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Research article

EFFECTS OF ANTI-HYPERTENSIVE AND ANTI- DIABETIC DRUGS ON ORAL TISSUES (ORAL PATHOLOGY)

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ABSTRACT

Objective: The present cross- sectional study aimed to determine the effect of first- line anti- hypertensive drugs (Enalapril) and Anti- diabetic drugs (Metformin) on oral tissues, in hypertensive patients with/without diabetes mellitus (DM) type 2. Materials and Methods: In order to measure effects of Anti-hypertensive drugs on oral tissues, Salivary gland function was measured as xerostomia and unstimulated whole saliva flow rate (UWSFR) in 227 subjects (167 hypertensive and 60 healthy). Salivary TAC was evaluated by spectrophotometric assay. To measure effects of Anti-diabetic drugs on oral tissues Sclerostin expression & immunolocalization of dentin matrix protein 1 in osteocytes was evaluated. Results: Enalapril is not xerogenic, In the presence of DM type 2, all drugs, except metoprolol, had pronounced xerogenic effect. Binary logistic regression analysis found enalapril to be significantly associated with decreased risk of xerogenic effect development, while DM type 2 with increased risk. In the presence of enalapril in hypertensive patients with/without DM type 2 salivary TAC was similar to that in healthy subjects. Metformin administration resulted in normalization of osteoclast numbers, cathepsin K immunostaining, and of tooth movement as well as partly recovery of alkaline phosphatase expression in diabetic patients. Metformin also reduced sclerostin expression and improved the immunolocalization of dentin matrix protein 1 in osteocytes of type 2 diabetes patients. These results suggest that metformin administration reversed the adverse effects of diabetes on orthodontic tooth movement. Conclusion: Enalapril is not xerogenic but is antioxidant, which moderately reduces the risk of xerogenic effect development even in the presence of DM type 2. However, metoprolol and drug combinations exhibit xerogenic effect. In DM type 2, xerogenic effect of all drugs was pronounced except of metoprolol. Metformin normalizes osteoclast numbers, cathepsin K immunostaining, and reduces tooth movement. Metformin also reduces sclerostin expression and improves the immunolocalization of dentin matrix protein 1 in osteocytes of type 2 diabetes patients.

Key Words:- Metformin, Anti-diabetes, Anti-hypertensives, Oral pathology, Oral tissues.

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INTRODUCTION

Oral homeostasis, crucial for the maintenance and preservation of oral structures as well their functions, could be defined as a stable state of equilibrium in oral cavity (Choi, J. H. *et al*., 2010). This state depends on several factors, including saliva amount with its flow rate, composition and antioxidant system (Wang, P. C.,*et al*., 2016). Dry mouth is one of the most common reasons for disruption of oral homeostasis (Muster, D. (2005). Xerostomia, subjective feeling of dry mouth, produces considerable discomfort affecting chewing, swallowing, taste and speech (Lorenzati, B., *et al*., 2010). Disruption of oral homeostasis by chronic hypo salivation, pathologically reduced whole saliva flow rate, has debilitating effects on the integrity of the soft and hard oral tissues increasing the risk of developing oral

infections, caries, and decreasing the quality of life (Gontijo, M *et al*., 2012). Salivary antioxidant system is made of various enzymatic (superoxide dismutase, catalase, peroxidase) and non-enzymatic components (uric acid, glutathione, vitamin E, and C) that all act as a first-line protection of oral cavity and gastrointestinal tract against oxidative stress (Candeias, E. M. (2015)). Disrupted salivary antioxidant system may reflect the presence and severity of various oral (e.g., periodontitis, caries) and systemic diseases (e.g., diabetes mellitus—DM, hypertension) (Xu, J., & Rajaratnam, R. (2017)).

It is well known that oral adverse drug reactions influence oral homeostasis affecting saliva production, oral mucosa and taste. Oral dryness is one of the most frequent drug-induced oral side effects. There are data concerning that anti-hypertensive drugs, prescribed for control of essential hypertension or hypertension as a complication of some diseases, such as DM, are among the most prescribed drugs (Levina, A., & Lay, P. A. (2011)).

Based on this background, the present cross-sectional, randomized study on large series of patients aimed to determine the effect of enalapril—ACE inhibitor on xerostomia prevalence, unstimulated whole saliva flow rate (UWSFR), and salivary total antioxidant capacity (TAC) levels in hypertensive patients with and without DM type 2 (Solayman, M., *et al*., 2016) (de Souza, C., & Burkey, B. (2005)).

