Oxidative stress status in hypertensive patients on amlodipine treatment

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ABSTRACT

Background: Oxidative stress may contribute to the etiology of hypertension in humans. Oxidative stress is an imbalance between reactive oxygen species (ROS) and antioxidant defense mechanisms, causing damage to biological macromolecules and dysregulation of normal metabolism and physiology. Amlodipine as an antihypertensive agent is a long-acting calcium channel blocker that dilates blood vessels and improves blood flow.

The aim of this study was to assess the oxidative stress in hypertensive patients on Amlodipine treatment through the assessment of salivary Malondialdehyde (MDA) and superoxide dismutase (SOD) as a marker of oxidative stress.

Material and method: 60 individuals were included in this study, divided into two groups; the first group composed of 30 hypertensive patients on Amlodipine antihypertensive agent. The second group, the control group, composed of 30 healthy subjects without any systemic disease and with almost healthy oral hygiene. Intraoral examination was done for each individual and salivary samples were collected with the salivary flow rate (F/R) which was calculated in ml per minute and pH was measured by pH meter. Salivary MDA and SOD were analyzed by using ELISA kit based on the principle of competitive enzyme immunoassay technique; the concentrations of markers were measured by spectrophotometer at 450nm in a microplate reader.

Results: Salivary MDA was significantly higher in hypertensive patients compared to control, while salivary SOD was significantly lower in patients than control group. Salivary flow rate and pH was significantly lower in patients as compared to the control group.

Conclusions: There is a relation between oxidative stress and hypertension. Salivary MDA and SOD can be used as potential marker for monitoring patients with Hypertension.

Keywords: hypertension, Oxidative stress, Amlodipine, MDA and SOD. **(Received: 10/1/2018; Accepted: 11/2/2018)**

INTRODUCTION

Hypertension is defined as a systolic blood pressure (SBP) of 140 mm Hg or more, or a diastolic blood pressure (DBP) of 90 mm Hg or more.[(1)] Hypertension may be primary, which may be developed as a result of environmental or genetic causes, or secondary, which has multiple etiologies, including renal, vascular and endocrine causes.[(2)] Primary or essential hypertension accounts for 90-95% of adult cases, while secondary hypertension accounts for only 2-10% of cases.[(3)] Channel blocker dilates blood vessels and improves blood flow. It is a dihydropyridine calcium antagonist (calcium ion antagonist or slow-channel blocker) that inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle.[(4)] Amlodipine (Norvasc), one of the antihypertension agents, is a long-acting calcium; Oxidative stress (OS) is an imbalance between the generation of reactive oxygen species (ROS) and nitrogen species (RNS) and the antioxidant defense systems in the body.[(5)]

Under normal conditions, ROS and the byproducts of their reactions with various biomolecules are neutralized and converted into harmless molecules by the natural antioxidant system. The antioxidant defense system is a highly complex biochemical organization that consists of numerous enzymes and a large number of scavenger molecules, the body's pool of antioxidant molecules is derived from endogenous and exogenous sources.[(6,7)]

Superoxide dismutase (SOD) has been identified as an endogenous antioxidant enzyme.[(8)] Reactive O_2- is converted by SOD into H_2O_2. In the next step, H_2O_2 is converted into H_2O and O_2 by salivary enzymes, catalase, peroxidase, and glutathione peroxidase.[(9)] Among the many different aldehydes which can be formed as secondary products during lipid peroxidation, malondialdehyde (MDA) propanol, hexanal, and 4-hydroxynonenal (4- HNE).[(10)] MDA appears to be the most mutagenic product of lipid peroxidation.[(11)] It is an end-product generated by decomposition of arachidonic acid and larger polyunsaturated fatty acids.[(12)] Once formed, MDA can be enzymatically metabolized or react

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on cellular and tissue proteins or DNA to form adducts resulting in biomolecular damages.[12] MDA is one of the most popular and reliable markers that determine oxidative stress in clinical situations[13] which is found to be contributed to the etiology of hypertension in humans.[14] Also, hypertensive patients have impaired endogenous and exogenous antioxidant defense mechanisms.[15]

MATERIALS AND METHODS

Sixteen individuals were included in this study, divided into two groups. The first group composed of 30 hypertensive patients on Amlodipine treatment. The second group (control) composed of 30 healthy subjects without any systemic disorder and they were almost with healthy oral hygiene. After explaining the experimental design and the purpose of the study, written informed consent was signed by each participant in this study. All patients were selected from Al-Manathera Primary Health Center in AL-Najaf city. After gathering information regarding age, sex, the dose of medication per day, family history of hypertension, oral soft tissue condition, burning mouth syndrome if existed, signs and symptoms of dry mouth, salivary samples were collected from individuals under the similar conditions.

