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Effect of cardiovascular disease and diabetes on the dental treatment

Author's abstract

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The dissertation contains 172 standard pages and is illustrated with 46 tables and 27 figures. The bibliography consists of 172 sources, of which 4 in Cyrillic and 168 in Latin.

The public defense of the dissertation will take place on 04/07/2022 at 12:00, in front of a scientific jury composed of:

Chairman:

Prof. Dr. Vladimir Panov, PhD, DSc – internal member

Members:

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The defense materials are available in the Scientific Department of MU – Varna and are published on the website of MU – Varna.

Note: The numbers of the figures and tables in the abstract do not correspond to the numbers in the thesis.

CONTENTS

ABBREVIATIONS

AH – arterial hypertension

ALT – alanine aminotransferase

Anti Xa – indicator for monitoring therapy with heparin and other low molecular weight heparin preparations

APTT – activated partial thromboplastin time

AST – aspartate aminostransferase

BH – blood pressure

Bone to implant contact – contact of the implant with bone

BOP – periodontal index

CBC – complete blood count

CBCT – cone-beam computed tompgraphy

COX-1 – cyclo-oxygenase-1

CRP – C-reactive protein

CVD – cardiovascular diseases

D-dimer – indicator of hypercoagulability and endogenous fibrinolysis

EF – the ejection fraction

F – fibrinogen

HF – heart failure

INR – internationally normalized relationship

PD – probing depth

SD – standart deviation – statistical index

SR – survival rate

TXA_2 – tromboxan A_2

WHO – World Health Organization

1. INTRODUCTION

Cardiovascular and endocrine diseases are socially important diseases and are widespread in the territory of the Republic of Bulgaria. Often cardiovascular disease is accompanied by diabetes or it manifests itself at a later stage. The risk factors for the two diseases overlap and therefore they often occur together in the same patient, in particular in patients with type 2 diabetes. Globally, there is also a widespread prevalence of both diseases, as well as their "rejuvenation". Dentists are not the specialists who deal with the actual treatment of this type of disease, but they are often the first to encounter the negative effects caused by the diseases and the medications that are taken by patients, as well as witnessing their specific oral manifestations. Dental treatment in this type of patients should be carried out in full, as in patients without common diseases. Untreated diseases in the oral cavity can lead to a deterioration in the general condition of patients, as well as to a worsening of local indicators of these diseases.

Cardiovascular disease and diabetes impair the overall health of patients. As part of the human body, the oral cavity is also affected by these diseases. Often, medications taken by patients can also make it difficult to treat patients. This can be most clearly reflected in the performance of various dental surgical and invasive manipulations.

Treatment of patients with CVD and diabetes should not be neglected. It is advisable to be carried out in full, without neglecting the patient's comfort and adequate therapy because of his underlying diseases. It is important to refine the approach to patients with this type of disease to maximize the success rate of their dental treatment.

2. AIM AND OBJECTIVES OF THE STUDY

AIM:

1. To compare the success rate of invasive dental treatment in patients with cardiovascular disease, diabetic patients and healthy subjects.

OBJECTIVES:

1. To build a profile of the patient in need of invasive dental treatment in terms of age, gender and clinical health.
2. To study the success rate of invasive treatment in healthy patients.
3. To investigate the success of invasive treatment in patients with CVD and anticoagulant/antiaggregant therapy or anticoagulant/antiaggregant therapy.
4. To investigate the success rate of invasive treatment in patients with diabetes.

3. OWN RESEARCH

3.1. MATERIAL AND METHODS

Patient selection and study design

The study included men and women divided into age groups according to WHO. Participants ranged in age from 18-44 to 75-89 years (Table 1). There are no participants in the under 18 group and none in the over 90 group. Participants with complaints of loss of one, several, or all teeth, as well as those with impending loss of one, several, or all teeth, those who are to have missing teeth in the tooth row restored with implants, and those who are to have invasive dental treatment were selected. Persons with mental illness are not included.

Table 1: Patient demographics

Age	Male	Female
18-44	**7**	**9**
45-59	**7**	**7**
60-74	**5**	**5**
75-89	**1**	**1**
90+	**0**	**0**

Patients were divided into three conditional groups - clinically healthy, patients with CVD taking antiaggregants or anticoagulants, and diabetics. Those who are clinically healthy are considered to be free of comorbidities (detected earlier or before the interventions) and are not taking medication systematically - they are controls.

Patients were examined and treated between 2018 and 2021, and the total number of invasive manipulations performed was 325 (Table 2).

Table 2: Delivery of invasive manipulations in different age groups

Age	Male	Female
18-44	**49**	**31**
45-59	**83**	**53**
60-74	**36**	**49**
75-89	**6**	**18**
90+	**0**	**0**

Everyone has a detailed history. If necessary, blood tests have been performed before and after surgical treatment with any of the above manipulations, restoration with prosthetic structures and monitoring over time.

The data from the anamnesis of all surveyed were recorded personally by us on a specially created map (Appendix 1).

In the clinical examination, **we examined the oral status** with a focus on dental rows, extracted teeth, teeth to be extracted, bone and soft tissue defects. The subject of the study is also the future protematic recovery of the sick. It is important to take into account the correct choice of dental implants and the accompanying procedures in order to ensure the durability of the treatment carried out.

We performed radiographic studies – sectoral graphs, orthopantographs or CBCT studies. Data from them and the clinical review we noted on a created clinical map (Appendix 2). Participants were also given 5 ml of venous blood. Blood sampling is carried out according to the instructions of the Ministry of

Health with individual sterile closed system Vascular. In vitro determination of CBC, AST, ALT, INR, CRP and other specific indicators of the disease, or those provoked by taking medications in a certified laboratory for blood tests, was performed on the blood samples taken by patients.

Each of the persons surveyed **signed** an informed consent to participate in the survey (Appendix 3).

In advance, each patient was **provided** with written instruction for the purposes and methods of the study (Appendix 4).

3.1.1. Material and methods for task 1: To build a profile of the patient in need of invasive dental treatment in terms of age, gender and clinical health

This was the largest group of patients in the study. After signing an informed consent, they underwent the entire set of paraclinical examinations required before starting treatment of such patients. If necessary, consultations with other specialists were made and treatment medication was adjusted. This group includes patients who take daily medication to treat a particular disease, as well as those who do not have inherited and acquired diseases and do not regularly take medication for a particular reason. All are treated by various invasive manipulations. If necessary, during or after the manipulations, an immediate X-ray control of the results is performed. The resulting surgical wounds are sutured and, if necessary, local haemostatic agents are placed. The sewing material most commonly used is 5/0, non-cutting, monofilament thread with 3/8 reverse cutting, 16mm. needle. Patients are followed up in the postoperative period for complications (early and late). The recovery times are compared with the data in the literature - from 1 to 6 months according to the type of treatment performed. In implant treatment, cases without complications are defined as those in which the placed implants are loaded with prosthetic constructs after the normal period of osseointegration without causing

functional and health disturbances. The other manipulations are tracked for different periods of time depending on their type - from 14 days to 6 months. In order for the results of the research to be objective, a standard treatment protocol is followed so as not to favour any of the treatment groups.

3.1.2. Material and methods for task 2: To investigate the success rate of invasive treatment in healthy patients

Under task 2, patients undergo various invasive manipulations. These are only the patients without concomitant diseases. These patients also serve as a "reference point" for treatment success rates for the research study. No circumstances of a general nature are expected to lead to a change in the success of invasive treatment.

In addition to the follow-up of patients after invasive treatment, a detailed analysis of blood tests was performed.

3.1.3. Material and Methods for Task 3: To investigate the success of invasive treatment in patients with CVD and anticoagulant/antiaggregant therapy or anticoagulant/antiaggregant therapy

In task 3, the same type of invasive manipulations are again performed as in the patients in task 2. The difference is that patients who suffer from CVD and take antithrombotic or anticoagulant medication fall into this group. According to the therapy in these patients, various modern treatment approaches are considered and their success rates are reported.

As in Task 2, patients' blood counts are reported in detail. Some of the indicators are examined according to the type of antithrombotic or anticoagulant medication taken.

3.1.4. Material and methods for task 4: To investigate the success of invasive treatment in patients with diabetes

In task 4, the same type of invasive manipulations are again performed as in patients in tasks 2 and 3. The difference is that patients who suffer from type 2 diabetes fall into this group. According to the therapy in these patients, various modern treatment approaches are considered and their success rates are reported.

Statistical processing of the data

For statistical processing of the data we used the Excel program, and $p<0.05$ was chosen as the significance level at which the null hypothesis was rejected.

- The first phase of the statistical survey consists in a descriptive analysis of all variables.
- The next step is a comparison of the continuous variables in terms of a definite variable for both population groups (patients with accompanying diseases and control group)
- **Graphical analysis** – for image visualization (MicrosoftExcel)• **Alternative analysis –** for reconciliation of dimensions and calculation of percentages
- **Correlation analysis –** to assess the presence of a linear relationship between quantitative signs; a correlation coefficient of variables and unchanged dimensions is calculated.
- **Variation analysis –** for calculation of standard deviation
- Determination of arithmetic mean dimensions, standard deviations, presentation error
- Variables are compared as a percentage.

3.2. RESULTS AND DISCUSSION

3.2.1. Results and discussion of task 1: To build a profile of the patient in need of invasive dental treatment in terms of age, gender and clinical health

Task 1 included 42 patients who underwent invasive dental treatment. Twenty-two (22) of the participants were female, 20 were male. Women predominate, but the difference is not statistically significant (Fig. 1)

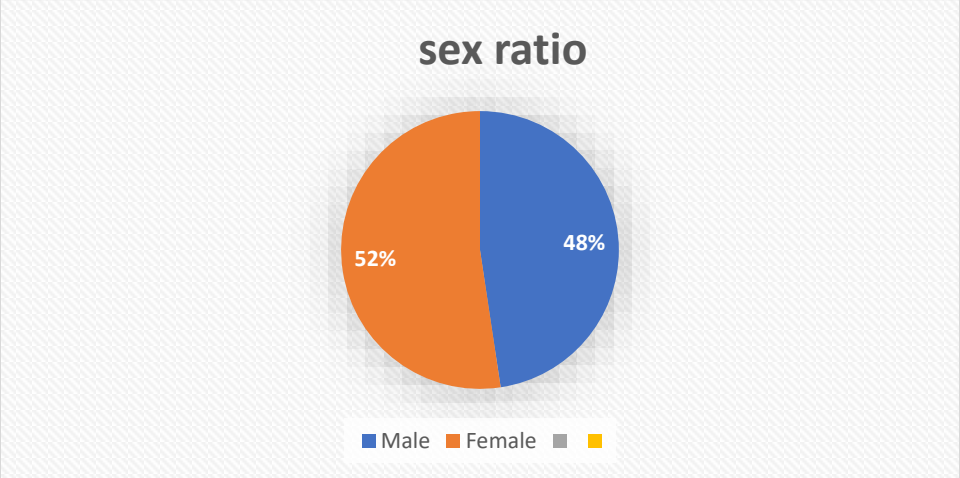

Figure 1: Sex ratio between men and women in the research

In the research study, 13 out of 20 men had 1 or more implants - that's 65% of the men. The remaining 35% underwent only other types of invasive manipulations (extractions, incisions, bone replacement, periodontal surgery, etc.) (Fig. 2). In the group of women, 63.6% of them (14) had implants placed and 36.4% had only other invasive manipulations (Fig. 2). This distribution is similar to the male distribution.