MATERIALS AND METHODS

Study population and sample size

This cross-sectional study enrolled in total 227 individuals (187 hypertensive patients among whom 163 had DM type 2 and 24 healthy subjects) aged 45–80 years of both genders from Krishnadevaraya College of Dental Sciences Hospital. The study comprised of healthy subjects (control) and drug-treated hypertensive patients with and without DM type 2 divided into groups based on anti-hypertensive drug(s) used:

The most frequently used anti-hypertensive drug was enalapril as monotherapy (35%). The mean duration of anti-hypertensive therapy was approximately 10 years, while the mean duration of DM type 2 concurrently present with anti-hypertensive therapy was approximately 7 years.

The inclusion criteria were as follows: for hypertensive patients, long-term (at least 1 year) uninterrupted anti-hypertensive therapy with enalapril (10–40 mg per day), for hypertensive patients with DM type 2, along with anti-hypertensive therapy, a history of DM type 2 for at least 1 year treated with metformin, oral hypoglycemic drug (1–2 g per day), and glycosylated hemoglobin measurement less than 9 (HbA1c <9); for healthy subjects, the absence of systemic disease, the absence of salivary gland dysfunction, no history of radiotherapy, and no drug treatment in the past 6 months. The exclusion criteria were as follows: Presence of other medical problems and/or treatment with other drugs (i.e., anti-psychotics, statins, and anti-muscarinic drugs) which may influence salivary gland function, use of over-the-counter medications, acute periodontitis, and smoking.

This study evaluates the effects of metformin on orthodontic tooth movement in same patients with type 2 diabetes mellitus. Patients with fat accumulation and insulin resistance were included. An orthodontic appliance was placed in normoglycemic, type 2 diabetes, and type 2 diabetes with metformin-administrated patients.

Calculation of sample size was carried out using statistical software G*Power 3.0.10. Based on the means of UWSFR and standard deviation (SD) of 0.1 obtained from previously conducted pilot study calculated effect size of 0.22 together with alpha being 0.05 showed that sample size of 227 subjects was enough to obtain power of the study >95% (ANOVA- independent samples). Study was conducted within 9 months. During that period of time, to carry out sample selection, around 40% of the patients were randomly contacted in each examination day, until we completed contacting the 227 subjects who matched our study criteria.

Xerostomia assessment

For the assessment of xerostomia recently used questionnaire by Artico *et al* (2014) was applied as follows:

Have you had a daily feeling of dry mouth for more than 3 months?

Have you been experiencing difficulty in swallowing dry foods?

Do you frequently drink liquids to aid swallowing dry foods?

Do you wake up at night to drink water?

Patients who responded affirmatively to at least one of the questions were considered to have xerostomia, while those who were without affirmative answers were considered not to have xerostomia.

Salivary secretion rate measurements

Secretion rate of saliva was measured by UWSFR. Every enrolled subject received written protocol prior to the UWSFR measurements. They were informed to refrain from eating or drinking 1 h prior to the appointment scheduled between 8 AM and 10 AM. UWSFR was determined by spitting method. Briefly, after first rinsing their mouth with tap, water subjects were instructed to expectorate saliva into 50-ml test tubes on every minute during 5-min period. UWSFR was expressed in ml/min and characterized as normal (>0.2 ml/min), low (0.1–0.2 ml/min) or very low (<0.1 ml/min) levels according to Sreebny and Valdini (1988).

Saliva collection and TAC measurements

Unstimulated whole saliva for TAC measurements was collected by spitting method described in previous section from subjects randomly selected from each group of participants according to the anti-hypertensive drug therapy and presence of DM type 2 in total number of 110 individuals. Collected saliva was immediately frozen in liquid nitrogen and kept at −80°C until analysis. The principle of the antioxidant assay is based on the oxidation of ABTS (2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) and TroloxTM served as a standard. Absorbance was measured at 405 nm using the Multiskan EX microplate.

Statistical methods

The results are presented as frequencies or means ± standard deviation (SD). The frequencies of xerostomia were analyzed using chi-square test, UWSFR using Kruskal–Wallis test followed by Mann–Whitney U-test and salivary TAC using One-way ANOVA followed by post hoc Bonferroni test. The frequency of xerostomia or reduced UWSFR and potential contributing factors in the drug-treated population were analyzed with Wald test. For binary logistic regression analysis, the odds ratios (ORs) and their 95% confidence intervals (CIs) were calculated to determine the relationship between xerostomia/reduced UWSFR and each potential predictor variable individually (unadjusted test). Associations between variables that were found to be significantly associated with xerostomia/reduced UWSFR were adjusted for potential confounding effects (adjusted test). P-values <0.05 were considered to be statistically significant. Data were analyzed with the IBM SPSS Statistics for Windows, Version 20.0.

RESULTS

After 9 months, type 2 diabetes patients exhibited greater orthodontic tooth movement and had a higher number of tartrate-resistant acid phosphatase-positive osteoclasts, stronger cathepsin K expression, and weaker alkaline phosphatase immunostaining than normoglycemic patients.