Methods: Intraoral examination was done using sterile dental mirror and probe with artificial light. The examination was performed systemically in the following sequence:

- Oral mucosa, examination of oral soft tissues was done in a sequence according to WHO (1997).
- Burning mouth syndrome according to (Scala, et al., 2003).
- Signs and symptoms of dry mouth.

The same dentist performed all examinations. A concordant diagnostic analysis was performed on 12 randomly selected patients by a second examiner.

Saliva samples were collected in restful and quiet circumstances. Saliva's production during the first 2 minutes was discarded to avoid any possible contamination, spitting saliva into graduated test tubes. After the collection of adequate amounts of saliva (5 ml) according to the biological needs, the salivary F/R was calculated ml per minute. pH of salivary secretion was measured by pH meter. Salivary samples were centrifuged at 3000×rpm for 15 minutes and then the clear supernatant was taken and transported frozen in ice crushed container to the laboratory and stored at -80C until analysis.

1- Estimation of Salivary Superoxide Dismutase:

2- The level of salivary superoxide dismutase was analyzed using commercially available, BG SOD ELISA kit. It was based on the principle of competitive enzyme immunoassay technique utilizing a monoclonal anti-SOD antibody and an SOD-Horseradish Peroxidase (HRP) conjugate.

The intensity of color was measured spectrophotometrically at 450nm in a microplate reader. The SOD concentration in each sample was interpolated from this standard curve.

Estimation of Salivary Malondialdehyde:

The level of salivary MDA was analyzed using commercially available BG MDA ELISA kit. It was based on the principle of competitive enzyme immunoassay technique utilizing a monoclonal anti-MDA antibody and an MDA-Horseradish Peroxidase (HRP) conjugate. The intensity of color was measured spectrophotometrically at 450nm in a microplate reader. The MDA concentration in each sample was interpolated from this standard curve.

3- Statistical analysis: Data were translated into a computerized database structure. An expert statistical advice was sought for study. Statistical analysis was computer assisted using SPSS version 24 (Statistical Package for Social Sciences) association with Excel version 5. The results were expressed as mean, standard deviation (SD). The differences between the groups were analyzed by using the Student's t-test and one-way ANOVA with the post hoc Tukey test and Pearson's correlation was applied to determine the relationships between the variables. The statistical significance was defined at a p value of <0.05.

RESULTS

Age & Gender

Hypertensive patients on Amlodipine were with a mean age of 56.53 year (±2.161 SD); 16 were males (53%) and 14 were females (47%). The age range was (52-60) years.

Regarding control group, the mean age was 54.77 year (±3.339 SD); 15 were males and 15 were females. The age range was (50-63) years, Table 1.

Table (1): Age range, mean and standard deviation of the study and control group

Groups	N	Age Range (years)	Mean age (year)	±SD	P-value
Control	30	50-63	54.77	3.339	>0.01
Amlodipine	30	52-60	56.53	2.161	

As shown in Table 1, no statistically significant differences in mean age were found between patient and control group (P>0.01).

Salivary flow rate (F/R) & pH: Both salivary flow rate & pH of hypertensive patients were found to be significantly lower than that of the control group, as shown in table 3.

Table (3): Salivary flow-rate and pH of the study and control group.

Variables	N	Mean	±SD	Std. Error	P-value
Salivary flow rate (ml/min)	Control= 30	0.37	0.14	0.02	<0.01
	Patient= 60	0.21	0.10	0.01	
Salivary pH	Control= 30	6.71	0.13	0.02	<0.01
	Patient= 60	6.51	0.18	0.03	

Salivary Malondialdehyde (MDA) level: As shown in Table 4, the mean salivary MDA was significantly higher in hypertensive patients compared to the healthy individuals (P<0.01). Mean salivary MDA of the study group was (0.67µmol/m ±0.13 SD), while that of control group was (0.23 µmol/m ±0.06 SD).

