



GOCE DELCEV UNIVERSITY - STIP  
FACULTY OF MEDICAL SCIENCES



International symposium at  
Faculty of medical sciences

# **CURRENT ACHIEVEMENTS AND FUTURE PERSPECTIVES IN MEDICAL AND BIOMEDICAL RESEARCH**



STIP, 24 NOVEMBER 2015  
MULTIMEDIA CENTRE – UGD, STIP

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INTERNATIONAL SYMPOSIUM AT FACULTY OF MEDICAL SCIENCES  
“Current achievements and future perspectives in medical and biomedical research”

SCIENTIFIC PROGRAM

November 24, 2015 - Stip

8:30 – 9:00

**Registration**

9:00 – 9:15

Rector / Vice rector/Dean

**SESSION 1**

**Chair: Prof. Emilija Janevik Ivanovska**

**Co-chair: Ass. Prof. Elena Drakalska**

9:15 – 9:35

**Ass. Marija Darkovska Serafimovska**  
Macedonian agency of drug and medical  
devices, Director  
University Goce Delcev Stip  
Republic of Macedonia

*Step forward of Macedonian agency for medicines and medical devices, establishment and strategic plan for development*

9:35 – 9:55

**Assoc. Prof. Zorica Arsovska Sarafinovska**  
Institute of Human Health, Skopje,  
University Goce Delcev Stip  
Republic of Macedonia

*Adherence to Therapy: A Modern Pharmacotherapeutic Approach*

9:55 – 10:15

**Prof. Biljana Gjorgjeska**  
University Goce Delcev Stip  
Republic of Macedonia

*Use of disinfectants and antiseptics in the health institution in Republic of Macedonia*

10:15 – 10:35

**Assoc. Prof. Bistra Angelovska**  
University Goce Delcev Stip  
President of Pharmaceutical Chamber  
of Macedonia. Republic of Macedonia

*Code of Ethics for Pharmacists – Pharmaceutical Chamber of Macedonia*

10:40 – 11:10

**Coffee break**

**Poster presentation**

**SESSION 2**

**Chair: Prof. Milka Zdravkovska**

**Co-chair: Ass. Prof. Darinka Gjorgieva Ackova**

10:10 – 11:50

**Prof. Neven Zarkovic**  
Rudjer Boskovic Institute, Croatia

*4-Hydroxynonenal – major bioactive marker of lipid peroxidation*

11:50 – 12:10

**Assoc. Prof. Tatjana Ruskovska** University  
Goce Delcev Stip Republic of Macedonia

*Nicotinamide adenine dinucleotide biosynthesis and consumption in dysfunctional white adipocytes*

12:10 – 12:30

**Prof. Rubin Gulaboski** University  
Goce Delcev Stip Republic of Macedonia

*New insights into the chemistry and functions of Coenzyme Q*

12:30 – 12:50

**Assoc. Prof. Darko Bosnakovski**  
University Goce Delcev Stip  
Republic of Macedonia

*Genetically modified systems to study muscular dystrophies*

12:50 – 14:00

**Coffee break**

**Poster presentation**

### SESSION 3

**Chair: Assoc. Prof. Cena Dimova**

**Co-chair: Ass. Prof. Nevenka Velickova**

14:00 – 14:40	<b>Prof. Lia Rimondini</b> Università del Piemonte Orientale, Novara, Italy	<i>Counteracting microbial biofilm formation onto dental materials</i>
14:40 – 15:00	<b>Prof. Elizabeta Zisovska</b> Agency for Quality and Accreditation of Healthcare Institutions, Skopje, Republic of Macedonia	<i>The endless potential of the umbilical cord blood for investigation, research and treatment</i>
15:00 – 15:20	<b>Ass. Misko Milev</b> University Goce Delcev Stip Republic of Macedonia	<i>The cytokinesis-blocked micronucleus assay: Good choice for detection and evaluation of genotoxicity in human cells</i>
15:20 – 15:40	<b>Prof. Lence Miloseva</b> University Goce Delcev Stip Republic of Macedonia	<i>Multiple predictive model for clinical and subclinical depression in adolescence</i>
15:40 – 16:00	<b>Coffee break</b>	<b>Poster presentation</b>

### SESSION 4

**Chair: Assoc. Prof. Darko Bosnakovski**

**Co-chair: Ass. Prof. Katarina Smilkov**

16:00 – 16:40	<b>Prof. Adriano Duatti</b> University of Ferrara, Ferrara, Italy	<i>Molecular imaging and radionuclide therapy of prostate cancer</i>
16:40 – 17:00	<b>Assoc. Prof. Vaso Taleski</b> University Goce Delcev Stip Republic of Macedonia	<i>Where Nanotechnology and Nanomedicine meet – Applications and Potential Risks</i>
17:00 – 17:20	<b>Dr. Aleksandar Cvetkovski</b> University Goce Delcev Stip Republic of Macedonia	<i>The role of molecular cocrystals in drug development</i>
17:20 – 17:40	<b>Prof. Emilija Janevik Ivanovska</b> University Goce Delcev Stip Republic of Macedonia	<i>Drug development based on radiolabeled antibodies</i>
17:40 – 18:00	<b>Closing remarks</b>	

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# INTERNATIONAL SYMPOSIUM AT FACULTY OF MEDICAL SCIENCES

## “Current achievements and future perspectives in medical and biomedical research”

November 24, 2015 – Stip

### ORAL PRESENTATIONS

- 1. Step forward of Macedonian Agency for medicines and medical devices. Establishment and strategic plan for development**  
*Author:* Ass. Marija Darkovska-Serafimovska
- 2. Adherence to Therapy: A Modern Pharmacotherapeutic Approach**  
*Author:* Ass. Prof. Zorica Arsovska Sarafinovska
- 3. Use of disinfectants and antiseptics in selected health institutions in Republic of Macedonia**  
*Author:* Prof. Biljana Gjorgjeska
- 4. Code of Ethics for Pharmacists – Pharmaceutical Chamber of Macedonia**  
*Author:* Prof. Bistra Angelovska
- 5. 4-Hydroxynonenal – major bioactive marker of lipid peroxidation**  
*Author:* Prof. Neven Zarkovic
- 6. Nicotinamide adenine dinucleotide biosynthesis and consumption in dysfunctional white adipocytes**  
*Author:* Prof. Tatjana Ruskovska
- 7. New insights into the chemistry and functions of Coenzyme Q**  
*Author:* Prof. Rubin Gulaboski
- 8. Genetically modified systems to study muscular dystrophies**  
*Author:* Prof. Darko Bosnakovski
- 9. Counteracting microbial biofilm formation onto dental materials**  
*Author:* Prof. Lia Rimondini
- 10. The endless potential of the umbilical cord blood for investigation, research and treatment**  
*Author:* Prof d-r Elizabeta Zisovska
- 11. The cytokinesis-blocked micronucleus assay: Good choice for detection and evaluation of genotoxicity in human cells**  
*Author:* Ass. Misko Milev
- 12. Multiple predictive model for clinical and subclinical depression in adolescence**  
*Author:* Prof. Lence Miloseva
- 13. Molecular Imaging and therapy with radionuclides of prostate cancer**  
*Author:* Prof. Adriano Duatti
- 14. Where Nanotechnology and Nanomedicine meet – Applications and Potential Risks**  
*Author:* Prof. Vaso Taleski
- 15. The role of molecular cocrystals in drug development**  
*Author:* Ass. Aleksandar Cvetkovski
- 16. Drug development based on radiolabeled antibodies**  
*Author:* Prof. Emilija Janevik

# INTERNATIONAL SYMPOSIUM AT FACULTY OF MEDICAL SCIENCES

## “Current achievements and future perspectives in medical and biomedical research”

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### POSTER PRESENTATIONS

- 1. Correlation between dynamic balance and gait parameters in patients with ischemic stroke in the chronic period**  
*Authors:* Danche Vasileva, Daniela Lubenova, Marija Mihova, Ivan Maznev, Lence Nikolovska, Zhu Jihe;
- 2. Effect of kinesitherapy on physical activity in patient with Guillain-Barré syndrome**  
*Authors:* Antoaneta Dimitrova, Kristin Petrova Grigorova, Daniela Lubenova, Danche Vasileva, Milena Nikolova;
- 3. Case Report :  
Oligoasthenoteratozoospermia, treatment with acupuncture**  
*Authors:* Jihe Zhu, Blagica Arsovska, Danche Vasileva, Andrijana Sterjovska-Aleksovska, Kristina Kozovska;
- 4. Treatment of cervical spondylosis with acupuncture**  
*Authors:* Kristina Kozovska, Jihe Zhu, Blagica Arsovska, Andrijana Sterjovska-Aleksovska;
- 5. Effect of kinesitherapy on static and dynamic balance in patient after vertebro-basilar system stroke**  
*Authors:* Milena Nikolova, Antoaneta Dimitrova, Danche Vasileva, Daniela Lubenova, Kristin Petrova Grigorova;
- 6. Malignant pleural effusions in lung cancer: the condition during the disease**  
*Authors:* Marija Karakolevska-Ilova, Elena Simeonovska Joveva, Aleksandar Serafimov, Lidija Petrovska;
- 7. Systemic fungal infections in hematological malignancies**  
*Authors:* Petar Kuzmanovski, Velo Markoski;
- 8. Morbidity and mortality of malignant neoplasms in Macedonia**  
*Authors:* Viktorija Vukovikj, Velo Markoski;
- 9. Cognitive behavioral program in treating insomnia among elderly patients**  
*Authors:* Knejinja Richter, Lence Miloseva, Guenter Niklewski, Anja Piehl;
- 10. Regulations and legal aspects in management of medical waste**  
*Authors:* Biljana Shikoska, Cena Dimova, Gjorgi Schumanov;
- 11. Control of the psychiatric disorders in the Republic of Macedonia**  
*Authors:* Leonid Ramov, Velo Markoski;
- 12. Monitoring of the renal function in Indometacin treated patients with rheumatoid arthritis**  
*Author:* Drita Yzeiri Havziu;
- 13. Incidence of breast cancer in Macedonia**  
*Authors:* Dijana Stojanova, Velo Markoski;
- 14. HPV virus as a cause of cancer of the cervix in R.Macedonia**  
*Authors:* Stefanija Joveva, Velo Markoski, Vaso Taleski;
- 15. Analysis of the Pap test results by age groups in the area of Kriva Palanka**  
*Authors:* Robert Nikolovski, Kristina Denchovska, Goran Mladenovski, Velo Markovski;
- 16. Giant rhinophyma treated by excision and full thickness skin grafting**  
*Author:* Emilija Lozanovska Doneva;

