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Oral Adverse Side Effects of Simvastatin in Relation to Salivary and Serum Copper

Mohammed J. Mohammed[1], Taghreed F. Zaidan[2]

[1]B.D.S, Department of Oral Diagnosis University of Baghdad, College of Dentistry, Iraq

[2]Prof. Department of Oral Diagnosis University of Baghdad, College of Dentistry, Iraq

Abstract: ***Hyperlipidemia is a medical condition characterized by abnormal increase lipids in circulation considered risk factors for cardiovascular disease. Aims of the study: To determine oral adverse side effects of simvastatin treatment (oral manifestations, taste detection threshold of the four basic tastes, salivary flow rate, teeth mobility by miller's mobility index) and estimation the level of copper in saliva and serum of patients with hyperlipidemia on simvastatin (20 mg tablet / day) at least for one year and compare all of these to healthy control subjects. Methods: Forty patients on simvastatin treatment age between (35-60) years and forty ages and sex matched healthy control subjects were participated in this study.Intraoral examination was done for all subjects to detect any oral manifestation and each subject was fulfilling case sheet information with consent form. Fifteen different concentrations of the four basic tastes solutions were used for estimation of taste detection threshold. Sip and spit with deionized water used as mouth wash interval. Serum and unstimulated saliva was obtained from each subject. Miller's mobility index was used to estimate teeth mobility. Salivary and serum copper was estimated by flame atomic absorption assay. Results: This study showed that there were no oral manifestations in patients on simvastatin treatment just complaining of dry mouth and bitterness. The taste detection thresholds of sweet, sour and bitter were highly significantly higher in those patients than that in control subjects, while saltiness was not affected. Salivary flow rate was significantly decreased in those patient than that in control subjects. The Miller's score 0 and 1 were highly significantly higher in patient on treatment with no patients presented with score 2 and 3 only presented in control subjects. Salivary and serum copper were highly significantly decreased in patients than those in control subjects. There was highly significant positive linear correlation between salivary flow rate and the mean of detection threshold of sweetness and sourness, and highly significantly negative linear correlation with the mean of detection threshold of saltiness and bitterness in both groups.***

Keywords: Hyperlipidemia, simvastatin, copper, salivary flow rate, mobility index, taste

1. Introduction

Hyperlipidemia or dyslipemia means that one or more fat proteins in the blood are high [1].Statins is the most efficient drug in lowering circulating lipids. *Aspergillusterreus* can produce simvastatin by fermentation of end products (simvastatin), which is an inactive lactone. Oral intake of simvastatin hydrolyzed to the corresponding β-hydroxyacid form. This is an inhibitor of 3-hydroxy-3-methylglutarylco enzyme A [2]. The HMG-CoA interact with statins reductase inhibit the opposing of HMG-CoA to L-mevalonate that leads to inhibition of the biosynthesis of circulating cholesterol [3]. Statins has pleotropic effects on bone turnover by encouraging bone formation and then decreases teeth mobilities [4] .Simvastatin therapy resulted in a considerable decrease of serum lipid profile but to a negligible decrease of parotid gland weight but can affect its flow rate [5]. Copper is incorporated in the functions of important enzymes and metabolic systems and essential dietary nutrient and periodic intake of copper is necessary for biological functions [6]. Taste detection threshold determine the ability of individuals to clearly differentiated taste solution from deionized water [7].

2. Materials and Methods

The study samples consisted of forty patients on simvastatin treatment of age range between (35-60) years. Forty healthy control subject's age between (35-60) years were collected from Al-Samawa teaching hospital. The laboratory works was done in the Ghazi Al- Hariri Hospital. Approved consent and fulfilled a case sheet was done for each subjects. Oral examination was done for each subject to detect any oral lesion.