Table (4): Salivary malondialdehyde level of hypertensive patients & control.

Salivary Malondialdehyde (µmol/m)	N	Mean	±SD	Std. Error	P-value
Control	30	0.23	0.06	0.012	<0.01
Amlodipine patients	30	0.67	0.13	0.024	

Salivary Superoxide Dismutase (SOD) level:

As shown in Table 5, the mean salivary SOD was significantly lower in hypertensive patients compared to the healthy individuals (P<0.01). Mean SOD in the hypertensive patients was 0.55 µg/ml (±0.16 SD), while that of control group was 1.14 µg/ml (±0.07 SD).

Table (5): Salivary superoxide dismutase level of hypertensive patients & control.

Salivary Superoxide Dismutase (µg/ml)	N	Mean	±SD	Std. Error	P-value
Control	30	1.14	0.07	0.01	<0.01
Amlodipine patients	30	0.55	0.16	0.03	

Regarding patients treated with Amlodipine SOD was significantly lower compared with control group (0.55, 1.14) (P<0.01) (Table 5).

In this study, a significant negative correlation was found between age of patients and saliva F/R (R= -0.61, P<0.01) (Figure 1).

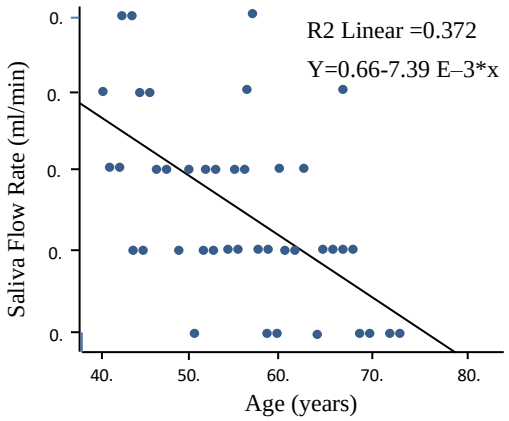

Figure (1): Negative Correlation between Age and Saliva F/R in Hypertensive Patients

Also, a negative significant correlation was found between age of patients and salivary pH (R= -0.556, P<0.01) (Figure 2).

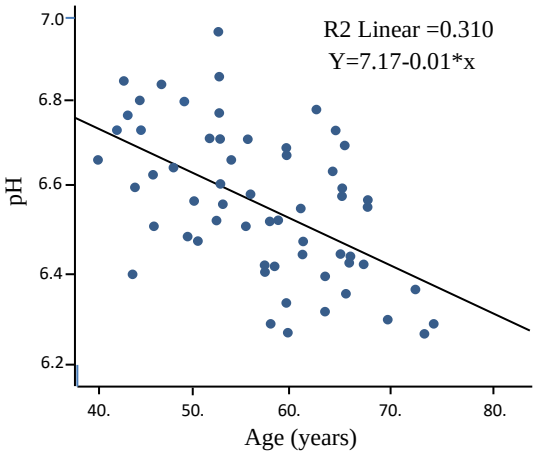

Figure (2): Negative Correlation between Age and Salivary pH in Hypertensive Patients.

Considering salivary markers, a significant positive correlation was found between age of patients and salivary MDA level in hypertensive patients (R= 0.591, P<0.01), Figure 3. The age of patients showed a significant negative correlation with salivary SOD (R= -0.570 P<0.01) (Figure 3).

