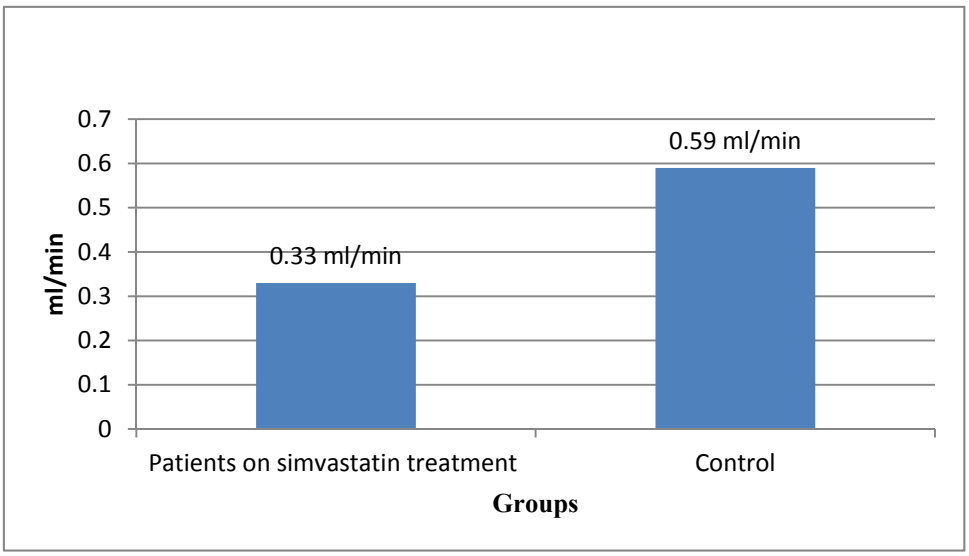

Figure (3-2):-Salivary flow rate in study groups

3.2.4 Miller's mobility index:-

The study showed that the mean and standard deviation of Miller's mobility score 0 for patients on simvastatin treatment was4.22±1.05, while for the control subjects was 1.44 ± 0.73 .

The mean and standard deviation of Miller's mobility score 1 for patients on simvastatin treatment 1.87±1.04, while for control subjects 3.77± 1.22. This study showed that there were no patients on simvastatin with Miller's mobility score 2 and 3, while for control, the mean and standard deviation of score 2 was 2.09±1.01 and for score 3 was 1.66±0.81 (Table 3-5) (Figure 3-3).

Statistical analysis using t- test showed that there was a significant differences between patients on simvastatin treatment and control subjects. The mean of Miller's mobility score 0 was highly significantly higher in patients on simvastatin than that in the control subjects ($p < 0.001$), while the mean of Miller's mobility score 1 was highly significantly lower in patients than that in the control ($p < 0.001$) (Table 3-5).

Table (3-5):- The mean and standard deviations of Miller's mobility score of patients on simvastatin and control subjects.

Groups	Miller's mobility score 0		Miller's mobility score 1		Miller's mobility score 2		Miller's mobility score 3	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Patient on simvastatin	4.22	1.05	1.87	1.04	No scores	-	No scores	-
Control	1.44	.73	3.77	1.22	2.09	1.01	1.66	.81
P -value	**P < 0.001		**P< 0.001					

** P < 0.001: high significant

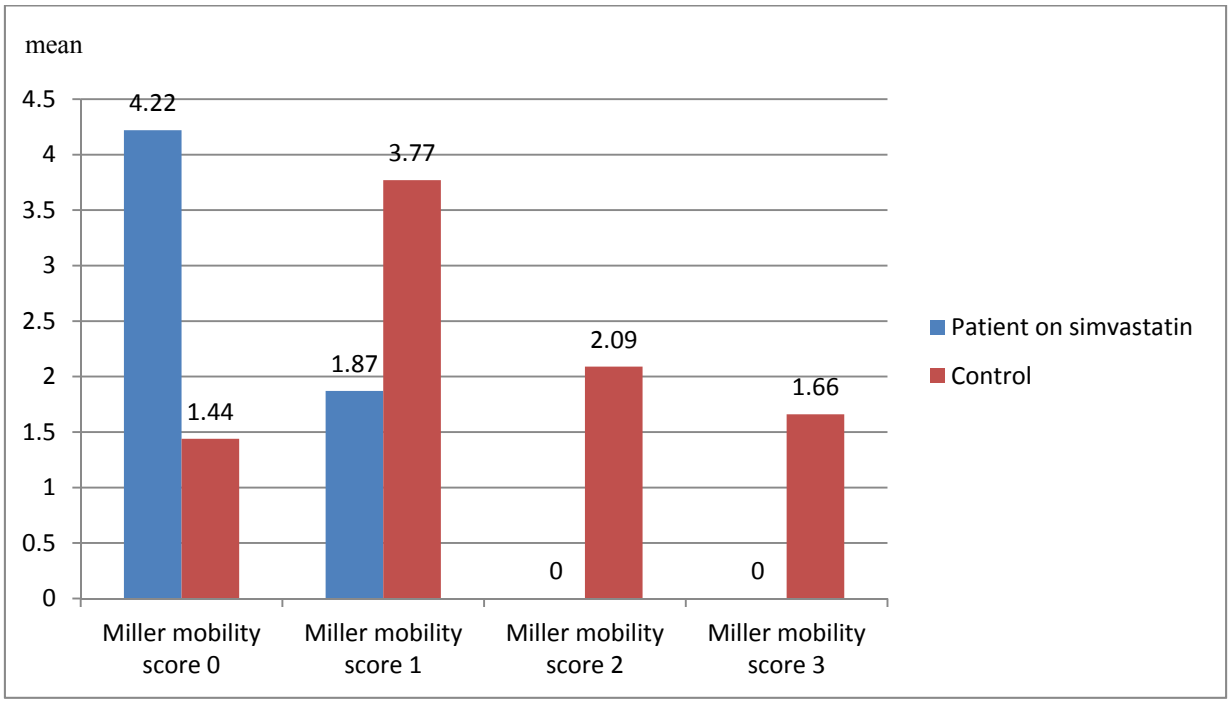

Figure (3-3):- The mean of Miller's mobility score of the study groups

3.3 Laboratory Findings (Trace elements):-

3.3.1 Salivary and serum zinc:-

It has been shown that the mean and standard deviation of salivary zinc of patients on simvastatin treatment was 2.03 µg/dl±0.58, while for the control subjects was 4.96 µg g/dl± 0.38.

This study showed that the mean and standard deviation of serum zinc level for patient on simvastatin was 58.85 µg/dl ±6.83, while for the control subjects, was 90.32 µg /dl ±7.81.

Statistical analysis showed that serum and salivary zinc were highly significantly decreased in patients on simvastatin treatment than that in control subjects ($p< 0.001$) (Table 3-6) (Figure 3-4).

3.3.2 Salivary and serum copper:-

The results showed that the mean and standard deviation of salivary copper in patients on simvastatin treatment was 1.99 µg /dl ± 0.46, while in the control subjects was 4.85 µg /dl ±0.96. It has been shown that, the mean and standard deviation of serum copper in patients on simvastatin treatment was 59.15 µg /dl±7.63, while in the control subjects, mean and standard deviation was 114.67 µg /dl±16.49 (table 3-6) (Figure 3-4).

The statistical analysis using t- test showed that salivary and serum copper were highly significantly decreased in in patients on simvastatin treatment than that in the control subjects ($p<0.001$)(Table 3-6).

Table (3-6):- The mean and standard deviations of serum and salivary zinc and copper in study groups with (t-test).

Group	Salivary zinc µg /dl		Serum zinc µg /dl		Salivary copper µg /dl		Serum copper µg /dl	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Patients on simvastatin	2.03	0.58	58.85	6.83	1.99	0.46	59.15	7.63
Control	4.96	0.38	90.32	7.81	4.85	0.96	114.67	16.49
p-value	** P < 0.001		** P < 0.001		** P < 0.001		** P < 0.001	

** P < 0.001: highly significant

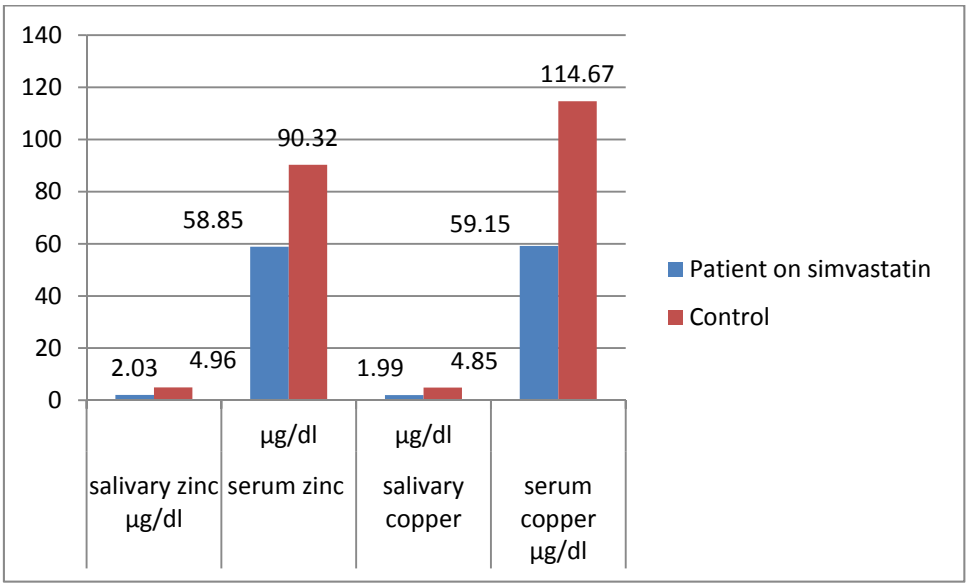

Figure (3-4): The mean of salivary and serum zinc and copper in the study groups

3.4 The correlations of parameters:

3.4.1 Duration of treatment:-

It has been shown that there was a significantly positive strong linear correlation between duration of treatment and age (p= 0.005), while a significantly negative linear correlation with salivary flow rate (p=0.005). Also there were a significantly negative linear correlation with serum zinc (p= 0.025) and with salivary copper (p= 0.026) as shown in (Table 3-7)

Table (3-7):- The correlation between duration of therapy and other study parameters in patient on simvastatin treatment.

Groups	Duration of treatment	
	Correlation coefficient (r)	P value
Age	0.615	0.005*
Sweet	0.212	0.190
Salt	0.042	0.795
Sour	-0.058	0.722
Bitter	0.033	0.840
Salivary flow rate ml/min	-0.585	0.005*
Miller mobility score 0	-0.053	0.89
Miller mobility score 1	0.171	0.292
Salivary zinc µg /dl	-0.164	0.312
Serum zinc µg /dl	-0.354	0.025*
Salivary copper µg /dl	-0.352	0.026*
Serum copper µg /dl	-0.226	0.161

* **Significant p < 0.05**

3.4.2 The correlations between salivary and serum trace elements:-

Statistical analysis using the correlation coefficient (r) showed no significant correlation between salivary and serum zinc in patients on simvastatin treatment and in control subjects and between salivary and serum copper in patients on simvastatin treatment and in control subjects $p>0.05$ (Table 3-8).

Table (3-8):- The correlation coefficient (r) between serum and salivary of zinc and copper in both groups.

Group / Trace element	Patients on simvastatin treatment		Control	
	r	p	r	p
Serum and salivary zinc	0.04	0.76 NS	0.32	0.30 NS
Serum and salivary copper	-0.03	0.84 NS	0.18	0.25 NS

NS:- None significant

3.4.3 The correlation between each of the four basic taste and serum and salivary trace elements:-

The results showed no correlation found between all the detection thresholds of the four basic tastes and salivary and serum trace elements ($p>0.05$) in both groups (Table 3-9).

Table (3-9):- The correlation and p-value between trace elements (zinc and copper) level in serum and saliva with the detection thresholds of the four basic tastes in both patients on simvastatin treatment and control subjects.

Trace elements Taste	Salivary zinc				Serum zinc				Salivary copper				Serum copper			
	Patient on simvastatin		control		Patient on simvastatin		control		Patient on simvastatin		control		Patient on simvastatin		control	
	(r)	P	(r)	P	(r)	P	(r)	P	(r)	P	(r)	P	(r)	P	(r)	P
Sweet	-0.06	0.71	-0.05	0.72	0.16	0.30	0.06	0.69	0.08	0.61	0.43	0.5	0.10	0.53	-0.05	0.71
Salt	-0.02	0.89	-0.01	0.91	0.08	0.59	-0.08	0.58	0.13	0.41	0.029	0.86	-0.05	0.97	-0.20	0.20
Sour	-0.10	0.51	0.12	0.44	0.11	0.49	0.10	0.52	0.003	0.41	0.11	0.49	0.17	0.29	0.004	0.97
Bitter	-0.10	0.50	-0.04	0.76	0.18	0.29	0.06	0.69	0.13	0.39	0.13	0.39	0.17	0.28	-0.15	0.33

*Correlation is significant at the 0.01

3.4.4 The correlation between salivary flow rate and other study parameters:-

Saliva flow rate showed a significantly negative linear correlation with age, and with duration of treatment. Also the results showed that there was a highly significant positive linear correlation between salivary flow rate and the mean of detection threshold of sweetness and sourness of both study groups ($p \leq 0.001$) , and highly significantly negative linear correlation with the mean of detection threshold of saltiness and bitterness in both groups ($p \leq 0.001$) (Table 3-10).

Regarding Miller's mobility scores, the results showed that there was a high significant positive linear correlation between salivary flow rate and score 0 and score 1in both groups.

For Miller's score 2 and 3 there was a significant negative linear correlation with flow rate in the control subjects (Table 3-10).

It has been shown that there were a high significant positive linear correlation between saliva flow rate and the mean of trace elements zinc and copper in serum and saliva of patients on simvastatin treatment and control subjects ($P \leq 0.001$) (Table 3-10).

Table (3-10):- The correlation coefficient and p-value between salivary flow rate and other study parameters in both study groups.