Any subjects with diabetes, thyroid and parathyroid disease, autoimmune disease, chemotherapy, smoking, alcoholics, neoplastic diseases were excluded. Trace element solution flame atomic absorption assay was used with standard solution cupric nitrate BDH Chemicals Ltd Poole England. Taste detection threshold was determined for each subject using 15 concentrations for each basic taste. Saliva was collected by spitting method with unstimulated whole saliva technique for 10 minutes then centrifuged at 3000rpm for 15 minutes, the supernatant layer was aspirated by pipette and stored in sterile plastic tubes and stored at -400 C in deep freezer until analysis [8]. Venous blood sample (5ml) was drawn from all subjects (fasting 12 hr.), The blood was allowed to clot at 370 C for 15-20 minutes and centrifuged at 3000 rpm for 15 minutes, the serum is obtained and divided in parts in sterile eppendroffs and was stored at -400 C in deep freezer until analysis .The tubes was labelled subject's name by water resistant marker. Collection was done at the morning from (9-11 a.m.).

Salivary flow rate is calculated as volume in ml of the sample divide by time in minutes required for collection [9] (Salivary flow rate =salivary volume /time = ml/min). The subjects asked to sit in upright position on a chair and their heads forward position to prevent stimulation of saliva by tongue.

Calculation the amount of taste substance in grams dissolved in deionised water for recommended

concentration according to (g= molecular weight x concentration x volume) [10]. A volume of 10 ml of each taste gradient solution, previously brought to room temperature (22-25 0C), was offered to the participants in disposable cups coded in random numbers, ordered progressively higher concentration starting from deionized water as blank [7] .

Miller's mobility index was used to determine degree of teeth mobility. In this method the teeth were selected according to Ramfjord teeth , these teeth are : upper right first molar ,central incisor , left upper first premolar , lower left first molar , central incisor , right lower first premolar was firmly held between 2 instruments handle to move back and forward and mobility is scored on a scale of 0-3 , 0: no detectable movement apart from physiologic tooth movement. 1: It indicates mobility greater than normal (physiologic), 2: Mobility up to 1mm in bucco-lingual direction, 3: Mobility >1mm in bucco-lingual in combination with vertical deformability is present [11]. A computerized program, the statistical package for the social sciences (SPSS) was used for data analysis. Both descriptiveand inferential statistics was used: .1-descriptive statistics Statistical tables, Mean, Standard Deviation (SD), and Range. 2-inferential statistics, Student t-test (paired) Pearson correlation. The results will be considered significant, when the level of significance is p<0.05.

3. Results

1) Age:
The mean age of patients on simvastatin treatment was 47.65± 7.63 years and 48.12±7.20 years for control subjects and age range (35-60) years for both study groups. The study showed that there were no significant differences between the age of patients on simvastatin treatment and ages of control subjects (p > 0.05) (Table 1).

Table 1: The range and mean of 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	7.20	

***NS:- None -Significant**

2) Gender:
The results showed that the number of male patients was higher 23 (57.5%) than the number of female patients 17 (42.5%).

3) Duration of treatment:
The results showed that mean and standard deviation of duration of treatment was 2.36±1.36 year , the number 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 2).

Table 2: The number and percentage of patients on simvastatin treatment according to the duration of treatment

Duration of treatment		*No. of patients*	*%*
Range1-6 years	Mean ±SD		
1-3	2.36±1.36	25	62.5
3-5		11	27.5
≥ 5		4	10

4) Oral Findings:
The study showed no oral lesions or other oral manifestations were found in the oral cavity of patients on simvastatin treatment , but some patients were complaining only of dry mouth 16 (40%) and bitterness 24 (60%).

5) Salivary flow rate:
This study showed that the mean of salivary flow rate of patients on simvastatin was 0.33±0.08 ml/min, while for the control subjects were 0.59± 0.04 ml/min. Statistical analysis showed that salivary flow rate was significantly decreased in patients on simvastatin treatment than that in control subjects (p < 0.05) (Table 3).

Table 3: The mean and standard deviation of salivary flow rate of patients on simvastatin treatment and control subjects.