- 17. Incidence of patients with chronic renal failure in Skopje**  
*Authors:* Simona Kamceva, Velo Markoski;
- 18. Calculation of effective dose to family members of patients with thyroid diseases**  
*Authors:* Marina Zdravevska Kochovska, Emilija Janjevik Ivanovska, Meri Angeleska, Sasho Nikolovski, Zlatko Filipovski;
- 19. Contemporary Microbiological Diagnostic Tests for Rapid Identification and Detection of Resistance of Mycobacterium tuberculosis**  
*Authors:* Oliver Taleski, Vaso Taleski;
- 20. Analysis of clinical features and complications in patients with  $\beta$ -thalassemia in the region of Strumica**  
*Authors:* Silvana Sinokapovska, Cena Dimova;
- 21. Lymphoepithelioma : A case report**  
*Author:* Vase Stojcheska;
- 22. F-ra Capitullum Radium L.Dex. – A Case report**  
*Author:* Svetlana Jovevska;
- 23. Patient with intracranial hemorrhage and arteriovenous malformation detected with transcranial color duplex sonography – case report**  
*Authors:* Elena Simeonovska Joveva, Marija Karakolevska-Ilova, Aleksandar Serafimov, Lidija Petrovska;
- 24. Hereditary supracondylar spur of the humerus: Case report**  
*Authors:* George Zafirovski, Strahil Todorov, Christian Lozanoski;
- 25. Prosthetic rehabilitation in patient with advanced degree of functional disorders (case report)**  
*Authors:* Natasa Denkova, Katerina Zlatanovska, Ana Radeska-Panovska, Sanja Nashkova, Ivona Kovacevska;
- 26. Marginal Implants Bone Loss – a Case Report**  
*Authors:* Kiro Papakoca, Ana Radeska-Panovska, Katerina Zlatanovska;
- 27. Ectodermal Dysplasia, a Case Report: Challenge for Prosthodontic Solution**  
*Authors:* Emilija Bajraktarova Valjakova, Bajevska Jagoda, Vesna Korunovska Stevkovska, Biljana Kapushevskaja, Nikola Gigovski, Aneta Mijoska, Katerina Zlatanovska, Cvetanka Bajraktarova Mishevskaja;
- 28. Alveolar socket preservation and shaping using temporary prosthetic construction – case presentation**  
*Authors:* Nikola K. Gigovski, Vesna Korunovska- Stevkoska, Emilija Bajraktarova, Aneta Mijoska, Ana Radeska-Panovska;
- 29. Porcelain veneers produced by refractory die method**  
*Authors:* Katerina Zlatanovska, Julija Zarkova-Atanasova, Ana Radeska, Natasa Denkova, Kiro Papakoca;
- 30. Correlation of Two Different Local Hemostatic Modalities in Oral Surgery Patients with Oral Anticoagulants**  
*Author:* Cena Dimova;
- 31. Assessment of orthodontic treatment need among school children by using iotn (index of orthodontic treatment need)**  
*Authors:* Ana Radeska-Panovska, Kiro Papakoca, Natasa Denkova, Ivona Kovacevska, Katerina Zlatanovska;
- 32. Oral Hygiene Level Maintenance among Dental Medicine Students**  
*Authors:* Darko Kochovski, Verica Toneva;
- 33. Poor oral hygiene and show of caries in 12 year old children**  
*Author:* Sanja Naskova;
- 34. Implant-prosthetic therapy failure in smoker and nonsmoker patients**  
*Authors:* Aneta Mijoska, Mirjana Popovska, Nikola Gigovski, Vesna Korunovska- Stevkoska, Emilija Bajraktarova, Katerina Zlatanovska;

- 35. Oral surgery treatment in the patients with combination syndrome**  
*Authors:* Vesna Korunoska Stevkovska, Nikola Gigovski, Katerina Zlatanovska, Emilija Bajraktarova, Aneta Mijoska;
- 36. Iatrogenic mistakes, cause for a failure at surgical treatment of a chronic periapical processes**  
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- 37. Evaluation of Different Preparation of Artificial Teeth and Acrylate Prosthetic Base**  
*Authors:* Pavle Apostoloski, Cena Dimova, Katerina Zlatanovska, Julija Zarkova;
- 38. Analysis of the dimensional stability of elastomeric silicone impression materials**  
*Authors:* Galaba Veresa, Cena Dimova, Julijana Miloseva
- 39. Use of gypsum into working everyday in dental technician**  
*Author:* Hadis Arslanov
- 40. Mobile dental NOG-types used in working dental models**  
*Author:* Julija Vladikova
- 41. Determining normal tissue toxicity of non-radioactively Lu/Y-labeled rituximab-conjugates in rat animal model**  
*Author:* Darinka Gjorgieva Ackova;
- 42. Genetically Engineered Mouse Models For Human Pancreatic Cancer: A Review Of The KC, KPC And iKRas\*P53\* Models**  
*Authors:* David Mwanza Wanjeh, Joel Munene Muchira, Aschalew Alemu Marie, Darko Bosnakovski;
- 43. Mouse Models For Human Prostate Cancer: Xenograft Vs Genetically Engineered Mouse Model**  
*Authors:* Aschalew Alemu Marie, Joel Munene Muchira, David Mwanza Wanjeh, Darko Bosnakovski;
- 44. HER2 Transgenic Mouse Models: A Way To HER2+ Breast Cancer Targeted Therapy**  
*Authors:* Joel Munene Muchira, David Mwanza Wanjeh, Aschalew Alemu Marie, Darko Bosnakovski;
- 45. Types of scaffolds and thier application in bone tissue engineering**  
*Author:* Milena Volcheva, Darko Bosnakovski;
- 46. Significance of preparation of tissue samples for electron microscopy for observation and diagnosis**  
*Authors:* Jovanka Laskova, Gordana Petrusevska, Darko Bosnakovski;
- 47. Design and characterization of nanoparticles as platforms for delivery of curcumin**  
*Author:* Elena Drakalaska;
- 48. Freeze-drying approach to enhance antibody stability**  
*Author:* Katarina Smilkov;
- 49. An overview of phytosomes as a novel herbal drug delivery system**  
*Authors:* Emilija Apostolova, Brankica Spaseska, Maja Simonoska Crcarevska, Maja Glavash Dodov, Renata Slaveska Raichki;
- 50. Determination of active pharmaceutical ingredient – chloropyramine in dragées**  
*Author:* Vesna Kostik;
- 51. Comparison of volatile aroma compounds between cultivated and spontaneous flowering stems of *Sideritis scardica* Griseb. from R. Macedonia**  
*Author:* Bujar Qazimi;
- 52. Bioactive compounds of cold-pressed oil from the seeds of Gojy Berry (*Lycium barbarum*)**  
*Author:* Sanja Kostadinovik Velickovska;
- 53. Development and validation of HPLC method for determination of flavonoids in herbal preparations**  
*Authors:* Tanja Janeva, Zorica Arsova-Sarafinovska;
- 54. Atomic emission spectrometry with inductively coupled plasma (ICP-AES) analysis of trace elements in *Camellia sinensis* teas**  
*Authors:* Dragica Doneva, Trajce Stafilov, Zorica Arsova-Sarafinovska, Katerina Starkoska, Maja Shishovska;



- 55. Determination of trace elements analyzed by atomic emission spectrometry with inductively coupled plasma (ICP-AES) in Matricaria chamomilla L. teas present on macedonian market**  
*Authors:* Dragica Doneva, Trajce Stafilov;
- 56. Human health risks from heavy metals via consumption of contaminated food**  
*Authors:* Biljana Balabanova, Rubin Gulaboski;
- 57. Development of an ultrasonic method for effective extraction of capsaicin as a potent bioactive compound**  
*Authors:* Viktorija Maksimova, Liljana Koleva Gudeva, Blaga Radovanovic, Rubin Gulaboski;
- 58. Electrochemical analysis of the properties of benzene-1,2,4-triol**  
*Authors:* Milkica Janeva, Rubin Gulaboski;
- 59. Comparison of the procedure for registration of medicines in the European Union and the Republic of Macedonia**  
*Author:* Sofija Petkovska;
- 60. Pharmaco-economic evaluation of the antibiotic prophylaxis in orthopedic surgeries**  
*Authors:* Dijana Atanasova, Bistra Angelovska, Biljana Lazarova;
- 61. Therapeutic approach in the treatment of benign prostatic hyperplasia**  
*Authors:* Rozeta Aceva, Zorica Arsova – Sarafinavska;
- 62. Oxidative stress, aging and antioxidants**  
*Authors:* Viktorija Trajkoska, Zorica Arsova Sarafinavska;
- 63. Oxidative stress, oxidative DNA damage and prostate cancer**  
*Authors:* Evgenija Nedelkoska, Zorica Arsova-Sarafinavska;
- 64. RNA interference (RNAi) mechanism as a basis for future successful treatment of chronic hepatitis B infection**  
*Author:* Ana Nikolova, Darko Bosnakovski;
- 65. Anti-cancer target therapy based on drugs conjugated to hyaluronic acid**  
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- 66. Cancer specific conjugated monoclonal antibodies for anticancer therapy**  
*Authors:* Daniela Todosiova, Darko Bosnakovski, Emilija Janevik Ivanovska;
- 67. Accreditation of the Laboratory of Radiopharmacy – requested requirements or need of challenge**  
*Author:* Katarina Delipetrevska;
- 68. Quality control of PET radiopharmaceuticals, with reference to its specifics vs quality control of conventional pharmaceuticals**  
*Authors:* Filip Jolevski, Maja Velickovska, Maja Chochevska, Marija Atanasova, Katerina Kolevska, Emilija Janevik-Ivanovska;
- 69. Production of [11C] Choline in The University Institute for PET – new perspective in diagnostics of prostate malignancy in R. of Macedonia**  
*Authors:* Katerina Kolevska, Maja Chochevska, Marija Atanasova, Maja Velickovska, Filip Jolevski, Emilija Janevik-Ivanovska;
- 70. PET radiopharmaceuticals in the diagnosis of neurological diseases**  
*Authors:* Marija Pandeva, Emilija Janevik-Ivanovska;
- 71. Achievements and perspectives in formulation of stable immunoconjugate of the HER2-targeting trastuzumab – potential for rapid labelling with Gallium-68**  
*Author:* Marija Sterjova



*Faculty of Medical Sciences*

*University Goce Delcev – Stip, Macedonia*

**INTERNATIONAL SYMPOSIUM AT FACULTY OF MEDICAL SCIENCES**

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# **BOOK OF ABSTRACTS**

*November 24, 2015 – Stip*

## Contents

ORAL PRESENTATIONS .....	10
Step forward of Macedonian Agency for medicines and medical devices	
Establishment and strategic plan for development.....	11
Adherence to Therapy: A Modern Pharmacotherapeutic Approach.....	12
Use of disinfectants and antiseptics in selected health institutions in Republic of Macedonia .....	14
Code of Ethics for Pharmacists – Pharmaceutical Chamber of Macedonia.....	15
4-Hydroxynonenal – major bioactive marker of lipid peroxidation .....	16
Nicotinamide adenine dinucleotide biosynthesis and consumption in dysfunctional white adipocytes.....	17
New Insights into the Chemistry and Functions of Coenzyme Q.....	18
Genetically modified systems to study muscular dystrophies .....	19
Counteracting microbial biofilm formation onto dental materials.....	20
The endless potential of the umbilical cord blood for investigation, research and treatment.....	21
The cytokinesis-blocked micronucleus assay: Good choice for detection and evaluation of genotoxicity in human cells .....	23
Multiple predictive model for clinical and subclinical depression in adolescence .....	24
Molecular Imaging and therapy with radionuclides of prostate cancer .....	25
Where Nanotechnology and Nanomedicine meet – Applications and Potential Risks .....	27
The role of molecular cocrystals in drug development.....	29
Drug development based on radiolabeled antibodies.....	30
POSTER PRESENTATIONS .....	31
Correlation between dynamic balance and gait parameters in patients with ischemic stroke in the chronic period.....	32
Effect of kinesitherapy on physical activity in patient with Guillain-Barré syndrome.....	33
Case Report : Oligoasthenoteratozoospermia, treatment with acupuncture .....	34
Treatment of cervical spondylosis with acupuncture.....	36
Effect of kinesitherapy on static and dynamic balance in patient after vertebro-basilar system stroke .....	37
Malignant pleural effusions in lung cancer: the condition during the disease.....	38
Systemic fungal infections in hematological malignancies .....	40
Morbidity and mortality of malignant neoplasms in Macedonia .....	41
Cognitive behavioral program in treating insomnia among elderly patients .....	43
Regulations and legal aspects in management of medical waste .....	44
Control of the psychiatric disorders in the Republic of Macedonia.....	46
Monitoring of the renal function in Indometacin treated patients with rheumatoid arthritis.....	47
Incidence of breast cancer in Macedonia .....	48
HPV virus as a cause of cancer of the cervix in R.Macedonia .....	49
Analysis of the Pap test results by age groups in the area of Kriva Palanka .....	50
Giant rhinophyma treated by excision and full thickness skin grafting.....	52
Incidence of patients with chronic renal failure in Skopje.....	53
Calculation of effective dose to family members of patients with thyroid diseases .....	54
Contemporary Microbiological Diagnostic Tests for Rapid Identification and Detection of Resistance of Mycobacterium tuberculosis.....	56
Analysis of clinical features and complications in patients with $\beta$ -thalassemia in the region of Strumica .....	57
Lymphoepithelioma: A case report.....	59

