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Comparative evaluation of the effectiveness of antioxidants in the complex treatment of periodontal diseases in patients with duodenal ulcer with fixed metal-containing dentures

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ABSTRACT

An open, prospective study was conducted in which 37 patients with periodontal disease (PD) and duodenal ulcer (DU) in the scarring phase with fixed metal dentures (FMD) and fixed metal-ceramic dentures (FMCD) participated. To determine the treatment effectiveness, two groups of patients were formed: the 1st group (16 people), which in addition to traditional therapy of PD, received vitamin E 100 mg once a day for 30 days; Group 2 (21 people) additionally received reduced L-glutathione (250 mg) with astaxanthin (40 mg) (Hepaval ASN) 1 capsule 2 times a day for 30 days. Complex therapy of patients with PD on the background of DU with fixed dentures with the inclusion of GSH and astaxanthin for a month helped to reduce the intensity of lipid peroxidation (LPO), oxidative modification of proteins (OMP) and endotoxicosis, reducing the activity of PD, which can be considered a preventive measure to prevent further loss of teeth and the need for prosthetics.

Keywords: periodontal disease, duodenal ulcer, fixed metal-ceramic dentures, oxidative-antioxidant homeostasis, glutathione.

1. INTRODUCTION

Periodontal diseases (PD) are diagnosed in 92–100 % of patients with duodenal ulcer (DU), and are mainly represented by chronic generalized gingivitis and chronic generalized periodontitis (Shadieva and Gijazova, 2021). Tooth loss after PD is observed in 4–6 times more often than after caries and its complications (Hermanchuk and Bida, 2019). The high prevalence and features of the clinical course of PD and DU, the increased need for prosthetics of dentition defects is a significant medical and social problem of modern society, which needs immediate solution (Doroshenko and Bida, 2021). Traditional methods of treatment of PD are aimed at eliminating microbial factors and include control of plaque formation, use of antimicrobial, anti-inflammatory drugs for local and systemic usage, improvement of surgical methods to

eliminate pathological foci in periodontal tissues (Iarov, 2020). In addition, materials used for prosthetics are not always indifferent to both periodontal tissues and digestive organs (Sailer et al., 2018). For example, the literature data indicate lots of negative effects of fixed metal dentures on the progression of PD due to induction of oxidative stress (OS) by metals (Chen et al., 2019; Avetisyan et al., 2021).

The processes of lipid peroxidation (LPO) and oxidative modification of proteins (OMP) play important role in the mechanisms of recurrence of PD with concomitant DU (Lobanets et al., 2015; Ostrovska et al., 2020). This becomes more complicated in the presence of metal inclusions in the oral cavity (Herman et al., 2016; Muris et al., 2015). Therefore, it is necessary to use such treatments that not only have anti-inflammatory effects, but also have a beneficial effect on the structural and functional state of periodontal tissues. The main representative of the antioxidant defense system (AODS), the most important regulator of redox processes, as well as an active factor in the natural detoxification system is reduced glutathione (GSH), which controls the activity of inflammatory processes, including PD (Bains and Bains, 2015). It has been proved that the total capacity of AODS in saliva and lower concentrations of GSH in serum and gingival fluid are reduced in patients with PD with concomitant DU (Kumar et al., 2017).

Published research results indicate that periodontal therapy with products containing GSH restores the redox balance of this area (Alkadasi, 2020; Toczewska and Konopka, 2019). Therapeutic considerations regarding the additional use of GSH in the treatment of PD to limit tissue damage associated with OS and enhance wound healing cannot be underestimated, but should be further evaluated in randomized researches (Richie et al., 2015). In this perspective, no study has yet been conducted on the effect of the natural antioxidant GSH on the clinical course of PD in comorbidities with DU in remission stage at the presence of fixed metal dentures (FMD), on OS intensity, endotoxicosis and AODS status.

The aim of the study was to explore the effect of the reduced glutathione and astaxanthin on the clinical course of periodontal disease, oxidative-antioxidant homeostasis, on the basis of which to develop a method of treatment of PD in patients with DU with fixed metal and metal-ceramic dentures.

