To the Chairman of the Scientific Jury
Based on Order P-109-213/19.05.2022
Of the Rector of Medical University – Varna

R e v i e w

From **Prof. Dr. Rosen Gospodinov Kolarov, DMD, PhD**

Medical University – Varna, Faculty of Dental medicine, Department of Oral surgery, of a PhD-thesis for the award of the educational and scientific degree „**Doctor (PhD)**".

Higher education: 7. Health care and sports

Professional domain: 7.2. Dental medicine

PhD-programme: „Oral surgery"

Author: Dr. Gergana Diyanova Slivovska, DMD

a self-training PhD-student

Department: Oral surgery

Topic:

„**Influence of chronic inflammatory processes of the teeth on the mucociliary transport of the maxillary sinus"**

Scientific supervisors: Prof. Dr. Tihomir Georgiev, DMD, PhD, DSc – Department of Oral surgery; Assoc. prof. Dr. Mario Milkov, MD, PhD – Department of Dental materials science and propaedeutics of prosthetic dental medicine, Faculty of Dental medicine, Medical University – Varna

1. **General presentation of the procedure and the PhD student**

The following Review is prepared on the basis of the Order of the Rector of MU - Varna № P-109-213 / 19.05.2022, with appointed Scientific Jury under the procedure for public defense of the described dissertation.

The presented set of materials on paper and electronic media are in accordance with Art. 24, para. 6 and Art. 30, para. 3 of Law on the Development of Academic Staff in the Republic of Bulgaria and art. 68, para. 1 of the regulations for the development of the academic staff of MU - Varna, and were provided to me within the statutory period.

The doctoral student has submitted a total of 3 publications related to the topic of the dissertation published in scientific journals.

All documents are prepared and presented properly.

2. Brief biography of the doctoral student

Dr. Gergana Diyanova Slivovska was born on 06.05.1986 in the town of Burgas, Republic of Bulgaria. In 2006 she was admitted to the Faculty of Dental medicine, Medical University – Varna and in 2011 she graduated as a Master of Dental medicine.

In October 2011 she was a part-time assistant professor at the Department of "Oral and maxillofacial surgery and special imaging diagnostics" at the Faculty of Dental medicine, Medical University-Varna.

In the period 2012-2013 Dr. Slivovska was an intern at the Clinic of Oral and maxillofacial surgery, University Hospital for active treatment "St. Marina"-Varna.

Since 09.2013, Dr. Slivovska is a full-time assistant at the Department of Oral Surgery, Faculty of Dental medicine, Medical University-Varna.

Since 2020, Dr. Slivovska is a specialist in "Oral Surgery".

Dr. Slivovska has a total work experience of 11 years, of which 11 as an academic teacher.

Dr. Slivovska is a member of:

➤ Bulgarian Dental Association, BAOI,

Fluent in English.

3. Relevance of the subject and expediency of the set goals and objectives

The topic of the dissertation deals with an important problem for dental science and practice. The goal is clearly stated, the tasks are defined correctly and are performed with modern research methods.

4. Understanding of the problem

Odontogenic maxillary sinusitis is a common problem and a well-known condition in dental practice. According to various sources, its frequency varies from 10-12% to 50-75% among cases of maxillary sinusitis. Diagnosis includes in-depth dental and clinical assessment of the patient's condition and appropriate imaging.

The etiology of maxillary sinusitis is diverse. It may be caused by nearby or in contact with the maxillary sinus maxillary teeth. In addition, the most common causes of chronic maxillary odontogenic sinus are apical periodontitis, inflammatory periodontal disease, odontogenic cysts, oroantral communication during extraction of nearby teeth, secondary irritation in the presence of a foreign body in maxillary sinus or unsuccessful endodontic treatment. The roots of the maxillary premolars, molars, have an intimate connection with the maxillary sinus. In this sense, the inflammatory processes of the teeth could be the cause of inflammation in the Highmore's cavity.

The typical odontogenic infection is represented by a mixed aerobic-anaerobic microflora, with a predominance of the anaerobic species. Isolated microorganisms differ from those found in neodontogenic maxillary sinusitis. This necessitates the introduction of a specific diagnostic and therapeutic approach in patients with chronic maxillary odontogenic sinusitis. Medical treatment should take this fact into account.

The maxillary sinus communicates with the homolateral nasal cavity through osteum sinus maxillae, which is oval in shape and opens in the middle nasal passage. The location of the osteum does not change throughout life. This shows that the drainage system is not based on the force of gravity, but instead on a complex active transport system carried out by the ciliated epithelium that covers the inner walls of the maxillary sinus.