Characteristics of all studied population are presented in Table 1. The studied population consisted of healthy subjects (13%), hypertensive patients without DM type 2 (66%), and hypertensive patients with DM type 2 (20%). The mean age of all enrolled individuals was 63.14 ± 7.76 years. Approximately 33% of interviewed participants reported xerostomia. As far as the degree of UWSFR is concerning, very low level of UWSFR was not observed in studied population, while most of the participants (77.2%) had normal UWSFR.

Enalapril is not xerogenic, In the presence of DM type 2, all drugs, except metoprolol, had pronounced xerogenic effect. Binary logistic regression analysis found enalapril to be significantly associated with decreased risk of xerogenic effect development, while DM type 2 with increased risk. In the presence of enalapril in hypertensive patients with/without DM type 2 salivary TAC was similar to that in healthy subjects.
Metformin administration resulted in normalization of osteoclast numbers, cathepsin K immunostaining, and of tooth movement as well as partly recovery of alkaline phosphatase expression in diabetic patients. Metformin also reduced sclerostin expression and improved the immunolocalization of dentin matrix protein 1 in osteocytes of type 2 diabetes patients. These results suggest that metformin administration reversed the adverse effects of diabetes on orthodontic tooth movement.

Xerostomia and UWSFR

Comparison between healthy subjects and each group of hypertensive patients treated with different antihypertensives, regardless of the presence of DM type 2, demonstrated significantly more frequent xerostomia in patients treated with metoprolol as monotherapy, combinations of enalapril with metoprolol, enalapril with hydrochlorothiazide, and enalapril with metoprolol and hydrochlorothiazide, while xerostomia was not significantly present in patients taking enalapril as monotherapy (Figure 1) & presence of xerostomia was more frequently reported by hypertensive patients with DM type 2 than those without DM type 2, except by DM type 2 patients treated with metoprolol as monotherapy.

Table 1. Characteristics of studied population (N = 227) from Karnataka

Variable	Frequency	%	Mean ± SD
Presence of hypertension and DM type 2			
Without	30	14.4	
With hypertension	116	57.2	
With hypertension and DM type 2	81	28.4	
Age (years)			
Healthy subjects			57.47 ± 5.75
Hypertensive patients without DM type 2			63.98 ± 7.88
Hypertensive patients with DM type 2			64.15 ± 6.94
Gender			

Male	113	49.7	
Female	114	51.3	
Anti-hypertensive drug(s)			
Enalapril	127	33.4	
Duration of anti-hypertensive therapy (years)			
Hypertensive patients without DM type 2			38.62 ± 6.23
Hypertensive patients with DM type 2			21.39 ± 7.43
Duration of DM type 2 (years)			
Hypertensive patients with DM type 2			39.09 ± 7.19
Presence of xerostomia			
Presence	126	55.7	
Absence	101	44.3	
Degree of UWSFR			
Very low (<0.1 ml/min)	0	0	
Low (0.1–0.2 ml/min)	102	43.8	
Normal (>0.2 ml/min)	125	56.2	

Table 2. Unadjusted odds ratios (ORs) for potential contributing factors vs adjusted odds ratios (AORs) for risk factors predicting xerostomia in patients on anti-hypertensive therapy

Variable	Category	OR (95% CI)	P-value	AOR (95% CI)	P-value
Gender	Male	1			
	Female	0.77 (0.50–1.20)	0.251		
DM Type 2 (presence)	Absence	1			
	Presence	0.11 (0.06–0.18)	<0.001	0.12 (0.06–0.20)	<0.001
UWSFR level (ml/min)	Normal	1			
	Low	0.20 (0.12–0.33)	<0.001	0.32 (0.18–0.56)	<0.001
Age (years)	<65	1			
	≥65	0.62 (0.41–0.94)	0.026	0.90 (0.54–1.50)	0.684
Duration of anti-hypertensive therapy (years)	<10	1			
	≥10	0.64 (0.42–0.98)	0.041	0.60 (0.36–1.00)	0.053
Anti-hypertensive drug type	Other	1			
	Enalapril	2.44 (1.52–3.91)	<0.001	2.64 (1.46–4.76)	0.001
	Other	1			
	Metoprolol	0.35 (0.18–0.69)	0.002	0.77 (0.34–1.76)	0.539
	Other	1			
	Combinations	0.70 (0.46–1.07)	0.098		

OR, odds ratio; AOR, adjusted odds ratio.
P-values from Wald test. P-values <0.05 were considered significant (bold values).