S.F.R / Parameters		Patients on simvastatin			Control		
		(r)	**p**	**Sig.**	**(r)**	**p**	**Sig.**
Age	**35-60 years**	-0.32	*0.03	S	0.03	0.83	NS
Duration of treatment	**1-6 years**	-0.585	*0.005	S			
Taste detection threshold	**Sweetness**	0.005	**0.0001	HS	0.64	**0.0001	HS
	Saltiness	-0.06	**0.0001	HS	-0.20	**0.0001	HS
	Sourness	0.21	**0.0001	HS	0.25	**0.0001	HS
	Bitterness	-0.21	**0.0001	HS	-0.17	**0.0001	HS
Miller's mobility index	**Score 0**	0.15	**0.001	HS	0.26	**0.001	HS
	Score 1	0.11	**0.001	HS	0.09	**0.001	HS
	Score 2	No score			-0.03	*0.03	S
	Score 3	No score			-0.03	*0.02	S
Saliva	**Zinc**	0.16	**0.0001	HS	0.23	**0.0001	HS
	Copper	0.21	**0.0001	HS	0.04	**0.0001	HS
Serum	**Zinc**	0.25	**0.0001	HS	0.20	**0.0001	HS
	Copper	0.30	**0.0001	HS	0.26	**0.0001	HS

****P ≤0.001 (HS) Highly significant, *P< 0.05 (S) Significant, (NS) None significant p>0.05 . S.F.R: Salivary flow rate.**

Chapter Four

Discussion

Discussion

Hyperlipidemia is a medical condition characterized by an elevation of any or all lipid profile and/or lipoproteins in the blood (Kathleen, 2017). Simvastatin is a lipid-lowering medication .It is used along with exercise, diet, and weight loss to decrease elevated lipid (fat) levels. It is also used to decrease the risk of heart problems in those at high risk (The American Society of Health-System Pharmacists, 2015).

4.1 Age:-

Data obtained from this study showed that age's ranges of patients on simvastatin treatment were (35-60 years) with a mean age and standard deviations of 47.65 ± 7.63 years, at that age the primary hyperlipidemia are common. This was agreed with other studies (Plaza *et al*., 2000) who found that hypercholesterolemia was high among people of Spain with age range 35-64 years. Others like (Pascual *et al.,* 2008) found that those patients on simvastatin treatment with oral adverse side effects of this medication were of age range (50-70) years.

Typically, in old age patients with hyperlipidemia the mechanisms behind this age-related hyperlipidemia are incompletely described. Some clues indicated that the causes of age-related disorders of lipid homeostasis comprised the precise drop in fractional clearance of low density lipoprotein (LDL) with growing age, the advanced reduced capability to remove cholesterol out of transformation to bile acids, and the lowering activity of the rate-limiting enzyme in bile acid biosynthesis, cholesterol 7-hydroxylase (C7OH). Furthermore, a good hypothesis by (Matasconi *et*

al., 2005) announced that critical change in cholesterol and lipoprotein metabolism depends on the aging.

Rudling *et al*., 1997 stated that growth hormone (GH) functions a remarkable role in cholesterol homeostasis by either amending the expression of hepatic LDL, or overnighting activity of cholesterol 7-hydroxylase.

4.2 Gender:-

The current study showed that male patients on simvastatin were 23 and females were 17 of total patients, which mean the number of male patients was higher than females, this was agreed with (Plaza *et al*., 2000). This disagreed with the previous study displayed by (Upmeier *et al.*, 2012) found that conflicting results as to gender differences, reporting higher use in women of ages below 60 years, while (Sheppard *et al*., 2012) and others reported no gender differences in Statin prescribing, in particular, incident prescribing, tended to be lower in women than in men, but after age 60 years, gender differences were negligible. In contrast, (Helle *et al*., 2016) found incidences as well as prevalence of therapy among individuals aged 50 years were considerably higher in women than men and the proportion of statin users in primary prevention decreased with age, this proportion was higher in women than men.

4.3 Duration of simvastatin treatment:-

This study showed that duration of simvastatin treatment ranged from (1-6) years and highest percentage of duration of simvastatin treatment was at (1-3) years (62.5%), this agreed with Aldeman , 2011

who found that the benefits of statins can be reached one to two years after initiation of treatment and increased as duration of treatment extended from (1-6) years .

4.4 Oral Findings:-

The study showed that there were no oral lesions or other oral manifestations in hyperlipidemic patients on simvastatin treatment except they were complaining of dry mouth and bitterness because little is known regarding the side effects of oral treatment with statins, this results coincided with (Pascual *et al*., 2008) who found that most of patients on statins were complaining of dry mouth, itchiness, parasthesia and bitterness. These results may disagree with (Smith *et al.*, 2016), who suggested that statins were potential causes for oral ulceration.

4.4.1 Taste detection thresholds:-

Sweet detection threshold for sucrose was 14.90±0.63mmol/l in patients on simvastatin treatment, this was significantly higher ($p<0.05$) than that of control subjects 9.40±0.74 mmol/l in such away those patients can only detect sweet taste in higher level due to drug-induced xerostomia (dryness of the mouth) this agreed with (Tomita and Yoshikawa , 2002), who found that less saliva is obtainable to transport tastants to the taste buds and medication can pass from the blood to taste cells or may influence the turnover of these cells. Also, Ackerman and Kasbekar (1997) stated that zinc deficiency is related to taste disturbances, and many medications chelate zinc in the body. Mann and Lafreniere (2006) referred problems in taste function may be due to progress age (i.e. Hypogeusia).

Salt detection threshold in patients on simvastatin treatment was 17.63±5.21 mmol/dl, while for control subjects 16.55±4.88 mmol/l. Although, it was high in patients on simvastatin treatment but it does not reach the significant level ($p>0.05$); this agreed with (Dioclécio *et al*., 2004) Who suggested that due to, in most of these cases, shortage of appetite which was not accompanied by any other symptoms and is fixed to a certain types of food, particularly those with a salty flavor.

Sour detection threshold in patients on simvastatin treatment was 330.40±44.75 µmol/l was significantly increased ($p<0.001$) than those of control subjects 172.80±30.35 µmol/l, this agreed with (Davies and Ng LL, 1993) who stated that simvastatin can cause dose-dependent drop in intracellular pH, allowed to a reduction in Na+/H+ exchange, and disagreed with (Roberto *et al.*, 2013) found that the buffering capacity of the saliva was normal and no changes in saliva pH were observed in patient on statins treatment.

The taste detection threshold for bitterness in patients on simvastatin treatment was 104.15±1.72 mmol/l which was significantly higher ($p<0.001$) than those of control subjects 97.10±1.75 mmol/l, this agreed with (Walravens *et al*., 1989) who found that simvastatin could damage peripheral nerves in the function of mitochondria enzymes.

Gaist *et al*. ,(2002) found that in the respiratory chain of mitochondria, and an intracellular shortage of respiratory enzyme because of statins has the cause of blocking energy consumed by neuron or functional changing in the nerve membranes, but

(Gauvin *et al.*,2015) and (Merkonidis *et al.*, 2015) suggested that, chemosensory disorders may be caused by statins.

4.4.2 Salivary flow rate:-

The present study showed that salivary flow rate was 0.33±0.08 ml/min in patients on simvastatin treatment, it was highly significant decreased ($p<0.001$) than that of control subjects which was 0.59± 0.04, this was corresponded with (Pascual *et al*., 2008) who ensure a frequent association between oral symptoms like dry mouth and treatment with statins.

The probable explanation for decrease salivary flow rate in patients on simvastatin was revealed by (Ferreira *et al* ., 2007) who stated that simvastatin treatment resulted in significant decrease of serum lipid profile but has less effect on the weight of parotid gland or may be due to recover parotid gland's changes from hyperlipidemia, resulting consequently to gland's acinar cells remodeling . Izumi *et al* . ,(1997) found that the deposition of fat in the major salivary glands and the severity of fat deposition could be correlated with compromised rates of salivary flow in those patients, the clinical findings of salivary glands in patients with hyperlipidemia include enlargement of parotid gland, lipid infiltration, and impaired salivary flow.

Rabia *et al*., (2009) suggested that the accumulation of lipid intracellular in the parotid and sublingual glands without changing in any structures but submandibular gland demonstrates a partial resistance to the accumulation of intracellular lipids.

4.4.3 Miller's mobility index:-

This study showed that the Miller's mobility score 0 was highly significantly higher ($p \leq 0.001$) in patients on simvastatin treatment than that in control subjects in such a way that those patients had the high score number indicates low or very undetectable tooth mobility , while the low number indicates there are various degrees of teeth mobility , the significant decline in teeth mobility presented in those patients might be demonstrated by the anti-inflammatory effects of this drug, this agreed with (Ilanna *et al.*,2015) and agreed with (Shemin *et al*., 2015) who stated that simvastatin provoke the expression of bone morphogenetic protein-2, a potent promoter of osteoblast differentiation and its activity, and encourage mineralization by cultured osteoblasts, (Horiuchi and Maeda ,2006) pointed out statins have an anabolic effect with a significant effect on the concentrations of systemic cytokine.

Other study by Shilpa *et al.,* 2014 stated that the week effects of antimicrobial action of statins increased bacterial clearance from the infected site or by promoting the apoptosis of microbial cells with hydrophobic nature of simvastatin. Also explained its antibacterial action, where it disturbs the bacterial membrane in a "soap like" manner could cause their death.

Also this study showed there were no patients on simvastatin treatment with score 2 and 3 due to decrease teeth mobility, this agreed with the results of (Pradeep *et al.,* 2013) who stated that, the decrease of teeth mobility in patients on simvastatin treatment may be due to the simvastatin anabolic effect on bones.

Lima *et al.,* (2011) found that Simvastatin has been reported to have generative effect on bone. Garrett *et al*., 2001 stated that statins are able of increasing bone mass as subsequent to bone formation.

Zongze et *al.,* (2016) found that identified statins use significantly increased bone mineral density (BMD) indicates that statins use could be a potential prevention or treatment for bone health. Moreover, an observational study by (Liu *et al.,* 2013) found that the association of statins use with improved BMD. Simvastatin at any dose for duration of more than one year, have no additive effect on 25- hydroxyvitamin D (25OHD) level but have a positive effect on the BMD at the lumbar spine and femoral neck (Abrar *et al.,* 2014).

Solomon *et al.*, (2005) support the hypothesis that statin use is associated with higher BMD, while it is unclear whether their relationship is causal.

4.5 Laboratory Findings:-

4.5.1 Salivary and serum zinc:-

This study showed that salivary zinc was highly significant decreased in patients on simvastatin treatment (2.03±0.58 µg/dl) than that of control subjects (4.96±0.38 µg/dl) , serum zinc was also highly significant decreased in patients on simvastatin treatment (58.85±6.83 µg/dl) than that in control subjects (90.32±7.81µg/dl), this results agreed with study by (Ghayour *et al.* , 2005) who found that the trace elements status may be affected significantly by treatment with statins at doses used in routine

practice. These effects may be due to the anti-inflammatory properties of the statins.

Jain *et al.,* (2005) explained salivary and serum zinc decreasing level because of simvastatin treatment may attribute the propagated serum depletion and alteration may be linked to the known anti-inflammatory properties of the statins class of medications.

Tatiana *et al*., (2001) proposed that the down regulate matrix metalloproteinases (MMPs) by simvastatin spends anti-inflammatory expression.

This results also agreed with (Coyle *et al*., 2002) who found that the decreased salivary and serum levels of zinc by simvastatin due to its effect on metallothionein (MT) 2A that belongs to metallothionein (MTs) family. These low-molecular weight proteins characterized by an extremely high percentage of cysteine remnants (up to 30%) that containing zinc.

4.5.2 Salivary and serum copper:-

This study showed that the patients on simvastatin treatment with salivary copper(1.99±0.46 mcg/dl)and serum copper(59.15±7.63 mcg/dl) were highly significant decreased than that in control subjects with salivary copper (4.85±0.96 mcg/dl) and serum copper (114.67±16.49mcg/dl) , this results was agreed with study of (Ghayour *et al* ., 2005) who proposed that statins reduced serum copper and serum concentration of ceruloplasmin which was not observed in the control patient.

Sparks *et al.,* (2005) stated that this reduction may be due to a tendency reduction of ceruloplasmin levels in circulation after a year of simvastatin treatment parallel to levels observed. Since the anti-oxidant properties of known relation to ceruloplasmin has on LDL was found by (Robinson *et al.,* 2005) who explained the way of blocking Cu^{2+} that mediated lipid oxidation comprised antioxidant properties.

Another possible explanation for decrease salivary and serum copper level by Pizzi *et al.,* 2004 who found that simvastatin treatment accompanied with a lessening in zinc-copper superoxide dismutase dependent activity and recovered endothelial response, this may be due to reduced production of superoxide anion.

Wassmann *et al.,* (2007) found that simvastatin also enhance the expression of catalase, but not superoxide dismutase or glutathione peroxidase by vascular smooth muscle cells in vitro.

Hung *et al.*, (2009) noticed that the opposite nature of copper allocation to cholesterol-rich lipid be gathered to relative concentrations of cellular copper reinforced an environment conducive to oxidative stress.

Duriez, (2003) stated that the suppression of HMG-CoA reductase and diminution synthesis of cellular cholesterol ,with subordinated waning copper by decreasing oxidative low density lipoprotein in circulation , an effect that was lean upon the amount of reduction.

Manuella *et al*., (2003) ;Ghaffari and Ghiasvand, (2010) ;Gyeong *et al.,* (2014) stated that copper has paramount role in low density lipoprotein oxidation. Simvastatin decreases antioxidant capacity of LDL, and elevates LDL vulnerability to copper oxidation.

It has been established that serum copper was positively connected with total and LDL cholesterol concentrations (Abiaka *et al.,* 2003).

Daniela *et al* ., (1999) found that copper ions are presumed to be rapport for the inducement of LDL oxidation and for the outgrowth of atherosclerosis in vivo , the oxidation of polyunsaturated fatty acids with copper has out come in the formation of peroxyl, alkaloxyl and other radicals.