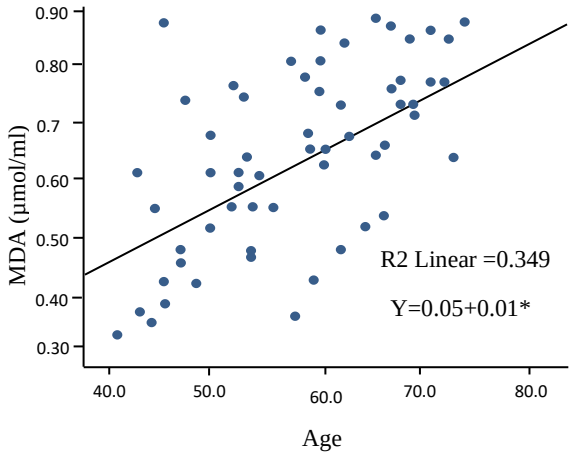

Figure (3): Positive Correlation between Age and MDA of Hypertensive Patients.

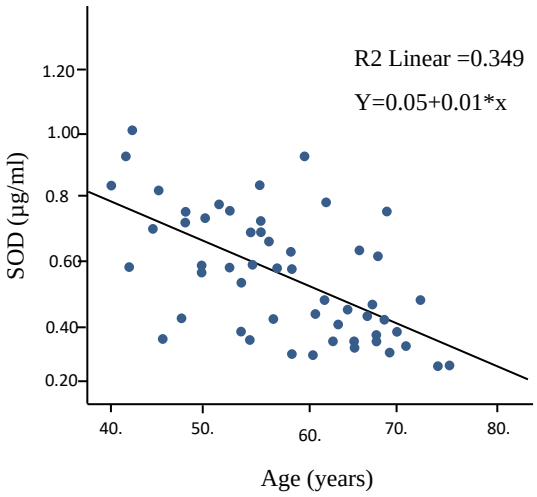

Figure (4): Negative Correlation between Age and SOD of Hypertensive Patients.

History of Hypertension and Study Parameters

The age range was 2-12 (years) and the mean was (6.3 years). There was a significant positive correlation between MDA and history of hypertension (r=0.70, P<0.01). But a significant negative correlation was found between history of hypertension and SOD (r=0.65, P<0.01), salivary F/R (r=0.53, P<0.01) and pH (r=0.56, P=0.01), Table 6.

Table (6): Correlation between history of hypertension and salivary parameters.

	Variables	Pearson's correlation (r)	P-value
Amlodipine patient	MDA	0.70	<0.01
	SOD	-0.65	<0.01
	F/R ml/min.	-0.53	<0.01
	pH	-0.56	<0.01

DISCUSSION

Hypertension, a serious medical problem, occurs when blood flows with force greater than normal. Amlodipine is a dihydropyridine calcium antagonist inhibits the transmembrane influx of calcium ions into vascular smooth muscle and cardiac muscle.[4]

In this study, 30 patients who were previously diagnosed with hypertension were enrolled. Those patients were under either Amlodipine (1-6) years. Generally, the age of hypertensive patients showed no statically significant difference from normotensive individuals (56.53, 54.77 years). However, hypertensive patients were older than normotensive control subject, which comes with the fact that hypertension is systemic disease mostly of old age.[16]

Salivary Flow Rate and pH

In the present study, salivary F/R of hypertensive patients was significantly lower than normal control subjects (0.21, 0.37 ml/min). These findings are in agreement with Böhm, et al., (1985)[17] who found that salivary F/R is lower in borderline hypertensives than in normotensives. The data support the assumption that in subjects with hypertension the parasympathetic influence on the salivary glands is reduced. However, Amlodipine results in a decrease in renal vascular resistance and an increase in glomerular filtration rate.[19] Also, as the salivary F/R decreases, the concentrations of total protein, sodium, calcium, chloride, and bicarbonate as well as the pH decrease to various levels, whereas the concentrations of inorganic phosphate and magnesium raise.[20,21]

This disagrees with Nimma, et al. (2016)[22] who found that there was no significant relation between hypertension and unstimulated salivary F/R. Also, kagawa, et al., (2013)[23] found no significant correlation between either hypertension or intake of antihypertensive medication and unstimulated salivary F/R, which also disagrees with the current study.