F-ra Capitulum Radii L.Dex. – A Case report .....	60
Patient with intracranial hemorrhage and arteriovenous malformation detected with transcranial color duplex sonography – case report.....	61
Hereditary supracondylar spur of the humerus: Case report.....	63
Prosthetic rehabilitation in patient with advanced degree of functional disorders (case report) ....	64
Marginal Implants Bone Loss – a Case Report.....	65
Ectodermal Dysplasia, a Case Report: Challenge for Prosthodontic Solution .....	66
Alveolar socket preservation and shaping using temporary .....	68
prosthetic construction – cases presentation .....	68
Porcelain veneers produced by refractory die method.....	69
Correlation of Two Different Local Hemostatic Modalities in Oral Surgery Patients with Oral Anticoagulants.....	70
Assessment of orthodontic treatment need among school children by using iotn (index of orthodontic treatment need) .....	72
Oral Hygiene Level Maintenance among Dental Medicine Students .....	73
Poor oral hygiene and show of caries in 12 year old children .....	74
Implant-prosthetic therapy failure in smoker and nonsmoker patients .....	75
Oral surgery treatment in the patients with combination syndrome .....	76
Iatrogenic mistakes, cause for a failure at surgical treatment of a chronic periapical processes ....	77
Evaluation of Different Preparation of Artificial Teeth and Acrylate Prosthetic Base.....	78
Analysis of the dimensional stability of elastomeric silicone impression materials.....	79
Use of Gypsum Into Working Everyday in Dental Technician .....	81
Mobile dental NOG types used in working dental models .....	82
Determining normal tissue toxicity of non-radioactively Lu/Y-labeled rituximab-conjugates in rat animal model.....	83
Genetically Engineered Mouse Models For Human Pancreatic Cancer: A Review Of The KC, KPC And iKRas*P53* Models.....	84
Mouse Models For Human Prostate Cancer: Xenograft Vs Genetically Engineered Mouse Model .....	85
HER2 Transgenic Mouse Models: A Way To HER2+ Breast Cancer Targeted Therapy .....	86
Types of scaffolds and their application in bone tissue engineering.....	87
Significance of preparation of tissue samples for electron microscopy for observation and diagnosis.....	88
Design and characterization of nanoparticles as platforms for delivery of curcumin.....	90
Freeze-drying approach to enhance antibody stability.....	91
An overview of phytosomes as a novel herbal drug delivery system .....	92
Determination of active pharmaceutical ingredient – chloropyramine in <i>dragées</i> .....	94
Compariton of volatile aroma compounds between cultivated and spontaneous flowering stems of <i>Sideritis scardica</i> Griseb. from R. Macedonia.....	95
Bioactive compounds of cold-pressed oil from the seeds of Goji Berry ( <i>Lycium barbarum</i> ).....	96
Development and validation of HPLC method for determination of flavonoids in herbal preparations .....	97
Atomic emission spectrometry with inductively coupled plasma (ICP-AES) analysis of trace elements in <i>Camellia sinensis</i> teas.....	98
Determination of trace elements analyzed by atomic emission spectrometry with inductively coupled plasma (ICP-AES) in <i>Matricaria chamomilla</i> L. teas present on macedonian market..	99
Human health risks from heavy metals via consumption of contaminated food .....	100

Development of an ultrasonic method for effective extraction of capsaicin as a potent bioactive compound.....	101
Electrochemical analysis of the properties of benzene-1,2,4-triol.....	102
Comparison of the procedure for registration of medicines in the European Union and the Republic of Macedonia .....	103
Pharmacoeconomic evaluation of the antibiotic prophylaxis in orthopedic surgeries.....	104
Therapeutic approach in the treatment of benign prostatic hyperplasia.....	105
Oxidative stress, aging and antioxidants.....	106
Oxidative stress, oxidative DNA damage and prostate cancer .....	108
RNA interference (RNAi) mechanism as a basis for future successful treatment of chronic hepatitis B infection .....	110
Anti-cancer target therapy based on drugs conjugated to hyaluronic acid .....	112
Cancer-specific conjugated monoclonal antibodies for anticancer therapy.....	113
Accreditation of the Laboratory of Radiopharmacy – requested requirements or need of challenge .....	115
Quality control of PET radiopharmaceuticals, with reference to its specifics vs quality control of conventional pharmaceuticals .....	117
Production of [ <sup>11</sup> C]Choline in The University Institute for PET – new perspective in diagnostics of prostate malignancy in R. of Macedonia .....	118
PET radiopharmaceuticals in the diagnosis of neurological diseases .....	120
Achievements and perspectives in formulation of stable immunoconjugate of the HER2-targeting trastuzumab – potential for rapid labelling with Gallium-68.....	121

## **ORAL PRESENTATIONS**

# **Step forward of Macedonian Agency for medicines and medical devices**

## **Establishment and strategic plan for development**

**Marija Darkovska – Serafimovska**<sup>1,2</sup>

<sup>1</sup>*Faculty of Medical Sciences, University “Goce Delcev”, Stip, R. Macedonia*

<sup>2</sup>*Macedonian Agency for drugs and medical devices, Skopje, R. Macedonia*

*E-mail address: marija.darkovska@ugd.edu.mk*

### **Abstract**

Macedonian Agency for Medicines and Medical Devices (hereinafter: the Agency) on September 16 2014 has been established as an independent regulatory authority. Founder of the Agency is the Government of the Republic of Macedonia. Institutional building of the Agency is an important part of implementation of national medicines and medical devices policy aimed at ensuring access to medicines meeting recognized EU standards of quality, safety and efficacy as well as access to medical devices, meeting essential requirements set in EU legislation. It can be ensured by setting up efficient regulatory system, so the Agency should quickly develop its capacity in order to be able to ensure unimpeded transition from the Drug Bureau, to ensure its proper development and to play a key role in implementing the said aims. First strategic plan for the development of Macedonian Agency is for the period 2015-2017. This is a key period of action of this institution because it sets the groundwork for future work of the new competent authority for medicines and medical devices, which is built on the foundations of the Bureau of medicines. Agency Strategic Plan reflects not only the present moment, but also our duty to make the best possible way we fulfill our mission and develop the Agency in accordance with our vision. The new legal organizational structure allows us professional independence and the necessary flexibility. The strategic plan of the Agency allows to be based on an analysis of the current situation and the vision of who we want to become at the end of a given period.

### **Keywords**

Macedonian Agency for Medicines and Medical Devices, national medicines, Strategic Plan.

# Adherence to Therapy: A Modern Pharmacotherapeutic Approach

**Zorica Arsova-Sarafinovska**<sup>1, 2</sup>

<sup>1</sup>*Institute of Public Health of the Republic of Macedonia, 50 Divizija 6, 1000 Skopje, Republic of Macedonia*

<sup>2</sup>*University Goce Delcev – Stip, Faculty of Medical Sciences, Krste Misirkov 10-A, Stip, 2000, Republic of Macedonia*

Telephone: (+389-70) 337 572; Fax: (+389-2) 322 33 54; e-mail address: [zorica.arsova@ugd.edu.mk](mailto:zorica.arsova@ugd.edu.mk)

## **Abstract**

Medication adherence is a crucial contributor to effective chronic diseases management. On the contrary, poor adherence leads to significant worsening of disease, death, and increased healthcare costs. Moreover, patient non-adherence is not limited to medications only. It can also take other forms, such as the failure to keep appointments, to follow recommended dietary or other lifestyle changes, and to follow recommended preventive health practices. According to the most recent report of the World Health Organization the global adherence among patients with chronic diseases averages 50 % in developed countries, with rates decreasing as the co-morbidities increase. The rates are lower in developing countries. Over the last decade, extensive research on the efficacy of adherence-enhancing strategies has been done. However, the rates of nonadherence have not changed significantly. One of the most significant improvements has been achieved with the inclusion of the patient in the process of determination of therapy. As a consequence, the term “compliance” was replaced with the term “adherence” seeming to indicate a greater involvement of the patient in the therapy decision making process. The World Health Organization identified five sets of factors that are important for patients to adhere to the long-term therapeutic regimens. These include: the social and economic factors, the health care team and system, the characteristics of the disease (for example, mental or physical disability), the characteristics of the treatment (for example, number of the medicines prescribed, the frequency of administration and side effects), and patient-related factors. In general, medical adherence is better for drugs that provide symptom relief, as opposed to ones used to treat a generally asymptomatic condition. For example, chronic conditions (such as high blood pressure, hyperlipidemia, diabetes, osteoporosis, and depression) are common diseases characterized with few symptoms and poor adherence, consequently. Additionally, studies have shown that compliance rates decrease when the treatment is long-term, involves multiple medications taken concurrently, several times daily. This problem can be overcome by simplifying the therapeutic regime (for example, use of extended-release formulations and / or fixed-dose combination finished pharmaceutical products). Furthermore, medication side effects remain a significant issue. However, the clinical pharmacists can reduce non-adherence suggesting ways to manage minor side effects or identifying alternative treatments with fewer side effects. Educating patients about disease, importance of treatment or prevention, and consequences if not treated, could be successful strategy in enhancing patient adherence. Finally, the frequent follow-up appointments provide an opportunity to discontinue the medication, change the prescription (e.g., dose, frequency) if needed, and overcome barriers responsible for



poor adherence. In conclusion, we should emphasize that a coordinated action from health professionals, researchers and policy makers is needed to achieve progress in this area.

**Keywords**

Medication adherence; compliance; chronic disease; comorbidity.

# Use of disinfectants and antiseptics in selected health institutions in Republic of Macedonia

**Biljana Gjorgjeska**

*Department of Pharmacy, Faculty of Medical Sciences, Goce Delcev University,  
str. "Krstev Misirkov" no.10-A, 2000 Shtip, Republic of Macedonia  
+389 75 499 912, biljana.gorgeska@ugd.edu.mk*

## **Abstract**

**Introduction** - Intra-hospital or hospital infections are caused by organisms acquired during hospitalization of the patient and clinically manifest from 48 to 72 hours after their administration. Disinfection procedures, type and quantity of used disinfectant is directly related to the effects of their use.

**Objective** – The aim of this study was to review of the use of antiseptics and disinfectants in selected hospitals in Republic of Macedonia over five years period, to make analysis of the amount of antiseptics and disinfectants consumed annually on each department in hospitals, to analyze of the total amount of consumed antiseptics and disinfectants in selected hospitals for five years and to compare the results to the microbiological data conducted periodically in each department in hospitals in Strumica, Ohrid, Veles, Stip and Kavadarci for five years.

**Materials and Methods** - Data from the annual reports collected from hospitals in Strumica, Ohrid, Veles, Stip and Kavadarci over five years were used. Data from annual reports for disinfectants and antiseptics (Bactosol, Ecosol, Dezintal, Betadine, Hydrogen peroxide, Formaldehyde, Ethanol) used on the selected departments for gynecology, surgery and transfusion were collected. Data from annual reports collected from public health centers in Strumica, Ohrid, Veles, Stip and Kavadarci over five years were used. Routine testing period for microbiological controls in hospitals was 15 days.

**Results** - The results indicate a significant reduction of contamination with conditionally pathogenic bacteria when disinfection is conducted according to the standardized procedures controlled by the IHI times established in each hospital from 2012. The number of conditionally pathogenic bacteria detected is reduced starting from 2012. The reduction of the quantity of disinfectant used is also noted from 2012.

**Conclusions** - In general disinfectants and antiseptics are used optimally and correctly according to the needs of the hospitals investigated. The amount of disinfectants and antiseptics consumed comparing with the microbiological data indicates their rational utilization starting from 2012. Use of disinfectants according to the standardized procedures established by the IHI times allows current daily care for patients and staff in the hospitals investigated. The processed data from public health centers in Strumica, Ohrid, Veles, Stip and Kavadarci confirm the above and point out the precautions to be taken when conditionally pathogenic bacteria have been detected. It is pointed out the role of IHI times in the hospitals, as well as the role of hospital pharmacists. We would like to suggest the implementation of disinfection process validation as standardization measure as well as more often routine microbiological controls in the hospitals.