It has been shown that statins, which block HMG-CoA reductase, possess both pleiotropic effects and low-density lipoprotein (LDL)-lowering properties. Simvastatin antioxidant effects versus lipid peroxidation happened through lipid-lowering-dependent and -independent mechanisms (Tuñón *et al*., 2007; Gyeong *et al.,* 2014).

Stancu and Sima ,(2001) found that there was a consequent lowering serum copper and following low salivary copper as an outcome of their capability to minimize cholesterol biosynthesis.

Galhardi *et al*., (2004) found that large amounts of dietary copper cause significant increases in cholesterol levels in rats. Furthermore, (Ghayour *et al*., 2005) stated that statin treatment in humans alters plasma copper and zinc levels.

4.6 Correlations of parameters:-

4.6.1 Duration of simvastatin treatment:-

This study showed significant positive linear correlation ($p<0.05$) between duration of treatment and age of patients on simvastatin treatment which was agreed with (Pascual *et al.,* 2008) who found that all patients on

simvastatin treatment their age range (50-70) years with primary hyperlipidemia.

This study showed significant negative linear correlation ($p<0.05$) between duration of treatment and salivary flow rate which means patients with long duration of treatment have a decreased salivary flow rate and this agreed with (Pascual *et al*. , 2008) who found that dry mouth was a common adverse side effect of statin treatment.

Also this study showed significant negative linear correlation ($p<0.05$) between duration of treatment and serum and with salivary copper. This agreed with (Ghayour *et al., 2005*) who found that zinc status may be affected significantly by treatment with statins and copper was decreased significantly with the treatment.

4.6.2 Salivary flow rate:-

4.6.2.1 With age:-

In this study salivary flow rate was significantly negative correlated with age this agreed with (Percival *et al.,*1994) who found that significant decrease in the secretion rates of unstimulated whole saliva in relation to age and their results suggest that elderly subjects have no impairment in their ability to respond to sialogogues but that resting saliva rates are significantly lower than in younger individuals and may contribute to the increase in oral mucosal diseases seen in the elderly.

Vissink *et al*., (1996) found that salivary secretion reduces with age. About 25% of the elderly suffer from oral dryness and related complaints.

With regard to salivary gland morphology and composition of saliva, age-related changes have been reported in healthy individuals, too with increasing age, the number of acini reduces and the amount of fatty and fibrous tissue increase, but (Rafael *et al.,* 2005) found that salivary function remains remarkably intact in healthy older persons who are not being treated for medical problems or receiving pharmacological therapy. Conversely, xerostomia in geriatric population is due to systemic diseases, or medications and head and neck radiotherapy. In spite of these two papers, there is still some controversy regarding whether the often-noted xerostomia in elderly is age-related or disease-and-drug-related, or maybe both. Part of this controversy results from various studies reporting a reduction in saliva secreted in resting conditions which is related to age. Further support for the primary role of age itself comes from the fact that there is substantial age-related replacement of functional parenchymal tissue by non-functioning adipose and fibrous tissue, accompanied by a reduction in salivary protein production and other induced alterations in composition.

4.6.2.2 With Miller's mobility scores:-

The study showed that there was highly significant positive linear correlation ($p \leq 0.001$) between salivary flow rate and Miller's mobility index score 0 and score 1 for patients on simvastatin treatment and control subjects.

Majed *et al*., (2012) found that statins were shown to have immunomodulatory, and antioxidative actions, and a significant effect on the concentrations of systemic cytokine.

4.6.2.3 With taste detection threshold:-

The study showed that there was highly significant correlation between amount of salivary flow and the detection thresholds of the four basic tastes of the study groups and this agreed with (Cathrine *et al.*,2011) who showed that subjects with a high flow rate had a higher taste detection threshold than subjects with a low flow rate, and saliva has modulating effects on sweet, salt, sour, and bitter taste keeping the fundamental role which consists of transporting the taste substances to and defending of the taste receptors.

In the incipient process of taste perception, saliva plays a role as a solvent for taste substances; salivary water dissolves taste substances, and the latter diffuse to the taste receptor sites. During this process, some salivary contents will interact chemically with taste substances. Salivary buffers (e.g., bicarbonate ions) decrease the concentricity of free hydrogen ions (sour taste), and there are some bitter taste substances which may bind with salivary proteins. This agreed with study of (Matsuo, 2000) who stated that another effect of saliva on taste transduction in a way that stimulation the taste receptor by some salivary constituents can persist, resulting in changing of taste sensitivity with salivary flow.

Salivary flow rate and sweetness detection threshold, there was highly significant positive linear correlation ($p \leq 0.001$) of both study groups ,this agreed with (Rodrigues *et al* ., 2017) who stated that the enzymatic activity of salivary amylase per minute takes into account the rate of salivary flow, and can better reflect what happens in the mouth per unit of time .

Nagai *et al.,* (2014) suggest that the main function of salivary α-amylase was cleaving glycoside bonds of complex carbohydrates, thus initiating digestion of the starch in the mouth but this disagreed with (Cathrine *et al*. ,2011) who stated that perception of sweetness remained unaffected with flow rate changes.

Salivary flow rate and saltiness detection threshold, there was highly significant negative linear correlation ($p \leq 0.001$) this agreed with (Cathrine *et al*., 2011) who stated that intensity of saltiness can be modified by a change in the salivary flow rate. Other explanations by (Behrens and Meyerhof, 2006) who stated that, the composition of saliva is known to influence the perception of salts due to its buffering action and salt content.

Spielman (1990) showed that salt taste is detected only when above salivary sodium-chloride concentrations; thus saliva influences salt taste threshold levels. It also provides the ionic environment for taste cells, probably critical in signal transduction.

For salivary flow rate and sour detection threshold showed highly significant positive linear correlation ($p \leq 0.001$) in both study groups, this agreed with (Christensen *et al*., 1987) who found that the flow rate and composition of saliva is important for taste perception, i.e. the neutral pH of saliva along with its buffering action is of importance for the perception of sour stimuli.

Salivary flow rate with detection threshold of bitterness has highly significantly negative linear correlation in patients on simvastatin treatment and controls, this agreed with (Pascual *et al*.,

2008) who found bitterness in those patients was a common side effect of simvastatin treatment than in control subjects and this agreed with (Matsou, 2000) who showed that the role of saliva includes transport of taste substances to and protection of the taste receptor. In the initial process of taste perception, saliva acts as a solvent for taste substances; salivary water dissolves taste substances, and the latter diffuse to the taste receptor sites.

4.6.2.4 With salivary and serum zinc and copper:-

The study showed that there were a highly significantly positive linear correlation between saliva flow rate and zinc and copper in saliva and serum of patients on simvastatin treatment and control subjects this disagreed with (Marcela *et al.,* 2016) who found that salivary zinc concentration was inversely proportional to the salivary flow rate.

Watanabe *et al.,* (2005) reported that serum zinc may sustain homeostatic concentration patterns, whereas salivary zinc is thought to be highly influenced by diet. There was no data available about salivary and serum copper related to salivary flow rate to be compared with this study and requires more investigations.

The levels of these elements in saliva were changed continuously, which depend on the presence of these trace elements in the systemic environment that affected by many factors such as the type of life style and the food. Saliva as other body fluids become one of the most effective factor in test trace elements status in human, that it can help in identification the presence of deficiency or any abnormality (Queimado *et al*., 2008).

Chapter Five

Conclusions & Suggestions

Conclusions and Suggestions

5.1 Conclusions:-

1- The only oral manifestations were found as adverse effects of simvastatin treatment were dry mouth (decrease salivary flow rate) and bitterness.

2- As a part of simvastatin lipid lowering properties, it can affect taste detection thresholds of sweet, sour and bitter taste in such a way that patients on simvastatin treatment detect taste with high concentrations of taste solutions, but salt taste was not affected.

3- Simvastatin can increase bone generation and /or bone mass indicates their possible beneficial effects on alveolar bone and teeth mobility that was significantly decreased in patients using simvastatin than those in control subjects.

4- The trace elements status (zinc and copper) in saliva and serum were decreased significantly by treatment with simvastatin.

5.2 Suggestions:-

1- Study oral adverse side effects and taste detection thresholds of the four basic tastes in patients on other anti-lipid medications such as fibric acid derivatives, niacin and cholysteramine.

2- Study the Miller's mobility index with bone turn over markers in saliva and serum of patients treated with simvastatin.

3- Study the bone mineral density (BMD) of the lower jaw in patients on simvastatin of different treatment durations.

4-Study of using statins as one modality in treatment of tooth mobility locally.

5- Study the prevalence of diabetes mellitus in patients on simvastatin treatment.

6-Study of oral ulceration as a possible adverse effect of statins treatment.

7- Study the effects of simvastatin on the tongue papillae .

References

(A)

- ABIAKA C, OLUSI S, AL AWADHI A. 2003 .Serum micro minerals and the indices of lipid metabolism in an apparently healthy population. J Clin Lab Anal; Vol.17, Issue 1, p.p: 61–65.
- ABRAR T, ABDULLAH A, RAZAN A , SAMEH N, AMEEN M , SOHA M, MOHAMMED Q, MOHAMMED A. 2014. Effect of Simvastatin and Atorvastatin on Serum Vitamin D and Bone Mineral Density in Hypercholesterolemia Patients: A Cross-Sectional Study, Journal of Osteoporosis Vol. 2014, Article ID 468397, p.p:1-9.
- ACKERMAN BH & KASBEKAR N. 1997 .Disturbances of taste and smell induced by drugs. J of Pharmacotherapy; Vol. 17, Issue 3, p.p:482-496.
- ADA S, JULIE C. FRITH, MICHELE H. FRENCH, JOANN S, TIMU GU, NGO R, THOMAS WH, JOSEPH T , MICHEAL JR AND JEAN HM FEYEN, 2003 . The Ability of Statins to Inhibit Bone Resorption Is Directly Related to Their Inhibitory Effect on HMG-CoA Reductase Activity .J of Bone and Mineral Research , Vol. 18, Issue 1 , p.p : 88-96
- AL –OMARY , W . 2009 .Threshold sensitivity of taste perception and the role of saliva and zinc level in some physiological and pathological conditions. M.Sc. thesis, college of dentistry, Baghdad University. J. Fac. Med. Baghdad , Vol. 51, Issue 1, p.p: 25-32
- ALDELMAN C. 2011. Optimal duration of statin therapy, Repatriation General Hospital Pharmacy E-Bulletin ,Vol. 42 , Issue 6 .
- ALEXANDRA MB .2014 .Taste Disorders: Hypogeusia, Ageusia, and Dysgeusia. A Critical Literature Review submitted in partial fulfillment of the requirements for the Senior Research Thesis .Wofford College edu/pittmandw/psy451/spring14AB.p.p: 11-12

- ALIANI M1, UDENIGWE CC, GIRGIH AT, POWNALL TL, BUGERA JL, ESKIN MN. 2013. Zinc deficiency and taste perception in the elderly. Critical Reviews in Food Science and Nutrition.Vol. 53, Issue 3, p.p: 245-250.
- AMERICAN HEART ASSOCIATION.2016 ."Cholesterol medication". AHA Website ,Issue 1, p.p:1-5
- AMERINE, MA, &PANGBORN, RM .1965. : Principles of sensory evaluation of food. Book 1st edition. New York: Academic Press. p.p. 75-105.
- AMERONGEN, AV & VEERMAN, EC.2002. Saliva: the defender of the oral cavity. J of Oral Diseases .Vol.8, Issue 1, p.p:12-22.
- AMIT G, VANDANA S, SIDHARTH M .2011. Hyperlipidemia: An Updated Review. Inter J of Biopharma & Toxicology Res. Vol.1, p.p:81-89.
- ARAYA M, PIZARRO F, OLIVARES M, ARREDONDO M, GONZALEZ M ET AL. 2006. Understanding copper homeostasis in humans and copper effects on health. J of Biological Res. Vol.39, p.p: 183-187
- AXELSSON P. 2000. Diagnosis and risk prediction of dental caries. Quintessence Publishing Co. Volume 2, 1st Edition. p.p: 91-150.

(B)

- BACHMAKOV I, GLAESER H, FROMM MF, AND KOENIG J .2008. Interaction of oral antidiabetic drugs with hepatic uptake transporters: focus on organic anion transporting polypeptides and organic cation transporter 1. J of Diabetes. Vol. 57, Issue 6, p.p:1463-1472.

- BADIYE A , KAPOOR N ,KHAJURIA H .2013 ."Copper Toxicity: A Comprehensive Study. Research Journal of Recent Sciences. Vol. 2, p.p: 58-67
- BARBARA G WELLS, JOSEPH T DIPIRO, TERRY L SCHWINGHAMMER, CINDY H .2005. Pharmacotherapy Handbook, McGraw-Hill publications, 6th edition, p.p: 92-96.
- BEHRENS M, MEYERHOF W .2006. Review Bitter taste receptors and human bitter taste perception. J of Cell Mol Life Sci. Vol. 63, Issue 13 , p.p:1501-1510.
- BELLOSTA S, PAOLETTI R, CORSINI A, CHIBA Y, SATO S, MISAWA M .2008. Inhibition of antigen-induced bronchial smooth muscle hyper responsiveness by lovastatin in mice. J Circulation. Vol.109 Issue 23 Supp. 1, p.p: III50-57.
- BERG JM & SHI Y. 1996 .The galvanization of biology: a growing appreciation for the roles of zinc. J of Science. Vol. 271, Issue 5252, p.p:1081-1086.
- BERKOVITZ BKB, HOLLAND GR, MOXHAM BJ.2002. Oral Anatomy, Histology and Embryology. 3rd edition. New York: Mosby.
- BOTTORFF M & HANSTEN P.2000. Long-term safety of hepatic hydroxymethyl glutaryl coenzyme A reductase inhibitors: the role of metabolism – monograph for physicians. Arch. Internal Medicine .Vol.28, Issue 160, p.p: 2273–2280.
- BROMLEY & STEVEN M. 2000. "Smell and Taste Disorders: A Primary Care Approach". J of American Family Physician. Vol.61, Issue 2, p.p:427–436.
- BRUNO S ,PATRICK P ,CLAUDE MH. 2004. Method of assessing taste abilities and hedonic responses in human and non-human primate. J of

Researching Food Habits : Methods and Problems, Oxford : Berghahn Books, p.p: 87-99

- BRZÓSKA, MM & MONIUSZKO J. 2001. Interactions between cadmium and zinc in the organs. Food. Chem. Toxicology. Vol.39, Issue 10, p.p:967-980.
- BRZÓSKA, MM. MONIUSZKO J, JURCZUK, GALAZYNSIDORCZUK J. ROGALSKA. 2000. Effect of short-term ethanol administration on cadmium retention and bio element metabolism in rats continuously exposed to cadmium. J of Alcohol and Alcoholism. Vol. 35, Issue 5, p.p:439-445.
- BUCK LB, 2000. ‘‘Smell and Taste: The Chemical Senses’’ 4th Edition, eds. Kandel ER, Schwartz JH, and Jessell TM, McGraw-Hill, New York, pp. 625–647.