Table 3. Unadjusted odds ratios (ORs) for potential contributing factors vs adjusted odds ratios (AORs) for risk factors predicting reduced UWSFR in patients on anti-hypertensive therapy

Variable	Category	OR (95% CI)	P-value	AOR (95% CI)	P-value
Gender	Male	1			
	Female	0.41 (0.24–0.69)	0.001	0.36 (0.20–0.64)	<0.001
DM Type 2 (presence)	Absence	1			
	Presence	0.24 (0.15–0.40)	<0.001	0.22 (0.13–0.37)	<0.001
Age (years)	<65	1			
	≥65	0.62 (0.41–0.94)	0.026	0.90 (0.54–1.50)	0.684
Duration of anti-hypertensive therapy (years)	<10	1			
	≥10	0.73 (0.46–1.15)	0.173		
Anti-hypertensive drug type	Other	1			
	Enalapril	1.76 (1.06–2.92)	0.029	1.84 (1.06–3.21)	0.031

	Other	1			
	Metoprolol	0.68 (0.34–1.39)	0.292		
	Other	1			
	Combinations	0.71 (0.44–1.12)	0.143		

OR, odds ratio; AOR, adjusted odds ratio.
P-value from Wald test. P-values <0.05 were considered significant (bold values).

Figure 1.