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

*** P≤0.001**

6) Taste detection threshold:
The study showed that the mean of the detection threshold for sucrose (sweetness) of patients on simvastatin treatment was 14.90 ±0.63 mmol/l ,salty taste was 17.63 ± 5.21 mmol/l , sour taste was 330.40 ±44.75 µmol/l, , for the bitter taste , was 104.15±1.72 mmol/l ,while for control subjects, sweet was 9.40 ±0.74 mmol/l, , salty taste was 16.55 ±4.88 mmol/l , sour taste was 172.80±28.72 µmol/l, bitter taste was 97.1±1.75mmol/l. Statistical analysis showed that 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 higher (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 (p>0.05) (Table 4) .

Table 4: The mean and standard deviation of the four basic 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**

7) Miller's mobility index:

The study showed that the mean and standard deviation of Miller's mobility score 0 for patients on simvastatin treatment was 4.22±1.05 , while for the control subjects was 1.44 ± 0.73 .The mean of Miller's mobility score 1 for patients on simvastatin treatment was 1.87±1.04, while for control subjects was 3.77± 1.22 .

This study showed that there were no patients on simvastatin treatment 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 5) .

Table 5: The mean and standard deviation of Miller's mobility index of patients on simvastatin treatment and control subjects

Groups	Miller mobility score 0		Miller mobility score 1		Miller mobility score 2		Miller 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**

Miller's mobility score 0 and 1 were highly significantly higher (p< 0.001) in those patients than that in the control subjects .

Laboratory findings of salivary and serum copper

The results showed that the mean and standard deviation salivary copper of patients on simvastatin treatment was 1.99 mcg/dl ± 0.46, while in the control subjects; the mean was4.85mcg/dl ±0.96. Serum copper for patients on simvastatin treatment was 59.15mcg/dl±7.63, for control subjects 114.67mcg/dl±16. Statistical analysis showed that salivary and serum copper were highly significantly decreased in patients on simvastatin treatment than that in control subjects (p<0.001) (Table 6).

Table 6: The mean and standard deviation of salivary and serum copper in study groups.

Group	Salivary coppermcg/dl		Serum copper mcg/dl	
	Mean	SD	Mean	SD
Patients on simvastatin	1.99	0.46	59.15	7.63
Control	4.85	0.96	114.67	16.49
P-value	**0.001		**0.001	

**** P ≤0.001**

4. The Correlation of parameters

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 between duration of treatment and salivary flow rate (p=0.005) and with salivary copper (p=0.026) as shown in (Table 7).

Table 7: The correlation between duration of treatment and other study parameters of patients on simvastatin

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 copper mcg/dl	-0.352	0.026*
Serum copper mcg/dl	-0.226	0.161

* **Significant p < 0.05**

2) Salivary and serum copper and taste detection threshold:

The results showed that no correlation has been found between all the detection thresholds of the four basic tastes and salivary and serum copper (p>0.01) (Table 8).

Table 8: The correlation and p-value between saliva and serum copper with the detection threshold of the four basic tastes in both study groups

Taste	Salivary copper				Serum copper			
	Patient on simvastatin		control		Patient on simvastatin		control	
	(r)	P	(r)	P	(r)	P	(r)	P
Sweet	0.08	0.61	0.43	0.5	0.10	0.53	-0.05	0.71
Salt	0.13	0.41	0.029	0.86	-0.05	0.97	-0.20	0.20
Sour	0.003	0.41	0.11	0.49	0.17	0.29	0.004	0.97
Bitter	0.13	0.39	0.13	0.39	0.17	0.28	-0.15	0.33

5. Discussion

Age

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,which agree with other studies who found thathypercholesterolemia was high among people of Spain of age 35-64 years **[12]**. While others found that those patients on simvastatin treatment with oral adverse side effects of this medication were of age range (50-70) years **[13]**.critical change in cholesterol and lipoprotein metabolism depend on the aging**[14]**. 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 [15].