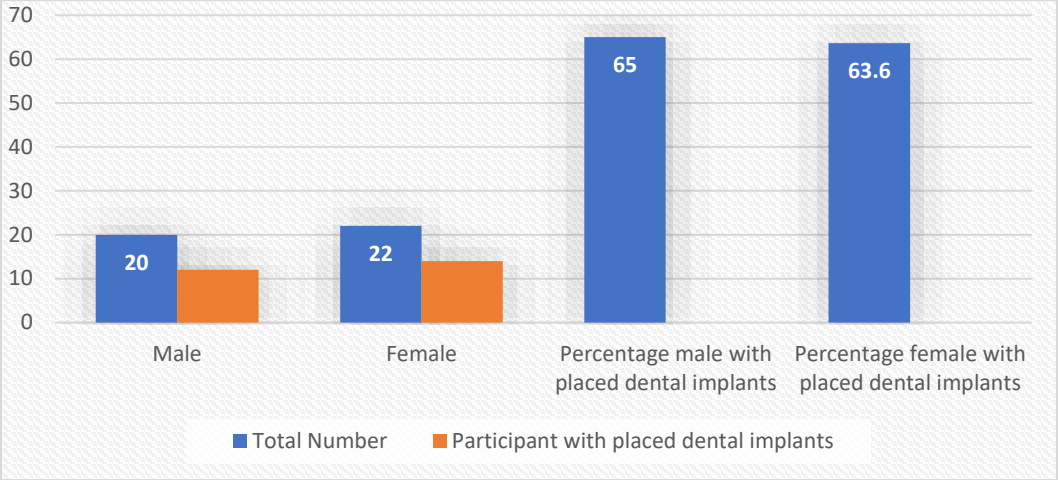

Figure 2: Implants placed by sex and percentage

The results showed that invasive manipulations were performed in 19 of the men (95%) (Fig. 3). The number of women who underwent invasive manipulation was also 19, but with the higher number in the study, this was 86.3% of them (Fig. 3)

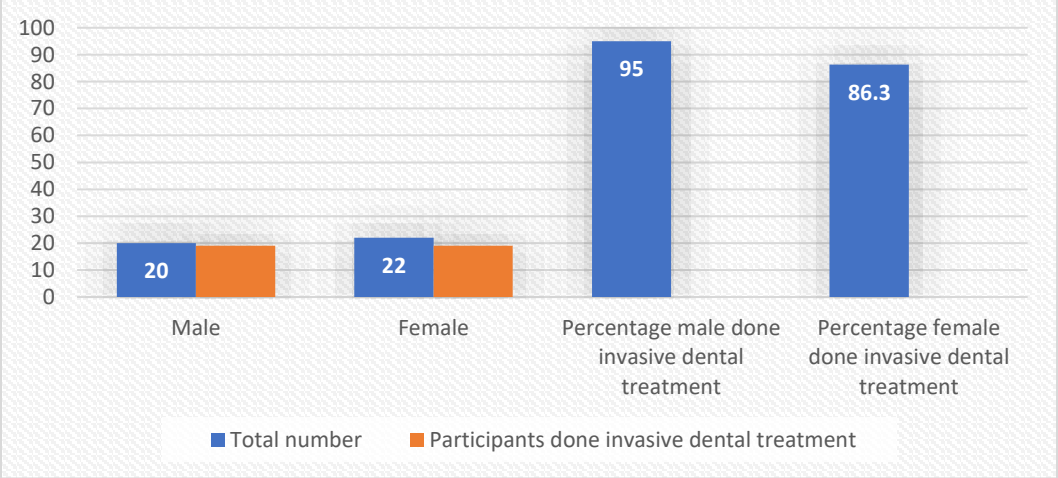

Figure 3 Invasive manipulations performed by sex and percentage

All patients in Task 1 were divided into five subgroups according to their age and general medical status (Table 3), consistent with WHO. The group of children and young people up to 18 years of age are not exposed in the statistics for

objective reasons. As can be inferred from the schematized data in the table, patients older than 89 years did not participate in the research study.

Table 3: Age-sex distribution of patients in the study

Age	Male		Fenale	
	Healthy	With accompanying. diseases	Healthy	With accompanying. diseases
18-44	**7**	**0**	**6**	**3**
45-59	**1**	**6**	**3**	**4**
60-74	**0**	**5**	**0**	**5**
75-89	**0**	**1**	**0**	**1**

Figure 4 shows the gender distribution of patients in the different age groups.

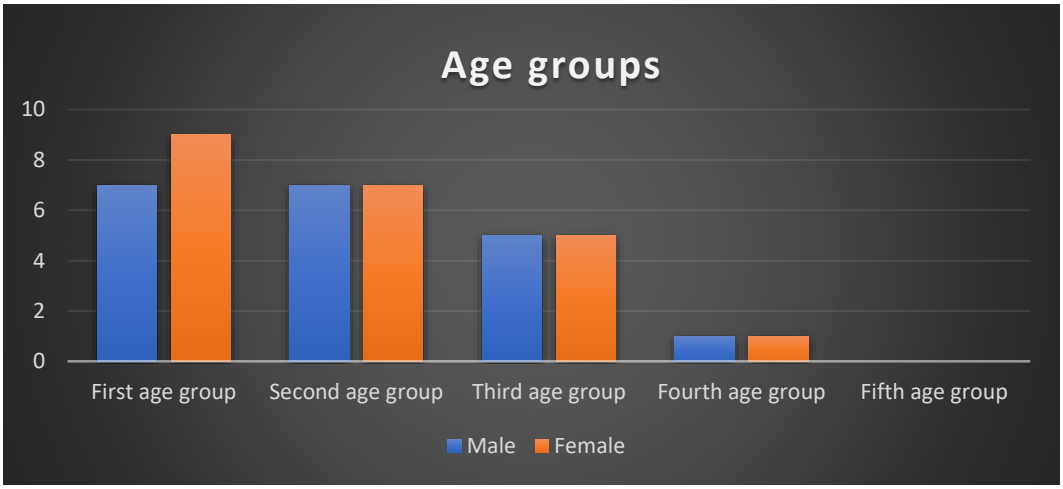

Figure 4: Graphical representation of the number of participants, disaggregated by gender and age

Different numbers of invasive dental manipulations were performed on the included patients. Most implants were placed in men in the second age group - 44

pieces, followed by women in the third age group - 21, men in the third age group - 20, men in the first age group - 13, women in the second and fourth age groups - 12, and women in the first age group - 7 (Fig. 5).

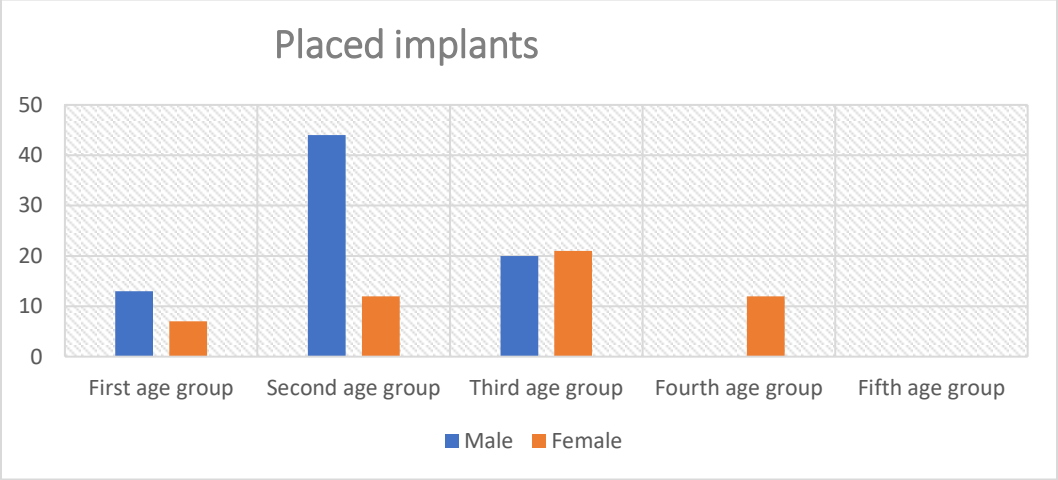

Figure 5: Graphical expression of implant placement in different age and sex groups

Most other invasive manipulations were performed on women in the 44-59 age group - 41 in total. (Fig. 6).

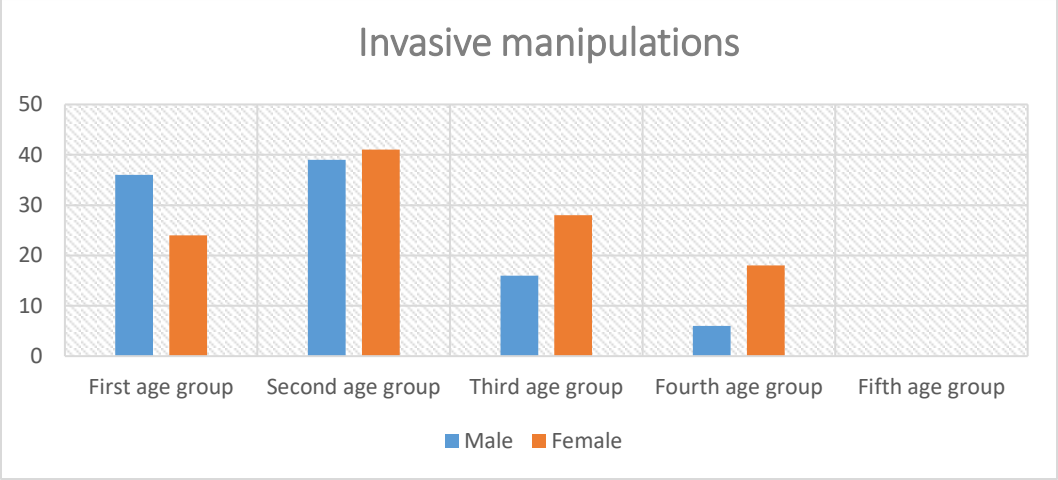

Figure 6: Graphical expression of invasive manipulations performed in different age and sex groups

Participants in the third and fourth age groups who received one or more dental implants were found to have comorbidities, regardless of their gender (Table 4). In the first age group, the number of healthy participants was significant as a proportion - 100% for men and 87.5% for women; in the second age group, 25% of participants were observed in women without concomitant diseases.

Table 4: Age group distribution of participants without concomitant dental implant disease

Age	Male	Female
18-44	**100%**	**87,5%**
45-59	**0%**	**25%**
60-74	**0%**	**0%**
75-89	**0%**	**0%**

Data for patients with other invasive manipulations were similar to those for participants who had implants. (Table 5).

Table 5: Age distribution of participants without concomitant dental implant disease

Age	Male	Female
18-44	**100%**	**70,8%**
45-59	**5%**	**14,6%**
60-74	**0%**	**0%**
75-89	**0%**	**0%**

Blood tests were performed on the study participants. This is a good approach to preventing complications at work from "hidden" diseases or conditions. After analyzing the results, the following patterns were found and presented in Table 6. The reference values are also presented for better overview and easy comparability.

Table 6: Blood values in study subjects

	Leu.	Ery.	Pl.	Hem.	AST	ALT	Gl.	INR
Reference values	4.5 – 10.5	3.5 – 5.5	150 – 450	120 – 180	<37	<41	<6.4	<1.2
Average values	8.36	4.86	258.54	143.18	21.38	20.25	5.73	1.045
SD	1.83	0.49	56.52	15.45	5.09	7.56	0.76	0.06

We also present the values of blood indices by age groups for both sexes (Fig. 7, 8, 9, 10).