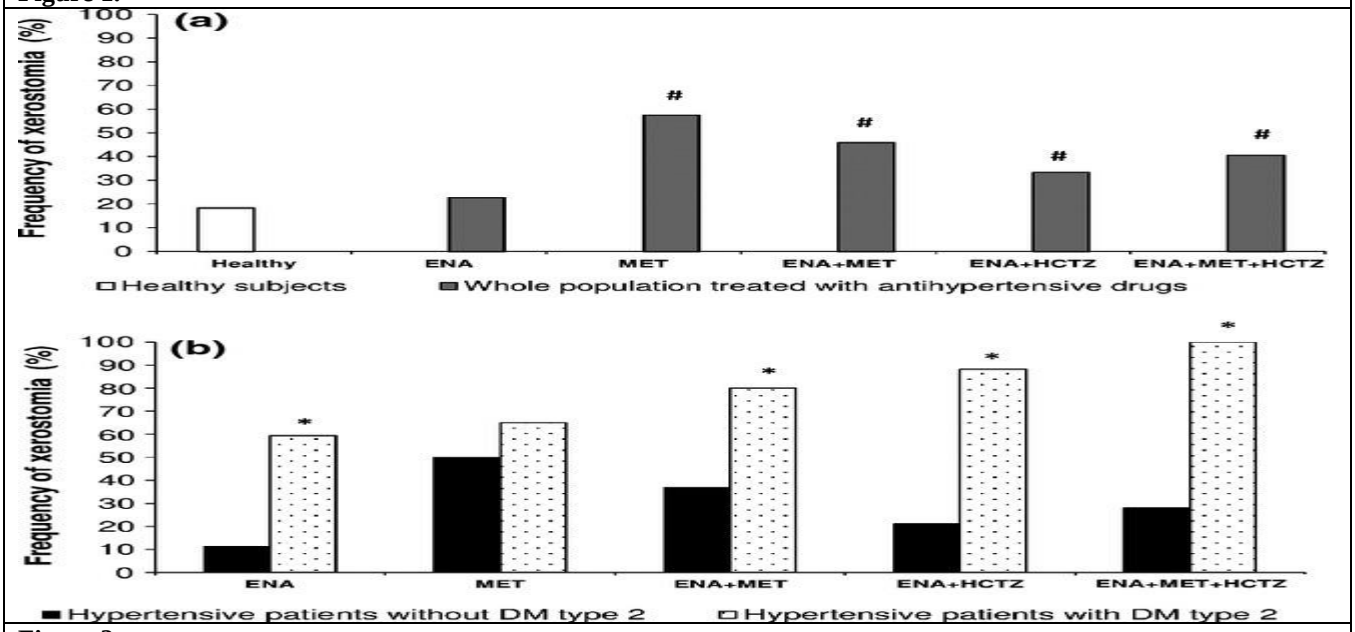


Figure 2

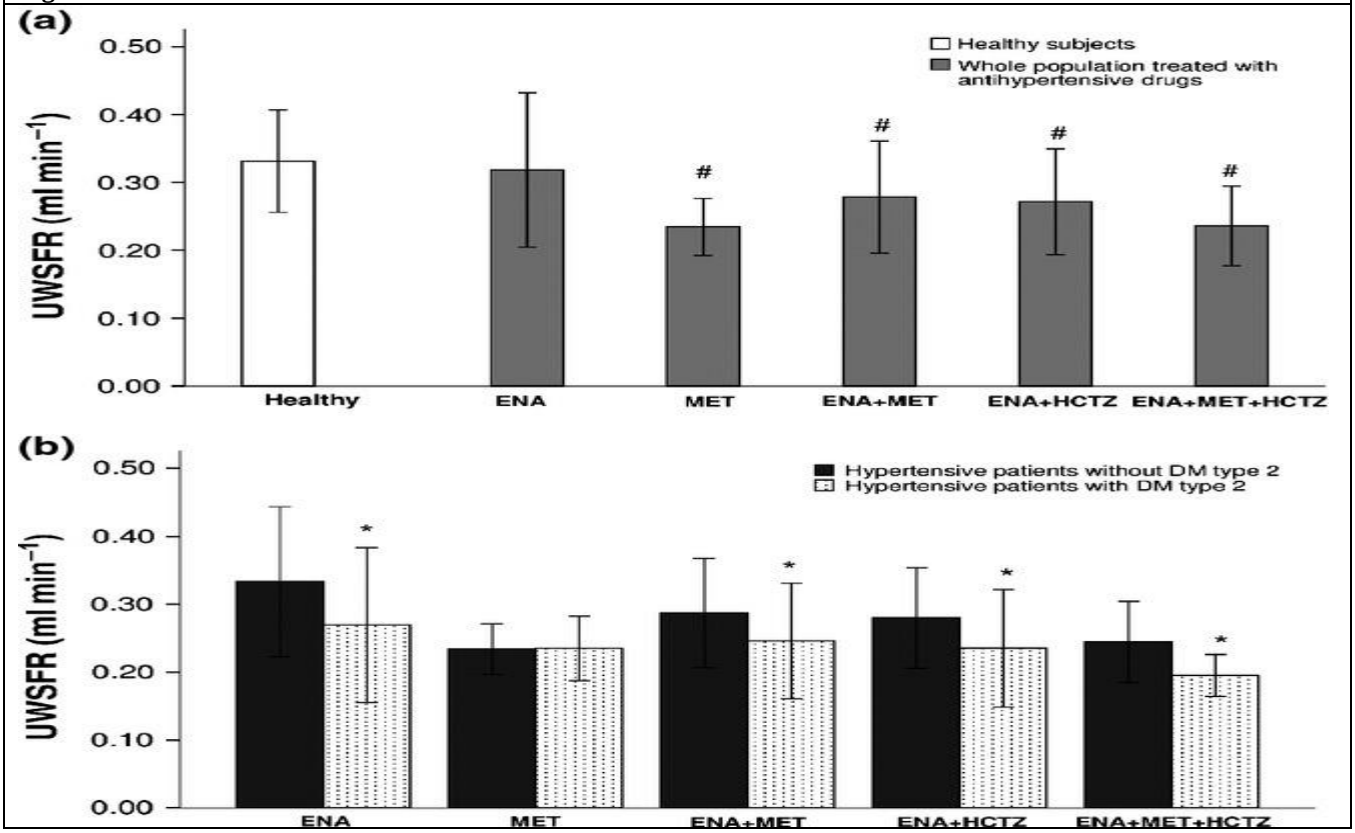
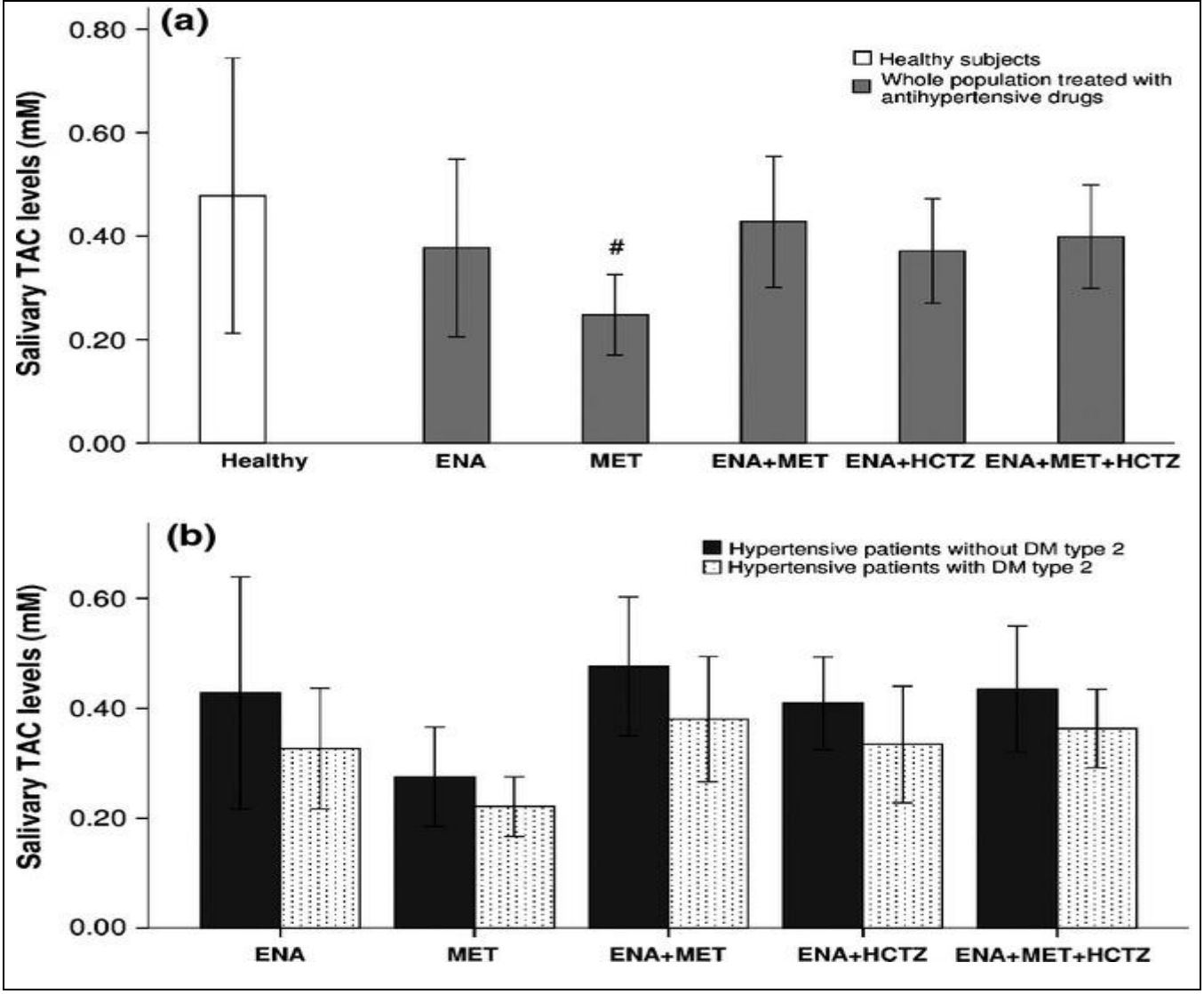