2. METHODS

An open, prospective study was conducted in which 37 patients with PD and DU in the scarring phase with FMD and FMCD took part. The average age of patients was (57.1 ± 1.17) years. The study was performed from September 2020 to March 2021 on the basis of the Educational and Treatment Center «University Clinic», Chernivtsi, Ukraine). To correct our violations of oxidative-antioxidant homeostasis, antioxidant medicines were selected: vitamin E and Hepaval ASN (Valartin Pharma LLC), containing reduced L-glutathione – 250 mg; astaxanthin 10% (equivalent to 4 mg of astaxanthin) – 40 mg, with antioxidant, anti-inflammatory and detoxifying action. Two groups of patients were formed: Group 1 (16 people), which in addition to traditional therapy of PD, received vitamin E 100 mg once a day for 30 days; Group 2 (21 people) additionally received reduced L-glutathione (250 mg) with astaxanthin (40 mg) (Hepaval ASN) 1 capsule 2 times a day for 30 days. The control group consisted of 20 practically healthy patients of the appropriate age, sex.

The periodontal status of patients was studied: the intensity of the inflammatory response in the gums was assessed using the papillary-marginal-alveolar index (PMA), modified by Parma (1960). The complex periodontal index (CPI) was used to determine the intensity of PD (Leus, 1988). Sulcus Bleeding Index (SBI) was evaluated by (Mühlemann and Son, 1971). The hygienic condition of oral cavity was assessed using the Oral Hygiene Index - Simplified (OHI-S) (Greene and Vermillion, 1964). The level of tongue hygiene was determined using the Winkel Tongue Coating (W.T.C.) Index (Winkel et al., 2003).

Saliva collection was performed in the morning on an empty stomach without stimulation by spitting into a sterile test tube. After two hours of standing in the refrigerator, the saliva was centrifuged for 15 minutes at 3 thousand rpm (centrifuge OS - 6M). Blood for biochemical examination was taken from the ulnar vein in the morning on an empty stomach. The intensity of OS was assessed by the content in the blood plasma and saliva of molecular products of LPO by spectrophotometric method (spectrophotometer SF - 2000): the content of isolated double bonds (IDB) in the compounds (Volchegorskyj et al., 1989), malondialdehyde (MDA) (Yagi et al., 1976). The intensity of OMP in blood plasma and saliva was determined by the method of (Meshchyshen, 1998). The content of GSH in the blood was determined by the titration method (Meshchyshen and Petrova, 1983). Medium molecular weight peptides (MMP) were determined in blood plasma by the spectrophotometric method (Gabrielyan, 1985). The activity of the AODS system was assessed by the activity of catalase in blood plasma and saliva (Korolyuk et al., 1988) and the activity of copper-zinc superoxide dismutase (SOD) (Fried, 1975).

Statistical processing of the material was performed using modern methods of variation statistics. Before testing the statistical hypotheses, the normality of the distribution of values in randomized samples was analyzed by determining the asymmetry and excess coefficients using the Khan-Shapiro-Wilk test. The probability of the difference between the arithmetic mean (M) and its error (m) between the study groups was determined using the bilateral odd Student's t-test. The difference was considered significant at a significance level of $p < 0.05$. Student's t-test was used only in the case of a normal distribution of the equality of the general variances of the compared samples, which was checked using Fisher's F-test. In other cases, the nonparametric Mann-Whitney U test was used to compare the results. Mathematical processing of the obtained data was performed using Statistica for Windows software packages version 8.0 (Stat Soft inc., USA), Microsoft Excel 2007 (Microsoft, USA).

3. RESULTS

In the analysis of the structural and functional state of periodontal tissues in patients with DU, it was found that index PMA probably did not change in patients of group 1, although it tended to decrease (p=0.072) (Table 1). Similar data on PMA were obtained by observing patients in this group one month after treatment. In patients of the group 2, PMA decreased in 1.6 times after treatment (p=0.045), although it did not reach the normative level with stabilization at this level during the month (p=0.049).