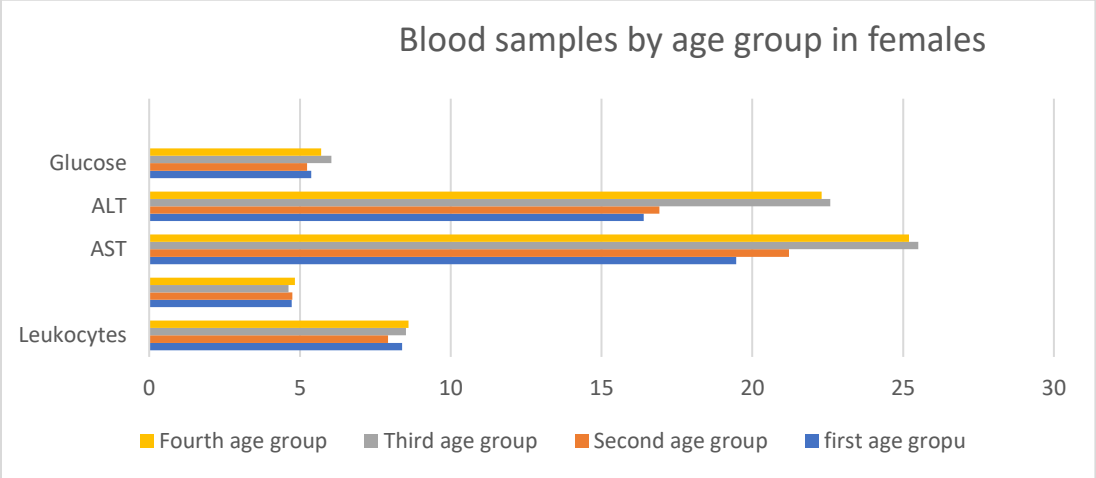

Figure 7: Alteration of glucose, ALT, AST, erythrocytes and leukocytes in women

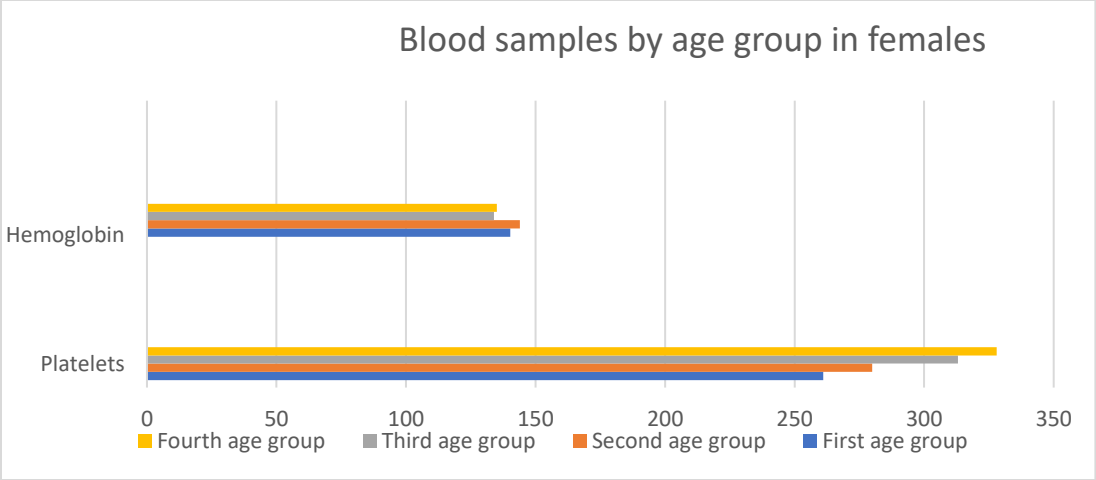

Figure 8: Alteration of hemoglobin and platelets in women

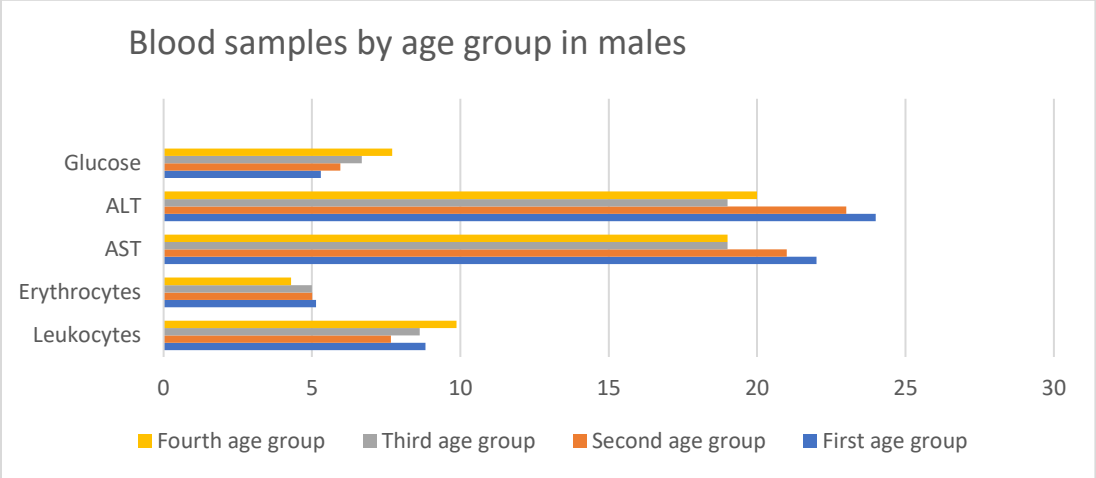

Figure 9: Alteration of glucose, ALT, AST, erythrocytes and leukocytes in men

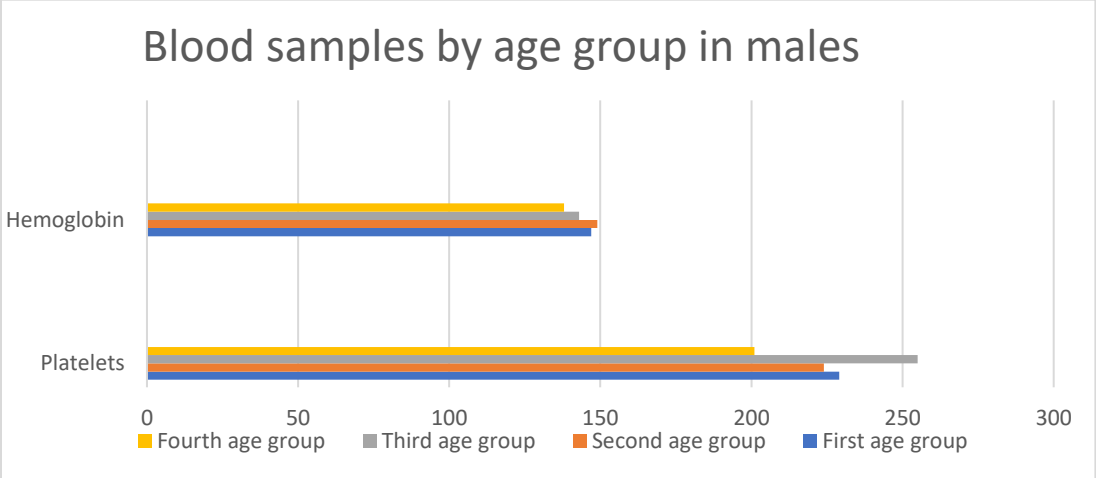

Figure 10: Change in haemoglobin and platelets in men

Analysis of the result of task 1. From the data collected in the scientific study, it should be established that the number of men and women in need of invasive dental treatment is approximately equal. Approximately the same are the data for the population of Bulgaria as of 2022 – 48.3% men and 51.7% women. It can be concluded that the scientific study is presentational to this criterion.

From a statistical point of view, both sexes need approximately the same invasive dental procedures, yet it is slightly more likely to be performed on a woman.

From the data it should be concluded that patients without concomitant diseases are mainly those of the first age group, regardless of their sex. The number of "healthy" patients decreased significantly in the second age group, and in the third and fourth all participants had comorbidities. Of all participants, only 38% were in the first age group. Taking into account that 100% of patients without concomitant therapy are not seen in women in the first age group, it should be considered that at least 2/3 of patients who require invasive dental treatment have one or more concomitant diseases. This requires the constant updating of treatment approaches in line with modern guidelines.

- The highest number of dental implants was placed in the second age group in males - an average of 6. 3 implants per participant. Most invasive manipulations were performed on women in the second age group - 5.85 per participant.
- From a statistical point of view, patients in the 45-59 age group undergo invasive dental treatment most often, with an approximately equal sex ratio (women are about 4% more). But, in this age group, the number of patients with comorbidities significantly outweighs that of healthy patients. If a

statistical profile of a patient in need of invasive dental treatment were to be created, it would look like this:

- **A patient aged between 45-59 years with an accompanying disease, slightly more likely to be female..**

From the examined blood pictures of the patients, it is found that they are within the reference values for the individual blood parameters and we can conclude that this is a representative sample of the community. Patient averages for erythrocytes and hemoglobin were higher in men compared to those in women. This is normal in view of the anatomical-physiological features of the human organism. Blood glucose values were relatively elevated in the participants, especially in males at 5.99 (vs. normal of 5.5). The participants in this study cannot be taken as a representative sample of the Bulgarian society, because this would mean that every Bulgarian over 18 years of age is in a pre-diabetic state or an early form of diabetes. The elevated blood sugar levels were attributed to the diabetics included in the study. The discrepancy in blood glucose values between men and women was due to the unequal distribution of participants with diabetes in the two groups and the different severity of the disease itself. The values of AST and ALT were normal in both groups (men and women) - therefore, the hepatic function of the study participants was normal and normal levels of coagulation factors were expected. With these indicators, it should be said that any hemorrhages resulting from invasive interventions are due to the medications taken or an inappropriate treatment approach, not to reduced production of clotting factors. Patients' blood counts were divided by gender and age groups. Thus, the dynamics of blood indicators in different age groups can be traced. We also compare the different trends in men and women:

The number of leukocytes in men and women remains relatively unchanged in the four age groups – no different immune response to the treatment carried out is expected in different age groups.

- The number of erythrocytes does not change significantly in different age groups – this is also the expectation in a normal process of hematopoiesis and an adequate diet.
- The number of platelets in men remains unchanged in different age groups, and women tend to increase values, leaving them within the reference values for the blood laboratories concerned. In patients with GPA and taking antithrombotic or anticoagulant therapy, normal platelet counts in all age groups give a clear sign that these drugs do not lead to a serious change in platelet count. This proves the need for an individual approach in different groups of patients, so as not to miss important hemostatic indicators. Hemoglobin values remain unchanged in different age groups, which corresponds to erythrocyte levels.
- AST and ALT values tend to increase slightly in the age groups in women and in men for a slight decline, but the changes are not significant and this speaks to unchanged liver function and the same hepatic response in patients of a given therapy and "healthy".
- Both men and women tend to increase blood sugar levels in age groups. This is characteristic of the type of scientific examination, as well as the nature of the disease. In patients of higher age groups, it is advisable to screen for diabetes in order to prevent future complications.

3.2.2. Results and discussion of task 2: To investigate the success rate of invasive treatment in healthy patients

In Task 2, 83 manipulations were performed on 22 healthy control patients who reported no chronic diseases, such as systemic medication intake.

