10.21608/ADJC.2022.173231.1187 Advanced Dental Journal
Volume 5 (2023) | Issue 1| Pages 12- 23

Original Article

Prevalence of Oral Mucosal Alterations in A Sample of Egyptian Cardiovascular Patients Secondary To Cardiovascular Drugs: A Hospital Based Cross-Sectional Study

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Abstract:

Aim: The current study aimed to determine the prevalence of oral mucosal alterations in cardiovascular patients secondary to cardiovascular drugs and to investigate the presence of a possible relation between different cardiovascular drugs and oral manifestations.

Methodology: Three hundred and thirty-eight adult patients diagnosed with cardiovascular diseases at Kasr Al-Einy Hospital, Faculty of Medicine, Cairo University, were exanimated for oral signs and symptoms such as oral dryness dysphagia, and burning sensation. The patients were also clinically examined to report any oral lesions in oral mucosa such as lichenoid reactions, xerostomia, and gingival enlargements.

Results: Oral manifestations were founded in 253 (74.8%) patients as an adverse effect of cardiovascular drugs. The most common manifestations were gingival overgrowth in170 (50.3%), followed by xerostomia in 87(40%), burning sensation in 71 and (21%), dysphagia in36 (10.65%), and lichenoid reaction in 5(1.47%). Drugs were found to most commonly cause xerostomia a combination of NGDs + antiplatelet, congestive heart failure, beta-blocker, and BBDs +diuretics, while the most common cause of burning sensation was CCBs+ antiplatelet and Congestive heart failure drugs. The most known cause of gingival overgrowth was calcium channel blocker drugs in 100% of patients.

Conclusions: Most patients who are being treated for cardiovascular disease will always experience an adverse oral manifestation such as xerostomia, burning sensation, and gingival overgrowth. Concomitant symptomatic oral care should be provided to these patients to better their quality of life.

Keywords:

Introduction

Cardiovascular diseases (CVD) are the main cause of death in all regions of the world. Sociodemographic change over the past 25 years has been related to the rapid decrease in CVD in areas with very high sociodemographic index (SDI), but only a slow decrease or no change in

most areas of the world especially those with low SDI **(Roth et al. 2017)**.

In Egypt, CVD has been an important reason for early death since 1990. In 2017, CVD was reported ted 46.2% of the overall death in Egypt **(Hassanin et al. 2017).**

The mouth act as "a reflection of health or disease, as a guard or early warning sign, as a reachable perfect for the study of other tissues and organs, and as a possible cause of diseases affecting body systems **(Arunkumar 203).**

The mouth acts as a window to the body because oral manifestations go together with numerous systemic diseases. In many situations, mouth affection first is seen earlier than other symptoms or lesions at other sites. These oral alternations essential be accurately known if the patient is properly non-diagnosed and recommended for treatment **(Mehrotra 2010).**

CVD is the most reason for premature death in people with diabetes. People with diabetes also have hypertension, dyslipidemia, and obesity, which lead to an increased frequency of CVD (**Malik and Dwivedi 2015).**

CVD is considered the main cause of death in the world as well as in the Middle East. This is because of the abnormality of adipose tissue causing an increase in the creation of pro-inflammatory adipokines and a decrease in cardio-protective adipokines for example adiponectin **(Abu-Farha 2014).**

There are numerous drugs were used in the treatment of CVD like anticoagulants, antiplatelet drugs, dual antiplatelet remedies, ACE Inhibitors, angiotensin II receptor blockers, neurolysin inhibitors beta-blockers, calcium channel blockers, cholesterol-lowering medications, and diuretics **(Muir 2017).**

Indeed, numerous cardiovascular drugs working clinically have been reported to cause oral detrimental effects along with xerostomia, oral lichen planus, angioedema, aphthae, dysgeusia, and gingival enlargement, scalded mouth syndrome, cheilitis, glossitis, etc…. Oral complications may in turn worsen the cardiovascular disease situation as some reviews endorse an unfavorable correlation between periodontal diseases and CVD **(Balakumar et al 2015).**

Table (1) shows different cardiovascular drugs, their mechanism of action, and potential side effects local to the oral cavity. The exact frequency of the effects of cardiovascular drugs on the oral mucosa is unknown; thus, it is impossible to expect if in the future there will be a necessity for particular attention to these diseases. The prevalence of the negative effects of cardiovascular drugs is not known possible to predict if we need specialized care for these effects in the future.