(C)

- CAFFORIO P, DAMMACCO F, GERNONE A, SILVESTRIS F.2005. Statins activate the mitochondrial pathway of apoptosis in human lymphoblasts and myeloma cells. J Carcinogenesis. Vol.26, Issue 5, p.p:883-891.
- CALLISTA H, ADAM L. REINHARD T, MARIAN J. SCHMID, DAVID B. MARX , RICHARD A. REINHARDT.2015 . Impact of local steroid or statin treatment of experimental temporomandibular joint arthritis on bone growth in young rats, Vol. 147, Issue 1, p.p80–88
- CATHRINE IH, MARKUS SJ, HENDRIKUS F, BULTAND, GERRIT SMI 2011. Individually Modified Saliva Delivery Changes the Perceived Intensity of Saltiness and Sourness. J of Chemosens Perception. Vol.4, Issue 4, p.p: 145–153.

- CHAIT A1, BRUNZELL JD.1990. Acquired hyperlipidemia (secondary dyslipoproteinemias). J of Endocrinology Metabolism Clin. North Am. Vol.19,Issue 2,p.p:259-278.
- CHENG H, ROGERS JD, SWEANY AE, DOBRINSKA MR, STEIN EA, TATE AC, AMIN RD, AND QUAN H .1992. Influence of age and gender on the plasma profiles of 3-hydroxy3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitory activity following multiple doses of lovastatin and simvastatin. J of Pharmaceutical. Research.Vol. 9, Issue 12 ,p.p:1629–1633.
- CHOU HC, CHIEN CL, HUANG HL, LU KS.2001.Effects of zinc deficiency on the vallate papillae and taste buds in rats. J Formos Med Assoc. Vol.100, Issue 5, p.p: 326–35.
- CHOW SC .2009. Immunomodulation by statins: mechanisms and potential impact on autoimmune diseases. Arch. Immunological Therapy Experiment. Vol.57, Issue 4, p.p:243-251.
- CHRISTENSEN CM, BRAND JG, MALAMUD D.1987. Salivary changes in solution pH: a source of individual differences in sour taste perception. J of Physiology Behavior. Vol.40, Issue 2, p.p:221-227.
- CHRISTENSEN M, SU A, SNYDER R, GRECO A, LIPSCHUTZ J, MANDAIO M.2006. Simvastatin protection against acute immune-mediated glomerulonephritis in mice. J of Kidney international .Vol.69, Issue 3, p.p:457-463.
- CHUENGSAMARN S1, RATTANAMONGKOULGUL S, SUWANWALAIKORN S, WATTANASIRICHAIGOON S, KAUFMAN L. 2010.Effects of statins vs. non-statin lipid-lowering therapy on bone formation and bone mineral density biomarkers in patients with hyperlipidemia. Bone.Vol.46, Issue 4, p.p:1011-1015.

- CHUN T, YAO-HSIEN W, CHUNG-HWAN C, , SHU-CHUN C, JE-KEN CHANG, MEI-LING .2015. Simvastatin enhances Rho/actin/cell rigidity pathway contributing to mesenchymal stem cells' osteogenic differentiation. Int. J Nano medicine. Vol.10, p.p: 5881–5894
- CILLA DD JR, GIBSON DM, WHITFIELD LR, AND SEDMAN AJ .1996. Pharmacodynamics and Pharmacokinetics of Atorvastatin after Administration to Normocholesterolemic Subjects in the Morning and Evening, Volume 36, Issue 7,. p.p 604–609
- CORSINI A, MAGGI FM, AND CATAPANO AL .1995. Pharmacology of competitive inhibitors of HMG-CoA reductase. Pharmacol Res. Vol.31 , Issue 1 , p.p :9–27.
- COUZY, F., MANSOURIAN, R., LABATE, A., GUINCHARD, S., MONTAGNE, D. H., AND DIRREN, H. 1998. Effect of dietary phytic acid on zinc absorption in the healthy elderly, as assessed by serum concentration curve tests. British Journal of Nutrition.Vol. 80, Issue 1,p.p: 177–182.
- COWART BJ, KLOCK C, VAINIUS A, PRIBITKIN E, BRESLIN P .2007. Relative impact of taste vs. smell dysfunctions on quality of life. J of Chemical Senses. Vol. 32 , p.p: A16.
- COWART. 2010. "Taste dysfunction: a practical guide for oral medicine" .J of Oral Diseases. Volume17, Issue1, p.p: 2-6.
- COYLE P, PHILCOX JC, CAREY LC, ROFE AM. 2002. Metallothionein: the multipurpose protein. Cellular and Molecular Life Science .Vol. 59, Issue 4, p.p: 627–647.

(D)

- DANIELA H, THOMAS H, VOLKER K, KLAUS B .BERND E .1999.Contribution of copper binding to the inhibition of lipid oxidation by plasminogen phospholipids .J Biochim.Vol. 340,Issue 2.p.p: 377–383.
- DAVIDSON MH .2002. Rosuvastatin: a highly efficacious statin for the treatment of hyperlipidemia. Expert opinion on investigational drugs. Vol.11, Issue 1, p.p :125-141.
- DAVIES JE & NG LL.1993.Simvastatin and intracellular pH regulation by the Na+/H+ anti port of SV40-virus-transformed human MRC5 fibroblasts. Clinical Science (Lon.). Vol.84,Issue 6, p.p :633-643.
- DAVIS CD .2003. Low dietary copper increases fecal free radical production, fecal water alkaline phosphatase activity and cytotoxicity in healthy men. J of Nutrition .Vol.133, Issue 2, p.p: 522-527.
- DESIMONE JA & LYALL V.2006. Taste Receptors in the Gastrointestinal Tract III. Salty and sour taste: Sensing of sodium and protons by the tongue. Am. J. Physiol. Vol.291, Issue 6, p.p: G1005–G1010.
- DIOCLÉCIO C. JR., MAGNO C. VERAS NETO, VALERIANO L. SILVA FILHO, MÔNICA F. LEITE, MICHELE B. S. HOLANDA, NARA F. CUNHA .2004. Zinc supplementation may recover taste for salt meals ,J of Pediatric . Vol.80, no.1,p.p :55-59
- DIRKS AJ, JONES KM.2006. Statin-induced apoptosis and skeletal myopathy. Am. J. of Physiol. Cell Physiology.Vol. 291, Issue 6, p.p:C1208–1212
- DITTMER DS .1991. Collection of saliva. in physical properties and chemical composition of saliva .8th edition .London , Philadelphia :Univ. Press ; pp. 78-93

- DORIS VS. 1997. Registry of toxic effects of chemical substances. NIOSH Pocket Guide to Chemical Hazards, p.p:3-4

- DSAMOU M., PALICKI O., SEPTIER C., CHABANET C., LUCCHI G., DUCOROY P., CHAGNON M.-C., MORZEL M. 2012 .Salivary protein profiles and sensitivity to the bitter taste of caffeine. Chemical Senses, Oxford University Press (OUP).Vol. 37, Issue 1, pp.87-95.
- DUGGAN D, VICKERS S .1990. Physiological disposition of HMG-CoA-reductase inhibitors. J of Drug Metabolism Reviews .Vol. 22, Issue 4, p.p:333–362.
- DUNCAN RE, EL-SOHEMY A, ARCHER MC. 2004 .Mevalonate promotes the growth of tumors derived from human cancer cells in vivo and stimulates proliferation in vitro with enhanced cyclin-dependent kinase-2 activity. J Biological Chemistry, Vol.279, Issue 32, p.p: 33079 – 33084.
- DURIEZ P . 2003. Mechanisms of actions of statins and fibrates. J of Therapie. Vol.58, Issue 1, p.p:5-14.

(E)

- EDGAR, M., DAWES, C. O'MULLANE, D. 2004. Saliva and Oral Health. 3rd edition. British Dental Association.
- ELIZABETH B & REGINALD C. 2009. Taste buds. Encyclopedia Britannica Online. Wikipedia and free encyclopedia. https://www.britannica.com/science/taste-bud.
- ENBERG N, ALHO H, LOIMARANTA V, LENANDER-LUMIKARI M.2001. Saliva flow rate, amylase activity, and protein and electrolyte concentrations in saliva after acute alcohol consumption.. J Oral Surg. Oral Med. Oral Path. Oral Rad. Endod. Vol.92, Issue 3, p.p:292–298.

- ERTUGRUL F, ÇIGDEM E , ERTUGRUL S, SEVGI M .2003. The oral health status of children undergoing hemodialysis treatment. The Turkish J of Pediatric. Vol.45. p.p : 108-113

(F)

- FÁBIÁN T.K., HERMANN P., BECK A., FEJÉRDY P., FÁBIÁN G.2012. Salivary defense proteins: Their network and role in innate and acquired oral immunity. Int. J. Molecular Sciences . Vol.13, Issue 4, p.p:4295–4320.
- FAJARDO ME, ROCHA ML, SÁNCHEZ-MARIN FJ, ESPINOSA-CHÁVEZ EJ. 2010 .Effect of atorvastatin on chronic periodontitis: a randomized pilot study. J Clin. Perio.Vol 37 , Issue 11, p.p :1016-1022.
- FASSBENDER K, SIMONS M, BERGMANN C, STROICK M, LUTJOHANN D, KELLER P, RUNZ H, KUHL S, BERTSCH T, VON BERGMANN K, ET AL. 2001. Simvastatin strongly reduces levels of Alzheimer's disease beta -amyloid peptides Abeta 42 and Abeta 40 in vitro and in vivo. J of Proc. Natl. Acad. Sci. U S A. Vol.98, Issue 10, p.p:5856-61.
- FEJERSKOV O & KIDD E. 2008. Dental caries : The disease and its clinical management. 2nd ed. Oxford: Blackwell Munksgaard; chap. 12
- FELIX, F., TOMITA, S., PEREIRA, B., CORDEIRO, J., CARLETI, G., BARROS, S., & CABREL, G. 2009. Gustatory alteration evaluation in patients with chronic otitis media. Braz. J Otorhinolaryngology. Vol.75, Issue 4, p.p:550-555.
- FEMIANO, F., ET AL.2002. "Idiopathic Dysgeusia; an Open Trial of Alpha Lipoic Acid (ALA) Therapy," International J of Oral and Maxillofacial Surgery, Vol.31, Issue 6, p.p: 625-627.
- FERREIRA WP, BERTOLAMI MC, SANTOS SN, ET AL.2007. One-month therapy with simvastatin restores endothelial function in

hypercholesterolemia children and adolescents. Pediatric Cardiology. Vol. 28, Issue 1, p.p:8–13.

- FLEET JC. 2000. Zinc, copper, and manganese. 1st edition .editor .Biochemical and Physiological aspects of Human Nutrition .New York; Saunders: p.p: 741-759
- FONG T, VIJ R, VIJAYAN A, DIPERSIO J, BLINDER M. 2007. Copper deficiency: an important consideration in the differential diagnosis of myelodysplastic syndrome. J of Haematologica .Vol.92, Issue 10, p.p:1429-1430.
- FREDDY JT, ROBERT MB, JACK D, JURIAN A HOOGEWERFF, VICKY JB, AND WH .2003. Iron supplements inhibit zinc but not copper absorption in vivo in ileostomy subjects. The American J. of Clinical Nutrition, Vol. 78, Issue 5, p.p:1018–1023
- FREDRICKSON, DS AND LEES, Rs (1965). "A System For Phenotyping Hyperlipoproteinemia". J Circulation.Vol. 31, Issue 3, p:321.
- FUKASAWA T, ORII T, TANAKA M, SUZUKI N, KANZAKI Y.2008. Relation between drug-induced taste disorder and chelating behavior with zinc ion; statistical approach to the drug-induced taste disorder, part II. Chem Pharm Bull (Tokyo). Vol.56, Issue 8, p.p :1177-1180.

(G)

- GAIST D, JEPPESEN U, ANDERSEN M, ET AL.2002: Statins and risk of polyneuropathy: a case-control study. J of Neurology .Vol.58 , Issue 9 , p.p :1333-1337
- GALHARDI CM, DINIZ YS, FAINE LA, RODRIGUES HG, BURNEIKO RC, RIBAS BO, NOVELLI EL.2004. Toxicity of copper intake: lipid profile, oxidative stress and susceptibility to renal dysfunction. J Food Chem. Toxicology. Vol.42, Issue 12, p.p:2053-2060.