## **Keywords**

disinfectants, antiseptics, disinfection.

# Code of Ethics for Pharmacists – Pharmaceutical Chamber of Macedonia

***Prof. Bistra Angelovska, PhD***

*University “Goce Delcev”, Faculty of Medical Sciences*

[\*bistra.angelovska@ugd.edu.mk\*](mailto:bistra.angelovska@ugd.edu.mk)

## **Abstract**

Code of ethics represents the principles that form the fundamental basis of the roles and responsibilities of pharmacists in pharmaceutical practice.

According to pharmacy practice, pharmacists are confirmed as healthcare professionals with unique knowledge, skills and responsibilities for safe and efficient medication therapy management in order to optimize therapeutic outcomes.

The scope of pharmacy practice includes technical aspects of pharmaceutical services, the preparation of pharmaceutical dosage forms, drug supply and also patient care services.

Therefore, Pharmaceutical Chamber of Macedonia, as professional association of pharmacists, in accordance with Code of Ethics, promotes the basic principles of professional ethics of pharmacists in order to establish professional behavior in implementation of pharmaceutical care.

## **Keywords**

Code of ethics, pharmacists, Pharmaceutical Chamber of Macedonia.

## 4-Hydroxynonenal – major bioactive marker of lipid peroxidation

**Neven Zarkovic<sup>1</sup> & Kamelija Zarkovic<sup>2</sup>**

1- LabOS Rudjer Boskovic Institute, Zagreb, Croatia

Tel.+385 (0)1 4560 937; Fax.+385 (0)1 456 1010

[zarkovic@irb.hr](mailto:zarkovic@irb.hr)

2 - University of Zagreb School of Medicine

Clinical Hospital Centre Zagreb, Division of Pathology, Croatia

### **Abstract**

While oxidative stress is generally considered mostly as pathogenic component of stress and age associated diseases, reactive aldehydes such as 4-hydroxy-2-nonenal (HNE) are considered mostly as the end-products of lipid peroxidation, which act as a “second toxic messenger of free radicals”. However, findings of growth regulating activities of HNE that overlapped with the development of the first monoclonal and polyclonal antibodies specific for the HNE-protein adducts led to the introduction of qualitative and quantitative determinations of the HNE presence in various (patho)physiological processes and to the change of consideration of the aldehyde’s bioactivities from toxicity into cell signaling, growth regulation and hormesis.

Thus, the progress in the fields of the redox signaling and broad bioactivities or reactive oxygen and nitrogen species changed our overall approach to oxidative stress and to consideration of HNE not only as toxic but more general as a “second messenger of free radicals” and the growth regulating factor. Moreover, findings of the HNE-protein adducts in various organs under physiological circumstances support the concept of “oxidative homeostasis”, which implies that oxidative stress and lipid peroxidation are not only pathological but also physiological processes. Accordingly, HNE could play important role in oxidative homeostasis, while complementary research approaches might reveal the relevance of the aldehydic-protein adducts as major bioactive markers of oxidative stress, lipid peroxidation and oxidative homeostasis.

### **Keywords**

4-Hydroxynonenal, lipid peroxidation, oxidative stress, pathophysiology, reactive aldehydes.

# Nicotinamide adenine dinucleotide biosynthesis and consumption in dysfunctional white adipocytes

***Tatjana Ruskovska***<sup>1</sup>, David Bernlohr<sup>2</sup>

<sup>1</sup>Faculty of Medical Sciences, Goce Delcev University, Stip, Republic of Macedonia

<sup>2</sup>Department of Biochemistry, Molecular Biology and Biophysics, University of Minnesota  
- Twin Cities, U.S.

Presenter's e-mail address: [tatjana.ruskovska@ugd.edu.mk](mailto:tatjana.ruskovska@ugd.edu.mk)

## **Abstract**

In addition to its role in storage of dietary energy in a highly concentrated form, the white adipose tissue (WAT) is an active endocrine organ that regulates various physiological processes in the body. It plays a central role in insulin responsiveness and energy homeostasis, which is mediated by the action of a wide range of biologically active molecules - adipokines.

During its "remodeling", the obese WAT becomes inflamed and dysfunctional, which causes insulin resistance. Dysfunctional WAT in obesity exhibits increased production of reactive oxygen species (ROS) and decreased activity of some of the key antioxidant enzymes, which leads to oxidative stress. Indeed, protein carbonyls in the visceral adipose tissue are considered as a reliable biomarker of the level of oxidative stress in this tissue. Their negative correlation with serum adiponectin is indicative of systemic effects of oxidative stress in the visceral WAT.

Glutathione S-transferase isoform A4 (GSTA4) has an important role in protection of the white adipocytes from oxidative stress and protein carbonylation. However, Gsta4 is downregulated in adipocytes treated with tumor necrosis factor  $\alpha$  (TNF $\alpha$ ), as well as in adipose tissue from obese mice, suggesting the link between oxidative stress, inflammation and insulin resistance.

Gsta4 silenced 3T3L1s are a good experimental model to study the consequences of oxidative stress in dysfunctional adipocytes in obesity induced insulin resistance. Among other findings, it has been shown that the expression of Sirtuin 3 (Sirt3) is decreased in Gsta4 silenced 3T3-L1 adipocytes (Bernlohr lab., unpublished results).

Sirtuins are enzymes that deacetylate lysine residues on both histone and nonhistone proteins. Mammals have seven sirtuins with different subcellular localization. SIRT3 is located in mitochondria. There is evidence that SIRT3 can delay the onset of a number of oxidative stress- and age-related pathologies. Sirtuin activity is nicotinamide adenine dinucleotide (NAD<sup>+</sup>) dependent and is directly linked to the energetic and redox status of the cell.

We explored the expression of some of the key genes involved in NAD<sup>+</sup> biosynthesis and consumption in a model of inflamed white adipocytes. Our experiments demonstrated a significant disturbance of NAD<sup>+</sup> metabolism, and decreased Sirt3 expression. These findings indicate that Sirt3 and NAD<sup>+</sup> pathway can be considered as potential therapeutic targets in obesity induced insulin resistance.

## **Keywords**

Adipocyte, Insulin resistance, Nicotinamide adenine dinucleotide, Oxidative stress, Sirtuin.

## **New Insights into the Chemistry and Functions of Coenzyme Q**

**Rubin Gulaboski**<sup>1,2,3,4</sup>, Valentin Mirceski<sup>2</sup>, Ivan Bogeski<sup>4</sup>, Sasa Mitrev<sup>3</sup>, Kokoskarova Pavlinka<sup>2</sup>, Velo Markovski<sup>2</sup>, Reinhard Kapp<sup>4</sup>, Markus Hoth<sup>4</sup>

<sup>1</sup>Faculty of Medical Sciences, "Goce Delcev" University, Stip, Macedonia

<sup>2</sup>Faculty of Natural Sciences and Mathematics, "Ss Kiril i Metodij" University, Skopje, Macedonia

<sup>3</sup>Faculty of Agriculture, "Goce Delcev" University, Stip, Macedonia

<sup>4</sup>Faculty of Medicine, Saarland University, Homburg, Germany

Email address: rubin.gulaboski@ugd.edu.mk

### **Abstract**

The oxidative phosphorylation is a crucial physiological process that leads to energy production in the living cells. In this processes, Coenzyme Q10 acts as a redox mediator in the mitochondrial membrane, where it facilitates the electron transfer between the complexes I, II and III, while transferring protons across the inner mitochondrial membrane. We have recently shown that Coenzyme Q undergoes structural changes in highly alkaline media, but also in neutral media in presence of Cytochrome P-450 enzymes. The chemical reactions of Coenzyme Q with NaOH or with Cytochrome P-450 lead to scission of one or two methoxy groups from the Coenzyme Q structure, while giving as products hydroxyl derivatives of Coenzyme Q. The new hydroxylated Coenzyme Q derivatives have a chemical potential to bind Ca<sup>2+</sup> and other earth-alkaline cations, and to transfer them across biomimetic membranes. Additionally, the newly synthesized hydroxyl Coenzyme Q derivatives can act as powerful antioxidants. The findings elaborated in this lecture explicitly show that the processes in the mitochondrial electron transfer chain can be switched in another direction under certain physiological conditions.

### **Keywords**

Antioxidants, Calcium transport, Coenzyme Q, Electrochemistry, Reactive Oxygen Species.

# Genetically modified systems to study muscular dystrophies

**Darko Bosnakovski**

*Faculty of Medical Sciences, University Goce Delcev, Stip 2000, R. Macedonia  
darko.bosnakovski@ugd.edu*

## **Abstract**

We developed different approaches to utilize genetically modified cells and animal models to understand molecular mechanism of Facioscapulohumeral muscular dystrophy (FSHD).

Main obstacle with primary cell lines is to obtain sufficient number of tissue specific progenitors that will be able extensively to proliferate and maintain the phenotype to be used for relevant in vitro studies. As an alternative solution for obtaining appropriate cells are induced pluripotent stem (IPS) cells. IPS cells can be made from different somatic cells by cell reprogramming. Patient specific IPS cells retain the genotype of the patient, they are good models to study molecular mechanism of diseases and they are suitable for autologous cell transplantations. We generated IPS cells from myoblasts from FSHD patients using common reprogramming factors (Oct4, Sox2, KLF4 and c-Myc), incorporated in viral vectors. Mesenchymal stem cells were obtained by differentiation of IPS cells in 3D culture conditions in presence of cocktail of growth factors. Myogenic progenitors were obtained by overexpressing Myf5 in mesenchymal cell fraction. Generated cells revealed typical characteristics of myoblast and were able functionally to recover damaged mouse muscle. Furthermore, we were able to genetically correct affected locus in FSHD IPS cells by removing 4qA161 allele using zinc finger nucleases. Gene corrected cells did not express DUX4 and displayed normal myogenic properties compared to the affected ones.

To be able to study FSHD in vivo and test various therapy approaches we developed transgenic mouse model that has incorporated DUX4 gene on X chromosome. IDUX4 mouse expressed DUX4 in different tissue. Male pups have runt phenotype, with prominent skin, testis and retina pathological changes.

In this talk, advantages and methods for cell manipulations for generating in vitro and in vivo diseases models will be discussed.

## **Keywords**

FSHD, IPS cells, animal models, myogenesis.

# Counteracting microbial biofilm formation onto dental materials

**Lia Rimondini**

*Università del Piemonte Orientale - Department of Health Sciences,  
via Solaroli 17, 28100 Novara Italy  
Tel. + 39 0321 660673 - email: [lia.rimondini@uniupo.it](mailto:lia.rimondini@uniupo.it)*

## **Abstract**

Bacterial contamination of dental materials is a common cause of their failure. Microbial contamination of the biomaterials differs from that of natural tissues. In fact, the contamination modalities of medical devices depend on many peculiar factors related to them: the chemistry of the biomaterial, the physical properties of the surface, the design of the medical device, the extension of surgical invasion, and the time of application. The environment and/or the conditions and response of the host also contribute to the development of infection.

Viruses, fungi, protozoa and bacteria are all involved in biomaterial contamination. They are endogenous commensals of the mouth, not virulent in planktonic form, but pathogens when arranged in biofilm. In this presentation the physical chemical aspects of the materials surfaces that mainly affect the biofilm formation will be reviewed. The current available strategies to develop materials with intrinsic antibacterial properties bioactive coatings with bactericide agents including Gallium and Silver doping and nanostructured anti-adhesion surfaces including anatase will be presented. Technologies to clinically remove biofilm and counteract its re-formation will be discussed.

## **Keywords**

Bacteria, biofilm, dental materials, surface.



# **The endless potential of the umbilical cord blood for investigation, research and treatment**

**Prof d-r Elizabeta Zisovska**

*Agency for Quality and Accreditation of Healthcare Institutions, Skopje, Macedonia*

## **Abstract**

The umbilical cord is not only tissue, but a whole organ connecting mother and fetus. Many of the UCB features can be used for research and therapeutic purposes, because of the following properties: biochemical analysis of blood gasses, full blood count, bilirubin; testing for abnormalities in 24-32 gestational week; catheterization of the cord blood vessels is the best way to reach neonatal circulation, and can be used as a route for venous catheter (infusion and medication, performing blood exchange in hemolytic disease of the newborn); immunological analysis for determination of the blood group, Rhesus factor, etc.; delayed cord clamping can prevent from anemia of prematurity and therefore improving their health status.