These 83 invasive manipulations (extractions, incisions, periodontal surgery, implant placement, bone replacement, etc.) accounted for approximately 25% of all 325 manipulations in the study. They were performed on patients in the first and second age groups (individuals aged 18 to 59 years), as no participants without comorbidities were identified in the third and fourth age groups. In terms of gender, 51 of the manipulations were performed on men and 32 on women (Fig. 11) .

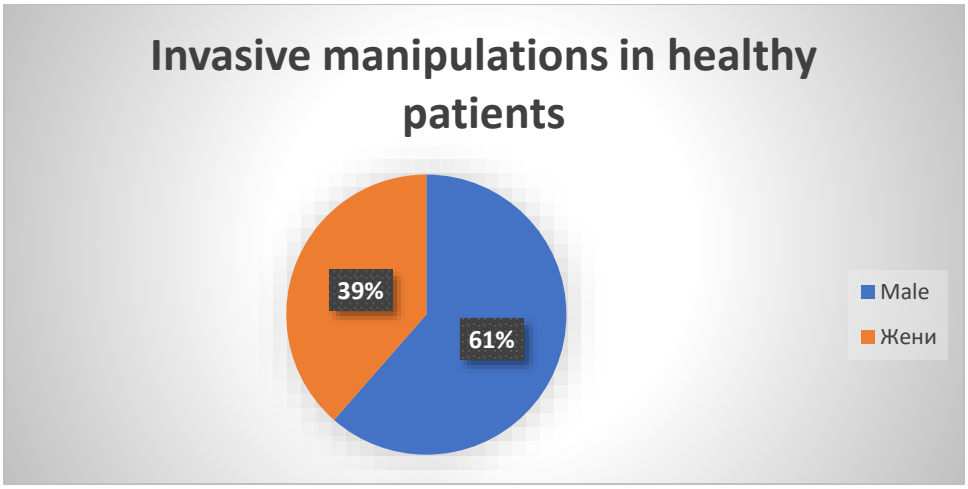

Figure 11: Percentage of manipulations in men and women

The specificity of the analysis of the results necessitates the precise grouping of the data according to the age group of the participants. In males, it was found that 49 out of 51 manipulations were performed on participants in the first age group (Fig. 12).

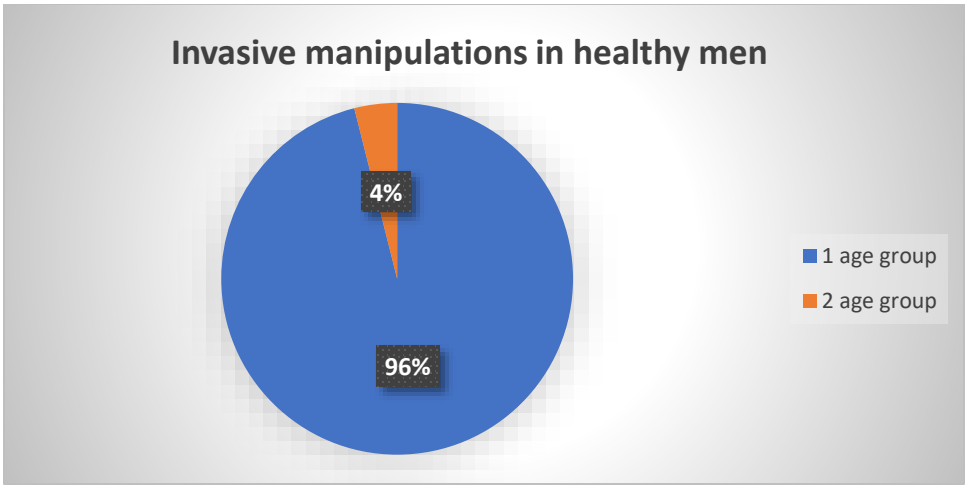

Figure 12: Percentage of invasive manipulations performed in healthy men across age groups

In ladies, 23 out of 32 manipulations were performed on participants in the first age group (Fig. 13). Overall, 86.7% of all manipulations were performed on patients aged 18 to 44 years.

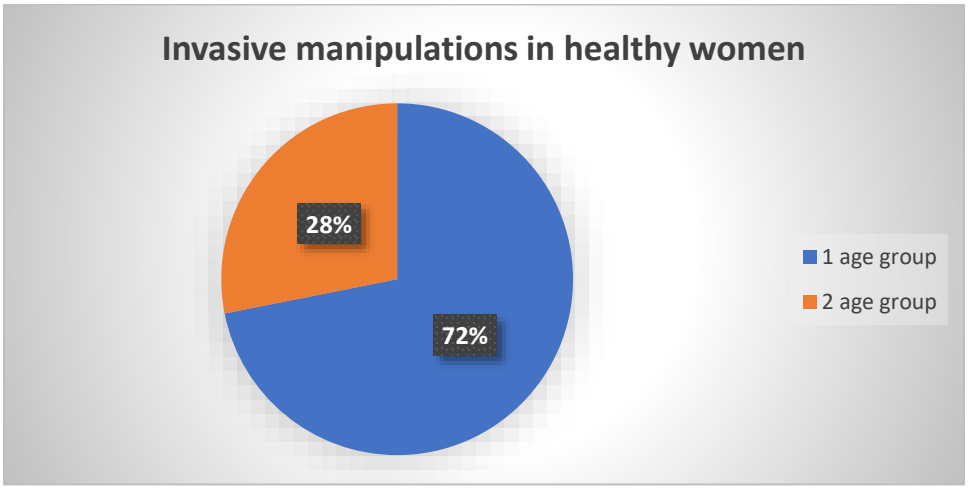

Figure 13: Percentage of invasive procedures performed in healthy women across age groups

A total of 22 implants have been inserted for task 2. During the early postoperative period, normal healing is observed in all of them, without objective and subjective evidence of violation of the natural restoration of periimplant tissues

– this is a 100% success rate. In no implant, inflammation and delayed healing period are observed. This allows for load with prosthetic structures.

Of all implants given to patients on task 2, 13 were given to men (59%) and 9 to women (41%).

The breakdown by age group shows that in men 100% of the implants placed were in the first age group (patients 18 to 45 years). For women, the distribution structure was heterogeneous, with 6 cases (66.6%) placed in women in the first age group and 3 in the second age group (33.3%).

Of all implants placed in Task 2, approximately 59% were those of males in the first age group, 27% of females in the first age group, and 14% of females in the second age group (Fig. 14).

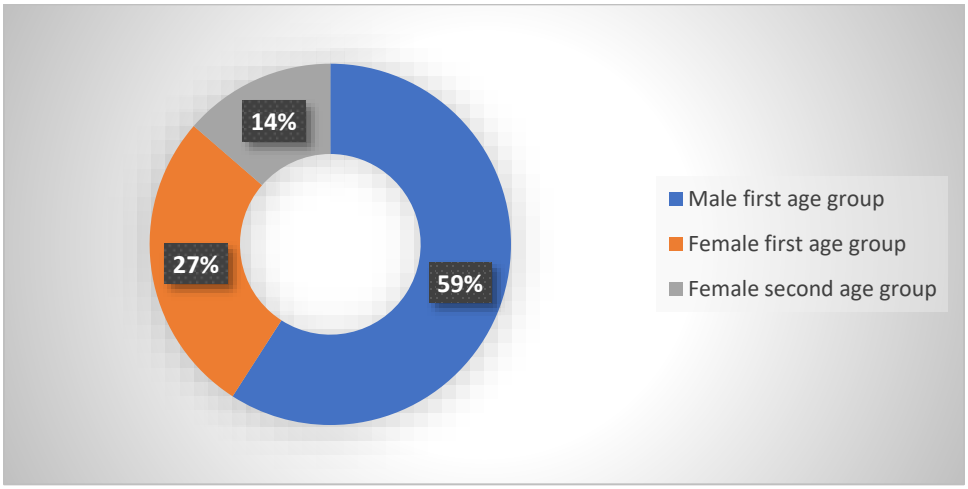

Figure 14: Percentage distribution of implants placed in Task 2 by age group and sex

On task 2, a total of 61 invasive manipulations of another type were performed. Of these, 59 went with a normal healing period – that's 96.7% of surgical manipulations with normal recovery. In a total of 3.4% of cases (these are 5% of manipulations in men) there was a modified recovery period (Fig. 15).

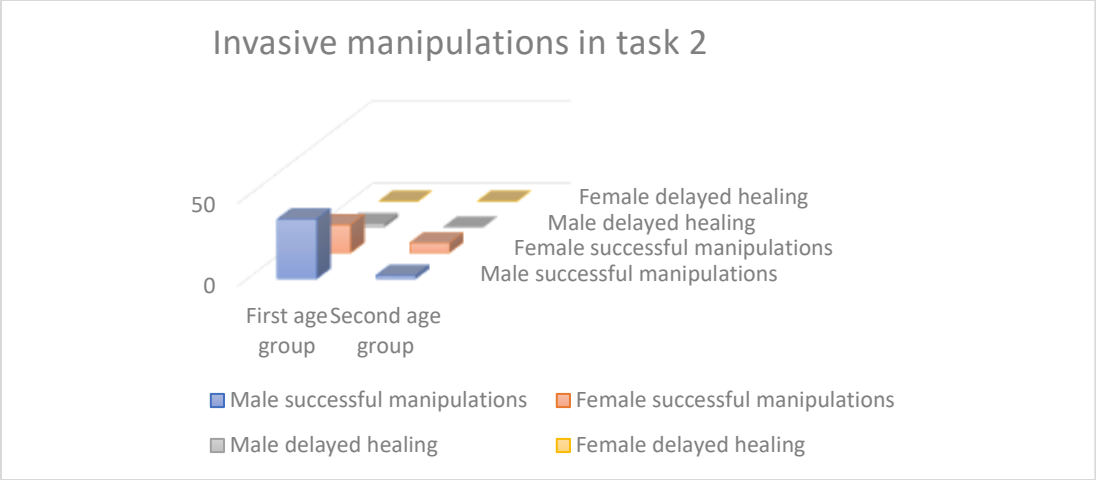

Figure 15: Invasive manipulation success rates, stratified by sex and age group

Blood tests were conducted on the control group of patients without association diseases under Task 2. The following results, presented in Table 7, can be derived from them.