Table 1 Indicators of the structural and functional state of periodontal tissues in patients with fixed metal and metal-ceramic dentures on the background of duodenal ulcer in the dynamics of treatment (M ± m)

Term of observation	Indicators, units of measurement	Groups of examined patients	
		Group 1 (n=16)	Group 2 (n=21)
Control group	PMA	0.19±0.04	
	SBI	0.6±0.09	
	CPI	0.52±0.25	
	OHI-S	0.75±0.2	
	W.T.C.	2.8±0.2	
Before treatment	PMA	0.51±0.03 *	0.50±0.02 *
	SBI	3.02±0.05 *	3.09±0.06 *
	CPI	1.63±0.10 *	1.62±0.11 *
	OHI-S	2.31±0.05 *	2.32±0.07 *
	W.T.C.	7.1±0.2 *	7.1±0.1 *
After treatment	PMA	0.43±0.02 *	0.31±0.01 */**/#
	SBI	2.55±0.03 */**	2.13±0.03 */**/ #
	CPI	1.49±0.06 *	1.27±0.02 */**/ #
	OHI-S	1.98±0.04 */**	1.45±0.03 */**/#
	W.T.C.	4.4±0.2 */**	4.3±0.1 */**
1 month after treatment	PMA	0.42±0.03 *	0.32±0.01 */**/#
	SBI	2.37±0.05 */**	1.98±0.02 */**/#
	CPI	1.46±0.03 *	1.19±0.01 */**/ #
	OHI-S	1.93±0.05 */**	1.43±0.02 */**/ #
	W.T.C.	4.0±0.2 */**	3.9±0.1 */**
Note. * - the difference is probable in comparison with the indicator in practically healthy people (p<0.05); ** - the difference is probable in comparison with the indicator before treatment (p<0.05); # - the difference is significant compared to the indicator after treatment in patients of group 1 (p<0.05).			

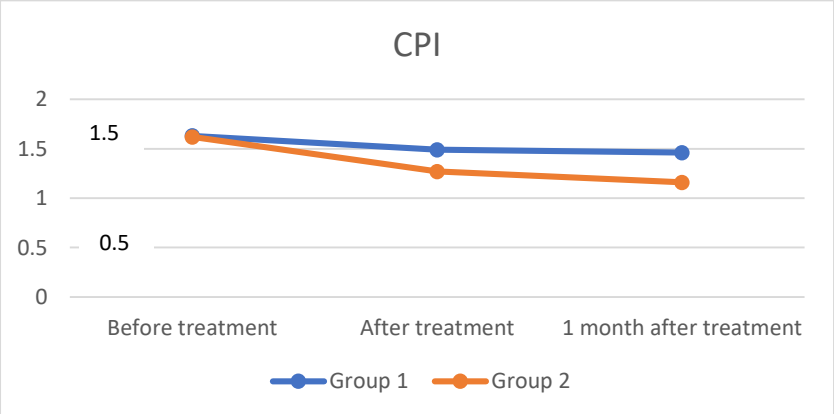

Figure 1 Indicators of the Complex periodontal index in the dynamics of treatment of periodontal diseases in patients with duodenal ulcer with existing metal and metal-ceramic dentures.

The average value of the SBI after treatment probably changed in patients of both groups: in patients of group 1 – in 1.2 times, group 2 – in 1.5 times (p1, 2 <0.05) with the maintenance of the achieved indicators during month (p=0.036). The CPI significantly increased before treatment in all patients with DU and after treatment it probably decreased only in the 2nd group: in 1.3 times with a subsequent decrease in 1.4 times one month after treatment (p=0.017) (Figure 1). That indicates on the higher anti-inflammatory action of GSH in terms of its effect on the course of PD, but in both groups, it didn't reach the normative values (p=0.031).