The current study aimed to determine the prevalence of oral mucosal manifestations in cardiovascular patients secondary to cardiovascular drugs and to examine the presence of a possible relation between cardiovascular drugs and oral manifestations.

Subjects and Methods

The present study is a cross-sectional study including 338 patients with different CVD who were receiving cardiovascular drugs and were selected from the cardiovascular clinic at Kasr Al-Ainy Hospital, Faculty of Medicine, Cairo University. The study was approved by the ethical committee of the faculty of dentistry, Cairo University under approval number 4720

Eligibility criteria

All Patients were more than 18 years old, were diagnosed with CVD, and received cardiovascular drugs included in this study.

Table (1) : different cardiovascular drugs, their mechanism of action, and potential side effects local to the oral cavity.

Cardiovascular Drugs	Mechanism of action	Oral side effect
Antiplatelet Agents	Prevent platelets from forming a plug	Cause acid burn and angioedema
Angiotensin-Converting Enzyme (ACE) Inhibitors	Expand blood vessels and decreases resistance	Cause angioedema, dry mouth, ulcerations, lichenoid eruptions, manifestations of hematological turbulences, lack of flavor, and 'scalded mouth syndrome
Beta-Blockers	Decreases the heart rate and force of contraction by beta-adrenergic receptor block	Cause angioedema, dry mouth, oral ulcerations, lichenoid drug eruptions, lupus erythematosus, SJS, oculo-mucocutaneous syndromes
Calcium Channel Blockers	Interrupt the movement of calcium into the cells of the heart and blood vessels	Cause gingival enlargement or overgrowth
Digitalis Preparations	increase the force of the heart's contractions.	Cause xerostomia
Diuretics	Cause the body to rid itself of excess fluids and sodium through urination	Cause dry mouth, taste disturbances, angioedema and oral manifestations of hematologic conditions, drug hypersensitivity disorder, lichenoid reaction, and lupus erythematosus-like eruptions
Antiarrhythmic Drugs	Treat inappropriate shocks from implantable cardioverter-defibrillators (ICDs	Cause xerostomia, fixed drug eruptions, oral manifestations of hematologic disorders, lupus erythematosus, gingival enlargement, SJS, TEN
Anticoagulant drugs	Affect coagulation cascade	Cause sublingual and retropharyngeal hematomas are uncommon and bleeding
Alpha-blocker drugs	Decrease blood pressure	Cause oral lichenoid eruptions and ulcerations

Patients who were not physically able to participate in a survey or clinical oral examination, or who were under immunosuppressive drug, had dementia or confusion, and who refused to participate in the study had been excluded from the study. Patients who had any medical conditions other than cardiovascular diseases and had taken any drugs other than cardiovascular drugs had also been excluded from the study.

Outcomes

Primary outcome

The primary outcome of this study was the prevalence of oral mucosa alternation which was

measured as a binary outcome by clinical examination according to WHO (World Health Organization 2010).

Secondary outcomes

1-Gingival overgrowth was measured as an ordinary outcome by clinical examination using a gingival overgrowth score **(Archana et al. 2018)**.

2-Salivary gland function

a-Oral dryness was reported as an ordinary outcome after clinical examination of the oral cavity by using a clinical oral dryness score **(Jager et al. 2018)**

b-xerostomia was reported as an ordinary outcome using**(Wiener et al. 2010)**

Study sample size

The primary outcome is oral mucosal alternation in Egyptian patients with CVD on cardiovascular medication based on the previous study by**(Arunkumar, 2013)**. who described the oral symptoms in cardiovascular patients secondary to cardiovascular drugs by 67,4%.

We used OpenEpi, Version 3, open-source calculator to calculate the sample size. At the power of study of 80%, an alpha level of significance of 5%, and a confidence interval of 95%; a total of 338 patients were needed to achieve the study objective.

Statistical methods

All Data were collected, tabulated, and subjected to statistical analysis. Statistical analysis is performed by SPSS in general (version 20), while Microsoft Office Excel is used for data handling and graphical presentation. Qualitative categorical variables are described by frequencies and percentages. Significance level is considered at $P < 0.05$ (S); while for $P < 0.01$ is considered highly significant (HS). Two-Tailed tests are assumed throughout the analysis for all statistical tests. Chi-squared test of independence was applied.