Figure 3



The influence of antihypertensive drugs on xerostomia in hypertensive patients regardless of the DM type 2 presence compared to healthy subjects (a) and among hypertensive patients divided by the DM type 2 presence (b). ENA, enalapril; MET, metoprolol; HCTZ, hydrochlorothiazide. #P < 0.05 drug(s) treated vs healthy (Chi-square test). *P < 0.05 hypertensive patients with DM type 2 vs hypertensive patients without DM type 2 (Chi-square test).

Figure 2a shows that UWSFR in patients treated with anti-hypertensive drugs in comparison with healthy subjects was significantly lower in patients treated with metoprolol as monotherapy and combinations of enalapril with metoprolol and/or hydrochlorothiazide, while it was not changed in patients taking enalapril as monotherapy. Hypertensive patients with DM type 2 exhibited a significant decrease of UWSFR with respect to those without DM type 2 treated with all investigated anti-hypertensive drugs except metoprolol as monotherapy (Figure 2b).

Open in figure viewer PowerPoint

The influence of antihypertensive drugs on UWSFR (ml/min) in hypertensive patients regardless of the DM type 2 presence compared to healthy subjects (a) and among hypertensive patients divided by the DM type 2 presence (b). ENA, enalapril; MET, metoprolol; HCTZ, hydrochlorothiazide. #P < 0.05 drug(s) treated vs healthy (Kruskal-Wallis test followed by Mann–Whitney U-test). *P < 0.05 hypertensive patients with DM type 2 vs hypertensive patients without DM type 2 (Mann–Whitney U-test). Error bars represent SD.

Risk factors for xerostomia and reduced UWSFR

The binary logistic regression model presented in Table 2 shows that the risk of xerostomia was 5 times greater in patients with low UWSFR than in those with normal UWSFR. DM type 2 increased the risk of xerostomia 9.09 times. In patients over 65 years of age, the risk of xerostomia was 1.61 times greater than in younger ones, while the duration of anti-hypertensive therapy over 10 years increased the risk of xerostomia 1.56 times. The risk of xerostomia was decreased 2.44 times with enalapril as monotherapy while increased 2.86 times with metoprolol as monotherapy. After adjustment with other confounders (DM type 2, low UWSFR, age over 65 years, duration of anti-hypertensive therapy over 10 years, enalapril and metoprolol as monotherapy), only factors: DM type 2, low UWSFR, and enalapril treatment remained significantly associated with xerostomia.

The binary logistic regression model presented in Table 3 shows that the risk of reduced UWSFR was 2.44 times greater in female patients than in males. DM type 2 increased the risk of reduced UWSFR 4.17 times, while the risk was 2.86 times greater in patients over 65 years of age. Enalapril as monotherapy decreased the risk of reduced UWSFR development 1.76 times. After adjustment, significant association of DM type 2, age over 65 years, female gender, and enalapril as monotherapy with reduced UWSFR remained.