In the medical-diagnostic planning, it is discussed that after the removal of the etiological factor and the improvement of the ventilation of the sinus, the mucosa shows the ability for reverse development and regeneration with restoration of the area and the full function of the ciliary layer.

Dr. Slivovska has made an in-depth critical analysis of the literature, formulating unresolved issues on the topic.

In her work, Dr. Slivovska demonstrates skills for conducting of independent research.

Based on the analysis of research conducted so far on the problem, the purpose of the research is logically derived, namely:

"To study the peculiarities of the normal metabolism of the mucosa of the maxillary sinus and in various chronic inflammatory processes of an odontogenic origin"

The text is written in an appropriate scientific language.

5. **Methodology of the research**

The fulfillment of the goal was achieved through three (3) main tasks and 6 subtasks:

1. To determine the main pathomorphological changes of the mucosa of the maxillary sinus, formed as a result of the presence of a chronic inflammatory process in the teeth near the maxillary sinus.

1.1. To determine the changes in the X-ray images of the mucosa of the maxillary sinus near endodontically treated teeth, dividing into 2 main groups depending on the height of the alveolar bone between the apices of the distal teeth and the floor of the maxillary sinus (first group - alveolar bone - less than 3 mm, second group - alveolar bone - more than 5 mm).

1.2. To determine the changes in the X-ray images of the mucosa of the maxillary sinus near teeth with odontogenic cysts, divided into 2 main groups depending on the height of the alveolar bone (first group - alveolar bone is less than 3 mm, second group - alveolar bone is over 5 mm).

1.3. To determine the changes in the X-ray image of the mucosa of the maxillary sinus near teeth with inflammatory processes of the dental periodontium, divided into 2 main groups depending on the height of the alveolar bone (first group - alveolar bone is less than 3 mm, second group - the alveolar bone is over 5 mm).

2. To conduct a comparative analysis of the results of bacteriological examination in the maxillary sinus from materials taken from the pathologically altered mucosa of the maxillary sinus and chronic inflammatory processes developing around the maxillary teeth (while determining the most effective antibacterial medications).

3. To establish the activity of mucociliary transport in the norm and in chronic inflammatory diseases of the maxillary sinus.

3.1. To establish the activity of mucociliary transport in the norm.

3.2. To evaluate mucociliary transport pre- and postoperatively in the treatment of chronic odontogenic maxillary sinusitis.

3.3. To determine the activity of mucociliary transport in the maxillary sinus intraoperatively during a surgical treatment of oroantral communication

The formulated tasks allow the goal to be proven.

6. Patient selection and study design:

On task 1

For the realization of task 1, analysis of the data obtained from an examination with a conical-beam computed tomography was used, and different criteria for the presence of an inflammatory process around the upper teeth, close to or in contact with the maxillary sinus, were evaluated as the cause of pathophysiological changes.

When performing task 1.1, 536 maxillary CBCT-images were analyzed, of which 180 were of patients with adentia in the distal parts of the maxilla and therefore were dropped out of the study. In the present task 356 CBCT-images were selected, on which 356 endodontically treated teeth were registered. The following measurements were subsequently performed on patients' CBCT images - the thickness of the Schneider's membrane over endodontically treated teeth with and without obvious clinical manifestations was assessed, and the patients were divided into 2 groups:

Group I - In this group, endodontically treated teeth in which there was less than 3 mm of alveolar bone between the apex of the tooth and the floor of the maxillary sinus were included.

Group II - In this group, endodontically treated teeth, in which the alveolar bone between the apex of the tooth and the floor of the sinus was over 5 mm were included.

For the implementation of task 1.2, 108 CBCT-images of patients with odontogenic cysts in the upper jaw, located in the maxillary sinus area were studied. Above each tooth with an odontogenic cyst, the thickness of the mucosa of the Highmore's cavity was measured. In the study the following odontogenic cysts were included - radicular and periodontal cysts. Above each of the cysts abovementioned, the thickness of the maxillary sinus membrane was measured by assessing the thickening of the sinus mucosa in 2 groups:

Group I - In this group, odontogenic cysts were included, where there was less than 3 mm of alveolar bone between the cyst and the floor of the maxillary sinus.

Group II - In this group, odontogenic cysts were included, where there was more than 5 mm of alveolar bone between the cyst and the floor of the maxillary sinus.