Table 7: Average values of blood parameters of patients in task 2

	Leu.	Ery.	Pl.	Hem.	AST	ALT	Gl.	INR
Average values	8.19	4.97	241.13	144.35	21.97	20.72	5.32	1.05
SD	1.95	0.47	39.93	12.24	3.77	7.48	0.47	0.06
Reference values	4.5 – 10.5	3.5 – 5.5	150 – 450	120 – 180	<37	<41	<6.4	<1.2

These same values are presented in comparison to the data for the entire study group in Figure 16 - the data have similar characteristics:

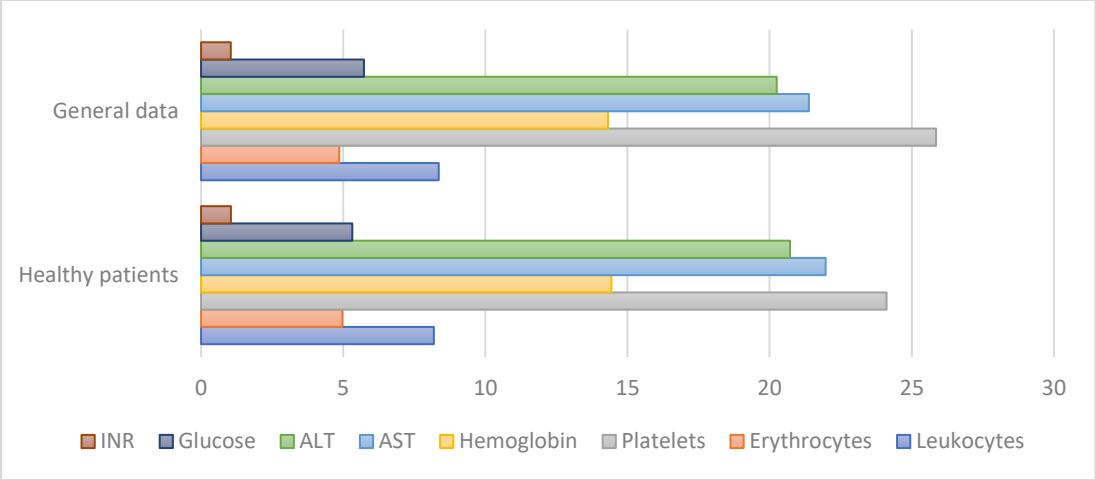

Figure 16: Comparative presentation of blood test results

(Note.: For clarity of the data in Figure 17, platelet and hemoglobin results are reduced 10-fold in both groups)

Analysis of the results of task 2

From the data submitted, it should be established that a total of 83 dental-surgical manipulations related to tissue integrity injury were performed under Task 2. Of these, 26.5% were related to the placement of dental implants and 73.5% to other invasive manipulations. Implant cases have a 100% success rate versus early complications, as well as a 100% prosthetic load.

Patients on this task are "healthy control individuals", without accompanying diseases and systemic intake of medications. They are representatives of the first and second age groups. The majority of manipulations were performed on patients in the first age group (86.7%).

Relative to the success rate of treatment in patients from Task 2, there was a 100% success rate in implantological treatment and 96.7% in other invasive manipulations (95% in men and 100% in women).

Compared to literary data, a 100% success rate in the treatment of patients with dental implants is slightly higher, but this is related to the smaller number of

patients on whom the scientific study was conducted. A success rate of over 95% can be compared with similar results in identical scientific studies as well as in larger studies. The success rate of 96.7% for the remaining surgical manipulations is comparable to literature data.

An overall treatment success rate of 97.5% can be reported in healthy patients, which is similar to that of the literature data.

The following patterns can be deduced from the results of the blood tests:

1. The mean blood values for this statistical group of the study provide no information about the presence of a disease or process leading to a change in the reference values of the individuals studied. Based on these, it can be considered that these patients can be defined as "healthy", as they are referred to in the study.
2. The presence of normal values of INR, AST, ALT serves as a prerequisite for a normal blood coagulation process, which is key for a smooth postoperative period in invasive interventions, as well as for the smooth surgical activity itself.
3. The presence of normal values in the blood counts of these patients may define them as a control group of healthy patients and, as such, serve as a comparison with the groups of patients with CVD and diabetes in Tasks 3 and 4.
4. Comparing the blood parameters of the patients in task 2 with those of the patients in task 1 resulted in a statistically significant difference in the mean values of the diabetic patients. This is an expected phenomenon, as Task 1 also included patients with diabetes.
5. The blood parameters of patients in task 2 are a prerequisite for a good healing process in any type of manipulation. The acute performance of any

dental manipulation in this group of patients should lead to comparability with the literature for the type of intervention performed.

3.2.3. Results and discussion on Task 3: Study the success rate of invasive treatment in patients with GS and anticoagulant/antiaggregant therapy or anticoagulant/antiaggregant therapy.

In task 3, 216 manipulations were carried out on 20 patients with CVD who were systematically taking an antithrombotic or anticoagulant drug – implantation and other invasive manipulations.

The results will be considered for patients on therapy with platelet antiaggregants, as well as direct, and indirect anticoagulants.

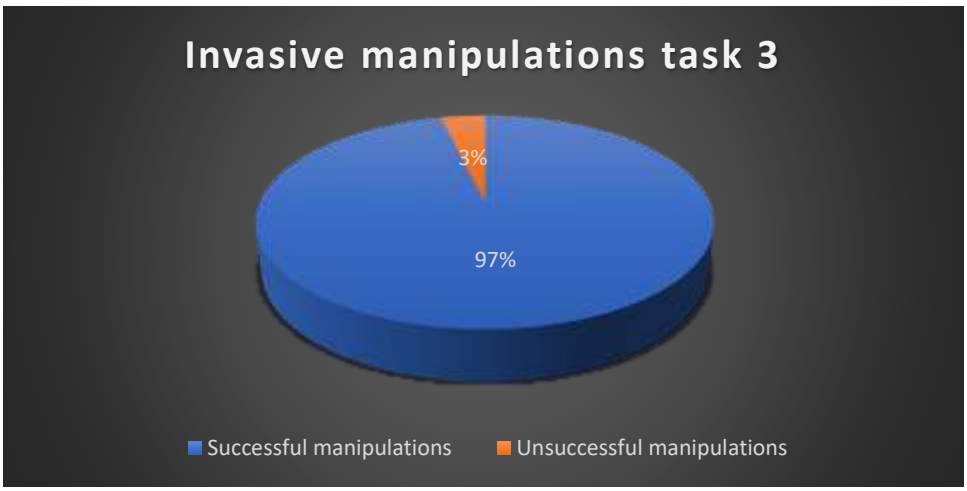

Figure 17: Percentage of successful and unsuccessful invasive manipulations under Task 3

In 8 (3.38%) of all 216 manipulations, inflammation and an incorrect healing process were observed. These cases may be considered unsuccessful (Fig. 17). In the remaining 96.62% there were no signs of inflammation or delayed recovery

and they were marked as successful.A total of 95 implants were placed in Task 3. During the early postoperative period, 92 of them (96.85%) showed normal healing, with no evidence of disruption of natural peri-implant tissue repair. Complications occurred in 3.15% of patients (Fig 18). The data for implant treatment in patients with cardiovascular disease are identical to those of the general group of invasive manipulations in the same patients.

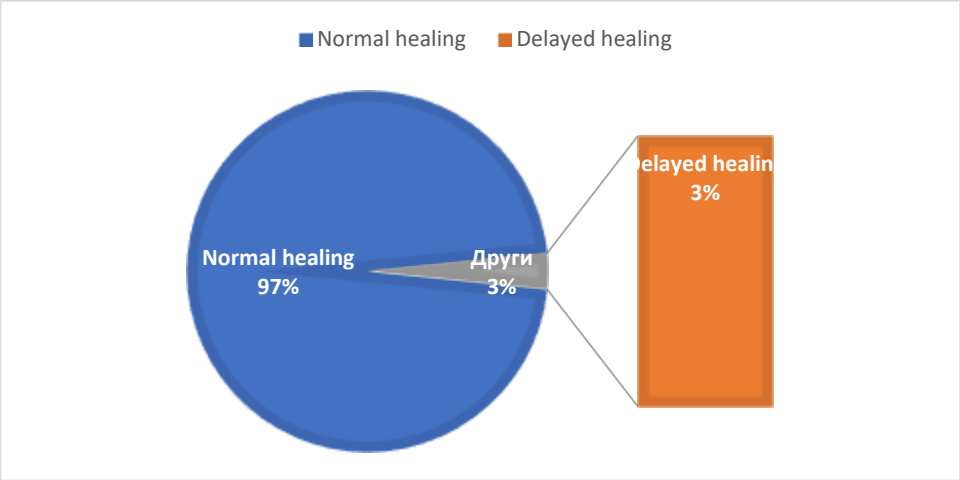

Figure 18: Percentage of healing time of implant-treated patients in task 3

A total of 121 other manipulations were performed on task 3. In 116, normal healing process was observed, while in the remaining 5 - inflammation and delayed recovery.

From Figure 19, it should be found that 95.87% of the participants did not show any disruption in the recovery process and the patients' invasive manipulations were performed without complications. Complications in the healing period were observed in 4.13% of the performed manipulations.

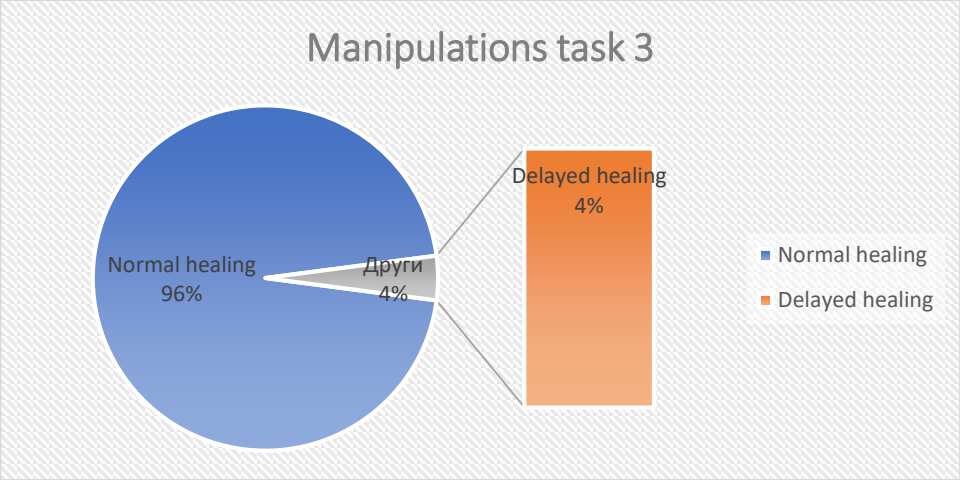

Figure 19: Percentage of healing time of other invasive manipulations in task 3

In 96.8% of implants placed in patients with CVD, successful osseointegration was found and they could be loaded with prosthetic constructs. The proportion of implants dropped in Task 3 coincides with the number of implants that developed early complications.

From the results obtained in task 3, a success rate in patients with CVD and antithrombotic or anticoagulant therapy of 96.3% should be found as follows:

- implant placement success rate 96.8% - 97.1% in men and 94.8% in women,
- overall success rate in surgical manipulations 95.87% - 96.4% in men and 93.8% in women.The age distribution in Task 3 differs strongly from the data in Task 2.

Here, invasive manipulations were mainly performed in the second, third and fourth age groups. The distribution is characteristic, related to the nature of CVD development. Figure 20 visualizes the distribution of patients by age group and sex. The predominant number of manipulations of patients in the second and

third age groups is seen. The presence of female patients in the first age group may indicate that they eliminate their health problems earlier and in a timely manner.

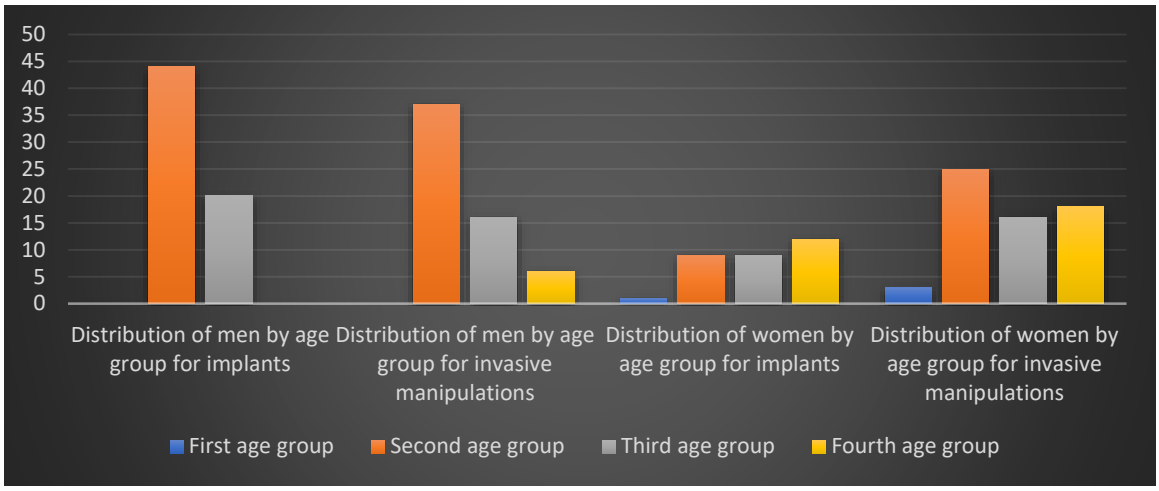

Figure 20: Distribution of patients by age group and sex

For the purpose of the scientific work, statistical models were built to compare the number of complications and the success rate of treatment versus anticoagulant therapy in patients.