Salivary TAC levels

The salivary TAC in patients treated with anti-hypertensive drugs was significantly lower only in patients treated with metoprolol as monotherapy in comparison with healthy subjects (Figure 3a). Also, hypertensive patients with DM type 2 exhibited a trend of a decrease of salivary TAC with respect to those without DM type 2 (Figure 3b). However, comparison between all hypertensive patients with DM type 2 and all those without DM type 2, regardless of antihypertensive therapy, showed significant reduction of salivary TAC in hypertensive patients with DM type 2 (0.32 ± 0.10 mM vs 0.40 ± 0.15 mM, $P < 0.05$, data not shown).

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The influence of antihypertensive drugs on salivary TAC (mM) in hypertensive patients regardless of the DM type 2 presence compared to healthy subjects (a) and among hypertensive patients divided by the DM type 2 presence (b). ENA, enalapril; MET, metoprolol; HCTZ, hydrochlorothiazide. #$P < 0.05$ drug(s) treated vs healthy (One-way ANOVA followed by post hoc Bonferroni test). Error bars represent SD

DISCUSSION

The present cross-sectional, comparative study deals with the effects of the first-line anti-hypertensive drugs affecting oral homeostasis by their adverse xerogenic (xerostomia and reduced UWSFR) and protective antioxidant effects in hypertensive patients with and without DM type 2.

The obtained results, concerning xerogenic effect of investigated anti-hypertensive drugs, showed that enalapril was without while metoprolol was with most prominent such effect. Even more, unadjusted ORs from binary logistic regression analysis indicated that enalapril is an independent factor which moderately reduces the risk of development of xerostomia and reduced UWSFR, while metoprolol is independent risk factor for development of xerostomia. In connection with this, combinations of enalapril with metoprolol and/or hydrochlorothiazide are not independent risk factor confirming such beneficial effect of enalapril.

Investigating the 7 day treatment with captopril, ACE inhibitor similar to enalapril, in placebo-controlled study on healthy volunteers, Nederfors *et al* (1995) found a tendency toward an increased flow rate for unstimulated and stimulated whole saliva with captopril. In a large study on cardiovascular patients, Habbab *et al* (2010) found that among cardiovascular drugs, as group's not individual drugs, ACE inhibitors induced xerostomia less frequently.

To analyze the possible mechanisms of the ACE inhibitors effect on salivary gland flow, it is noteworthy to mention the following. Main pharmacodynamic effect of ACE inhibitors is inhibition of not only the conversion of angiotensin I into angiotensin II, but also degradation of bradykinin, potent vasodilator. Investigating the effect of captopril and bradykinin on salivation in the cat submandibular gland, Stojic (1999) showed that captopril induced salivation through endogenously accumulated bradykinin due to ACE inhibition.

Concerning xerogenic effect of metoprolol, in a study on hypertensive patients receiving beta blockers as a group (not specified drugs), de Matos *et al* (2010) also demonstrated reducing effect of these drugs on resting salivary flow in comparison to non-medicated controls. Investigating salivary secretion rate of metoprolol on hypertensive patients, Nederfors and Dahlöf (1996) reported significant increase in UWSFR during withdrawal of and decrease after re-exposure to the drug. The authors suggested that increased cardiac output followed by an increase in salivary gland blood flow during withdrawal of metoprolol and opposite mechanisms during the drug re-introduction are responsible for observed effects. Another possible mechanism for xerogenic effect of beta blockers could be the prevention of upregulation of Na+-K+-2Cl− cotransporter (followed by major chloride uptake and consequent increase of chloride and fluid secretion in salivary glands) through beta1 adrenoceptor blockage observed by Paulais and Turner (1992).

Although in our study, none of the patients received hydrochlorothiazide as monotherapy, results

showing that the combination of enalapril and hydrochlorothiazide possesses significant xerogenic effect in investigated population suggest that this effect derives from hydrochlorothiazide but not from enalapril which was, as mentioned earlier, without xerogenic effect. Xerogenic effect of combinations which include hydrochlorothiazide, with enalapril or enalapril and metoprolol, was similar. In a study on hypertensive patients taking hydrochlorothiazide with potassium sparing component, spironolactone, significant reduction of stimulated parotid salivary flow rates was observed when compared to normotensive and uncontrolled hypertensive patients (Streckfus *et al*, 1994). In a small study on healthy female volunteers, a modest xerogenic effect of bendroflumethiazide, thiazide diuretic similar to hydrochlorthiazide, was observed after 7 days treatment (Nederfors *et al*, 2004). It seems that anti-hypertensive mechanism of action of hydrochlorothiazide, inhibition of Na+-Cl− cotransport, is not involved in its xerogenic effect, as acinar cells operate without Na+-Cl− cotransporters (Turner and Sugiya, 2002), while vasodilation contributes to salivary secretion (Edwards, 1998). Most probably, hydrochlorothiazide exhibits effect on salivary secretion through inhibition of $HCO3^{-}$ transport as a consequence of its ability to inhibit carbonic anhydrase which operates in acinar cells (Turner and Sugiya, 2002).