Result

All patients were more than 18 years. Young adults represented 10% of the study sample (34 patients), whereas the majority of patients were middle-aged (46.75%, 158 patients) and senior citizens (43.2%, 146 patients). Males represent 62.43% (211 patients) of the study sample while females represent 37.57% (127 patients). 317 (91%) patients were married and 21 (9%) patients were single. The BMI was evaluated, 4.4% of the patients were underweight (<18.5) (15 patients), and 51.18% of the patients had normal BMI (18.5-24) (173 patients). 35% of the patients were overweight (25-29.9) (121 patients), while 8.58% of the patients were obese (>30) (29 patients) Table (2) shows the Distribution of cardiovascular diseases among the study participants.

As for CVD distribution among patients in the study, 55.62% patients had hypertension (188 patients), 19.82% patients had coronary heart disease (67 patients), 11.54% had cardiac arrhythmia (39 patients), 7.1% patients had heart surgery (24 patients), 3.85% had congestive heart disease (13 patients), 1.48% patients had arrhythmia and hypertension (5 patients) and 0.59%patients had heart pacemaker (2 patients). Figure (1) shows the frequency of cardiovascular drugs were taken by study participants.

Outcomes

Oral mucosal alternations secondary to cardiovascular drugs were found as follows:
Oral manifestations were recorded in 253 (74.8%) patients as adverse effects of cardiovascular drugs (Table 3). The most common manifestation was gingival overgrowth in 170(50.3%), followed by xerostomia in 87

(40%), burning sensation in 71(21%), dysphagia in36 (10.65%), and lichenoid reaction in 5(1.47%). The drugs found to most commonly cause xerostomia were a combination of NGDs + antiplatelet, congestive heart failure drugs, beta-blockers, and BBDs +diuretics, while the most common to cause burning sensation was CCBs+ antiplatelet and Congestive heart failure drugs (Table 4) .

Lichenoid drug reaction

In the current study lichenoid drug reaction was found in only 5 patients (1.47%) of all patients in the present study as an oral adverse effect of the cardiovascular drugs.

Clinical oral dryness

Almost a quarter of the study participants (25.74%) had severe clinical oral dryness (87 patients), 13% had moderate oral dryness (44 patients), 1.48 % had mild oral dryness (5 patients), while almost 60% of the patients had none (202 patients) (table 5).

Gingival overgrowth

The most known cause of gingival overgrowth was calcium channel blocker drugs. According to the score by **(Archana et al. 2018)**;49.7% (168 patients) of the patients had normal gingiva, 28.4% of patients had mild gingival enlargement (96 patients), 18.93% of patients had moderate gingival enlargement (64 patients) and 2.96% of patients had severe enlargement (10 patients)

Discussion

In the present study, 253 (74%) patients had oral manifestation as an adverse effect of cardiovascular drugs. The most common manifestations were vertical gingival overgrowth (50.2%), xerostomia (40%), burning sensation (21%) followed by dysphagia (10.65%), and lichen planus (1.47%). **Arunkumar (2013)** reported similar results, where the overall oral manifestations seen had a prevalence of 67.4%, with the dry mouth being the most frequent finding (25.5%) followed by dysgeusia (17.7%), the combination of xerostomia with dysgeusia (12.4%) and burning sensation (6%). On the other hand,**(Habbab 2010)** reported markedly fewer oral manifestations (14.1%). Interestingly, xerostomia remained the most common finding with a prevalence of 7.5% followed by lichenoid lesions (3.6%) and dysgeusia (1.9%).

A burning sensation was reported in 21% of patients who were taking cardiovascular drugs. The drugs found to most commonly cause these symptoms were CCBs+ antiplatelet (15.4%), Congestive heart failure drugs (14.08%), NGDs+ antiplatelet (14.08%), and BBDs+diuretics (9.8%) Arunkumar's results were comparable to the present findings, like the following, patients had medicated for coronary artery disease (60%), the combination of BABs with diuretics (20%), and in patients were taking both anti-diabetic and cardiovascular drugs (20%). Conversely, (Habbab 2010)**.** reported a burning sensation in only 0.6% of the study population.

In the current study lichenoid drug reaction was reported in only 5 patients (1.47%) of all patients in the present study as an oral adverse effect of the cardiovascular drugs.