Model: The total number of failed manipulations is thought to be determined by anticoagulant therapy. "A" is the selected dependent variable and represents the number of failed manipulations. The independent variable is "A1", which indicates the health status of patients. The data series includes 42 values corresponding to the independent variable. A linear regression model was constructed with one independent variable, β2, representing the parameters of the regression model and εi the residual. The linear regression equation is as follows:

$$\log(A) = \beta_1 + \beta_2 * \log(A2) + \varepsilon_i.$$

The regression coefficient was not statistically significant - Sig > 0.05. Consequently, there is no regular statistical correlation between anticoagulant therapy of patients and the success rate of manipulations.

There is also a lack of correlation between patients' anticoagulant therapy and manipulation complications.

Blood tests were performed on patients in task 3. From these, the following results can be derived, presented in Table 8.

Table 8: Mean values of patients' blood parameters in task 3

	Leu.	Ery.	Pl.	Hem.	AST	AlT	Gl.	INR
Average values	8.24	4.38	260.5	143.5	20.5	18.8	6	1.05
SD	1.48	0.47	56.23	16.39	5.26	5.98	0.84	0.05
Reference values	4.5 – 10.5	3.5 – 5.5	150 – 450	120 – 180	<37	<41	<6.4	<1.2

These same values are presented in comparison to the data for the entire study group and the healthy group in Figure 21 - the data have similar characteristics.

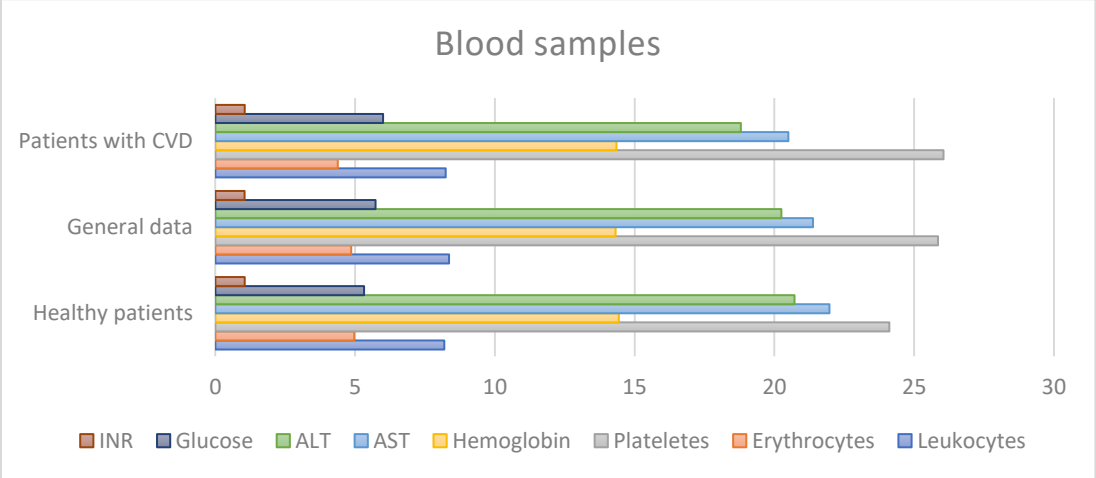

Figure 21: Comparative presentation of blood test results

(Note.: For clarity of the data in the figure, the platelet and haemoglobin results are reduced 10-fold in all three groups)

Taking so many different medications can potentially lead to a risk to patients. The purpose of the scientific study is to track treatment in this type of patient. In a consideration before the treatment is carried out, blood indicators also enter. They are essential for planning the volume of interventions carried out, both for detecting "hidden" diseases. For the purposes of the study, regression models are set, which take into account the dependence of leukocytes, erythrocytes, platelets, hemoglobin, AST, ALT, blood sugar, INR from the presence of CVD. All acknowledge that there is no consequential statistical correlation between patients' CVD and those indicators.

The assessment of the risk of bleeding and, accordingly, of thrombus formation should also be carried out with specific blood tests.

In therapy with Fraxiparine for an extended period of time, the indicators of hemostasis are monitored in order to achieve optimal dosing of the preparation. A change is only registered in the Anti Xa factor, which is specific to treatment with fraxiparin. Other indicators such as APTT, prothrombin time and INR remain at normal values, therefore not sufficiently informative in this case.

When treated with aspirin, bleeding time, prothrombin time, INR, APTT, D-dimer and fibrinogen can be studied. D-dimer is the most telling in this case.

Analysis of task results 3

In task 3, a total of 216 manipulations were performed on patients on platelet antiaggregant and anticoagulant therapy. The higher number of participants in the second, third, and fourth age groups on Task 2 is typical of the type of disease being studied on Task 3. No case of severe postoperative bleeding requiring further wound management was found in these patients.It is important to mention that

preoperatively blood pressure levels were strictly monitored and if necessary patients were referred to their attending physician for adjustment of therapy. Often the treatment of AH in incomplete volume and the maintenance of high blood pressure values may be the reason for the more difficult control of intra- or postoperative bleeding, which on the background of antithrombotic or anticoagulant therapy occurs with even more effort. Therefore, it is important to examine patients carefully before performing invasive manipulations and to consult other specialists if necessary. Other important criteria for the ultimate success of treatment are adherence to surgical protocols and proper determination of surgical volume in order to make the best decision to stop, modify, or continue antithrombotic or anticoagulant therapy. The determination of the operative volume should be in accordance with the principles of oral surgery.

The results of Task 3 clearly show that modern trends in working in patients of antiaggregant and anticoagulant therapy can be successfully administered in invasive dental treatment, without changing the results in patients. To confirm this and because of the relatively small volume of scientific research, it is necessary to apply our treatment approach to larger groups of the population.

It is important to mention that modern methods of anticoagulant therapy are not applied in patients with high surgical volume. Further studies need to be carried out.

From the results obtained in the blood tests carried out in this group, the following regularities can be derived:

1. Patients with CVD and antithrombotic or anticoagulant therapy have normal leukocyte values that are not significantly different from those of "healthy"

controls. Therefore, the same immune response is expected as in "healthy" patients.

2. Patients on task 3 had normal erythrocyte and hemoglobin values. We can conclude that they do not have impaired hematopoiesis function and no internal bleeding due to medications. Normal platelet counts in the systemic circulation were found in patients in task
3. The regression analysis showed no difference in the values of patients in task 3, i. e. they were similar to the data in healthy patients. This, together with the normal INR values, gives reason to believe that blood clotting in this type of patients is similar to that in "healthy" patients, which is not true and will be commented further.
4. AST and ALT values are normal in task 3 patients. No statistically significant difference in data was found in the regression analysis. It can be concluded that the intake of specific medications by patients with CVD does not lead to a change in liver function – the medications taken by patients are metabolized in normal values and no change in their reactivity is expected.
5. Blood sugar values in this group of patients are increased against the background of those on task 2. However, from a statistical point of view, no significant difference was found. The higher glucose values in task 3 patients, against the background of those of task 2–6 in patients with CVD and 5.32 in "healthy", is mainly due to the fact that the majority of patients on Task 3 are also diabetics. CVD occurs in 70% of diabetics, with hypertension occurring 2 times more common in diabetics than in patients without diabetes. In such patients, the cumulative risk of developing complications associated with the nature of both diseases increases. Invasive manipulations in this type of patient must be carried out in compliance with all the norms of art, because of the above mentioned risk of

complications of a general nature. This also requires a strictly precise change in their therapy.

6. Performing invasive manipulations in dental practice without proper assessment of the risk of bleeding in patients on antithrombotic or anticoagulant therapy can lead to difficult-to-control hemorrhages in outpatient conditions. The follow-up of a common indicator such as prothrombin time or APTT does not provide sufficient information on the general condition of the sick and should not be considered a "golden standard" in the study of homeostasis. The effect of different blood-saging medications should be reported by specific indicators. Taking a blood indicator as "universal" can lead to an incorrect preoperative assessment of the risk of bleeding and complications during manipulations.

Treatment of patients with GSC and anticoagulant or antiaggregant therapy – recommendations derived from scientific work

- **Patients with prolonged aspirin intake**In patients with prolonged aspirin intake, platelet count, APTT, bleeding time and clotting time should be investigated. It is recommended to stop taking the drug for a period of 3-5 days for surgical manipulations of medium and large volume. In small invasive interventions, patients can be treated without stopping the medication. It is important to mention that in this type of patients, doctors should have good surgical skills and apply local haemostatics.
- **Patients with intake of indirect anticoagulants:** In patients with prolonged intake of vit. K-dependent anticoagulant anticoagulation levels can be established using the INR. It is an accurate indicator of the effect of the treatment carried out so far. In medium and large surgical volumes, it is

necessary to stop taking the medication and replace it with low molecular weight heparin. Small-volume invasive manipulations can be performed without change of therapy at INR values up to 3.5.

- **Patients taking direct anticoagulants:** In Xa anticoagulants, the maximum discontinuation of medicines should not exceed 5 days. The action of the anticoagulant can be measured by a specific blood test anti-Ha, which is the only indicator of hemostasis aimed at this type of medication. The examination is done 3-4 hours after taking the drug, because then its maximum bioavailability in the blood is recorded. The use of the drug may not be discontinued with a small volume of surgical manipulations, but its reception should be carried out after manipulation, and not before, and it is advisable not to be immediately after surgical intervention. With a medium and large volume of surgical manipulations, it is advisable to temporarily stop the drug, it can be for a period of 2-3 days. It is important to mention that extations and manipulations associated with opening lamba and choosing a bone lead to a high risk of bleeding and it is recommended to temporarily stop medications.
- **Patients at high risk of thromboembolism:** In patients at high risk of thromboembolism, any change in therapy can lead to a fatal accident. On the other hand, in patients with severe antithrombotic or anticoagulant therapy, it is strongly contraindicated to conduct invasive manipulations without a change in medication intake. They recommend taking totokinase, which increases the body's ability to break down formed thrombi without changing the bleeding time. It is also necessary to co-ordify them with the relevant specialist who leads the main treatment and, if necessary, adjust the therapy.

3.2.4. Results and discussion on Task 4: Study the success rate of invasive treatment in patients with diabetes.

In task 4, 125 manipulations were performed on 11 diabetic patients who were taking a systemic medication to reduce blood glucose values. As mentioned, in this research study, diabetic patients had good and moderate blood sugar control. Routine surgical interventions are not recommended for patients with poor glycemic control. In these patients, it is desirable to initially establish stable control of blood glucose levels and then proceed to routine invasive manipulations.