UCB has become a new obstetrical trend. It means that the UCB, a once discarded material, is an organ that could be transplanted to either oneself or to another recipient, because of the relative immaturity compared to adult cell sources, having higher proportion of immature T-lymphocytes and decreased numbers of mature memory T-lymphocytes. UCB cells also produce fewer absolute levels of cytokines than adult cell sources. This lack of mature immune function is attributed to UCB's low incidence of Graft versus Host Disease (GvHD) and viral transmission. Such cellular constitution could allow for less stringent donor–recipient matching requirements, hence leading to shorter waiting period for treatment. UCB contains a large population of hematopoietic stem/progenitor cells compared to adult sources. These easily procured, low immunogenic sources of multipotential cells are thought to have the capability to become any type of cell in the body under specific conditions. The non-hematopoietic stem cell, the mesenchymal stem cell (MSC) can give rise to such diverse phenotypes as osteoblasts, chondroblasts, adipocytes, and hematopoietic and neural cells (astrocytes and neurons) because they are multipotent. The advantages of the UCB compared to bone marrow in treatment of leukemia and other diseases mainly are the following: no risk or discomfort to donors, lower incidence of viral contamination (38.2%) compared to BM, able to be stored at cryogenic temperatures indefinitely without significantly affecting cell viability, immediately available and easily shipped and many others. There is a high immune tolerance of UCB cells because they are unable to generate cytotoxic T-Lymphocytes, which respond to allogenic antigens.

The most recent researches on animals have demonstrated UCB's growth as a multidimensional treatment, mostly as a neurotrophic, neuroprotective, and anti-inflammatory agent.

But, besides many advantages, there are some hazardous effects of the UBC. In multiple American and international studies, cancer-causing chemicals have been found in the blood of umbilical cords. These originate from certain plastics, computer circuit boards, fumes and synthetic fragrances. Over 300 toxic chemicals have been found, including bisphenol, tetrabromobisphenol A teflon-related perfluorooctanoic galaxolide, and many other air pollutants among others.

The research will never come to its end, because the umbilical cord is one of the most unexplored organ, and on the other hand, the most harmless target organ for research.

**Keywords**

umbilical cord, blood, research.

# The cytokinesis-blocked micronucleus assay: Good choice for detection and evaluation of genotoxicity in human cells

Velickova, N., **Milev, M.**, Petrova, B., Gorgieva, P., Nedeljkovic, B.

Faculty of medical science, University "Goce Delcev" – 2000 Stip, R. Macedonia

presenting author phone +38978477313, e-mail [misko.milev@ugd.edu.mk](mailto:misko.milev@ugd.edu.mk)

## **Abstract**

**Introduction:** Chromosomal damage measurement is one of important ways to evaluate the toxicity, carcinogenicity, and mutagenicity of drugs, chemicals, and rays. Measurement of micronucleus (MN) frequency in lymphocytes is extensively used to evaluate the presence and the extent of chromosomal damage in human populations exposed to genotoxic agents or bearing a susceptible genetic profile.

The aim of this study was to evaluate the effect of ionizing radiation on peripheral lymphocytes using the MN assay and to determine the level of genetic damage. The study population included 20 individuals in the exposed group of medical personnel who are professionally exposed to ionizing rays and 20 individuals in the control group (healthy people who have never been exposed to ionizing rays and other chemical or physical agents).

**Results:** The mean of MN frequencies in the exposed group increased in comparison with the mean of MN frequencies in the control group. Although men dominated the exposed group, all the women from this group showed increased MN frequency. Clear evidence of increased number of MN formation appeared in smoking women within the control group. Also, we found BN cells with nucleoplasmic bridges (NPBs) and binucleated cell with nuclear buds (NBUDs).

**Conclusion:** The formation of small and large micronuclei indicates that medical personnel who are exposed on radiation in their work place, have a chromosomal instability and a risk of cancer.

## **Keywords**

Micronucleus, lymphocytes, genotoxicity, ionizing radiation, cancer.

# Multiple predictive model for clinical and subclinical depression in adolescence

**Lence Miloseva**<sup>1</sup>, Tatjana Vukosavljevic-Gvozden<sup>2</sup>

<sup>1</sup>University Goce Delcev Stip, Faculty of Medical Science, R. Macedonia

<sup>2</sup>University of Belgrade, Dept. of Clinical Psychology, R. Serbia

lence.miloseva@ugd.edu.mk

## **Abstract**

**Introduction:** Identification of potential groups of differences and similarities between clinical and subclinical depression in adolescence, compared to the risk factors of cognitive vulnerability and psychosocial risk factors, contributes to shedding light on the etiological picture of clinical and subclinical depression.

**Objectives:** The present study investigated whether we can build multiple predictive model for clinical and subclinical depression in adolescence, based on risk factors of cognitive vulnerability and psychosocial risk factors.

**Material and Methods:** Multiple predictive model for group membership in three groups: clinical, subclinical and control group, has been built by using canonical discriminant analysis. The final survey sample consists of 412 adolescents (61.7% female and 38.3% male) aged 13-17 years. The data were collected from Psychiatric wards and Centers for Mental Health for children and adolescents from three Clinics in Macedonia (for clinical sample) and schools (for subclinical and control sample) during last four years, including one year of pilot study for psychological instruments.

Cognitive vulnerability factors for depression (dysfunctional attitudes, negative inferential style, ruminative response style) and psychosocial risk factors (negative life events and perceived social support) were measured by a set of psychological instruments.

**Results:** The discriminant analysis showed that it was possible to statistically significantly distinguish groups on the basis of the mentioned predictors and it allocated two discriminant functions. The overall test of the first discriminant function was significant ( $p < .001$ ) indicating that scores discriminated between the three groups accounting for 99.3% of the total variance of depression. The first discriminant function consists of all listed predictors, ruminative response style, dysfunctional attitudes, negative inferential style, and negative life events in a positive direction and perceived social support in a negative direction, and in this function the highest scores are for the clinical and the lowest for the control subjects. Subclinical respondents were in-between. The overall test of the second discriminant function was significant ( $p < .001$ ) indicating that scores discriminated between the three groups accounting for 0.7% of the total variance of depression. Only ruminative response style makes the second discriminant function and the subclinical sample has the highest scores, while the clinical sample has the lowest. The control group is in-between.

**Conclusion:** We have confirmed our expectations that we can build multi predictive model of clinical and subclinical depression in adolescence. The clinical, subclinical group and control group differ significantly with respect to the factors of cognitive vulnerability and psychosocial risk factors. We believe that this research has scientific and applicative value and that it has not only theoretical and empirical contributions, but has contributions to clinical practice as well.

## **Keywords**

adolescence, clinical depression, predictive model, risk factors, subclinical depression.

# Molecular Imaging and therapy with radionuclides of prostate cancer

**Adriano Duatti**

*Department of Chemical and Pharmaceutical Sciences, University of Ferrara, Italy  
adriano.duatti@unife.it*

## **Abstract**

Prostate cancer (PC) is the most common type of cancer in men worldwide leading to substantial morbidity and mortality. At present, imaging of PC is indicated for primary diagnosis, staging and re-staging, as well as for the detection of (biochemical) recurrent disease. Currently, conventional imaging modalities, including ultrasound, bone scintigraphy, and computed tomography (CT) are used to detect primary and metastatic PC for staging and risk stratification. Despite significant efforts, conventional imaging of PC does not contribute to patient management and do not allow tumor-specific imaging. Radionuclide imaging techniques such as single-photon emission computed tomography(SPECT/CT) and positron emission tomography (PET)/CT provide both high sensitivity to detect tumor lesions, and characterization of the disease at the molecular level (molecular imaging).

Choline radiolabeled with C-11 or F-18 is currently used as PET tracer for (re)staging of PC. Since choline is a key precursor in the biosynthesis of phosphatidylcholine, a major component of the cell membrane, increased levels of total choline incorporation have been observed in several malignancies. However, this molecular approach has limited sensitivity due to the lack of target specificity inherently to its uptake mechanism.

The prostate-specific membrane antigen (PSMA) is a type II integral membrane glycoprotein that is selectively overexpressed in 90-100% of local PC lesions, as well as in cancerous lymph nodes, and bone metastases. Increased PSMA expression is correlated with an increase in tumor grade, pathological stage, aneuploidy, and biochemical recurrence. Most importantly, PSMA expression is upregulated when tumors become androgen-independent, showing elevated PSMA expression after anti-androgen therapy. This characteristic makes PSMA a reliable tissue marker for PC and is considered an ideal target for theranostic applications.

Imaging probes specifically targeting PSMA are actively investigated and a number of highly promising agents radiolabeled with Tc-99m, F-18, Cu-64 and Ga-68 are currently under extensive clinical evaluation. Besides diagnostic imaging, radiolabeled PSMA ligands also have potential for radionuclide therapy of PC and a new therapeutic agent radiolabeled with Lu-177 has been developed and tested in patients. These promising preliminary clinical data encourage further studies to evaluate the potential for diagnosis and therapy (theranostic) of PC using PSMA ligands. The added value of this therapeutic regimen needs to be compared to conventional PC therapies.

Recently, it has been surprisingly reported the observation of high and specific accumulation of copper ions in prostate cancer cells after administration of Cu-64 under the simple chemical form of dichloride salt. This result will open a new and unexpected route to PC diagnosis and treatment since the nuclear characteristics of Cu-64 allow using this radionuclide as both imaging and therapeutic agent. Clinical studies in patients are ongoing and showing high potential for this new approach.

In this presentation, the clinical status of radiopharmaceuticals for theranostic applications in PC will be discussed.

**Keywords**

Prostate cancer, Molecular imaging, Imaging probes, radiopharmaceuticals.

## Where Nanotechnology and Nanomedicine meet – Applications and Potential Risks

Vaso Taleski<sup>1</sup>, Darko Bosnakovski<sup>1</sup>, Milka Zdravkovska<sup>1</sup>, Velo Markoski<sup>1</sup>, Zdenka Stojanovska<sup>1</sup>, Svetlana Jovevska<sup>1</sup>,

<sup>1</sup>Faculty of Medical Sciences, Univ. „Goce Delchev“ Shtip, Republic of Macedonia

Presenter's telephone 389 70 266 822, e-mail address: vaso.taleski@ugd.edu.mk

### **Abstract**

Most definitions describing concept of nanotechnology includes control, understanding, design, imaging, measuring and manipulating matter at dimensions between 1 and 100 nanometers. Nano-structure poses unique physical, chemical and biological properties exclusively due to its nanoscale dimensions, significantly different from the properties of bulk materials and single atoms or molecules. Gravity loses impact and importance, surface tension and Van der Waals constants has more importance in system of nano particles. Extremely small size enables nano particles to enter the human body through usual or unusual routes, pass through cell membranes, cross the blood-brain barrier and access new sites, interact with DNA or small proteins at different levels, in blood or within organs, tissues or cells.

Nowadays nanotechnology is being used in a range of applications, with potential to be applied at any stage in food industry: production, processing, packaging, labelling, transporting, tracing, keeping the quality of food product and extend the product shelf-life.

The use of nanotechnologies to solve medical problems can dramatically improve the quality of life. Nanomedicine has the potential to enable early detection, prevention and significantly improve diagnosis, treatment and follow-up of many diseases.

Based on nano (bio) sensors, rapid and sensitive detection of pathogenic bacteria and trace levels of viruses in small sample volumes and lower costs than current in-use technologies are developed. Early detection enables accurate and prompt treatment. Likewise, sensors to detect biofilm formation by bacteria on surfaces are developing

Over 70 products are under clinical trials, covering important diseases including cardiovascular, neurodegenerative, musculoskeletal and inflammatory (such as cancer, atherosclerosis, diabetes, eye diseases, antimicrobial resistance, tissue engineering, Alzheimer disease, arthritis). Nanomedicine delivered over 70 products, including nano-delivery, pharmaceuticals, imaging, diagnostics and biomaterials. Researchers have developed "nano-sponges" that absorb toxins and remove them from the bloodstream, absorb free radicals, monitor the level of nitric oxide (which indicate inflammation, important to monitor inflammatory diseases) in the bloodstream.