Table (2) : Distribution of cardiovascular diseases among the study participants

Cardiovascular diseases	Frequency	Percent
Hypertension	188	55.62%
Coronary heart diseases	67	19.82%
Cardiac arrhythmia	39	11.54%
Heart surgery	24	7.10%
Congestive heart disease	13	3.85%
Arrhythmia and hypertension	5	1.48%
Heart pacemaker	2	0.59%
Congenital heart disease	0	0.00%
Total	338	100%

Table (3) : Frequency of oral adverse reactions to cardiovascular drugs

Drug	Adverse Effect		Total
	No	Yes	
Beta-adrenergic blocker drugs (BBDs)	7	13	20
	35.0%	65.0%	100.0%
Calcium channel blockers (CCBs)	0	2	2
	0.0%	100.0%	100.0%
Antiplatelet drugs	1	0	1
	100.0%	0.0%	100.0%
Sodium channel blockers (SCBs)	6	2	8
	75.0%	25.0%	100.0%
Potassium channel blockers (PCBs)	3	8	11
	27.3%	72.7%	100.0%
Nitrates (NCDs)	5	3	8
	62.5%	37.5%	100.0%
Angiotensin-converting enzyme inhibitors (ACEIs)	1	1	2
	50.0%	50.0%	100.0%
BBDs +CCBs	0	1	1
	0.0%	100.0%	100.0%
NGDs+ antiplatelet	8	37	45
	17.8%	82.2%	100.0%
ACEIs+ antiplatelet	2	4	6
	33.3%	66.7%	100.0%
BBDs+ anticoagulant	0	4	4
	0.0%	100.0%	100.0%
NGDs+ BBDs	0	6	6
	0.0%	100.0%	100.0%
BBDs+ Diuretics	4	23	27
	14.8%	85.2%	100.0%
BBDs +CCBs+ diuretics +antiplatelet	7	19	26
	26.9%	73.1%	100.0%
Congestive heart failure drugs	8	27	35
	22.9%	77.1%	100.0%
ACIBs+ anticoagulant	3	5	8
	37.5%	62.5%	100.0%
BBDs+ CCBs+ diuretics +anticoagulant	0	1	1
	0.0%	100.0%	100.0%

NGDs+ anticoagulant	0	5	5
	0.0%	100.0%	100.0%
CCBs+ diuretics	1	3	4
	25.0%	75.0%	100.0%
BBDs+ anticoagulant +antiplatelet	2	13	15
	13.3%	86.7%	100.0%
SCBs+ antiplatelet	1	5	6
	16.7%	83.3%	100.0%
ACIBs+ BBDs	6	8	14
	42.9%	57.1%	100.0%
CCBs+ antiplatelet	3	18	21
	14.3%	85.7%	100.0%
ACIBs+ CCBs+ antiplatelet	0	1	1
	0.0%	100.0%	100.0%
BBDs+ antiplatelet	2	7	9
	22.2%	77.8%	100.0%
ACEIs+ BBDs+ diuretics	4	9	13
	30.8%	69.2%	100.0%
NGDs+ CCBs	0	10	10
	0.0%	100.0%	100.0%
ACEIs+ diuretics	3	4	7
	42.9%	57.1%	100.0%
ACEIs +diuretics +antiplatelet	2	3	5
	40.0%	60.0%	100.0%
ACEI +BBDs+ anticoagulant	1	2	3
	33.3%	66.7%	100.0%
BBDs +diuretics +antiplatelet	2	1	3
	66.7%	33.3%	100.0%
PCBs+ antiplatelet	0	5	5
	0.0%	100.0%	100.0%
BBDs +antiplatelet +anti arrhythmia	3	3	6
	50.0%	50.0%	100.0%

The lesion was found in one patient for each of the following therapeutics groups: BBDs+diuretics, BBDs +antiplatelet, NGDs+ antiplatelet, NGDs+ anticoagulant, and ACEI +antiplatelet+ antiarrhythmic drugs. Arunkumar et al (2013) had noticed lichenoid reaction when they used the following combinations as Beta-adrenergic blockers (BABs) with CCBs (18.5%), CCBs with anti-anxiety drugs (18.5%), BABs with diuretics and coronary disease medication (14.8%), and patients on antidiabetic drugs with cardiovascular drugs (3.7%), while in other drug groups the lichenoid lesions were found to be less than 2%. **Arunkumar et al** reported lichenoid drug reaction to be more than the present study, however, these patients were on anti-anxiety and anti-diabetic medication. **(Mccartan and Mccreary 1997)** also noted a reaction with BABs where 14 of the 19 patients had lichenoid drug reactions (73.6%).