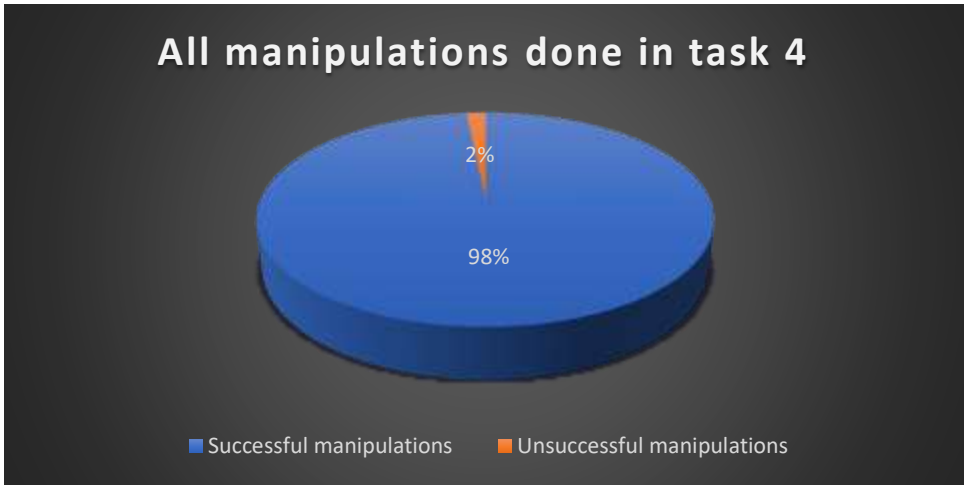

Figure 22: Percentage of successful and unsuccessful invasive manipulations in task 4

Inflammation and improper healing occurred in 2 of the 125 manipulations of patients with diabetes and were considered unsuccessful, accounting for 1.6% of cases (Fig. 22). The remaining 98.4% showed no signs of inflammation or delayed recovery - they were classified as successful.

A total of 59 implants were placed in Task 4. During the early postoperative period, 58 of them showed normal healing, with no objective and subjective criteria for impairment of natural repair of peri-implant tissues. Inflammation and a delayed healing period were observed in 1 implant case. Regarding the patients - in

1.69% of them complications were observed, and in the remaining 98.31% the healing period was uneventful (Fig. 23).

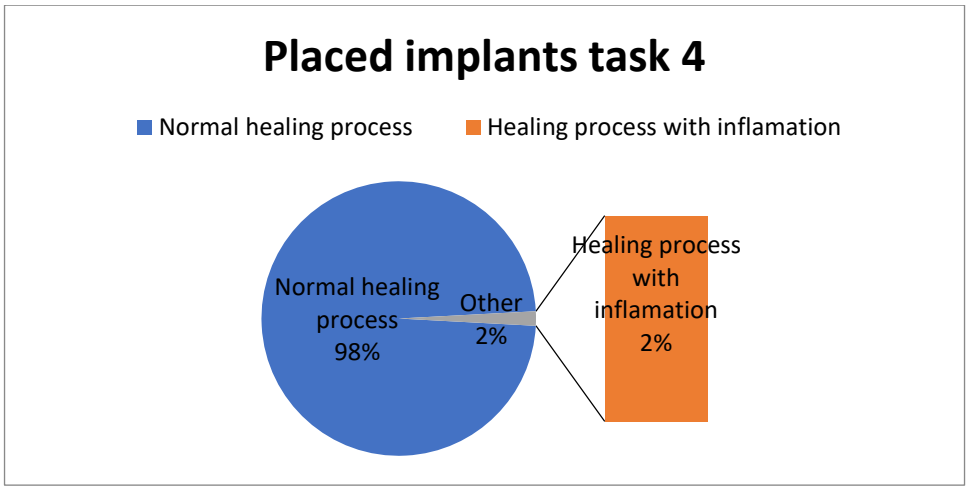

Figure 23: Percentage of healing time of implant-treated patients in task 4

A total of 66 other manipulations were performed on task 4. Normal healing process without complications was observed in 63 (95.46%) cases, whereas 3 (4.54%) cases had inflammation and delayed recovery (Fig. 24).

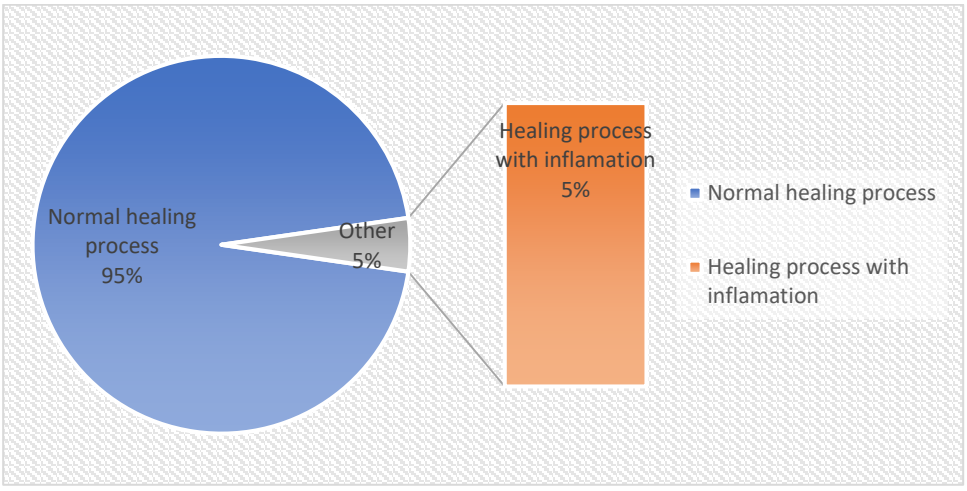

Figure 24: Percentage of healing time of other invasive manipulations in task 4

In 98.31% of implants placed in diabetic patients, successful osseointegration was found and they could be loaded with prosthetic constructs. The proportion of implants dropped in Task 4 was the same as the number of implants that developed early complications, 1.

From the results obtained in Task 4, the success rate in diabetic patients should be found to be 98.4% overall, as follows:

- implant placement success rate 98.31% - 97.5% in men and 98.4% in women,
- overall success rate in surgical manipulations 95.46%-96.1% in men and 94.8% in women.

The age distribution in Task 4 differs strongly from the data in Task 2. Here, invasive manipulations were mainly performed in the second and third age groups (Fig. 25).

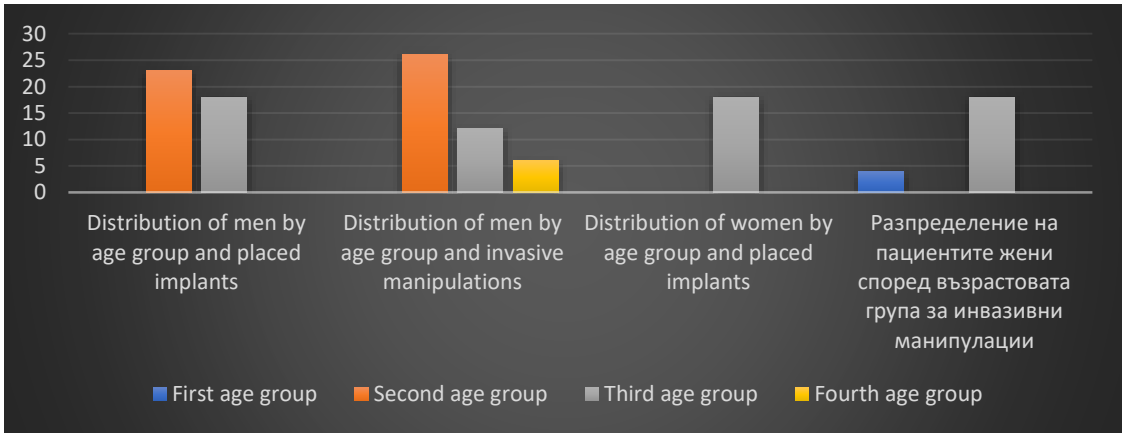

Figure 25: Distribution of patients by age group and sex

For the purpose of the research work, statistical models were built to compare the number of complications and the success rate of treatment in diabetics. They found that there was no consistent statistical relationship between the presence of diabetes and manipulation success rates, nor between the presence of diabetes and the development of manipulation complications.

Blood tests were performed on patients in task 4 (Table 9).

Table 9: Average values of patients' blood parameters in task 4

	Leu.	Ery.	Pl.	Hem.	AST	ALT	Gl.	INR
Average values	8.98	4.83	278.27	139.9	20.3	20.31	6.78	1.03
SD	2.04	0.53	63.47	20.81	6.08	9.65	0.49	0.08
Reference values	4.5 – 10.5	3.5 – 5.5	150 – 450	120 – 180	<37	<41	<6.4	<1.2

These same values are presented in comparison with the data for the whole study group, the CVD group and the healthy group in Figure 26 - the data have similar characteristics.

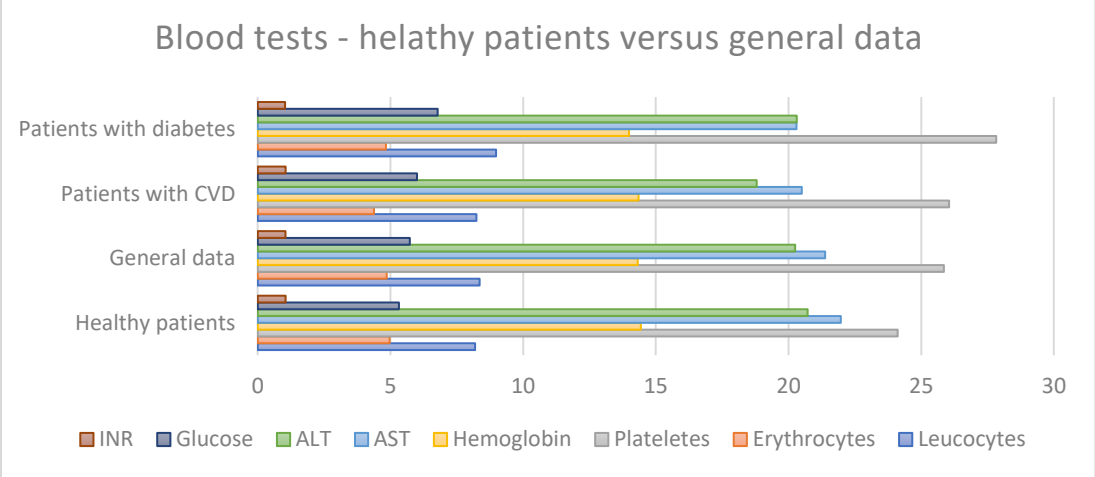

Figure 26: Comparative presentation of blood test results

(NOTE: For clarity of the data in the figure, the platelet and haemoglobin results are reduced 10-fold in all three groups)

For the purpose of the study, regression models were set to account for the dependence of leukocytes, erythrocytes, platelets, hemoglobin, AST, ALT, blood

sugar, INR on the presence of diabetes as a comorbidity. In all but blood glucose, it was reported that there was no regular statistical relationship between patients' diabetes and the indicated indicator. There was a strong correlation between diabetes and blood sugar of 0.82 (Sig 0.05).