Nanomedicine is understood to be a key enabling instrument for targeted and regenerative medicine by delivering of drugs (increases efficiency and minimizes side effects), treatments, implantable devices, early diagnosis of cancers, accurate cancer imaging, cancer therapy and drug delivery.

Multy drug resistant microorganisms present one of the most serious and increasing global, public health threat. This problem causes approximately 25,000 deaths each year and over 1.5 billion expenses in healthcare and productivity losses in Europe.

New strategies to combat MDR are urgently needed and nanomaterials are very promising approach. Metal nanomaterials (silver, gold, copper, titanium, zinc, magnesium, cadmium and alumina) possess unique antimicrobial activities. Silver ions showed strongest bactericidal effect.

Regenerative medicine based on tissue engineering is currently a great exciting challenge for science and industry.

Nanoparticles are also used to stimulate the body's innate repair mechanisms, artificial activation and control of adult stem cells and to deliver vaccine, allowing a stronger immune response

Nanomedicine provides important new tools to deal with the grand challenge of an ageing population.

Future applications of nanomedicine will be based on the ability to build nanorobots. These nanorobots could be programmed to repair specific diseased cells („genetic surgery“), functioning in a similar way to antibodies in our natural healing processes and elimination of bacterial infection. Intense research is going on to make changes in the DNA structure of human beings as it can bring about a way to cure gene-related diseases.

Risks of nanotechnology are still unknown and unpredictable.

Potential problem with is the lack of knowledge and understanding the impact these products will have on the nanoscale. Initial scientific studies showed negative effects on living organisms and a potential for serious threat to human health in connection with disposal of nanowaste and environmental contamination. Scientists are primarily concerned with toxicity, characterization and exposure pathways.

Number of ethical and societal concerns raised, ranging from possible health risks of using or consuming nanoenabled products, intellectual property rights governing them, and the new challenges they may raise.

There are concerns that strong economic competition may be taking precedence over scientific prudence when it comes to public health and the potential dangers of nanotechnology.

However, currently the benefits of nanomedicine definitely outweigh the risks.

## **Keywords**

antimicrobial, ions, nanoparticles, nanomedicine, nanotechnology.



# The role of molecular cocrystals in drug development

***Aleksandar Cvetkovski, PhD***

*Faculty of Medical Sciences, University "Goce Delcev", Stip, R. Macedonia*

*aleksandar.cvetkovski@ugd.edu.mk*

## **Abstract**

The selection of the crystalline phases in a form of molecular cocrystals has become scientific challenge at the early stage of drug development of pharmaceutical formulations and in the late stage of synthesis and isolation of Active Pharmaceutical Ingredients (APIs) in desirable defined crystalline forms. Optimal crystal form of API interactively interrelates and impacts its aqueous solubility and dissolution rate that are benchmark for drug delivery and absorption determining the extent of its bioavailability and pharmacokinetics profile. Hence, determining the crystal structure and revealing the crystal packing forces and geometry of the API impact upon its physicochemical properties what it is a threshold for controlling the performance of the API. The range of crystal forms in which molecular cocrystals of APIs may exist are advantageous comparing to its polymorphs, salts, solvates and hydrates due to the vast number of potential cofomers which extend the limited counterions for salt formation implying the existence of more complex intermolecular interactions based on different H-bonding patterns with API that lead to conformational changes and flexibility for crystal packing in process of cocrystallization.

Selected case-studies of cocrystallization screening reveals determined crystal structures of pharmaceutical cocrystals composed of APIs that belong to different pharmacotherapy and functional group classes, respectively. The case study underline the crystal growth and the method of preparation for "drug-drug" type of pharmaceutical cocrystals wherein two different APIs cocrystallized in single crystal cell, and that represent new paradigm for approaching in development of "fixed-doses" or "combo" pharmaceutical formulations. Preliminary results of the Structure-Activity Relationship study on the cocrystals composed of metformin with dichloroacetic acid indicate dual and complementary pharmacological activities of the two selected drug models for cocrystallization.

## **Keywords**

Active Pharmaceutical Ingredients, molecular cocrystals, pharmaceutical cocrystals.

# Drug development based on radiolabeled antibodies

**Prof. Emilija Janevik**

*University Goce Delcev, Faculty of medical sciences*  
[emilija.janevik@ugd.edu.mk](mailto:emilija.janevik@ugd.edu.mk)

## **Abstract**

During the past decade, the efficacy of new molecular targeted drugs such as monoclonal antibodies has been proven worldwide, and molecular targeted therapies have become the mainstream in cancer therapy. However, clinical use of these new drugs presents unexpected adverse effects or poor therapeutic effects. Therefore, it was require diagnostic tools to estimate the target molecule status in cancer tissues and predict therapeutic efficacy and adverse effects. Although immunohistochemical, polymerase chain reaction (PCR) and fluorescence in situ hybridization (FISH) analyses of biopsy samples are conventional and popular for this diagnostic purpose, molecular imaging modalities such as positron emission tomography (PET) and single photon emission computed tomography (SPECT) are also useful for noninvasive estimation of gene and protein expression and drug pharmacokinetics and in the same time using beta and alfa radionuclide to shoe therapeutical efficacy.

This presentation is a short review of the antibodies that are already used in preclinical and clinical application and to introduce new radiolabeled antibodies, and their clinical application in molecular targeted therapy and discuss the issues of these imaging probes.

Radiolabeling techniques for labeling of antibodies are well established and radiolabeled antibodies are a clinical and commercial reality that deserves further studies to advance their application in earlier phase of the diseases and to test combination and adjuvant therapies including radiolabeled antibodies in hematological diseases. In solid tumors, more resistant to radiations and less accessible to large molecules such as antibodies, clinical efficacy remains limited. However, radiolabeled antibodies used in minimal or small-size metastatic disease have shown promising clinical efficacy. In the adjuvant setting, ongoing clinical trials show impressive increase in survival in otherwise unmanageable tumors. New technologies are being developed over the years: recombinant antibodies and pretargeting approaches have shown potential in increasing the therapeutic index of radiolabeled antibodies. In several cases, clinical trials have confirmed preclinical studies. Finally, new radionuclides, such as lutetium-177, with better physical properties will further improve the safety of radioimmunotherapy. Alpha particle and Auger electron emitters offer the theoretical possibility to kill isolated tumor cells and microscopic clusters of tumor cells, opening the perspective of killing the last tumor cell, which is the ultimate challenge in cancer therapy. Preliminary preclinical and preliminary clinical results confirm the feasibility of this approach.

## **Keywords**

molecular targeted therapies, radiolabeled antibodies, radionuclides.

## **POSTER PRESENTATIONS**

# Correlation between dynamic balance and gait parameters in patients with ischemic stroke in the chronic period

**Vasileva D<sup>1</sup>**, Lubenova D, PhD<sup>2</sup>, Mihova M, PhD<sup>3</sup>, Maznev I, PhD<sup>4</sup>, Nikolovska L, PhD<sup>1</sup>, Jihe Dz, PhD<sup>1</sup>

<sup>1</sup> Faculty of Medical Sciences - University "Goce Delchev" – Shtip, Macedonia

<sup>2</sup> Department of "Kinesitherapy and rehabilitation" - Faculty of kinesitherapy, tourism and sports animation, National Sports Academy "Vasil Levski", Sofia, Bulgaria

<sup>3</sup> Faculty of Computer Sciences and engineering – University "Ss. Cyril and Methodius" – Skopje, Macedonia

<sup>4</sup> Department of "Sports medicine" - Faculty of kinesitherapy, tourism and sports animation, National Sports Academy "Vasil Levski", Sofia, Bulgaria

Address for correspondence:

Dance Vasileva, MSc

Telephone: 00389 78 493 331

e-mail: dance.vasileva@ugd.edu.mk

## **Abstract**

The aim of the study was to trace the correlation between dynamic balance and gait parameters during the application of specialized kinesitherapeutic methodology (SKTM) in patients with ischemic stroke in the chronic period (ISChP) which is developed on the grounds of the principles of motor control, motor learning and modern guidelines for neurodevelopment treatment (NDT).

## **Material and Methods**

The study was conducted with 56 patients with ISChP. The Berg Balance Scale is used for the evaluation of the balance reactions. Tracking changes in gait before and after the applied treatment is evaluated cadence of gait and maximum speed of movement. To determine the cadence, the number of steps is measured for covering 6 meters and 10 meters. The maximum speed of the gait is determined in m / min by dividing undergone distance (m) / time (min), for which they have walked it. All indicators were assessed at the baseline, on the 10th day, 1st month and 3rd months after the beginning of the kinesitherapy. The patients studied were treated with a specialized 10-day kinesitherapy, which later continues to be performed by patients as an adapted exercise program at home for a period of three months.

## **Results**

After applying SKTM, the highest tendency towards improvement in dynamic balance and gait is established in the 1st month, with a level of significance  $p = 0.000$ . The correlations between the studied parameters were most visible in the 1st month after the start of the applied SKTM with a significance level of  $p < 0.01$ .

## **Conclusion**

The applied specialized kinesitherapeutic methodology continued later as an adapted exercise program at home, significantly improving the dynamic balance and gait parameters in patients with functional impairment due to ISChP.

## **Keywords**

Dynamic balance, Gait, Ischemic stroke, Neurodevelopmental treatment, Kinesitherapy.

## Effect of kinesitherapy on physical activity in patient with Guillain-Barré syndrome

*Dimitrova A<sup>1</sup>, Grigorova-Petrova Kr<sup>1</sup>, Lubenova D<sup>1</sup>, **Vasileva D<sup>2</sup>**, Nikolova M<sup>1</sup>*  
*<sup>1</sup>Faculty of Kinesitherapy, Tourism and Sports Animation, National Sports Academy  
"Vassil Levski ", Sofia, Bulgaria*  
*<sup>2</sup>Faculty of Medical Sciences, University "Goce Delcev", Shtip, Macedonia*  
telephone: 00389 78 493 331  
E-mail: dance.vasileva@ugd.edu.mk  
Faculty of Medical Sciences, University "Goce Delcev", Shtip, Macedonia

### **Abstract**

**Introduction:** Guillain-Barré syndrome is an autoimmune disease characterized by sudden onset and progressive impairment of peripheral nerves. It is a rare disorder in which weakness and tingling in the extremities are usually the first symptoms.

**Aim:** To study the influence of the applied kinesitherapy in a patient with Guillain-Barré syndrome with severe and protracted course of the disease by deterioration with Landry ascending paralysis and assisted breathing.

**Material and Methods:** The study was conducted with a female, 34 years old in the subacute stage within two months at home. The kinesitherapy sessions are performed 2-3 times per week with 1-hour duration, moderate intensity, more breaks between exercises without reaching fatigue. We applied correct positioning in bed and seating, passive-active exercises, analytical exercises for upper and lower limbs, breathing exercises, training balance and coordination of sitting and standing and massage techniques. To monitor the effect of kinesitherapy the patient performed twice tests for transfers (turning from lying on his back to the left and right side; lying to sitting and sitting to standing). We use also the test "Five Times Sit To Stand" which is appropriate to assess the possibilities for transfer.

**Results and Discussion:** The results showed an improvement in the speed of response of the patient for changing the body position and transfer due to systematic applying of various therapeutic exercises including exercises for strength of lower limbs and abdominal muscles. The time for performing the test "Five Times Sit To Stand" decreased with 33 sec, which is indicative of the strength of the lower limbs and a big step towards the independence of the patient. The correct position of the body and speed is essential. If the speed of movement of the trunk is less, then it will be a greater loading of the lower extremities. The test also aims to establish coordination and consistency of movements between the trunk and lower limbs.