Gender

The current study showed that male patients on simvastatin were 23 and females were 17 of total patients, which means the number of male patients was higher than females. Others displayed a conflicting results of gender differences, reporting higher use in women of ages below 60 years [16], others reported no gender differences in statins 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, incidences as well as prevalence of therapy among individuals aged 50 years

were considerably higher in women than men [17] , and the proportion of statins users in primary prevention decreased with age, this proportion was higher in women than men [18].

Duration of simvastatin treatment

This study showed that duration of simvastatin treatment ranged from (1-6) years and highest percentage of duration of simvastatin was at (1-3) years (62.5%) . The fact of benefits of statins can be realized one to two years after initiation of treatment and increased as duration of treatment extended from (1-6) years [19] .

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, other study found that most of patients on statins were complaining of dry mouth, itchiness, parasthesia and bitterness [13]. Others suggested that statins were potential causes of oral ulceration [20].

Taste detection thresholds:

Sweet detection threshold for glucose was 14.90±0.63 mmol/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 concentration due to drug-induced xerostomia (dryness of the mouth) ,the 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 [21] [22]. Referredproblems in taste function may be due to progress age (i.e. Hypogeusia) [23].

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 ($p>0.05$). Studysuggested 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 [24].

Sour detection threshold in patients on simvastatin treatment was 330.40±44.75 mcmol/l was significantly increased ($p<0.001$) than those of control subjects 172.80±30.35 mcmol/l, simvastatin can cause dose-dependent drop in intracellular pH, allowed to a reduction in Na+/H+ exchange [25], but others foundthat the buffering capacity of the saliva was normal and no changes in saliva pH were observed in patient on statins treatment [26].

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 showed that simvastatin could damage peripheral nerves in the function of mitochondria enzymes [27].

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 studyrevealed a frequent association between oral symptoms like dry mouth and treatment with statins[13].

The probable explanation for decrease salivary flow rate in patients on simvastatin was revealed 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 eventually to gland's acinar cells remodeling [28] . The deposition of fat in the major salivary glands and the severity of fat deposition could be correlated with impaired 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 [29].

Miller's mobility index:

This study showed that the Miller's mobility score 0 was highly significantly higher ($p\leq0.001$) 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, because simvastatin boosts the expression of bone morphogenetic protein-2, a potent promoter of osteoblast differentiation and its activity, and encourage mineralization by cultured osteoblasts [30]. Other study stated that attributed the 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 distresses the bacterial membrane in a "soap like" manner causing its death [31].

Also this study showed also there were no patients on simvastatin treatment with score 2 and 3 due to decrease teeth mobility, because the decrease of teeth mobility in patients on simvastatin treatment was probably due to the simvastatin anabolic effect on bones [13].

Simvastatin has been reported to have generative effect on bone. Statins are able of increasing bone mass as subsequent to bone formation [32].

6. Laboratory Findings

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) was highly significantly decreased than thatin control subjects with salivary copper (4.85±0.96 mcg/dl) and serum copper (114.67±16.49mcg/dl) , this may be due to statins reduced serum copper and serum concentration of ceruloplasmin which was not observed in the control patient [33].

There was a consequent lowering serum copper and following low salivary copper as an outcome of statins capability to minimize cholesterol biosynthesis,

fundamentally in the liver, where they are selectively allocated, as well as to the modification of lipid metabolism [7], this was agreed with the results of this study.

Reduction may be due to a tendency reduction of ceruloplasmin levels in circulation after a year of simvastatin treatment parallel to levels observed [34].Since the anti-oxidant properties of known relation to ceruloplasmin (Cp) has on LDL was explained the way of blocking Cu2+ that mediated lipid oxidationcomprised antioxidant properties [35].

Another possible explanation for decrease salivary and serum copper level 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 [36].

There was a consequent lowering serum copper and following low salivary copper as an outcome of their capability to minimize cholesterol biosynthesis [37].

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