Analysis of task 4 results

No case of severe postoperative inflammation was found to correlate with elevated blood glucose levels in the patients in task 4. It is important to mention that blood sugar levels were monitored preoperatively and if necessary, patients were referred to their treating physician for adjustment of therapy. Patients had good and moderately good glycemic control. Diabetic patients with poor glycemic control were not treated - in the setting of outpatient surgery and the performance of non-emergency manipulations, our team believes that surgical intervention can be delayed until blood glucose levels are corrected in patients with poor glycemic control. Other important criteria for the ultimate success of treatment is adherence to surgical protocols and proper surgical volume determination. It is advisable to separate large surgical interventions, if possible, to allow better recovery of patients. The results of task 4 clearly show that with good preparation and adherence to modern surgical protocols, surgical treatment of diabetics can be predictable. Our results on task 4 are similar to those of other research studies. Results ranged from 90 to over 95%, which correlates with the study conducted. Therefore, the treatment of diabetics can be carried out successfully if certain rules are observed before, during and after manipulation. Despite the need for stricter control and measures in these patients, patients with diabetes can be treated to the full extent of dental manipulation.

The following patterns can be deduced from the results of the blood tests:

1. Patients with diabetes and therapy for its treatment have normal leukocyte values. In view of this, the same immune response is expected as in "healthy" patients. Hypothetically, failed manipulations should be related to disease management.
2. Patients in task 4 had normal erythrocyte and hemoglobin values, and we are justified in concluding that they did not have impaired hematopoiesis due to the medications they were taking, and no internal bleeding was found.
3. Normal platelet counts in the systemic circulation were found in patients in task 4. Regression analysis showed no difference in the values of these patients and healthy controls, i. e. no difference in platelet counts between healthy patients and those with diabetes. This, together with the normal INR values, gives reason to believe that blood clotting in this type of patients is similar to that in "healthy" patients. The statement about patients not taking antithrombotic medications or anticoagulants is true. However, a large proportion of patients with diabetes also have CVD and are taking various antithrombotic drugs or anticoagulants. Therefore, monitoring platelet counts and INR values to assess coagulation would be inappropriate in these patients.
4. The values of AST and ALT were within normal limits in the patients in task 4. Regression analysis revealed no statistically significant difference in the values of these patients and healthy controls. It can be considered that the medications taken by the patients on the task did not lead to a change in AST and ALT, respectively, and in liver function. In view of the type of research it can be concluded that the drugs taken by the patients are metabolysed in normal values and no change in their reactivity is expected, as well as no change in the reactivity of the organism is expected due to the drugs taken.

5. Blood sugar values are highly elevated in patients on task 4. The regression analysis also showed a statistically significant difference with respect to this blood indicator. The appearance of these values is sought. Otherwise, it may be difficult to differentiate Task 4 patients as diabetic. As mentioned, a large proportion of patients on this assignment had a combined course of CVD and diabetes. This significantly increases the risk of complications in such patients in view of the cumulative effect of the two diseases, and demonstrates the need for a tailored individual approach according to the type of disease and therapy administered in each patient.

Treatment approach for diabetics (study and literature conclusion)

Diabetics can be divided into three groups according to the control of their blood sugar values - patients with good, average and poor disease control.

Patients with good disease control: invasive manipulations can be performed as in healthy patients.

In patients with moderate control of the disease, more efforts need to be made to prevent infection. In these patients, mandatory antibiotic prophylaxis is necessary, regardless of the volume of invasive manipulation. With a large volume of surgical manipulation, it is advisable to separate it.

Because of the type of scientific research, patients with **poor glycemic control are not included**. In them, invasive manipulations should be minimized – only to urgency or when the lack of treatment would lead to complications. Regardless of the volume of invasive manipulations, they should be carried out under antibiotic protection. If surgical manipulation of a large volume is necessary, it is advisable to separate it.

3.2.5. General discussion of results

The research included a heterogeneous group of patients. A group of "healthy" patients, patients with diabetes and those with cardiovascular disease who are taking antithrombotic or anticoagulant medications are observed. All groups of patients underwent the same type of invasive manipulations and the results were recorded. Invasive manipulations are the object of scientific study and not other types of manipulations carried out in dentistry, because they result in tissue injury with a subsequent recovery process. It is these processes that are disrupted by both cardiovascular disease and diabetes, and by the drugs that are taken to treat them. Treatment success outcomes were recorded using the same criterion for the different groups studied. After their analysis, similar success rates were observed for the different groups in the research. The literature data have some heterogeneity in their success rates in patients with this type of comorbidities. The idea of any type of treatment is to complete it successfully, regardless of the patient's general condition.

Analysis of the data from the different groups studied showed similar success rates as well as complications during treatment when invasive manipulations were applied. This is due to the individual approach to each patient. The individual approach refers not only to the performance of the manipulation, but also to the preparation for it.Preoperative preparation includes: blood tests, which must be tailored to the patient's underlying disease and the medications he is taking, recording the parameters of the co-morbidities and, if necessary, consultation with a specialist, and last but not least, determining the operative volume in the domain of oral surgery. The comparison of these data leads to individualization of the approach in each patient. The templating of blood tests required prior to invasive manipulation can to some extent be performed in

"healthy" patients, as normal status is expected in these patients. However, this cannot happen in patients with diabetes and those with CVD and antithrombotic or anticoagulant therapy. With them, the approach must be individual.

In patients with cardiovascular disease and antithrombotic or anticoagulant therapy, the main indicators of concern to the dentist are blood pressure levels, assessment of thrombotic risk, and the type of antithrombotic or anticoagulant medication taken. Before performing the invasive manipulation, it is necessary to reflect the level of blood dilution by a specific indicator reflecting the action of the given drug. Patients' blood tests clearly highlight the need for specific investigations. After their analysis, it was concluded that there is no way to judge the action of all antithrombotic drugs and anticoagulants by one universal indicator, such as prothrombin time or APTT.

In diabetics, things can be even more complicated. Diabetes control can be monitored by blood glucose or glycated hemoglobin levels and accordingly, the control of their underlying disease can be judged and necessary measures taken before invasive manipulation is performed. However, diabetes is a disease that affects the whole body. Often diabetics (especially those with type II, who are the subjects of the study) also have CVD as well as common diseases of other genesis. Therefore, not only the control of diabetes, but also that of other diseases should be taken into account.

The treatment of patients with cardiovascular disease and diabetes, especially those associated with injury to their tissues and subsequent recovery, requires an individualized approach. This is the only way their treatment success is comparable to that of patients without this type of disease.

3.3. CONCLUSION

The dynamic development of all medical and paramedical sciences constantly leads to the discovery of new data on various diseases. Treatment protocols for many diseases are also being changed dynamically. In some, there is a refinement of drug intake, in others the discovery of a new type of medication - some with the same action but optimized pharmacodynamic and pharmacokinetic parameters, and others with a new type of action. In parallel, there has been a steady "rejuvenation" of cardiovascular disease and diabetes.Modern lifestyles associated with mass immobilisation and higher calorie intake, mainly from simple sugars and fats, further promote earlier development and diagnosis of this type of disease.

The treatment of diabetes and cardiovascular disease is constantly being refined. New drugs are discovered, new treatment strategies are developed. In parallel, dentistry is developing at a commensurate pace. New materials and techniques are being introduced in view of the constantly increasing medical and aesthetic criteria. Increasingly, invasive manipulations are required in outpatient practice such as dental implants, periodontal surgery, etc.

Dental treatment of diabetics and patients with cardiovascular diseases, and mainly those who take antithrombotic or anticoagulant medications, can not be left in the "background". They need to be able to apply all modern invasive manipulations, as well as to "healthy" patients. The treatment of this type of patient should be tailored on the one hand to the condition of their organism and to the type of medications they take and, on the other hand, to the very methodology of the manipulation to be applied to them. This symbiosis should not be disturbed,

because otherwise the absence of one can lead to severe complications during and after invasive manipulations.

A key factor for the ultimate success of treating a sick person with accompanying diseases is the individual approach. Before proceeding to treatment manipulation, it is necessary to take an accurate history of the patient and to do research related to the accompanying disease, the medications he takes for their response, and the impact of the latter. Templateization of a patient, according to his disease, can lead to gaps in the objective medical condition and, accordingly, failures and complications during his treatment.

3.4. FINDINGS

On the anamnestic study:

1. Over 90% of patients with arterial hypertension take beta-blocker as the main therapy or as part of the general therapy for the treatment of the disease.
2. Over 50% is the proportion of patients taking Aspirin, in parallel with therapy for arterial hypertension.
3. There is a "rejuvenation" of diseases such as diabetes and arterial hypertension. In practice, participants with therapy for the treatment of cardiovascular disease and diabetes (together or individually) can be established in all age groups.
4. Despite the "rejuvenation" of the diseases studied, they spread en masse in groups with older participants.
5. A good level of control of the main diseases in the sick is observed. In a small percentage of study participants, further consultation with the attending physician on the underlying disease was required.

On the clinical studies:

1. The success rate of invasive dental treatment of "healthy" participants in the scientific study is over 98% – 100% for implantological treatment and 96.7% for other manipulations.
2. Approximately the same success data in the group of patients with CVD and healthy controls – over 95%.

3. Approximately the same success data in the group of patients with diabetes and healthy controls – over 95%.
4. Properly conducted preparation of patients leads to comparable results of treatment of patients with accompanying diseases and clinically healthy patients.
5. Approximately the same success rates of invasive dental treatment were observed in men and women with accompanying diseases, with values in men marginally higher than in women.

On the laboratory studies:

1. No difference was observed in CBC, AST and ALT in the group of healthy patients and those with cardiovascular disease and diabetes.
2. No significant difference in blood tests was observed in different age groups by the main blood indicators with a similar general condition.
3. There is a difference in blood sugar values in different age groups due to the specificity of the study. However, screening for diabetes in the upper age groups is recommended.
4. The need for specific studies to determine the action of a type of medication shall be visualized.
5. The impossibility of determining a blood test to determine the influence of all medications altering normal hemostasis is visualized.

3.5. CONTRIBUTIONS

Scientific contributions

1. A thorough analysis of the epidemiological, etiological and clinical aspects of the treatment of healthy patients and those with cardiovascular disease and diabetes was performed.
2. An analysis of the results of blood tests performed on patients with various underlying diseases was performed, accounting for variability by sex and age groups.

Applied contributions

1. A protocol for treatment by invasive dental manipulation of patients with cardiovascular disease and ongoing antithrombotic or anticoagulant therapy is proposed.
2. A protocol for treatment by invasive dental manipulation of patients with type 2 diabetes is proposed.

Confirmatory contributions

1. It has been confirmed that the treatment of patients on antithrombotic or anticoagulant therapy can be predictive and comparable to that of "healthy" patients if certain measures are followed.
2. It has been confirmed that the treatment of patients with diabetes can be prediabetic and comparable to that of "healthy" patients if certain measures are followed.

3.6. PARTICIPATIONS AND PUBLICATIONS ON THE TOPIC

Participation in scientific forums:

1. Georgiev A. Implant treatment in patients with underlying diseases. 17th International Congress of ISLD, 10th Congress of BDLS and 2nd National Congress of BAOM, Plovdiv 6-8 June 2019
2. Georgiev A, Balcheva M. Surgical and implant treatment in patients with underlying diseases. 29th Annual Assembly of IMAB, Varna 09-12 May 2019.

Publications:

1. Georgiev A, Balcheva M. Invasive dental treatment in patients with diabetes type 2. Scripta Scientifica Medicinae Dentalis. 2021;7(2):45-8
2. Georgiev A, Balcheva M. Patients with hypertension – influence of hypertension therapy on the impending dental surgical treatment. Varna medical forum. 2020;9(2):177-81
3. Georgiev A, Balcheva M. Dental treatment and diabetes mellitus. Medinform J. 2020;7(2):1216-1222. ISSN 2367-6795