Considering salivary pH, hypertensive patients significantly showed lower pH than normal control subjects (6.51, 6.71). This finding is similar to kagawa, et al., (2013)[23] who found a

significant correlation between either hypertension or intake of antihypertensive medication and pH of unstimulated saliva. Several studies have reported that the reduction in salivary F/R is also the cause of reduction in salivary pH/salivary buffering capacity in individuals (Andrei, et al., 2015)[24] and the electrolytic concentration and tonicity of saliva decrease with decreasing salivary flow rates.[25]

Salivary markers

Salivary Malondialdehyde level

Malondialdehyde is one of the most reliable markers that determine oxidative stress in clinical situations.[13] The mean salivary malondialdehyde was significantly higher in hypertensive patients compared to the apparently healthy individuals. This agrees with Al-Rawi, et al., (2008)[26] who found that MDA level was significantly higher in hypertensive patients than that in healthy individual. Also, Ahmad et al., (2013)[27] found that the MDA levels was significantly increased in the hypertension groups as compared to those of the control group. Further, Nwanjo et al., (2007)[28] and Mahdi et al., (2002)[29] demonstrated an increase in the MDA levels in the essential hypertension cases. This can be attributed to ROS which contributes to the etiology of hypertension in humans.[14] Superoxide anion is produced by stimulation of the angiotensin II/angiotensin II type I receptor and nicotinamide adenine dinucleotide phosphate-oxidase (NADPH) oxidase by angiotensin II which in turn contribute in oxidation process products.[30]

In human with hypertension, ROS may increase due to a diminution of the activity of antioxidant enzymes[31] which could lead to increase oxidation process and in turn increasing lipid peroxidation process and its products (MDA).

Salivary Superoxide Dismutase level

The mean salivary SOD was significantly lower in hypertensive patients compared to the apparently healthy individuals. This agrees with Ahmad, et al., (2013)[27] who found that the activities of SOD was significantly lower in the hypertensive patients as compared to those in normotensive subjects. The data support the assumption that subjects with hypertension have impaired endogenous and exogenous antioxidant defense mechanisms.[15] Also, hypertensive patients have reduced activity and decreased content of antioxidant enzymes, including super oxide dismutase, glutathione peroxidase, and catalase.[32]

This disagrees with Al-Rawi, et al., (2008)[26] who found that SOD level was significantly higher in hypertensive patient than that of normotensive one.

Considering the correlation between age and salivary F/R, a significant negative correlation was found between age of patients and salivary F/R and this agrees with Heintze , et al., (1983);[33] Pendersen, et al., (1985);[34] Cowman, et al., (1994);[35] Michael, (1998)[36] who found that a reduction in salivary F/R with aging, but disagrees with Heft., et al., (1984)[37] who found that there was no significant correlation between age and salivary F/R. This could be due to the effect of antihypertensive medications.[19]

Also, this may be attributed to the effect of aging process on physiological homeostasis which can be separated in to two different major pathways, primary and secondary aging as proposed by Busse, (1997).[38]

According to Narhi, et al., (1992)[39] the concept of primary aging (chronological) is an alteration in physiological function with advancing age and is independent of extrinsic of physical and psychological disturbances such as stress, trauma and disease. Yet, secondary aging implies the result of external influences including systemic diseases and therapeutic treatment. It is well-recognized that alteration of salivary function in the elderly are commonly associated with age related diseases (secondary aging).

Since the reduction in salivary F/R could be a cause of reduction in salivary pH/salivary buffering capacity in individuals.[24] So, a negative significant correlation was found between age of patients and salivary pH.

A significant positive correlation was found between age of patients and salivary MDA level in hypertensive patients. However, the age of patients showed a significant negative correlation with salivary SOD. These findings suggested that increased lipid peroxidation in patients may be caused by increased free radical production and/or decreased antioxidant defense, which agrees with the previous studies Gonca Akbulut, et al., (1999);[40] Mine ErdenİInal, et al., (2001);[41] Ramazan Ozcankaya, et al., (2002);[42] Ümit Mutlu Türkoğlua, et al., (2003)[43] which hypothesized that increased oxidative stress may play an important role in the aging process or versa verse.

Furthermore, Ramazan et al., (2002)[42] concluded that increased MOD level is a result of aging so that lipid peroxidation increases due to aging.

Gonca, et al., (1999)[40] suggested that increased levels of lipid peroxidation products may play a role in aging. Mine ErdenİInal et al., (2001)[41] and Ümit, et al.,(2003)[43], hypothesized that higher

level of OS plays an important role in the aging process of individual.