**Conclusion:** After a two-month kinesitherapy an improvement of functional status of the patient was observed.

### **Key words:**

Guillain-Barré syndrome, kinesitherapy, physical mobility.

## Case Report : Oligoasthenoteratozoospermia, treatment with acupuncture

*B.Arsovska<sup>1</sup>, J. Zhu<sup>2</sup>, D.Vasileva<sup>2</sup>, A. Sterjovska-Aleksovska<sup>2</sup>, **K. Kozovska**<sup>2</sup>  
Institute of Biology, Faculty of Natural Sciences and Mathematics – Skopje,  
Macedonia<sup>1</sup>;  
Faculty of Medical Sciences, University Goce Delchev – Shtip, Macedonia<sup>2</sup>  
071-557-345; kika\_1993\_@hotmail.com*

### **Abstract**

**Background** - Oligoasthenoteratozoospermia (OAT) is one of the most common causes of male infertility. This condition includes oligozoospermia (lower number of sperm), asthenozoospermia (poor sperm movement) and teratozoospermia (abnormal sperm shape). The quality of semen can be affected by smoking cigarettes or marijuana, alcohol, medications, hormone preparations, varicocele, infections, genetics etc or it can be idiopathic when the cause for the condition is unclear. Acupuncture is very often used to enhance male fertility. With acupuncture the sperm quality and production can be increased, hormonal factor can be corrected by restoring balance to the entire body and mechanical blockages can be dissolved or reduced.

**Purpose** - The main purpose of this work is to show a case of oligoasthenoteratozoospermia, the results before and after the treatment with acupuncture and the effectiveness of the treatment in the cases of man's infertility.

**Methods** – The acupuncture treatment was done in 'Tong da Tang' clinic for Traditional Chinese Medicine and acupuncture in Skopje. The patient is 35 year old male diagnosed with moderate degree oligoasthenoteratozoospermia according to the criteria of WHO and KRUGGER. The patient noticed the condition two years ago. The condition is not genetic, no infections were diagnosed and no other symptoms were present. The patient is non-smoker, active and hard-working 12-13 hours a day. The patient done 7 treatments in a period of two weeks. The duration of the treatments was 35-40 minutes. The needles were sterile with 0.25x25mm dimensions, made by Wuijiang City Medical Health Material Co., LTD. The acupoints that were used in the treatment are: DU20 (BaiHui), RN12 (ZhongWan), ST25 (TianShu), RN6 (QiHai), RN4 (GuanYuan), ST26 (WaiLing), RN1 (HuiYin), DU1(CnagQiang), BL32 (CiLiao), BL28 (Bang GuangShu), LI4 (HeGu), PC6 (NeiGuan), ST36 (ZuSanLi), GB34 (YangLingQuan), SP9 (YinLingQuan), SP6 (SanYinJiao), LR3 (TaiChong), KI3 (TaiXi) and KI1 (YongQuan).

**Results** - The patient made two sperm analysis before and after the acupuncture treatment. The first analysis was made in 'Newborn clinic - Center for fertility and andrology' and the second in 'Avicena laboratory'. The volume of the sperm before the treatment was 3ml and after the treatment 5.2ml. The concentration of the sperm before was  $2 \times 10^6$ ml and after  $38,4 \times 10^6$ ml. The total number of spermatozoa before was  $6 \times 10^6$  and after  $199,7 \times 10^6$ . The total motility before was 25% with 0% rapidly progressive motility and after the treatment 60% total motility with 35% of rapidly progressive motility. Before the treatment 3% of the spermatozoa was with normal morphology and 75% after the treatment. The diagnosis in the second analysis was: Brought in material analysis - ejaculate with complete liquefaction, without presence of mucous fibers, not noticeable oligozoospermia or asthenospermia (with a moderate degree of agglutination of the

sperm). Normal ejaculate volume and normal viscosity with increased presence of leukocytes ( $4,2 \times 10^6/ml$ )

**Conclusion** – There is significant difference between the results before and after the treatments. Acupuncture can improve the overall quality and structural integrity of the sperm and increase men's fertility.

**Keywords**

Acupoints, acupuncture, infertility, oligoasthenoteratozoospermia, treatment.

# Treatment of cervical spondylosis with acupuncture

***K. Kozovska<sup>1</sup>, J. Zhu<sup>1</sup>, B.Arsovska<sup>2</sup>***

*Faculty of Medical Sciences, University Goce Delcev – Stip, Macedonia<sup>1</sup>*

*Institute of Biology, Faculty of Natural Sciences and Mathematics – Skopje, Macedonia<sup>2</sup>*

071-557-345; kika\_1993\_@hotmail.com

## **Abstract**

**Background:** Cervical spondylosis is common and progressive degenerative disease which occurs with the aging process. Cervical spondylosis affects 95% of patients over 65 years. The disease can be asymptomatic and symptomatic (in patients over 40 years). Acupuncture is well accepted and widely used as a treatment to treat symptoms caused by cervical spondylosis. The goal of acupuncture treatment is to improve and regulate the flow of Qi energy, to complement it where there is a deficit and reduced it if it has accumulated an excessive amount of energy. In this way the flow of the Qi energy and the overall health of the body is restored and balanced.

**Purpose:** The main purpose of this work is to show the results and efficacy of the research and analysis done for the patients diagnosed with cervical spondylosis treated with acupuncture.

**Material and methods:** In the research were included 30 patients, 14 male and 16 female aged from 35 to 82 years all diagnosed with cervical spondylosis in the past year. The diagnosis was confirmed by X-ray scan. The treatments were done in the clinic for Traditional Chinese Medicine and acupuncture 'Tong Da Tang' in Skopje. All the patients were effectively cured with the treatment, with certain number of treatments. The number of the treatments was different for all the patients and depends on gender, age, working status, duration of disease, type of symptoms, when they appeared, etc. The main symptoms were neck pain, variable blood pressure, insomnia, changes in urine and stool, dizziness, headache, pain, numbness, tingling in the shoulders, arms and hands i.e. irradiation to the left, right or both sides of the upper limbs. All the patients were treated with the same acupoints for cervical spondylosis, all located on the neck and head: Du16 (Fengfu), Du20 (Baihui), Du21 (Qianding), SJ16 (Tiannyou), B10 (Tianzhu), SI15 (Jianzhongshu), SI14 ( Jianwaishu). The duration of the treatments was 35-40 minutes. 0.25x25mm dimension disposable sterile needles were used, made by Wuijiang City Medical Health Material Co., Ltd

**Results:** After the treatments all the patients had satisfying results. The patients were relieved from the pain and the symptoms were gone. On average, 8 treatments were needed to achieve the effect of the treatment. Older patients have done more number of treatments. The most common age group is of 50-60 years, with average age for men – 55 and for women 64. Men are affected earlier, by the age of 50 and women by the age of 60. There was no significant difference between the gender of the patients of which 16 were female and 14 male. The most common symptom is neck pain (17 patients). Headache and dizziness are the most common symptoms in the younger patients by the age of 56.

**Conclusion:** Acupuncture is an effective treatment by using the acupoints located on the neck and head which can relieve the symptoms and physical signs of cervical spondylosis.

## **Keywords:**

Acupoints, acupuncture, cervical spondylosis, effect, treatment.



# Effect of kinesitherapy on static and dynamic balance in patient after vertebro-basilar system stroke

Nikolova M<sup>1</sup>, Dimitrova A<sup>1</sup>, Vasileva D<sup>2</sup>, Lubenova D<sup>1</sup>, Grigorova-Petrova Kr<sup>1</sup>

<sup>1</sup>Faculty of Kinesitherapy, Tourism and Sports Animation, National Sports Academy "Vassil Levski", Sofia, Bulgaria

<sup>2</sup>Faculty of Medical Sciences, University "Goce Delcev", Shtip, Macedonia

telephone: ++389 78 493 331

E-mail: dance.vasileva@ugd.edu.mk

Faculty of Medical Sciences, University "Goce Delcev", Shtip, Macedonia

## **Abstract**

**Aim:** To assess the effect of a kinesitherapeutic methodology in a patient who survived an ischemic stroke in the vertebro-basilar system (VBS) during the post-acute stage.

**Material and methods:** The case studied a 62 years old female patient, who survived an ischemic stroke and pulmonary thromboembolism and was administered to kinesitherapeutic regimen of individual sessions, 3 times weekly for a month. Functional status of the 62 year old patient is weakness and slight latent paresis according the test of Mingazzini-Strumpell on the right side of the body, mild impairment of balance and equilibrium and dizziness while changing the body position from sitting to standing. The kinesitherapeutic methodology included exercises for the general performance status, exercises for improving the lower limbs strength, exercises for improving the static and dynamic trunk control from different starting positions. The following methods of evaluation of changes have been used for the functional performance status in the patient at baseline and after the kinesitherapeutic sessions: "Berg Balance Scale", "Timed Up & Go", "Five Time Sit-To-Stand" and the test „Sit-to-Stand per 30 sec”.

**Results:** After applied kinesitherepy the static and dynamic balance and the strength of the lower extremities were improved.

**Conclusions:** The Case study has shown that the targeted methods of kinesitherapy for influencing the static and dynamic trunk controlres ulted in improved postural stability, balance and performance status in a female patient with VBS stroke.

## **Keywords**

postural stability, balance, VBS ischemic stroke.

## Malignant pleural effusions in lung cancer: the condition during the disease

**Marija Karakolevska-Ilova**<sup>1</sup>, Elena Simeonovska Joveva<sup>2</sup>, Aleksandar Serafimov<sup>3</sup>, Lidija Petrovska<sup>4</sup>

<sup>1</sup>Department of oncology and radiotherapy, Clinical Hospital Stip, Faculty of medical sciences, "General Mihajlo Apostolski 34/14" Stip

<sup>2</sup>Department of neurology, Clinical Hospital Stip, Faculty of medical sciences, "ASNOM" 5 Stip

<sup>3</sup>Department of pathology, Clinical Hospital Stip, Faculty of medical sciences, Roza Petrova br 15 1-1/3-1, Kocani

<sup>4</sup>Department of dermatology, Clinical Hospital Stip, Faculty of medical sciences, "Kozjak planina" 2 Stip

++389/ 70 270 284, marija.karakolevska@ugd.edu.mk

### **Abstract**

**Introduction:** Malignant pleural effusions are common pathology in clinical practice in patients with malignant disease. Malignant pleural effusion represents 40% of chronic pleural effusion and is the leading cause of recurrent pleural effusion, which has an additional impact on morbidity in patients with malignant disease. Lung cancer is the predominant cause of malignant pleural effusion confirmed by more research series. Primary lung cancer associated with malignant pleural effusion is metastatic disease (7-th edition of TNM classification of lung cancer at the American Cancer Committee). Primary lung cancer associated with malignant pleural effusion further increases the morbidity of these patients reducing therapeutic options and affect survival (a median survival of less than 4 months). Pleural metastases originating from bronchogenic origin appear relatively early in the disease unlike other primary visceral tumors and is sufficient reason to determine the incidence of pleural effusions among different histological types of primary lung cancer and the condition of the malignant pleural effusion in different histopathological types of lung cancer during the course of disease.

**Material and methods:** This is a retrospective study. Data from 800 patients (35-75 years old) with primary lung cancer classified according to the recommendations of the WHO were processed over a period of three years from 2010 to 2013 at the Clinic of Oncology and Radiotherapy, Medical Faculty - Skopje. The study included all patients with the presence of malignant pleural effusion associated with primary lung cancer regardless of the time of occurrence of pleural effusion. Data from patients for the purposes of the study were evaluated by the following parameters: Incidence of pleural effusion in evaluated lung cancer patients; Development of pleural effusion in certain histopathological types of lung cancer and Condition of the malignant pleural effusion in different histopathological types of lung cancer during the course of disease.