In the present study, xerostomia was divided into three categories mild (1.48%), moderate (13.2%), and severe (25.74%) which was the most commonly found grade of xerostomia. The drugs found to be the most common cause of xerostomia were a combination of NGDs + and antiplatelet, congestive heart failure drugs, beta-blockers, and BBDs +diuretics. **(Shinkai et al. 2006)** reported xerostomia in 40 patients (7.5%) as an adverse effect of many drug categories**. (Kumar et al. 2012)** had found that 79% of patients who were taking medications with diuretics presented with hyposalivation.

Table (4): Percentage and frequency of burning sensations among drugs categories

Cardiovascular drugs	Frequency	Percent
CCBs+ antiplatelet	11	15.4%
Congestive heart failure drugs	10	14.08%
NGDs+ antiplatelet	10	14.08%
BBDs+diuretics	7	9.8%
NGDs+ CCBs	5	7.04%
BBDs+ CCBs+ diuretics+ antiplatelet	4	5.6%
BBDs+ antiplatelet + anticoagulant	3	4.2%
NGDs+ anticoagulant	3	4.2%
ACEIs+ anticoagulant	2	2.8%
ACEIs+ BBDs+diuretics	2	2.8%
PCBs	2	2.8%
ACEIs+ diuretics +antiplatelet	2	2.8%
BBDs+ CCBs +diuretics +anticoagulant	1	1.4%
CCBs	1	1.4%
ACEIs	1	1.4%
NCDs +BBDs	1	1.4%
ACEIs +diuretics	1	1.4%
BBDs	1	1.4%
ACEIs+ BBDs	1	1.4%
BBDs+ anticoagulant	1	1.4%
BBDs+ antiplatelet	1	1.4%
CCBs+ diuretics	1	1.4%
Total	71	100%

Table (5): Frequency and percentage of clinical oral dryness among the study participants

Clinical oral dryness	Frequency	percent
No	202	59.76%
Mild 1-3	5	1.48%
Moderate 4-6	44	13.02%
Severe 7-10	87	25.74%
Total	338	100%