- GARCÍA MJ, REINOSO RF, SÁNCHEZ NAVARRO A, PROUS JR .2003. Clinical pharmacokinetics of statins. J of Methods Find Exp. Clin. Phar. Vol. 25, Issue 6, p.p :457-481.
- GARNETT WR .1995. Interactions with hydroxy methylglutaryl-coenzyme A reductase inhibitors. Am. J Health Syst. Pharm. Vol.52, Issue 15, p.p:1639–1645.
- GARRETT IR, GUTIERREZ G, MUNDY GR. . 2001. Statins and bone formation .Curr. Pharm. Des. Vol. 7, Issue 8, p.p :715-736..
- GAUVIN D. V., ABERNATHY M. M. , TAPP R. L. , YODER J. D. , DALTON J. A. , BAIRD T. J. 2015. The failure to detect drug-induced sensory loss in standard preclinical studies J. Pharmacol. Toxicol. Methods .Vol.74, p.p:53-74.
- GAZZERRO P, PROTO MC, GANGEMI G, MALFITANO AM, CIAGLIA E, PISANTI S, SANTORO A, LAEZZA C, BIFULCO M.2012. Pharmacological actions of statins: a critical appraisal in the management of cancer, J Pharmacol Rev. Vol. 64, Issue 1,p.p :102-146.
- GHAFFARI MA & T GHIASVAND .2010. Kinetic study of low density lipoprotein oxidation by copper. Indian J. of Clinical Biochemistry .Vol. 25, Issue 1, p.p: 29-36
- GHAYOUR M , LAMB DJ, TAYLOR A, VAIDYA N, LIVINGSTONE C, WANG T, FERNS GA.2005. Effect of statin therapy on serum trace element status in dyslipidaemic subjects J. Trace Elem Med Biol. Vol. 19 , Issue 1, p.p :61-67.
- GITLIN JD and ZAKIM D, BOYER T.2002. Wilson’s disease. eds. Hepatology. Philadelphia: W. B. Saunders , p.p : 1273-1287
- GIUDICE M .2006. "Taste Disturbances Linked to Drug Use," J Canadian Pharmacist's. Vol. 139, Issue 2, p.p :70-71

- GOMEZ, L , J C MORALES-DE-LEÓN H BOURGES.2004. ,"Detection and recognition thresholds to the 4 basic tastes in Mexican patients with Primary Sjögren's syndrome" European Journal of Clinical Nutrition .Vol.58 , Issue 4, p.p:629-636
- GRUNDY D.2006. Signaling the state of the digestive tract. J Auton. Neuro science. Vol.125, Issue 1-2, p.p:76-80
- GUTHRIE RM.2006. How safe is aggressive statin therapy? Progress in Cardiovascular Nursing, Vol. 21 , Issue 3, p.p : 140–145.
- GYEONG JM, SUK JK, YEON HC, SOOKYUNG RYOO, OH YB .2014.Antioxidant Effects of Statins in Patients with Atherosclerotic Cerebrovascular Disease. J Clin Neurol. Vol.10, Issue 2, p.p :140-147

(H)

- HAPER CR, JACOBSON TA. 2007. The broad spectrum of statin myopathy: from myalgia to rhabdomyolysis. Current Opinion in Lipidology. Vol.18, Issue 4, p.p:401–408
- HARIKUMAR, S. ABDUL ALTHAF, B. KISHORE KUMAR, M. RAMUNAIK, CH. SUVARNA .2013."A Review on Hyperlipidemic" International Journal of Novel Trends In Pharmaceutical Sciences. Vol.3 , Issue 4, p.p :51-71
- HARRIS ED .2001. Copper homeostasis: the role of cellular transporters. J of Nutr. Rev. Vol.59, Issue 9 , p.p: 281-285.
- HARVEY LJ1, DAINTY JR, HOLLANDS WJ, BULL VJ, HOOGEWERFF JA, FOXALL RJ, MCANENA L, STRAIN JJ, FAIRWEATHER-TAIT SJ. 2007.Effect of high-dose iron supplements on fractional zinc absorption and status in pregnant women. Am. J. Clin. Nutr. Vol. 85, Issue 1, p.p:131-136.

- HATANAKA T .2000. Clinical pharmacokinetics of pravastatin: mechanisms of pharmacokinetic events. J of Clin. Pharmacokinetics. Vol.39, Issue 6, p.p:397–412.
- HEATH, T., MELICHAR, J., NUTT, D., & DONALDSON, L.2014. Human Taste Thresholds Are Modulated by Serotonin and Noradrenaline. The J. of Neuro sci. Vol.26, Issue 49, p.p:12664-12671.
- HEINZERLING CI, MARKUS S, JOHANNES H, FRANSISCUS B, , GERRIT S .2011. J of Chemosens Percept. Vol. 4, Issue 4, p.p: 145–153.
- HELLE W, HENRIK S, EBBA H, KENNETH H AND HÁLFDÁN P .2016 .Statin prescribing according to gender, age and indication: what about the benefit–risk balance. J of Evaluation in Clinical Practice Vol.22, Issue2, p.p 235-246.
- HENRY Y. PAN, ANTHONY P. WACLAWSKI, PHILLIP TF, DAISY W.1993. Pharmacokinetics of pravastatin in elderly versus young men and women. J Ann. Pharmacotherapy. Vol.27, p.p:1029–1033.
- HEYNEMAN, C.1996. "Zinc Deficiency and Taste Disorders," Ann Pharmacotherapy. Vol.30, Issue 2, p.p:186-187.
- HONG SP, CHANG KS, KOH YY, CHOI DH, AND CHOI JS. 2009. Effects of lovastatin on the pharmacokinetics of verapamil and its active metabolite, norverapamil in rats: possible role of P-glycoprotein inhibition by lovastatin. J Archives of Pharmacol. Research .Vol. 32 , Issue 10, p.p :1447-1475.
- HORIUCHI N, MADEA T.2006. Statins and bone metabolism Oral Dis. J of Oral Dis. Vol.12, Issue 2, p.p :85-101.
- HSIAO, H., & LI, H. 2007. Taste disturbance after palatopharyngeal surgery for obstructive sleep apnea. J of Med Science.Vol. 23, Issue 4, p.p:191-194.

- HUMMEL, C., FRASNELI, J., GERBER, J., & HUMMEL, T. 2007. Cerebral processing of gustatory stimuli in patients with taste loss. J of Behavioral Brain Research. Vol.185, Issue 1, p.p: 59-64.
- HUMPHREY SP, WILLIAMSON RT.2001. A review of saliva: normal composition, flow, and function. J Prosthetic. Dent. Vol.85, issue 2 ,p.p:162-169
- HUNG Y. H., ROBB E. L., VOLITAKIS I., HO M., EVIN G., LI Q. X., ET AL. 2009. Paradoxical condensation of copper with elevated beta-amyloid in lipid rafts under cellular copper deficiency conditions: implications for Alzheimer disease. J Bio. Chem. Vol.284, Issue 33, p.p :21899-21907
- HUNT JR & BEISEIGEL JM .2009. Dietary calcium does not exacerbate Phytate inhibition of zinc absorption by women from conventional diets. Am J Clin. Nutr. Vol. 89, Issue 3,p.p: 839–843 .

(I)

- ILANNA M, GOMES E, ICRÓLIO R, COLARES T, MARIO R ,PONTES L, PATRÍCIA DB, ROSIMARY DS, RICARDO S, , AND MARIA M, STUDART M .2015. Pleiotropic effects of statins on the treatment of chronic periodontitis – a systematic review. Br J Clin Pharmacol. Vol.79, Issue 6, p.p:877-885.
- IMAI H, HIROSHI S, KEIGO K, KAZUNORI O, AND HIROYUKI S. 2013 .Preliminary estimation of the prevalence of chemotherapy-induced dysgeusia in Japanese patients with cancer, J of BMC Palliative Care. Vol.12, Issue 1 , page : 38.

- IOANNA D. , CHRISTINA C. TESSEROMATIS . 2015."Morphological Changes of Parotid Gland in Experimental Hyperlipidemia. J of Den. and Med. Sci .Vol.14, Issue 10 ,p.p: 93-100
- IZUMI M, EGUCHI K, NAKAMURA H, NAGATAKI S, NAKAMURA T. 1997 ,Premature fat deposition in the salivary glands associated with Sjogren syndrome: MR and CT evidence. American Journal of Neuroradiology. Vol.18 , Issue 5, p.p :951–958.

(J)

- JACOBSEN W, KUHN B, SOLDNER A, KIRCHNER G, SEWING KF, KOLLMAN PA, BENET LZ, AND CHRISTIANS U .2000. Lactonization is the critical first step in the disposition of the 3-hydroxy-3-methylglutaryl-CoA reductase inhibitor atorvastatin. Drug Metab Dispos. Vol.28, Issue 11, p.p:1369-1378.
- JAIN, MK; RIDKER, PM. 2005. Anti-Inflammatory Effects of Statins: Clinical Evidence and Basic Mechanisms. J of Nature Reviews Drug Discovery.Vol.4 Issue 12 , p.p : 977-987..
- JAISER, S. R., & WINSTON, G. P. 2010. Copper deficiency myelopathy. J Neurol. Vol. 257, Issue 6 ,p.p :869-881
- JAMAL SM, EISENBERG MJ, CHRISTOPOULOS S .2004. Rhabdomyolysis associated with hydroxy methylglutaryl-coenzyme A reductase inhibitors. Am Heart J. Vol.147, Issue 6, p.p:956–965.
- JAMES M. 2003. Pharmacologic Characteristics of Statins. J of Clin. Cardiol. Vol. 26 , Issue S3, 32–38
- JOHN S. BORELLO L . 1976 ."The Effect of Copper on Taste Sensitivity and Caries Activity", University Chicago . J of Neuro.Vol. 257 Issue 6, p.p: 869-881.

- JOSEPH T DIPIRO . 2005. Pharmacotherapy: A pathophysiological approach. 6th edition. The McGraw Hill companies, Inc. Chapter 21, Section 2 , p.p. 429.
- JUNG HS , AKITA K, KIM JY. 2004. Spacing patterns on tongue surface-gustatory papilla . Int. J Dev. Biol. Vol. l8 , Issue 2-3,p.p:157-161. .

(K)

- KARTHIKEYAN M, 2014. Saliva Composition and Function: A review. International J of Pharmaceutical Science and Health Care, Vol. 3, Issue 4, p.p: 72-77
- KATZ D, B., SIMON S. A., N. 2002. Taste-Specific Neuronal Ensembles in the Gustatory Cortex of Awake Rats. J Neuro Sci. Vol.22, Issue 5, p.p: 1850-1857.
- KAZUO Y & RIE K .2010. "Statin prevents chondrocyte aging and degeneration of articular cartilage in osteoarthritis (OA)". J of Aging (Albany NY). Vol. 2, Issue 12, p.p: 990–998.
- KIM J, PAIK H Y, JOUNG H, WOODHOUSE LR, LI S, KING, J C. 2007. Effect of dietary Phytate on zinc homeostasis in young and elderly Korean women. Journal of the American College of Nutrition. Vol.26, Issue 1, p.p: 1–9.
- KIM IS, JEONG BC, KIM OS, KIM YJ, LEE SE, LEE KN, KOH JT, CHUNG HJ. 2011. Lactone form 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) stimulate the osteoblastic differentiation of mouse periodontal ligament cells via the ERK pathway. J Periodontal Res.Vol. 46. Issue 2 .p.p: 204–213.
- KING JC, KEEN CL. SHILS ME, OLSONJA, SHIKE M, ROSS CA.2003. Zinc. editors. Modern Nutrition in Health and Disease. 9th Ed.NewYork ; Lippincott Williams& Wilkins. p p:.223-239

- KINRA P, GUPTA H, KHAN S.2010 . Evaluation of the Relative Efficacy of an Allograft used alone and that in Combination with Simvastatin in the with Simvastatin in the Treatment of Human Periodontal Infrabony Defects – A Clinical and Radiological Study. J of Taibah University Medical Sciences .Vol. 5, Issue 2, p.p: 75-88.
- KISHOR S, KATHIVARIN MK, RAHUL S, CHAMANAL J.2007 .The biology and chemistry of hyperlipidemia. Bioorganic and Medicinal Chemistry.Vol. 15, Issue 14, p.p: 4674-4699
- KITAMURA S, KAZUYA M, YI W, AND YUICHI S. 2008. Involvement of Multiple Transporters in the Hepatobiliary Transport of Rosuvastatin. J of Drug Metab Dispos. Vol. 36, Issue 10, pp:2014-2023
- KLEVAY, L. M. 2006 . "Myelodysplasia," myeloneuropathy, and copper deficiency. Mayo Clinic Proceedings . Vol.81, Issue 1,p.p: 132.
- KNOPP R.H.1999. Drug treatment of lipid disorders. N. Engl. J. Med. Vol. 341, Issue 7,p.p: 498–511.
- KOENIG J, CUI Y, NIES AT, KEPPLER D. 2000. A novel human organic anion transporting polypeptide localized to the basolateral hepatocyte membrane, Am J Physiology Gastrointestinal Liver Physiology .Vol.278, Issue 1, p.p:G156-164.
- KRUPANIDHI, ARUN S & C.B. SANJEEVI.2008. Copper & biological health. Indian J Med. Res. Vol.128, p.p 448-461
- KSOUDA, K., AFFES, H., HAMMAMI, B., SAHNOUN, Z., ATHEYMEN, R., HAMMAMI, S., & ZEGHAL, K. 2011. Ageusia as a side effect of clopidogrel treatment. J of Indian Pharmacol. Vol.43, Issue 3, p.p :350-351
- KUMAR, N. 2006. Copper deficiency myelopathy (human swayback). J of Mayo Clinic Proceedings. Vol.81, Issue 10, p.p 1371–1384

(L)

- LAINE M., TENOVUO J., LEHTONEN O. P., OJANOTKO-HARRI A, VILJA P., & TUOHIMAA P. (1988). Pregnancy-related changes in human whole saliva. J. of Archives of Oral Biology, Vol.33, Issue 12, p.p: 913–917.
- LAGO FE. 2005. FMC. J Med Contin Aten Prim.Vol. 12 , Issue 8, p.p:554-565.
- LARRY E. JOHNSON .2008.Aquired copper toxicity, Merck. Retrieved 07-19.
- LASTER L, LAUDENBACH KW, STOLLER NH. 1975 , An evaluation of clinical tooth mobility measurements. J Periodontol. Vol.46, Issue 10, p.p :603-607.
- LAZZERINI PE, CAPECCHI PL, NERUCCI F, FIORAVANTI A, CHELLINI F, PICCINI M, BISOGNO S, MARCOLONGO R, LAGHI PASINI F. 2004 .Simvastatin reduces MMP-3 level in interleukin 1beta stimulated human chondrocyte culture. Ann. Rheum. Dis. Vol. 63 ,Issue 7,p.p :867–869
- LELAND V. MILLER, NANCY F. KREBS, AND K. MICHAEL HAMBIDGE. 2013. Mathematical model of zinc absorption: effects of dietary calcium, protein and iron on zinc absorption .Br. J Nutrition. Vol.109, Issue 4, p.p: 695–700.
- LENNERNÄS H .2003. Clinical pharmacokinetics of atorvastatin. J Clinical Pharmacokinetics. Vol. 42, Issue 13, p.p :1141–1160.
- LIMA CE, CALIXTO JC, ANBINDER AL.2011. .Influence of the association between simvastatin and demineralized bovine bone matrix on bone repair in rats. Braz. J of Oral Res. Vol.25 , Issue 1, p.p :42-48.