For the implementation of task 1.3 a total of 490 CBCT-scans of the upper jaw were analyzed. 171 CBCT-scans were dropped out, because they belonged to patients with adentia in the distal areas of the upper jaw. The target group included 319 CBCT-images of 638 sinuses and a total of 814 teeth, with the youngest patient being 18 years old and the oldest - 75 years old.

On task 2

Twenty-seven patients were examined and six different types of microorganisms were found. These are Staphylococcs CNS, Peptostreptococcus and Prevotella sp., Fusobacterium spp., Alpha-hemolytic streptococcus and Porphyromonas sp.

All 27 patients underwent extraction of non-conservatively treatable molar teeth whose roots protrude into the maxillary sinus or are no more than 3 mm apart.

On task 3

When performing task 3, the drainage function of the maxillary sinus mucosa was assessed in the norm and in the presence of chronic odontogenic inflammation in the sinus cavity. Groups of 20 patients were selected for each of the three subtasks.

The number of logical units required for a clinical study for a doctoral dissertation is sufficient to formulate conclusions of good scientific value.

Clinical, paraclinical, therapeutic and statistical research methods were used in the dissertation. Through the selected methods the goal was achieved and the answer to the set tasks was obtained.

The clinical material selected for the implementation of the main goals and objectives is sufficient for the development of a dissertation work.

Units of observation: images of the upper jaw, inflammatory process around the upper teeth, cystic cavity and floor of the maxillary sinus, thickness of the Schneider's membrane.

Traits of the observation are:

➤ thickness of the Schneider membrane;
➤ CBCT-images of the upper jaw;
➤ floor of the maxillary sinus;
➤ inflammatory process of the maxillary sinus;
➤ odontogenic (radicular and periodontal) cyst.

Time of observation:

Patients were examined and treated in the period 2018 - 2021.

The place of observation is the Faculty of Dental Medicine, Medical University - Varna.

7. **Statistical methods and data analysis:**

IBM SPSS, specialized statistical software, was used for statistical data analysis. $p = 0.05$ was chosen as the significance level. This is the probability of making a mistake of the first kind.

The following statistical methods have been used for the purposes of this study:

➢ Descriptive statistical analysis (one-dimensional and two-dimensional distributions), where in a table form the frequency distribution of the considered characteristics is presented, broken down by study groups, mean values and standard deviations, 95% confidence intervals of change of mean values. Tables, pie charts and graphs were used to illustrate the results.

➢ One-Sample T-test.

➢ Independent Samples T-test for two independent samples to detect a statistically significant difference in the mean values of a given factor.

➢ One Way – ANOVA - Analysis of variance in order to determine the presence or absence of influence of two or more factors on the average values of the studied traits, without measuring the narrowness or strength of the dependence, as well as its direction.

➢ Test statistical hypotheses.

➢ Chi-square distribution.

➢ Regression analysis.

➢ Correlation analysis.

8. Characteristics and assessment of the PhD-thesis:

The dissertation contains 174 pages, illustrated with 32 histograms, 137 tables, 17 graphs and 12 images. The bibliography consists of 169 sources, all of which are in Latin

The results are comprehensively and correctly described, analyzed and interpreted.

The dissertation ends with conclusions based on the results, discussion and summaries of the study

9. Contributions and significance for the development of science and practice:

The dissertation outlines the following contributions of an original and a confirmatory origin, as follows:

Contributions of an original origin:

1. For the first time, the mucociliary transport of the maxillary sinus was measured, after local plastic surgery for closing of the communication between the oral cavity and the maxillary sinus. For the accuracy of the test, the saccharin granule was placed directly into the sinus cavity.

2. For the first time, the difference in the values when measuring the mucociliary transport of the maxillary sinus was taken into account, when the saccharin granule was placed on one side in the sinus cavity and on the other in the lower nasal passage.

Contributions of a confirmatory origin:

1. In the spread of the inflammatory process from the teeth in the distal parts of the upper jaw to the maxillary sinus, the available bone plays an essential role.

2. When the bone available between the apices of the teeth and the floor of the maxillary sinus is less than 3 mm, there was a high possibility that the process will ascend and affect the sinus mucosa - 96.7% of cases.

3. Chronic odontogenic sinusitis is most often caused by the following bacteria: Staphylococcs CNS, Peptostreptococcus, Prevotella sp., Fusobacterium spp., Alpha-hemolytic streptococcus and Porphyromonas sp.