Increased before treatment OHI-S, which indicates unsatisfactory oral hygiene in patients with PD and DU, in the dynamics of treatment decreased probably in both groups, but in patients of group 2 more intensely – in 1.6 times versus 1.2 times in patients of the 1st group (p1,2<0.05) with stabilization at the achieved level during the month (p=0.042). W.T.C. Index, which indicated unsatisfactory hygiene of tongue before treatment, in the dynamics of treatment probably decreased in patients of the 1st and 2nd groups – in 1.6 and 1.7 times, respectively (p1,2<0.05) with no probable intergroup difference (p>0.05). Thus, the proposed therapy for PD in patients with DU with the addition of GSH and astaxanthin was more effective in terms of impact on the clinical status of periodontal tissues, than similar therapy with vitamin E, which indicates about a significant reduction in the activity of inflammation of periodontal tissues and reducing the negative impact of metal-containing dentures on periodontal status.

When using the proposed therapy with GSH and astaxanthin, we found a significant reduction in the intensity of LPO. The content of MDA after treatment in the group 2 decreased by 28.2 % compared to baseline (p=0.023), and in group 1 the content of MDA had a tendency to decrease (p=0.067) (Table 2). One month later, the results of plasma MDA in patients of the 2nd group were significantly lower (by 38.9 %, p=0.036), compared with indicator on the 30th day of treatment and the data of the 1st group (p=0.012), which indicates a stronger antioxidant effect of the combination of GSH and astaxanthin than vitamin E, which probably adjusts the oxidative-antioxidant homeostasis.

Table 2 Indicators of the intensity of lipid peroxidation, oxidative modification of proteins, endogenous intoxication and the state of antioxidant protection factors in the blood of examined patients in the dynamics of treatment (M ± m)

Term of observation	Indicators, units of measurement	Groups of examined patients	
		Group 1 (n=16)	Group 2 (n=21)
Control group	MDA, μmol/L	2.53±0.07	
	IDB, E220/ml bl.	2.62±0.03	
	GSH, mmol/L	0.93±0.01	
	SOD, un.act./1min×1gHb	3.53±0.05	
	AKDNPH AC, op.un.g/L of protein	1.37±0.02	
	MMP 254, c.un./L	0.23±0.002	
Before treatment	MDA, μmol/L	4.52±0.13 *	4.48±0.12 *
	IDB, E220/ml bl.	6.48±0.06 *	6.49±0.07 *
	GSH, mmol/L	0.53±0.01 *	0.52±0.01 *
	SOD, un.act./1min×1gHb	2.04±0.01 *	2.03±0.02 *
	AKDNPH AC, op.un.g/L of protein	2.68±0.03 *	2.70±0.02 *
	MMP 254, c.un./L	0.36±0.003 *	0.36±0.004 *
After treatment	MDA, μmol/L	4.03±0.12 *	3.23±0.18 */**/#
	IDB, E220/ml bl.	4.50±0.14 */**	3.18±0.13 **/ #
	GSH, mmol/L	0.64±0.01 */**	0.89±0.01 **/ #
	SOD, un.act./1min×1gHb	2.49±0.03 */**	2.95±0.02 */**/ #
	AKDNPH AC, op.un.g/L of protein	2.11±0.06 */**	1.72±0.04 */**/ #
	MMP 254, c.un./L	0.32±0.004 */**	0.28±0.003 */**/ #
1 month after treatment	MDA, μmol/L	3.93±0.41 *	2.75±0.15 **/#
	IDB, E220/ml bl.	4.12±0.17 */**	3.08±0.11 */**/#
	GSH, mmol/L	0.68±0.02 */**	0.92±0.01 **/ #
	SOD, un.act./1min×1gHb	2.52±0.04 */**	3.36±0.01 */**/ #
	AKDNPH AC, op.un.g/L of protein	1.93±0.09 */**	1.50±0.02 */**/ #
	MMP 254, c.un./L	0.34±0.007 *	0.27±0.002 */**/#
Notes. * - the difference is probable in comparison with the indicator in practically healthy people (p<0.05); ** - the difference is probable in comparison with the indicator before treatment (p<0.05); # - the difference is significant compared to the indicator after treatment in patients of group 1 (p<0.05)			