- LIN J1, JUDD S, LE A, ARD J, NEWSOME BB, HOWARD G, WARNOCK DG, MCCLELLAN W. 2010. Associations of dietary fat with albuminuria and kidney dysfunction. Am. J Clin. Nutr. Vol.92, Issue 4, p.p :897-904.
- LIU J, ZHU LP, YANG XL, HUANG HL, YE DQ. 2013. HMG-CoA reductase inhibitors (statins) and bone mineral density: a meta-analysis. J of Bone. Vol. 54,Issue 1, p.p :151–156.
- LÖNNERDAL B .2000. Dietary factors influencing zinc absorption. J Nutr. Vol.130, Issue 5S Suppl. , p.p :1378S-1383S.
- LUGAZ O., PILLIAS A-M., BOIREAU-DUCEPT N., FAURION A. 2005.Time–intensity evaluation of acid taste in subjects with saliva high flow and low flow rates for acids of various chemical properties. J of Chem. Senses. Vol. 30 , Issue 1,p.p :89–103.
- LUNDY RF, NORGREN R. 2004 .Activity in the hypothalamus, amygdala, and cortex generates bilateral and convergent modulation of pontine gustatory neurons. J. Neurophysiol.Vol.91 , Issue 3, p.p:1143–1157.

(M)

- MAEDA T, MATSUNUMA A, KAWANE T, HORIUCHI N.2001. Simvastatin promotes osteoblast differentiation and mineralization in MC3T3-E1 cells. J of Biochem. Biophys Res. Commun. Vol. 280 , Issue 3, p.p :874–877.
- MAJED M, NIZAR M, KAREM A AL-AZZAM, AND ZIAD A.2012 Antibacterial activity of statins: a comparative study of Atorvastatin, Simvastatin, and Rosuvastatin. Ann. Clin. Microbiology and Antimicrobials.Vol. 11, page 13.
- MALAVOLTA M, PIACENZA F, BASSO A, GIACCONI R, COSTARELLI L, MOCCHEGIANI E.2015. Serum copper to zinc ratio:

Relationship with aging and health status. J of Mech. of Ageing Development. Vol.151, p.p:93-100.

- MANN NM & LAFRENIERE D. 2006. Anatomy and etiology of taste and smell disorders. https://www.uptodate.com/contents/anatomy-and-etiology-of-taste-and-smell-disorders.
- MANUELLA B, VAN CAMPENHOUT C, VERTOMMEN J, DE LEEUW I. 2003. Effects of atorvastatin on LDL sub-fractions and peroxidation in type 1 diabetic patients: a randomised double-blind placebo-controlled study. J of Diabetes Metabolism Research.& Review . Vol.19, Issue 6 , p.p :478–86.
- MARCELA L , FLÁVIA L , IRAN V , MARIANA D , WILSON D BENATO M , SERGIO A , JOÃO A , MARINA DE .2016. Analysis of zinc concentration in the saliva of individuals at different age ranges, Journal of Dental Science.Vol. 31, Issue 1, p.p :12-15
- MARIA F , FERNANDA L , MARIA B , MARILIA A.2005. Fluoride kinetics in saliva after the use of a fluoride-containing chewing gum. J of Braz. Oral Research. Pediatric Dentistry. Vol.19 , Issue 4 , p.p:256-260
- MARITZ FJ, CONRADIE MM, HULLEY PA, GOPAL R, HOUGH S. 2001.Effect of statins on bone mineral density and bone histomorphometry in rodents. J Arteriosclerosis Thromb Vascular Biol. Vol.21, Issue 10, p.p:1636–1641.
- MARTIN P.D., WARWICK M.J., DANE A.L., BRINDLEY C., SHORT T.2003. Absolute oral bioavailability of rosuvastatin in healthy white adult male volunteers. Clin. Therapy. Vol. 25, Issue 10, p.p:2553–2563.
- MATASCONI M, P. PARINI, B. ANGELIN, AND M. RUDLING, 2005. “Pituitary control of cholesterol metabolism in normal and LDL receptor knock-out mice: effects of hypophysectomy and growth

hormone treatment," J of Biochimica Biophysica Acta, Vol. 1736, Issue 3, pp. 221–227.

- MATSUMOTO I, EMORI Y, ET AL.2001. A comparative study of three cranial sensory ganglia projecting into the oral cavity: in situ hybridization analyses of neurotrophin receptors and thermosensitive cation channels. J of Brain Res Mol Brain Res. Vol.93, Issue 2, p.p :105-112
- MATSUO R .2000 . Role of saliva in the maintenance of taste sensitivity. J of Critical Review in Oral Biol, and Med. Vol. 11, Issue 2, p.p:216-229.
- MATTAR M, OBEID O. 2009 .Fish oil and the management of hypertriglyceridemia. J Nutr Health. Vol.20, Issue 1, p.p :41-49.
- MATTES RD, COWART BJ, SCHIAVO MA ET AL .1990. Dietary evaluation of patients with smell and ⁄ or taste disorders. Am J Clin Nutr.Vol51, Issue 2, p.p :233-240.
- MCCAREY DW, MCINNES IB, MADHOK R, ET AL. 2004 .Trial of atorvastatin in rheumatoid arthritis (TARA): double-blind, randomized placebo-controlled trial. J Lancet. Vol.363, Issue 9426, p.p :2015–21
- MEDINA MW, GAO F, RUAN W, ROTTER JI, AND KRAUSS RM .2008. Alternative splicing. of 3-hydroxy-3-methylglutaryl coenzyme A reductase is associated with Plasma Low-Density Lipoprotein Cholesterol Response to Simvastatin. J Circulation. Vol. 118, Issue 4, p.p: 355–362.
- MERK S& DOHME LTD. 1991 .Cramlington, Northumberland, UK . Zocor (simvastatin) Tablets. Approval. Package leaflet. https://www.scribd.com/document/258941417/Zocor-Application-Approval, p.p:1-8
- MERKONIDIS C. , GROSSE F.NINHT. , HUMMEL C , HAEHNER A , HUMMEL T. 2015. Characteristics of chemosensory disorders–results

from a survey. Eur. Arch. Otorhinolaryngology. Vol. 272, p.p:1403–1416.

- MERVYN G, GEORGE S, KHALIL S, HOWARD K, MICHAEL H, MARTIN B, ANA M .2004. "Double-blind randomized, placebo-controlled study of pilocarpine to salvage salivary gland function during radiotherapy of patients with head and neck cancer", Vol.98, Issue 1, p.p: 45-52
- METZGER BT, BARNES DM, AND REED JD .2009. A comparison of pectin, polyphenols, and phytosterols, alone or in combination, to lovastatin for reduction of serum lipids in familial hypercholesterolemic swine. J Med. Food .Vol.12, Issue 4, p.p:854–860.
- MILNE, D. 2000. Laboratory Assessment of Trace Element and Mineral Status. J of Clinical Nutrition of the Essential Trace Elements and Minerals, p.p :69-90
- MOGHADASIAN MH, FROHLICH JJ. 1999. Effects of dietary phytosterols on cholesterol metabolism and atherosclerosis: clinical and experimental evidence. Am J Medicine . Vol. 107, Issue 6, p.p: 588–594
- MOJET J , JOHANNES , HEIDEMA J , CHRIST-HAZELHOF E .2003 .Taste Perception with Age: Generic or Specific Losses in Supra-threshold Intensities of Five Taste Qualities?. J Chem. Senses .Vol.28 Issue 5,p.p: 397-413.
- MORRIS W J., SEGO R., BRINKLEY L., DOLCE C. 2000 .The effect of sialoadenectomy and exogenous EGF on taste bud morphology and maintenance. J Chem. Senses. Vol. 25, Issue 1, p.p:9–19.
- MOSEL, D., BAUER, R., LYNCH, D., & HWANG, S. 2011. Oral complications in the treatment of cancer patients. J Oral Dis. Vol. 17, Issue 6,p.p: 550-559.

- MUCK AO, SEEGER H, WALLWIENER D. 2004 .Class-specific pro-apoptotic effect of statins on human vascular endothelial cell Zeitschrift für Kardiologie. Vol. 93 , Issue 5 ,p.p:398–402

(N)

- NAGAI A, KUBOTA M, SAKAI M, ET AL.2014. Normal taste acuity and preference in female adolescents with impaired 6-npropylthiouracil sensitivity. Asia Pac. J Clin. Nutr. Vol.23 , Issue 3, p.p:423–428
- NAGLER RM.2004. Salivary glands and the aging process: mechanistic aspects, health-status and medicinal-efficacy monitoring. J Biogerontology. Vol. 5, Issue 4 ,p.p:223-233
- NAIK, C., & CLAUSSEN, C. 2010. Qualitative and quantitate representation of taste disturbances: how we do it by pentagon chart.Indian J orolaryngology. Head Neck Surgery. Vol.62 , Issue 4,p.p 376-380.
- NEZASA K, HIGAKI K, TAKEUCHI M, NAKANO M, AND KOIKE M .2003. Uptake of rosuvastatin by isolated rat hepatocytes: comparison with pravastatin. J of Xenobiotica. Vol.33, Issue 4, p.p:379-388.

(O)

- O'CONNOR A. 2008. "The Claim: The tongue is mapped into four areas of taste". The New York Times. Perception & Psychophysics. Vol.16 ,p.p: 169–174
- OISHI S , J NAKAGAWA AND M. ANDO. 2000. Effects of cadmium administration on the endogenous metal balance in rats. J Biol. Trace Elem. Res. Vol.76 , Issue 3, p.p:257-278.
- OLIVARES, M., ARAYA, M. , UAUY, R. 2000. Copper homeostasis in infant nutrition: deficit and excess. J. Pediatric Gastroenterology. Nutr. Vol.31, Issue 2, p.p:102-111.

- OSAMU W .2004 .What are Trace Elements? Their deficiency and excess states. Japan Med. Ass. J. Vol.47, Issue 8: p.p :351–358

(P)

- PADALA K, CHERYL K, PADALA R. 2006. "Mirtazapine Therapy for Dygeusia in the Elderly," The Primary Care Companion. J of Clinical Psychiatry. Vol. 8, Issue 3, p.p: 178-180.
- PASCUAL C , CHIMENOS E, GARCÍA JA, MEZQUIRIZ X, BORRELL E, LÓPEZ J. 2008 .Adverse side effects of statins in the oral cavity. J Med. Oral Patho. Oral Cir Bucal. Vol. 13, Issue 2: p.p: E98-101.
- PERCIVAL RS1, CHALLACOMBE SJ, MARSH PD.1994. Flow rates of resting whole and stimulated parotid saliva in relation to age and gender. J Dent Res. Vol.73 , Issue 8, p.p:1416-1420.
- PIJPE J, KALK W, VAN JE, VISSINK A, KLUIN PM, ROODENBURG JL, BOOTSMA H, KALLENBERG CG, SPIJKERVET FK.2006. Parotid gland biopsy compared with labial biopsy in the diagnosis of patients with primary Sjögren's syndrome. J Rheumatology Advance Access. Vol. 46, Issue 2, p.p:335-341.
- PINELES, S. L., WILSON, C. A., BALCER, L. J., SLATER, R., & GALETTA, S. L. 2010. Combined optic neuropathy and myelopathy secondary to copper deficiency. J Survey of Ophthalmology.Vol. 55 , Issue 4,p.p: 386-392.
- PIZZI C, MANFRINI O, FONTANA F, BUGIARDINI R.2004. Angiotensin-converting enzyme inhibitors and 3-hydroxy-3-methylglutaryl coenzyme A reductase in cardiac syndrome X – role of superoxide dismutase activity. J Circulation .Vol.109, Issue 1,p.p:53-58.

- PLATTIG, K.H.1988. The senses of taste. Chapter 1. In Sensory Analysis of Foods. 2nd edition. J Arterioscl. Thromb. Vas. Biology .Vol.29, p.p :706–711
- PLAZA I, VILLAR F, MATA P, PÉREZ F, MAIQUEZ A, CASASNOVAS JA, ET AL.2000. Control of cholesterolemia in Spain. A tool for cardiovascular prevention. Review in Esp. Cardiology. Vol.53 , Issue 6, p.p: 815-837.
- PRADEEP AR, RAO NS, BAJAJ P, KUMARI M. 2013. Efficacy of subgingivally delivered simvastatin in the treatment of patients with type 2 diabetes and chronic periodontitis: a randomized double-masked controlled clinical trial. J Periodontol.Vol .84, Issue 1, p.p :24–31
- PRADEEP AR, THORAT MS.2010. Clinical effect of subgingivally delivered simvastatin in the treatment of patients with chronic periodontitis: a randomized clinical trial. J Periodontol. Vol.81, Issue 2, p.p:214-222.
- PREETHA, A. AND R. BANERJEE .2005. "Comparison of Artificial Saliva Substitutes, Trends in Biomaterials and Artificial Organs: Vol.179, Issue 2 , p.p:178-186.
- PROHASKA, J. R., AND GYBINA, A. A. 2004. Intracellular copper transport in mammals .J. Nutr. Vol.134,Issue 5,p.p: 1003–1006
- PRUEKSARITANONT T, MA B, AND YU N .2003. The human hepatic metabolism of in statins. British J Clin Pharmacol. Vol. 56 , Issue1 : p.p:120–124.
- PURKAIT S, PRASANTA B, BAKUL M.2016. Research article classification of tooth mobility: International J of Recent Advances in Multidisciplinary Research Vol. 03, Issue 5, pp.1510-1512.