A significant positive correlation was found between history of hypertension and salivary MDA level in hypertensive patients suggests a relation between increased oxidative stress and hypertension which is in agreement with Am et al., (2007)[44] who reported an association between increased oxidative stress and higher blood pressure.

A significant negative correlation was found between history of hypertension and SOD which could be attributed to the fact that hypertensive patients have reduced activity and decreased content of antioxidant enzymes.[32] Also, the decrease in the antioxidant enzymes could be due to their inactivation as the result of a continuous exposure to hydrogen peroxide, hydrogen peroxynitrite and other free radicals.[45]

Moreover, a significant negative correlation was found between history of hypertension and salivary F/R, this could be the effect of aging.[38] Also a significant negative correlation was found between history of hypertension and salivary pH, this could be due to the reduction in salivary F/R which could be due to reduction in salivary pH/salivary buffering capacity in individuals.[26]

CONCLUSION

1. Over production of the free-radicals may lead to increased oxidative stress which leads to oxidative damage to the biological molecules, leading to several chronic diseases.
2. Salivary MDA increases in hypertensive patients which represent an increasing in oxidative process.
3. Salivary SOD decreases in hypertensive patients which represent a decrease in anti-oxidant enzyme system.
4. Salivary F/R & pH are negatively associated with hypertension due to the effect of antihypertensive medications or in hypertension the parasympathetic influence on the salivary glands is reduced.
5. This study recommends anti-oxidant supplements for patients with hypertension along with antihypertension medications.

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الخلاصة:

ارتفاع ضغط الدم هو الوضع الذي يكون فيه ارتفاع مستمر لضغط الأوعية الدموية والذي يضها تحت شد مستمر. الشد التأكسدي هوه عدم التوازن بين أنواع الاوكسجين التفاعلية وألية الدفاع ضد الاكسدة, تسبب ضرر أحيائي وعدم انتظام في العمليات الأيضية والوظيفية الطبيعة للجسم. الشد التأكسدي ممكن ان يساهم في اسباب ارتفاع ضغط الدم عند الكائن البشري .

اميلودبين Amlodipine هو علاج يستخدم لمعالجة ارتفاع ضغط الدم, يعمل كمثبط لقناة الكالسيوم ليؤدي الى توسعة الاوعية الدموية ويحسن سريان الدم.

الهدف من الدراسة: تقييم الشد التأكسدي في المرضى المصابين بارتفاع ضغط الدم ويستخدمون الاميلودبين Amlodipine كعلاج من خلال قياس مستوى مالوندالديهايدMDA و انزيم سبور أوكسيد دسميوتزSOD في اللعاب.

المواد والطريقة :هذه الدراسة مؤلفة من (60) شخص عراقي و مقسمين الى مجموعتين: المجموعة الاولى تتكون من (30) مريض مصاب بارتفاع ضغط الدم ويستخدم علاج الاميلودبين. المجموعة الثانية تتكون من (30) شخص سليم صحيا. تم فحص الفم لكل فرد, واخذ نموذج من اللعاب لقياس كمية اللعاب المفرز بالمليتر/دقيقة وحموضة اللعاب. تم قياس مستوى مالوندالديهايد و انزيم سبور أوكسيد دسميوتز في اللعاب باستخدام تحليل اليسا وقياس كمية التركيز باستخدام مقياس الطيف اللوني 450 نانومتر.

النتيجة :التحليل الإحصائي للقياسات اوجد انه مستوى مالوندالديهايد في لعاب مرضى الضغط اعلى بكثير من الاشخاص السليمين .بينما انزيم سبور أوكسيد دسميوتز اقل في لعاب مرضى الضغط مقارنه بالأصحاء, كمية جريان اللعاب ومستوى الحموضة اقل في مرضى ارتفاع ضغط الدم مقارنة بالأشخاص الاصحاء.
الاستنتاج: هنالك علاقة بين الشد التأكسدي وارتفاع ضغط الدم و مستوى مالوندالديهايد و انزيم سبور أوكسيد دسميوتز في اللعاب يمكن ان يستخدم كعلامه في متابعه المرضى المصابين بارتفاع ضغط الدم.