The content of IDB in the dynamics of treatment in patients of the 1st group decreased in 1.4 times, while in patients of the 2nd group –in 2.0

times (p1,2<0.05). One month after treatment, the content of IDB in patients of group 1 decreased compared to pre-treatment by 36.6 %, while in patients of group 2 – by 52.6 % (p1,2<0,05) compared with the indicator before treatment (p=0,033). A significant correction of the intensity of OMP processes in the dynamics of treatment was found: the content of aldehyde- ketone- dinitrophenylhydrazine of alkaline character (AKDNPH AC) in the blood probably decreased in both groups of comparison: in the 1st group – by 21.3 %, in patients of the 2nd group – by 36.3 % (p1,2 <0.05) with a significant difference between the groups (p=0.041). One month after therapy, the content of AKDNPH AC in patients of both groups continued to decline significantly: in patients of group 1 – by 28.5 %, in patients of group 2 – by 44.4 % (p1,2<0.05) with a probable difference between the groups (p=0.025).

The study of the impact of complex therapy on the state of the AODS revealed the following results. In patients of the 2nd group there was a more significant increase in the content of GSH in erythrocytes (in 1.7 times) with normalization of the indicator compared with group 1, where the indicator increased in 1.2 times (p1,2<0.05), but normative values have not been reached. One month after treatment: the content of GSH in erythrocytes was stably normalized in patients of group 2 (p=0.072) and increased compared to pre-treatment in 1.7 times (p=0.040). At the same time, in the 1st group the content of GSH in erythrocytes didn't reach the normative data (p=0.047). The activity of SOD in the blood of the examined patients was reduced before treatment, and after treatment it probably increased: in the 1st group – in 1.2 times (p=0.036), in the 2nd group – in 1.5 times (p=0.016) with a probable difference between the groups (p=0.039), but in the 1st group it didn't reach the normative values. One month after treatment, SOD activity in patients of group 1 remained at the positions reached right after the treatment (reduced in 1.2 times (p=0.043)), in patients of group 2 it increased in 1.6 times compared to pre-treatment (p=0.024). The obtained data allow us to conclude that the efficacy of complex therapy of PD in patients with DU with the inclusion of antioxidants GSH and astaxanthin is higher than the effect of natural antioxidants (vitamin E) to correct oxidative-antioxidant homeostasis at the systemic level and strengthen the natural detoxification system.

A study of the content in the blood of MMP, which is a marker of endogenous intoxication in the dynamics of treatment showed a probable decrease in the 2nd group by 22.2 % (p=0.032) against 11.1 % in the 1st group. One month after treatment, the content of MMP in the blood probably decreased only in group 2 by 25.0 % compared with pre-treatment, and in patients of group 1 the indicator returned to baseline (p>0.05). When applying the proposed therapy, we found a significant reduction in the intensity of the LPO at the local level – in the saliva (Table 3). Thus, the dynamics of the MDA content in the saliva of patients of the 1st group after of treatment indicated a tendency to decrease, but the changes were not reliable (p=0.058). In the 2nd group, the MDA content decreased in 1.5 times, compared with the initial values (p=0.038) with the presence of intergroup difference (p<0.05). On the 30th day after the end of treatment, the content of MDA in saliva of patients of the 2nd group decreased in 1.6 times (p=0.025), compared with before and after treatment, and data of the 1st group (p=0.41), where changes were not reliable (p>0.05).

Table 3 Indicators of the intensity of lipid peroxidation, the state of the antioxidant defense system in the saliva of patients in the dynamics of treatment (M±m)

Term of observation	Indicators, units of measurement	Groups of examined patients	
		Group 1 (n=16)	Group 2 (n=21)
Control group	MDA, μmol/L	1.50±0.23	
	Catalase, mmol/min × L	2.72±0.19	
Before treatment	MDA, μmol/L	4.53±0.21 *	4.55±0.17 *
	Catalase, mmol/min × L	1.36±0.07 *	1.34±0.09 *
After treatment	MDA, μmol/L	4.15±0.24 *	3.08±0.13 */**/ #
	Catalase, mmol/min × L	1.89±0.04 */**	2.37±0.03 **/ #
1 month after treatment	MDA, μmol/L	3.97±0.35 *	2.85±0.15 */**/#
	Catalase, mmol/min × L	1.96±0.15 */**	2.49±0.05 **/ #
Notes. * - the difference is probable in comparison with the indicator in practically healthy people (p<0.05); ** - the difference is probable in comparison with the indicator before treatment (p<0.05); # - the difference is significant compared to the indicator after treatment in patients of group 1 (p<0.05)			