- PURVES D, AUGUSTINE GJ, FITZPATRICK D, 2001.Editors. Neuroscience. 2nd edition. Sunderland (MA): Sinauer Associates. The Organization of the Taste System.

(Q)

- QUE´RIN S, LAMBERT R, CUSSON JR, GRE´GOIRE S, VICKERS S, STUBBS RJ, SWEANY AE, AND LAROCHELLE P .1991. Single-dose pharmacokinetics of 14C-lovastatin in chronic renal failure. Clin Pharmacol Therapy. Vol. 50, Issue 4, p.p:437–441.
- QUEIMADO, L.;OBESO, D.; HATFIELD, M. 2008. Dysfunction of Wnt pathway Component in human salivary gland tumors. Arch Otolaryngolo Head Neck Surg. Vol.134, Issue 1,p.p: 94-101.

(R)

- RABIA P, ESIN C, EBRU E, YURDAGUEL C .2009. Impact of Experiment Hyperlipidemia on Histology of Major Salivary Glands. J Trakya Üniversitesi Tip Fakültesi Dergisi.Vol.29, Issue 4 , p.p:283-229.
- RADANOVICH M, PEREIRA FR, STELLA F, ET AL.2013. White matter abnormalities associated with Alzheimer's disease and mild cognitive impairment: a critical review of MRI studies. Expert Review Neurotherapy . Vol.13, Issue 5, p.p:483–493
- RAFAEL M. NAGLER AND ODED H. 2005 .Age-related changes in unstimulated salivary function and composition and its relations to medications and oral sensorial complaints. J Aging clinical experiments Research. Vol.17, Issue 5, p.p: 358–366.
- RAMFJORD S P, 1967. The Periodontal Disease Index (PDI). J Periodontology, Vol.38, Issue 6, p.p: 602-610

- REJNMARK L, OLSEN M, JOHNSEN SR, ET AL.2004 . Hip fracture risk in statin users—a population-based Danish case-control study. J Osteoporosis Int . Vol. 15, Issue 6 , p.p: 452-458.
- RIBAS , E., & DUFFAU, H. 2012 . Permanent anosmia and ageusia after resection of a left temporo-insular low-grade glioma: anatomofunctional considerations. J Neurosurgery. Vol. 116 , Issue 5,p.p: 1007-1013.
- RIDGE, P. G., ZHANG, Y., AND GLADYSHEV, V. N. 2008. Comparative Genomic Analyses of Copper Transporters and Cuproproteomes Reveal Evolutionary Dynamics of Copper Utilization and Its Link to Oxygen. J PLoS ONE.Vol. 3, Issue 1, p.p: e1378.
- ROBERT A. KREISBERG, MD LAWRENCE A. LEITER, MD.2012. "hyperlipidemia " , Hormone Health Network, www.hormone,org , 4th Edition.
- ROBERT R, ANTHONY T, PETER K, NEETAN A. 2010. Statin induced myopathy presenting as mechanical musculoskeletal pain observed in two chiropractic patients. J Can Chiropractic Asso. Vol.54, Issue 1, p.p: 43–51
- ROBERTO P , DELANO O , DANILO B , CRÉSIO A . 2013 .Salivary Flow and Buffering Capacity in Patients with Cardiovascular Disease. J Pesq Bras Odontoped Clin. Integr, João Pessoa.Vol. 13 , issue 1, p.p:77-81.
- ROBINSON JG, SMITH B, MAHESHWARI N. 2005. Pleiotropic effects of statins: benefit beyond cholesterol reduction. A meta-regression analysis. J Am. Coll. Cardio Vol.46, p.p:1855-1862.
- RODRIGUES, G. COSTA, C. CORDEIRO, C. PINHEIRO, F. AMADO & E. LAMY ORCID .2017 .Salivary proteome and glucose levels are related with sweet taste sensitivity in young adults. J Food & Nutrition Research .Vol. 61, Issue 1, p.p: 1-12

- RUDLING M, PARINI P, ANGELIN B.1997. Growth hormone and bile acid synthesis: key role for the activity of hepatic microsomal cholesterol 7a-hydroxylase in the rat. J Clin. Invest. Vol.99, Issue 9, p.p:2239–2245

(S)

- SAKAGAMI M, IKEDA M, TOMITA H, IKUI A, AIBA T, TAKEDA N, et al. 2009 . A zinc-containing compound, Polaprezinc, is effective for patients with taste disorders: Randomized, double-blind, placebo-controlled, multi-center study. J Acta. Otolaryngol. Vol. 129, Issue 10, p.p:1115–1120.
- SASANO T, SATOH-KURIWADA S, SHOJI N., SEKINE-HAYAKAWA Y, KAWAI M , & UNEYAMA H. 2010. Application of umami taste stimulation to remedy hypogeusia based on reflex salivation. J Biological Pharm. Bull. Vol. 33, Issue 11, p.p: 1791-1795.
- SATO K, ENDO S, TOMITA H. 2009. Sensitivity of three loci on the tongue and soft palate to four basic tastes in smokers and non-smokers. Acta Otolaryngol Suppl. Vol. 122, Issue 4, p.p:74-82.
- SCHACHTER M. 2001. Drug interactions and cytochrome P450. Br. J. Cardiol. Vol. 8, p.p: 311–317.
- SCHLEPER B. & STUERENBURG H J. 2001. Copper deficiency-associated myelopathy in a 46-year-old woman. J of Neurology. Vol.248, Issue 8, p.p:705-706.
- SEYMOUR RA. DAVIES DM, FERNER RE, DE GLANVILLE H,1998, Editors : Davies's Textbook of Adverse Drug Reactions. 5th ed. London: Chapman & Hall Medical, Oral and dental disorders. p. 234-258
- SHAMIR R & FISHER EA. 2000. Dietary therapy for children with hypercholesterolemia. J Am. Fam. Physician. Vol. 61, Issue 3, 675-682

- SHEMIN V, ALIA E & SEIFELDIN Y. 2015. Xerostomia: an unseen consequence of statin use. Endocrine Abstracts. Vol. 38, p.p:100.
- SHEPPARD, J. P., SINGH, S., FLETCHER, K., MCMANUS, R. J. & MANT. 2012 . Impact of age and sex on primary preventive treatment for cardiovascular disease in the West Midlands, UK: cross sectional study. BMJ ,Clinical Research Ed. Vol. 345, p.p: e4535.
- SHIER D, BUTLER J, LEWIS R .2016. Hole's Human Anatomy and Physiology, 11th Edition. New York: McGraw-Hill Education, p.p:454–455. .
- SHILPA E, GAYATHRI V G, DHOOM S. 2014 . Determination of the antibacterial activity of simvastatin against periodontal pathogens, Porphyromonas gingivalis and Aggregatibacte actinomycetemcomitans: An in vitro study, J Contemp. Clin. Dent. Vol.5, Issue 3, p.p: 377–382.
- SILVA M, SWANSON AC, GANDHI PJ, TATARONIS GR.2006. Statin-related adverse events: a meta-analysis. Clin Therapy. Vol.28, Issue 1, p.p:26-35.
- SILVERTHORN, DU. 2004. Human Physiology, an Integrated Approach. San Francisco: Pearson Education Inc., 3rd Edition, p.p:1-32
- SMITH DJ, M. DILLON, J. RUSSELL, A. KANATAS .2016 .Statins and oral ulceration. BDJ .Vol.220, Issue 2, p.p:45–46.
- SOLOMON DH, FINKELSTEIN JS, WANG PS, AVORN J.2005. Statin lipid-lowering drugs and bone mineral density. J Pharmacoepidemiol. Drug Safety. Vol.14, Issue 4, p.p:219-26.
- SPARKS D. L. PETANCESKA, S SABBAGH, M CONNOR, D SOARES, H ADLER, C LOPEZ, J ZIOLKOWSKI, C LOCHHEAD, J BROWNE, PATRICK .2005 .Cholesterol, Copper and Aβ in Controls, MCI, AD and the AD Cholesterol- Lowering

Treatment Trial (ADCLT). J Curr. Alzheimer Res. Vol. 2,Issue 5, p.p : 529- 539.

- SPECTOR AC & TRAVERS SP. 2005. The representation of taste quality in the mammalian nervous system. J Behav. Cogn. Neuro. Sci. Rev. Vol.4, Issue 3, p.p:143-91.
- SPIELMAN AL ,1990 .Interaction Of Saliva And Taste .J Dent. Res., Vol.69 , Issue 3, p.p:838-43.
- STACK KM & PAPAS AS. 2001.Xerostomia: etiology and clinical management. J Nutr Clin Care. Vol.4, Issue 1, p.p:15-21.
- STANCU C & SIMA A. 2001. Statins: mechanism of action and effects. J Cell. Mol. Med. Vol.5, Issue 4, p.p: 378-387.
- STAPLETON J R., MICHAEL L. LAVINE, ROBERT L. WOLPERT, MIGUEL A. L. NICOLELIS AND SIDNEY A. SIMON .2006 . Journal of Neuroscience .Vo. 26 , Issue 15,p.p 4126-4138
- STEPHEN S, 2013. Heart, Health & Nutrition by Whole Foods Magazine Staff. https://health.clevelandclinic.org/15-heart-healthy-foods-to-work-into-your-diet/
- SVETLANA L, NATALIE L. BARNES, MEE Y. BARTEE, OLEG Y. DMITRIEV. 2007. Function and Regulation of Human Copper-Transporting ATP ases. J Physiol. Rev.Vol. 87 , Issue 87, p.p: 1011–1046.
- SYNTHON PHARMACEUTICALS. 2007. Inc. Research Triangle Park, North Carolina 27709 Synthon Pharmaceuticals, Inc. Vol.4, Issue 5 ,p.p: 83-77

(T)

- TANDON V, BANO G, KHAJURIA V, PARIHAR A, GUPTA S.2005. Pleiotropic effects of statins. Indian J Pharmacol. Vol. 37, Issue 2, p.p:77-85.
- TATIANA C., IZIDOR T, DANIELLE A. ,GUIMARAES A. , RAQUEL F. , JOSE E ,NAUNYN S.2011. Effects of statins on matrix metalloproteinases and their endogenous inhibitors in human endothelial cells. J Archives of Pharmacology, Vol. 383, Issue 6, p.p: 547–554.
- TEN CATE AR. 1998. Oral histology: development, structure and function. 8th Edition. St. Louis: Mosby.pp:4-5
- THE AMERICAN SOCIETY OF HEALTH-SYSTEM PHARMACISTS. 2015. https://en.wikipedia.org/wiki/American_Society_of_Health-System_Pharmacists.
- THOMPSON PD, MOYNA NM, WHITE CM, WEBER KM, GIRI S, AND WATERS DD .2002. The effects of hydroxy-methyl-glutaryl co-enzyme A reductase inhibitors on platelet thrombus formation. Atherosclerosis .Vol.161, Issue 2, p.p:301–306.
- TOMITA H & YOSHIKAWA T. 2002 .Drug-related taste disturbances.Acta Otolaryngol .Suppl. Vol. 546, p.p :116-121.
- TSARTSALIS AN , DOKOS C, KAIAFA GD, TSARTSALIS DN, KATTAMIS A, HATZITOLIOS AI, SAVOPOULOS CG. 2012. Statins, bone formation and osteoporosis: hope or hype? J Hormones (Athens).Vol. 11 , Issue 2, p.p :126-139
- TSIVGOULIS, G., IOANNIS, H., VADIKOLIAS, K., GALETTA, S., & PIPERIDOU, C. (2011).Bilateral ageusia caused by a unilateral midbrain and thalamic infarction. J Neuroimaging. Vol. 21, Issue 3, p.p: 263-265.

- TUÑÓN J, MARTÍN-VENTURA JL, BLANCO-COLIO LM, EGIDO J. 2007 .Mechanisms of action of statins in stroke. J Expert Opinion Therapy Targets. Vol. 11, Issue 3, p.p:273–278.

- TUPE RP, CHIPLONKAR SA. 2009. Zinc supplementation improved cognitive performance and taste acuity in Indian adolescent girls. J Am Coll. Nutrition. Vol. 28, Issue 4, p.p:388–396.

(U)

- UEDA C, TAKAOKA T, SARUKURA N, MATSUDA K, KITAMURA Y, TODA N, ET AL. 2006. Zinc nutrition in healthy subjects and patients with taste impairment from the view point of zinc ingestion, serum zinc concentration and angiotensin converting enzyme activity. Auris. Nasus. Larynx. Vol. 33, Issue 3, p.p:283–288.
- UNIVERSITY OF MARYLAND MEDICAL CENTER. 2009. Alpha-lipoic Acid, http://www.umm.edu/altmed/articles/alpha-lipoic-000285.htm, p.p:1-5.
- UPMEIER, E., KORHONEN, M. J., HELIN-SALMIVAARA, A. , HUUPPONEN, R.2012. Statin use among older Finns stratified according to cardiovascular risk. European Journal of Clinical Pharmacology.Vol. 69, Issue 2, p.p: 261– 267.
- UZZAN B, COHEN R, NICOLAS P, CUCHERAT M, PERRET GY. 2007. Effects of statins on bone mineral density: a meta-analysis of clinical studies. J Bone .Vol.40, Issue 6 , p.p: 1581-1587.

(V)

- VAQUERO MP, SA´NCHEZ MUNIZ FJ, JIME´NEZ REDONDO S, PRATS OLIVA´N P, HIGUERAS FJ, AND BASTIDA S .2010. Major diet-drug interactions affecting the kinetic characteristics and

hypolipidaemic properties of statins. J Hospital Nutrition .Vol. 25 , Issue 2, p.p :193–206.