Diabetes mellitus has been consistently reported to alter salivary gland function (Soell *et al*, 2007), through same mechanisms as in cardiovascular or renal diabetic complications: autonomic neuropathies, microvascular changes, underlined by oxidative stress (Chávez *et al*, 2000). The influence of dysfunctional autonomic nervous system in non-insulin-dependent diabetes mellitus patients was indicated by correlation between stimulated saliva secretion and heart rate sympathetic and parasympathetic components variability (Meurman *et al*, 1998). Having in mind, the significance of blood flow to salivary secretion, recent study on experimentally induced diabetes demonstrated decreased vasorelaxant response to acetylcholine, due to endothelial dysfunction, in the rabbit feeding artery of parotid gland (Roganović *et al*, 2011). Also, direct evidence of impaired salivary function in non-insulin dependent diabetes mellitus patients was established by quantitative salivary scintigraphy (Lin *et al*, 2002).

In the present study, binary logistic regression analysis showed that DM type 2 is independent risk factor for development of xerostomia and reduced UWSFR. After adjustment, we found moderate potentiation between DM type 2 with other established risk factors. To analyze the impact of DM type 2 on observed xerogenic effect of investigated drugs, we divided whole population of drug-treated hypertensive patients into hypertensive patients with and without DM type 2. In hypertensive patients with DM type 2 treated with enalapril, a significant xerogenic effect was observed in comparison with those without DM type 2. It could be suggested that observed xerogenic effect is rather the effect of DM type 2 than of enalapril, per se. This suggestion has been confirmed by adjusted binary logistic regression analysis showing that even in the presence of DM type 2 and other herein established risk factors for development of xerogenic effect enalapril still moderately reduces the risk of such adverse effects development (xerostomia: adjusted OR = 2.64, 95% CI 1.46–4.76, P = 0.001; reduced UWSFR: adjusted OR = 1.84, 95% CI 1.06–3.21, P = 0.031).

ACE inhibitors had been shown to attenuate the progression of cardiac and renal impairments related to diabetes by different mechanisms: suppression of ACE upregulation, improvement of endothelial function, and protective antioxidant action (O'Driscoll *et al*, 1997; de Cavanagh *et al*, 2001; Motawi *et al*, 2013). Our results showed that in the presence of enalapril salivary TAC, as an indicator of overall antioxidant protection, in hypertensive patients with and without DM type 2 was similar to that in healthy subjects while in the presence of metoprolol was reduced in hypertensive patients with and without DM type 2. It is noteworthy to mention that enalapril possesses antioxidant properties in different tissues while metoprolol does not (Arumanayagam *et al*, 2001; de Cavanagh *et al*, 2001; Baykal *et al*, 2003; Deoghare and Kantharia, 2013). An unexpected finding that in DM type 2 hypertensive patients xerogenic effect of metoprolol was not pronounced could imply a sort of protective effect of metoprolol against diabetic changes at the level of salivary glands. It remains to elucidate the protective mechanisms of metoprolol which according to our results does not include antioxidant protection.

CONCLUSION

In conclusion, this cross-sectional study found that first-line anti-hypertensive drugs differently affect salivary gland function and salivary antioxidant protection in hypertensive patients with/without DM type 2.

Enalapril is not xerogenic but is antioxidant and is the factor which moderately reduces the risk of xerostomia and reduced UWSFR development even in the presence of DM type 2. In contrast to that, metoprolol and combinations of enalapril with metoprolol and/or hydrochlorothiazide are xerogenic, with such stronger effect in DM type 2, with exception of metoprolol. These findings are of clinical importance, as they point out that enalapril does not seem to adversely affect the oral health-related quality of life of hypertensive patients with DM type 2, what is more enalapril could protect it.

Enalapril is not xerogenic but is antioxidant, which moderately reduces the risk of xerogenic effect development even in the presence of DM type 2. However, metoprolol and drug combinations exhibit

xerogenic effect. In DM type 2, xerogenic effect of all drugs was pronounced except of metoprolol.

Metformin normalizes osteoclast numbers, cathepsin K immunostaining, and reduces tooth movement. Metformin also reduces sclerostin expression and improves the immunolocalization of dentin matrix protein 1 in osteocytes of type 2 diabetes.

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