In the dynamics of treatment, the activity of catalase in the saliva in the 1st group increased in 1.3 times, although it didn't reach the norm, and in patients of the 2nd group – increased in 1.8 times (p1,2<0.05), i.e., with the normalization of the indicator (p>0.05). It should be noted that one month after treatment, catalase activity in saliva increased in patients of both groups: respectively, in patients of group 1 – in 1.4 times, in patients of group 2 – in 1.9 times (p1,2<0.05) with a probable difference between the groups (p=0.039).

4. DISCUSSION

Several previous studies also have reported a significant intensity of the inflammatory response of the gums of patients despite the anti-inflammatory and antioxidant therapy (Lobanets et al., 2015; Shadieva and Gijazova, 2021). However, in the majority of these studies alpha tocopherol was used as a main antioxidant. Therefore, in this work we have investigated the effectiveness of the therapy with the addition of GSH and astaxanthin. The results of this study demonstrated that it was higher compared with the use of vitamin E in the intensity of the impact on the clinical manifestations of PD, the intensity of LPO, OMP and endogenous intoxication. This is confirmed by the increase in the activity of AODS factors under the influence of GSH and astaxanthin treatment in both blood and saliva.

The reduction in metabolic intoxication due to level of MMP under the influence of GSH can be explained by its systemic detoxifying effect, as it is the main subject that provides the second phase of natural detoxification of xenobiotics in the liver (Berndt and Lillig, 2017). Sulfhydryl groups of cysteines, which is part of GSH, are powerful nucleophilic agents that neutralize electrophilic attacks of free radicals of oxygen and nitrogen, chemicals, their active metabolites (Allen and Bradley, 2011). Thus, GSH protects the membranes of intracellular organelles and plasma membranes of cells against the background of active OS and prevents the process of cell damage. In addition, GSH is an agent of conjugation of endotoxins and xenobiotics, with which it forms fewer toxic compounds that are metabolized and excreted in mercapturic acids (Palathingal et al., 2022).

5. CONCLUSION

Complex therapy of patients with periodontal disease on the background of duodenal ulcer with fixed metal and metal-ceramic dentures, with the inclusion of GSH and astaxanthin for a month, helped to reduce the intensity of LPO, OMP and endotoxicosis, strengthened the activity of factors of the AODS system and the natural detoxification system – GSH and SOD in the blood and catalase in the saliva, caused a significant reduction in the activity of periodontal disease. Patients with periodontal disease and concomitant duodenal ulcers with fixed metal-containing dentures are recommended to undergo a course of treatment with a combination of L-glutathione (250 mg) and astaxanthin (40 mg) 2 times a day for 30 days 2 times a year to eliminate the oxidative effects of dentures on periodontal tissues without replacement of dentures.

Author's Contributions

Oleksandra I. Roshchuk contributed to the design, study protocol, data collection, analysis and interpretation of the result.
Vasyl P. Havaleshko contributed to thedata collection, statistical processing of material.
Yaroslav R. Karavan contributed to the data collection, drafting of the manuscript.
Oksana S. Khukhlina contributed to consultation on gastroenterology, collection of research material, reviewing and editing the manuscript.
The final version of the manuscript was approved by all authors.

Ethical approval

The study was approved by the Biomedical Ethics Commission of the Bukovinian State Medical University, Chernivtsi, Ukraine (protocol number 1, dated September 17, 2020). All studies were performed after patients have signed an informed consent for permission to participate in project.

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Conflicts of interest

The authors declare that there are no conflicts of interests.

Data and materials availability

All data associated with this study are present in the paper.

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