- VAUGHAN C.J., GOTTO A.M., BASSON C.T.2000. The evolving role of statins in the management of atherosclerosis, J. Am. Coll. Cardiol.Vol. 35, Issue 1, p.p: 1-10.
- VERMA N .2017. Introduction to hyperlipidemia and its treatment: a review. Int. J of Current Pharmaceutical Research. Vol. 9, Issue 1, p.p: 6-14
- VISSINK A, SPIJKERVET FK, VAN NIEUW AMERONGEN A.1996 Aging and saliva: a review of the literature. J Spec. Care Dentist. Vol.16, Issue 3, p.p :95-103.

(W)

- WALRAVENS PA, GREENE C, FRERMAN FE. 1989. lovastatin isoprenes, and myopathy. J Lancet. Vol.2, Issue 8671, p.p:1097-1098.
- WANJEK C. 2011 .The Tongue Map: Tasteless Myth Debunked". Livescience.com. https://www.livescience.com/7113-tongue-map-tasteless-myth-debunked.html
- WASSMANN S, LAUFS U, MULLER K, KONKOL C, AHLBORY K, BÄUMER AT, LINZ W, BÖHM M, NICKENIG G. 2007 .Cellular antioxidant effects of atorvastatin in vitro and in vivo. J Arterioscl. Thromb Vas. Bio. Vol. 22, Issue , p.p:300-305
- WATANABE M, ASATSUMA M, IKUI A, IKEDA M, YAMADA Y, NOMURA S, IGARASHI A. 2005 . Measurements of several metallic elements and matrix metalloproteinases (MMPs) in saliva from patients with taste disorders. Chemical Senses .Vol. 30 , Issue 2, p.p :121-125.
- WHELTON H .2012. The anatomy and physiology of salivary glands. Saliva and oral health. 4th Edition, Chapter 1 , Editors ; Michael Edgar, Colin Dawes and Denis O'Mullane. Stephen Hancocks Limited. p.p:1-16

- WILLIAMS D & FEELY J .2002. Pharmacokinetic-pharmacodynamic drug interactions. J Clin. Pharmacokinetic. Vol.41, Issue 5, p.p :343-370.
- WORLD HEALTH ORGANIZATION, 2013. Oral health survey, Basic methods 5th edition, World Health Organization, Geneva, Switzerland.
- WU YS, HU YY, YANG RF . 2007. The matrix metalloproteinases as pharmacological target in osteoarthritis: statins may be of therapeutic benefit. J Med Hypotheses .Vol. 69, p.p :557–559.

(Y)

- YANAGISAWA, H., NOJIMA, Y. TAMURA J, WADA O, SATO M. 2002. Zinc deficiency aggravates hypertension in spontaneously hypertensive rats: Possible role of Cu/Zn-superoxide dismutase. J Clin. Exp. Hypertension. Vol. 24, Issue 5, p.p: 355–370.
- YASODA, A., KITAMURA, H., FUJII, T., KONDO, E., MURAO, N., MIURA, M., KANAMOTO, N., KOMATSU, Y., ARAI, H. AND NAKAO, K. 2009. Systemic administration of C-type natriuretic peptide as a novel therapeutic strategy for skeletal dysplasias. J Endocrinology. Vol. 150, Issue 7, p.p:3138–3144.
- YOSHIDA O, KONDO T, KUREISHI Y, SUGIURA T, MAEDA K, OKUMURA K, ANDYOSHIDA S, KAMIHATA H, NAKAMURA S, SENOO T, MANABE K, MOTOHIRO M, SUGIURA T,AND IWASAKA T .2009. Prevention of contrast-induced nephropathy by chronic pravastatin treatment in patients with cardiovascular disease and renal insufficiency. J Cardiology. Vol. 54, Issue 2, p.p:192-198.
- YUAN A, WOO S B. 2015 .Adverse drug events in the oral cavity. Oral Surg. Oral Med Oral Path. Oral Radiology. Vol.119, Issue 1, p.p : 35–47

- YUDOH K, KARASAWA R. 2010. Statin prevents chondrocyte aging and degeneration of articular cartilage in osteoarthritis (OA). J Aging (Albany NY) .Vol.2, Issue 12:990–998.

(Z)

- ZONGZE W, YING L, FENGXIN Z, ZHE P, JIAN H. 2016. Effects of Statins on Bone Mineral Density and Fracture Risk A PRISMA-compliant Systematic Review and Meta-Analysis. J Medicine (Baltimore). Vol.95, Issue 22, p.p : e3042.

Appendices

Appendix I

Case sheet

Name: **Date / /** **Case no.**

Gender:

Age:

Address:

Occupation:

Past medical and dental history:

History of hyperlipidemia:

Chronic systemic diseases:

Neoplastic diseases:

Steroid:

Smoking:

Clinical examination:

1-oral manifestation

2- Salivary flow rate:

3- Taste test

4- Miller's mobility index

Laboratory investigations:

1- Zinc

Serum **Saliva**

2- Copper

Serum **Saliva**

Appendix II

موافقة للاشتراك في البحث العلمي

اسم الباحث: د. محمد جاسم محمد

عنوان البحث : العوارض الفموية للسمفاستاتين وتأثيره على مستوى العناصر النادرة في مصل الدم واللعاب

مكان إجراء البحث: م. الحسين التعليمي في السماوة

أنت مدعو/ مدعوة للمشاركة ببحث علمي سريري سيجري في م. السماوة التعليمي . الرجاء أن تأخذ/ تأخذي الوقت الكافي لقراءة المعلومات التالية قبل أن تقرر/ تقرري إذا كنت تريد / تريدين المشاركة أم لا . بإمكانك طلب إيضاحات أو معلومات إضافية عن أي شئ مذكور في هذه الاستمارة أو عن هذه الدراسة ككل من طبيبك .

في حال وافقت على المشاركة في هذه الدراسة , سيبقى اسمك طي الكتمان ولن يكون لأي شخص , مالم ينص القانون على ذلك ,حق الاطلاع على ملفك الطبي باستثناء طبيبك المسئول عن الدراسة ومعاونيه .....

موافقة المشترك :

لقد قرأت استمارة القبول هذه وفهمت مضمونها .تمت الإجابة على أسئلتي جميعها . وبناء علية فأنني ,حرا مختارا ,أجيز إجراء هذا البحث و أوافق على الاشتراك فيه , وإنني اعلم بان الباحث الدكتور محمد جاسم محمد وزملاؤه ومعاونيه أو مساعديه سيكونون مستعدين للإجابة على أسئلتي وانه باستطاعتي الاتصال بهم على الهاتف ..... وإذا شعرت لاحقا إن الأجوبة تحتاج إلى مزيد من الإيضاح فسوف اتصل بأحد أعضاء لجنة الأخلاقيات كما اعرف تمام المعرفة بأنني حر في الانسحاب من هذا البحث متى شئت حتى بعد التوقيع على الموافقة دون أن يؤثر ذلك على العناية الطبية المقدمة لي .

اسم المشترك :

توقيع المشترك:

Appendix III

Modified Miller's mobility index

Case no.	Teeth selected																								Total scores				Mean
	5⌋				⌊1				⌊6				⌈5				1⌉				6⌉								
	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	0	1	2	3	

Notes:

0 indicates no tooth mobility

1 indicates normal or physiologic mobility less than 0.25 mm

2 indicates slight mobility more than 0.25 -1 mm in facial –lingual/palatal direction

3 indicates considerable mobility more than 1 mm in all direction (vertical and horizontal)

If the selected tooth has been lost the next tooth will be included

الخلاصة

الخلفية

فرط شحميات الدم هو ارتفاع الدهون في الدم ومعظمها من الكوليسترول والدهون الثلاثية. ترتبط هذه الدهون عادة بالبروتينات بما يسمى البروتين الدهني لتبقى تدورفي الدم . البروتين الدهني ذوالكثافة الخفيفة لديه خطر كبير لتطوير أمراض القلب التاجية أكثر من البروتين الدهني عالية الكثافة، وأكثر المضاعفات من البروتينات الدهنية هي احتشاء عضلة القلب والذبحة الصدرية وعجز القلب والسكتة الدماغية والأمراض الشريانية الطرفية مثل تضيق الشريان السباتي أو تمدد الأوعية الدموية في الشريان الأورطي البطني، وهذا المرض يصنف الى ابتدائي أو ثانوي .

يمكن تشخيص فرط دهون الدم عن طريق فحص البروتين الدهني بعد الصوم مثل الكولسترول الكلي، البروتين الدهني منخفض الكثافة، البروتين الدهني عالي الكثافة، والدهون الثلاثية في عينة دم. العلاجات الممكنة هي السيطرة الغذائية على الدهون،استخدام الستيرول النباتي التي تحتوي على الأحماض الدهنية أوميغا 3، ادوية خفض الدهون مثل سيمفاستاتين وهو من عائلة ستاتينز.

هدفت هذه الدراسة إلى تقييم النتائج الفموية (المظاهر الفموية، معدل جريان اللعاب ، عتبات الكشف عن التذوق للأذواق الأربعة الأساسية، وحركة الأسنان باستخدام مؤشر ميلر لحركة الاسنان) كأعراض جانبية ضارة لدى المرضى على الذين يتناولون علاج سيمفاستاتين وكذلك تقدير العناصر الشحيحة (الزنك والنحاس) في لعاب و مصل هؤلاء المرضى ومقارنتها مع عينات لعاب ومصل دم الاصحاء.

العينات, المواد وطرق العمل

تم مشاركة ثمانون عينة في هذه الدراسة؛ تم تقسيمها إلى مجموعتين: أربعين مريضا على علاج سيمفاستاتين (20 ملغ قرص / يوم) لمدة سنة واحدة (على الأقل) فما فوق ، مدى أعمارهم ما بين (35-60) سنة، وأربعين من الأشخاص الذين هم اصحاء والمتطابقين من ناحية العمر والجنس للمرضى، وليس لديهم أي علامات وأعراض أي أمراض جهازيةعامة.

تم الحصول على الموافقة للمشاركة بالبحث لكل العينات. تم إجراء الفحص داخل الفم لتحديد أي تغيير في الفم. وقد تم تقدير معدل جريان اللعاب عن طريق جمع اللعاب غير المحفز وتقسيم حجم العينة على 10 دقيقة. تم تقييم حركة الأسنان من قبل مؤشر الحركة لميلر. في هذه الطريقة يتم وضع الأسنان بين اثنين من نهاية ادوات الاسنان مثل مراة الاسنان وتسجل الحركة إلى الجهة الوجهية /اللسانية ، وتسجل على مقياس من 0-3. حيث 0: لاتوجد حركة بعيدا عن حركة الأسنان الفسيولوجية , 1: يشير إلى حركة طفيفة أقل من 0.25

ملم , 2: حركة طفيفة 0.25 ملم في الاتجاه الوجي واللساني , 3: الحركة كبيرة أكثر من 1 ملم في كل الاتجاهات مع حركة عمودية. وقد تم تقدير عتبة الكشف عن التذوق من أربعة أذواق رئيسية (الحلو والملح والحامض والمر) باستخدام 15 تركيز مختلف لكل ذوق باستخدام طريقة اسكب وابصق مع غسل الفم بالماء المقطر بين كل تركيز يجري اختباره . تم جمع العينات اللعابية والدم لتحديد مستوى العناصر الشحيحة (الزنك و النحاس)من خلال فحص الامتصاص الذري اللهبي.

النتائج

أظهرت النتائج أن متوسط الانحراف المعياري للاعمار كان (7.63 ± 47.65) سنة. لم يتم العثور على اعراض فموية عند المرضى على علاج سيمفاستاتين الا من شكوى جفاف الفم والطعم المر .

وقد تبين أن متوسط عتبة كشف الحلو لدى المرضى على علاج سيمفاستاتين كانت عالية بشكل ملحوظ ($p<0.05$)، كما أن عتبة الكشف عن الأذواق الحامضة والمرة لدى هؤلاء المرضى كانت أعلى بشكل كبير ($p<0.001$) عن تلك الموجودة عند الأشخاص الاصحاء في حين أن عتبة الكشف عن طعم الملح لدى المرضى على علاج سيمفاستاتين أظهرت عدم وجود فرق معنوي ($p> 0.05$). وقد انخفض معدل تدفق اللعاب بشكل كبير جدا في هؤلاء المرضى مما كانت عليه في الاصحاء ($p<0.001$).

كان متوسط مؤشر ميلر في درجة الحركة 0 أعلى بكثير في المرضى مقارنة مع الأشخاص الاصحاء ($p< 0.001$)، في حين كان مؤشر درجة ميلر للحركة 1 أقل بكثير في المرضى مقارنة بالاصحاء ($p <0.001$). لم يكن هناك مرضى على سيمفاستاتين مع ميلر درجة الحركة 2 و 3.

وانخفض الزنك والنحاس بشكل ملحوظ وإلى حد كبير في مصل دم ولعاب المرضى الذين يأخذون علاج السيمفاستاتين عما عند الاصحاء ($p< 0.001$).

الاستنتاجات

لم يكن هناك أي اعراض فموية قد شوهدت في المرضى على العلاج سيمفاستاتين فقط شكوى من جفاف الفم والمرارة، كانت عتبة الكشف عن التذوق عالية بالنسبة للحامض والحلو والمر، و ان حركة الاسنان كانت قليلة. كما انخفض أيضا الزنك والنحاس في اللعاب ومصل الدم.

وزارة التعليم العالي والبحث العلمي
جامعة بغداد
كلية طب الاسنان

التأ ثيرات الفموية الجانبية لعقار السمفاستاتين وعلاقته بحالة العناصر الشحيحة في مصل الدم واللعاب

رسالة

مقدمة إلى مجلس كلية طب الأسنان / جامعة بغداد

كجزء من متطلبات نيل درجة الماجستير

في علوم طب الفم

من قبل

محمد جاسم محمد

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بأشراف

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دكتوراه طب الفم

١٤٣٩ هجري ٢٠١٨ ميلادي