4. In chronic inflammatory disorders of an odontogenic origin, it is good to prescribe the following antibiotic substances: Amoxicillin with clavulanic acid.

5. Any surgical trauma or chronic inflammation affects the intimate process of mucociliary transport and its self-cleansing function for the maxillary sinus.

10. Assessment of the scientific publications in connection with the PhD-thesis

Dr. Slivovska has presented 3 full-text publications, published in Bulgarian scientific journals. She is a lead author in all three publications:

1. Gergana Slivovska. Analysis of mucociliary transport of the maxillary sinus mucosa after surgical trauma and in the presence of chronic inflammation nternational Bulletin of Otorhinolaryngology Vol 17, No 4 (2021)

2. Gergana Slivovska, Mario Milkov, Tihomir Georgiev Influence of the height of the alveolar bone in the distal parts of the upper jaw on the odontogenic inflammatory processes in the maxillary sinus International Bulletin of Otorhinolaryngology Vol 17, No 4 (2021)

3. Gergana Slivovska, Mario Milkov, Elitsa Dzhongova, Tihomir Georgiev Comparative bacteriological examination of materials, taken from the pathologically altered mucosa of the maxillary sinus and chronic inflammatory processes, developing around the maxillary teeth International Bulletin of Otorhinolaryngology Vol 17, No 4 (2021)

They are all published in prestigious journals, and the results obtained in them satisfy quantitatively and qualitatively the legal requirements for dissertation work.

11. Personal participation of the doctoral student:

The research and observations of patients and the resulting conclusions and contributions to the dissertation I accept as a personal work of the author.

12. Abstract of the PhD-thesis:

The abstract contains 80 pages, illustrated with 13 histograms, 12 images, 2 graphs and 28 tables. Correctly reflects the nature of the study and the results achieved in the dissertation. The conclusions made are reflected in it.

It has been prepared in accordance with the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria and the regulations of Medical University – Varna. Reflects the content of the dissertation.

13. Critical remarks and recommendations to the author:

The set of materials from the dissertation provided to me is complete and in accordance with the Law on the Development of Academic Staff in the Republic of Bulgaria and the regulations for its implementation, as well as with the Regulations of MU - Varna. I have no remarks or recommendations

14. Personal impressions:

Dr. Gergana Slivovska, DMD is established as an academic teacher and a dentist with a strong clinical thinking. She has in-depth theoretical knowledge and professional skills in the specialty. The text provided to me shows a thorough knowledge of the problem and gives me a reason to accept it as her personal work.

15. Recommendations for a future use of dissertation contributions and results

I recommend Dr. Slivovska to design and publish her dissertation as a monography. This would make her work more accessible to colleagues who work on this issue on a daily basis

CONCLUSION

The dissertation submitted to me for a Review by Dr. Gergana Diyanova Slivovska, DMD, a self-training PhD-student, on the topic: **„Influence of chronic inflammatory**

processes of the teeth on the mucociliary transport of the maxillary sinus" I take for completed. It meets the requirements and regulations of the laws regarding it.

The topic of the PhD-thesis is actual and well chosen.

The literature review is comprehensive and gives a clear idea of the current state of the problem. It ends with a critical analysis, which is a good basis for the research.

Based on the analysis of research conducted so far, the purpose of the study is derived. The set tasks give the opportunity to prove it.

The clinical material and the studies performed are of interest to dental science and practice. The results obtained in the dissertation, their interpretation, as well as the presented publications related to it, I accept as a personal work of the author.
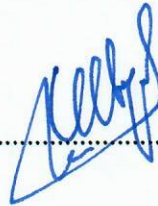
The dissertation work shows that the doctoral student Dr. Slivovska has in-depth theoretical knowledge and professional skills in the specialty, demonstrating qualities and skills for independent research.

Based on everything noted so far, I accept that the requirements of the Law on the Development of Academic Staff in the Republic of Bulgaria, the Regulations for the implementation of it, and the relevant Rules of MU - Varna are met. The presented materials and dissertation results **fully comply** with the specific requirements of MU - Varna.

To conclude: I **confidently give** a positive assessment of the dissertation on the topic: **„Influence of chronic inflammatory processes of the teeth on the mucociliary transport of the maxillary sinus"** and will vote with a **"YES"** for the award of educational and scientific degree "DOCTOR" on the scientific specialty "Surgical dentistry" to Dr. Gergana Diyanova Slivovska, DMD.

07.06. 2022   Reviewer: ....

(Prof. Dr. Rosen Gospodinov Kolarov, DMD, PhD)