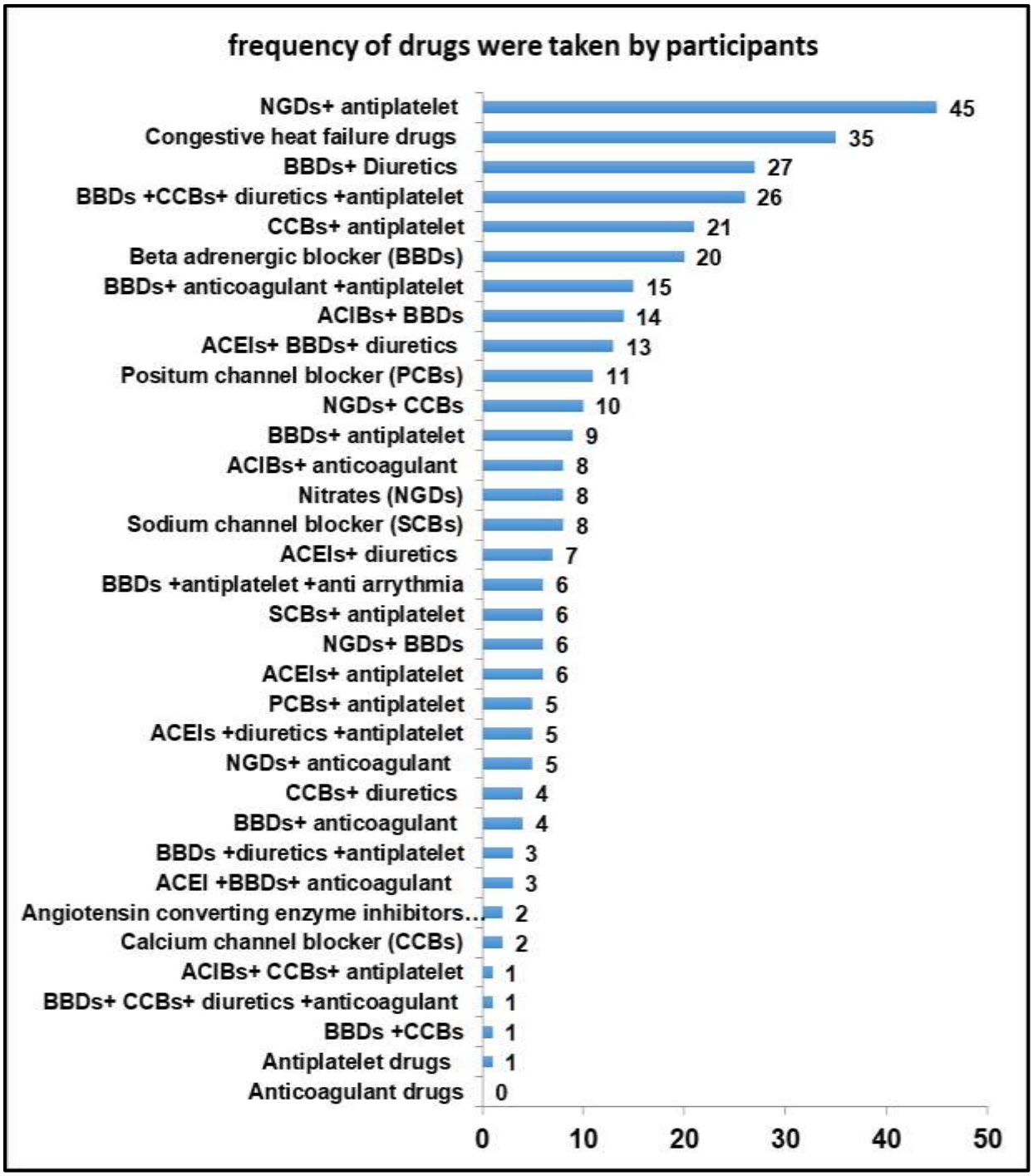

Figure (1): frequency of cardiovascular drugs taken by study participants

Vertical gingival overgrowth was found in 50.2% of the studied patients and categorized into three categories mild (28.40%), moderate (18.93%), and severe (2.96%) (The classification of gingival overgrowth according to papilla overgrowth into normal =0, mild less than 2 mm,

moderate from 2 to 4 mm, sever more than 4mm) **(Miranda et al. 2012).**

Interestingly, patients on antiplatelet drugs alone exhibited no oral adverse manifestation, while those on NGDs alone had only 3 patients (37%) who had any oral manifestations, yet the most adverse reactions were seen in patients taking a combination of the two previously stated drugs (17.8% showed an oral adverse reaction, 16.6% dysphagia, 14.08% burning sensation, 13.5% moderate gingival overgrowth and 10% severe gingival overgrowth). This means that drug combinations may increase the possibility of developing oral adverse reactions.

Actually, in the present study lichenoid reaction was reported in 5 patients who were taking the following combination ACEs +antiplatelet, BBDs+ antiplatelet + antiarrhythmic, BBDs +diuretics and NGDs+ antiplatelet although no patient suffer from this reaction with one type of drugs, this means a combination of drugs lead to more adverse side effects.

Clearly, calcium channel blocker causes gingival overgrowth. The present study showed moderate and severe gingival overgrowth with CCBs alone and with different drugs categories. In moderate gingival overgrowth 100% patients were on CCBs + BBDs, 100% CCBs+ BBDs+ diuretics + anticoagulant, 60% CCBs+ antiplatelet, 20% NGDs+ CCBs and 16.6% CCBs+ anticoagulant. In severe gingival overgrowth 11% patients were on CCBs+ NGDs and 11% CCBs +antiplatelet.

Some drug categories were found to induce severe and moderate gingival overgrowth this means not only do drug factor causes adverse effects but time factor also affect the degree of severity.

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The study has some limitations such as not having an equal number of patients for each drug category. Additionally, the author cannot prove that certain drug combinations have synergistic action as regards adverse effects related to the oral cavity.

CONCLUSION

Patients who are being treated for a cardiovascular illness will most of experience an adverse oral event such as xerostomia, burning sensation, or gingival overgrowth. Concomitant symptomatic oral care should be provided to these patients to improve their quality of life.

RECOMMENDATIONS

Further studies are needed with more patients included in each type of cardiovascular disease to detect oral adverse effects specific to each drug combination**.**

Physicians should anticipate the occurrence of an oral adverse event in patients with cardiovascular disease and should consult with an oral medicine specialist to decide the best approach for symptomatic management of these events**.**

Studies should be conducted on patients who are newly diagnosed with cardiovascular disease and have not received treatment yet to determine whether cardiovascular disease alone

could have any oral manifestations that would serve as a herald feature.

Conflict of interest:

The authors declare no conflict of interest.

Funding:

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sector.

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