**Results:** Research has shown that malignant pleural effusion associated with primary lung cancer appeared in 193 patients/28.1%. The right lung malignant pleural effusion appeared with 54.4% of the total number of pleural effusions, and left with 43.5%, and 10.9% of the difference was statistically significant. The right lung showed no statistically significant trend in the separate histopathological type development pleural effusion, while only adenocarcinoma in the left lung showed a tendency to develop pleural effusion

for 20.6% more than squamous cell carcinoma. In the right lung 59% of the effusions persisted, 14.3% withdrew and 6.7% progressed, while 63.1% of the effusions in the left lung persisted, 16.7% withdrew, 6% progressed during disease. In the right lung there wasn't difference in the condition of pleural effusion between different histological types, but in the left lung adenocarcinoma effusions withdrew as much as they progressed during the disease (13,6%) and squamous cell carcinoma effusions didn't progress. **Discussion:** Pleural effusions in lung cancer are a major problem (appearing in 28%) given that they mostly persist during illness regardless of histological type which increases the problem in the treatment and in survival of those patients.

### **Keywords**

lung cancer, malignant pleural effusion.

# Systemic fungal infections in hematological malignancies

***Petar Kuzmanovski**, Velo Markovski*

*Faculty of Medical Sciences, University "Goce Delcev", Shtip, Macedonia*

## **Abstract**

**Introduction:** In few centers around the world within a period of several decades were made autopsy studies of patients with any kind of cancer for the purpose to find systemic (invasive) fungal infection.

**Objective:** The objective of this paper is to find the relation between systemic (invasive) fungal infections and cancer. What's the correlation and connections between the two of them and why is this so important for the modern medicine.

**Materials and methods:** The data that we are going to use is from a research made in M.D. Anderson Cancer Center, Huston, Texas and from the medical book Carol A. Kauffman, Peter G. Pappas - Essentials of Clinical Mycology 2<sup>nd</sup> edition 2011.

**Results and discussions:** Results from the research made in M.D. Anderson Cancer Centre show that 57% (1990-1999) and 68% (2000-2008) of the patients with leukemia have had some kind of an invasive fungal infection. Results documented in "Essential of Clinical Mycology" show that 26% of the patients with leukemia worldwide have had invasive fungal infection confirmed by a autopsy. Authors assume that around 75% of the leukemia patients are with undiagnosed IFI during life. This rate lead to threatening cancer patient with antifungal therapy, which bring us to the discovery that patient easily go in remission while threated with antifungal medicaments such as itraconazole or voriconazole. Also an important data from this research is the change of the most commonly fungal pathogens, candida and aspergillus. We can see from the chart that before year 1990 the most common fungal infection were candida infections. Now we see that aspergillus has taken that place. This is due to involving of azole prophylaxis while threatening leukemia.

**Conclusion:** The autopsy show that average rate of leukemia patients with invasive fungal infection is 26%.

The use of azole prophylaxis in the treatment of leukemia lowered the rate of systemic candidiasis in patient by 5 to 10%.

When we treat cancer, we always have to think about the complications made from systemic fungal infections, which can be easily cured and can bring remission to the patients and prolong their lives.

## **Keywords**

Invasive fungal infections, leukemia, candida, aspergillus.

# Morbidity and mortality of malignant neoplasms in Macedonia

**Viktorija Vukovikj**, *Velo Markovski*

*Faculty of Medical Sciences, University "Goce Delcev", Shtip, Macedonia*

## **Abstract**

**Introductions:** Malignant neoplasms are the second cause of death among the population in Republic of Macedonia with representation of and represent 19.0% in the structure of total deaths.

**Objective:** To analyze the morbidity and mortality of the most common malignant neoplasms in Republic of Macedonia.

**Material and methods:** Were used a data from the Institute of Public Health of the Republic of Macedonia, National institute for statistic of Republic Macedonia.

**Results and discussions:** During analyzed period in 2003-2013, morbidity and mortality showed an upward trend. The lowest rate of mortality has was n 2004 (76.3), and highest in 2010 (164.4) per 100.000 inhabitants. In the distribution by gender, the number of deaths by malignant neoplasms shows an increase in both genders, with highest rate of mortality among males in 2012 (216.7), and among females in 2010 (145.1) per 100.000 inhabitants. Rates of mortality are higher among males. From 3654 deaths from malignant neoplasms in 2013 in Republic of Macedonia, males are represented in 60.1% (2196), and females in 39.9% (1458). In the structure of most common causes of deaths, by individual diagnoses among males, on first place are malignant neoplasms of bronchus and lungs with mortality rate of 66.5 (688 deaths), while the second is a followed by malignant neoplasm of the prostate with mortality rate of 19.6 (203 deaths) and the third place belongs to malignant neoplasm of stomach with mortality rate of 19.1 (198 deaths). Among the female population, the first place belongs to malignant neoplasms of the breast with mortality rate of 26.4 (240 deaths), while the second is followed by malignant neoplasm of bronchus and lungs at a rate of 15.3 (158 deaths). On the third place is malignant neoplasm of the stomach with mortality rate of 10.6 (109 deaths). In distribution by municipalities in 2013, the highest rates of mortality are in Krivogashtani with 21 total of deaths and with mortality rate of 368.4 per 100.000 inhabitants., Demir Hisar with 26 total of deaths or mortality rate of 303.9 per 100.000 inhabitants and Berovo with 34 total of deaths and a mortality rate of 252.9 per 100.000 inhabitants.

**Conclusion:** Malignant neoplasms are the second cause of death among the population of Republic of Macedonia, after the diseases of circulatory system. During period between 2003-2012, the morbidity and mortality showed an upward trend. In the distribution by gender, the number of deaths from malignant neoplasms shows a positive development tendency in both genders.

Mortality rates are higher among males. The most common cause of death from malignant neoplasms are malignant neoplasms of bronchus and lungs. The most

common cause of death from malignant neoplasms among females, is malignant neoplasm of the breast.

**Keywords**

breast, bronchus, lungs, morbidity, mortality, neoplasms, prostate, stomach.

# Cognitive behavioral program in treating insomnia among elderly patients

***Kneginja Richter***<sup>1,2</sup>, *Lence Miloseva*<sup>3</sup>, *Guenter Niklewski*<sup>1,2</sup>, *Anja Piehl*<sup>1</sup>

<sup>1</sup> *University Clinic Nuremberg*, <sup>2</sup> *Private Paracelsus Medical University, Germany*

<sup>3</sup> *University Goce Delcev Stip, Faculty of Medical Science, R. Macedonia*  
kneginja.richter@gmx.de

## **Abstract**

**Introduction:** Insomnia is a most common in elderly patients. World wide experience showed that Cognitive behavioral program in treating insomnia is one of the best effective model.

**Objectives:** The present study aim to present clinical experience from University Clinic Nuremberg, Centre for Sleeping Medicine with application of Cognitive behavioral program in treating insomnia among elderly.

**Material and Methods:** The sample consists of 22 patients with chronic insomnia (10 primary insomnia, 12 secondary insomnia; 16 women, 6 men; mean age 64.6 years) treated in two consecutive group sessions. Participants compliance was 82%. Treatment program was consists of: 6 Group meetings, 1 Activation week, with total duration during 10 week. It include: Sleep hygiene and stimulus control; Sleep restriction; Progressive Muscle Relaxation; Mental Relaxation, Cognitive restructuring; Light Therapy; Sport; Excursions and cultural program. In order to assess the results of the Sleep diary and for the total and possibly sub-scores of the questionnaires pre-post comparison were made with the Wilcoxon signed-rank test, as a non-parametric statistical hypothesis test used for comparing two matched samples. Statistical analyzes depending on the machining rate on subgroups (15 to 17 people). In order to asses : sleep quality, daytime sleepiness, depressive symptoms, cognitive performance, before and after the training, the participants were examined with Pittsburgh Sleep Quality Index, (PSQI); Epworth Sleepiness Scale (ESS); Beck Depression Inventory (BDI); Syndrome Short Test (SKT). In addition, sleep diary were conducted and completed an evaluation questionnaire at the last meeting of the patient.

**Results:** The high attendance compliance of 82% indicates a great motivation of the participating patients. The decisive factor here is probably a high psychological strain caused. The "poor" sleep quality of our sample showed both psycho-metric (PSQI) and in the sleep diary (sleep efficiency: 67.7%). Of the accompanying symptoms mentioned above in a means "light" depressive symptoms could be objectified, whereas daytime sleepiness and cognitive impairment were on the clinical border relevance.

**Conclusion:** The results of the pre-post comparisons lead us to the conclusion that sleep quality, daytime sleepiness, sleep time, and mood positively changed during the day among older insomnia patients under the described cognitive-behavioral group program. Is draw special-lift that just often complained of the elderly long sleep onset and increased daytime sleep were reduced. However, important parameters such as sleep efficiency and total sleep time were unaffected, suggesting the need for a more intensive therapy settings.

## **Keywords**

cognitive-behavioral, program, elderly, insomnia.

## Regulations and legal aspects in management of medical waste

**Shikoska Biljana**<sup>1</sup> Dimova Cena<sup>2</sup>, Schumanov Gjorgji<sup>3</sup>

<sup>1</sup> Professional dental assistant

UPHO University Dental Clinical center "Sveti Pantelejmon" – Skopje

[biljanashikoska@gmail.com](mailto:biljanashikoska@gmail.com)

<sup>2</sup>Associate Professor

Department of oral and maxillofacial surgery and dental implantology,

Faculty of Medical Science, University of "Goce Delcev", Stip

[cena.dimova@ugd.edu.mk](mailto:cena.dimova@ugd.edu.mk)

<sup>3</sup> Full Professor

Faculty of Medical Science, University of "Goce Delcev", Stip

[gorgi.sumanov@ugd.edu.mk](mailto:gorgi.sumanov@ugd.edu.mk)

### **Abstract**

Medical waste, according to the law of waste management is waste generated in medical and health institutions (dispensaries, hospitals, polyclinics and outpatient clinics, dental clinics, veterinary stations etc.), originated as a product of used items and materials during diagnosis, convalescence, treatment and prevention in humans and animals.

Medical waste is a risk to those who produce, package, store, transport, treat and perform disposition. The possibility of infection of some diseases and their spread in hospitals due to negligence in the handling of medical waste, have to inform the entire staff in management and disposition to reduce the risk to minimum.

The actual management of medical waste, is an organized process that consists of five elements: separation, identification, handling, treatment and disposal.

Medical waste, as a waste that is a result of the provision of informal care can be divided into two groups - municipal and hazardous medical waste. The municipal medical waste includes: paper, cartons, glass, food scraps and other common debris arising in the administration, kitchens and laundries.

On the other hand hazardous medical waste contains elements of chemical and biological threat, whether in the form of solid, liquid or gaseous waste. The properties of hazardous medical waste are virulence, toxicity, carcinogenicity, infection and so on. According to these properties hazardous medical waste differs from the municipal medical waste.

**Objective:** The aim of the study was to highlight the importance of knowledge of legal regulations and provisions of the proper management of medical waste with special emphasis on attitudes, division and recommendations of the World Health Organisation.

**Material and Methods:** As a special heterogeneous mixture of municipal, infectious, pathological, pharmaceutical, laboratory waste, disinfection agents and packaging, as well as radioactive and chemical waste, hazardous medical waste can be divided into several subgroups for easier and more accurate identification and, therefore, is divided on:

- Infectious (laboratory cultures, fluids, materials and equipment that have been in contact with infected patients);
- Pathological (blood, other body fluids, body parts, fetuses);
- Sharp (objects of needles, scalpels, knives, broken glass);
- Pharmaceutical (drugs, residues of drugs);



- Genotoxic (cytostatic, genotoxic chemicals);
- Chemical (solvents, laboratory reagents, disinfectants);
- Heavy metal (batteries, sphygmomanometers, thermometers);
- Pressure vessels (gas cylinders, metal vessels) and
- Radioactive waste (scrap used in radiation therapy, urine and fluids of patients treated with radio-nuclides).

**Results:** The World Health Organization recommends as protective gear for anyone who comes into contact with medical waste to wear: helmet; protective face mask; goggles; Special jumpsuits; industrial aprons; feet guards; boots etc.

**Conclusion:** Firstly, it's important to clearly define the responsibility for proper waste management, to the process of its final processing. It is necessary to develop a comprehensive and planned management system that beside responsibility, should provide funds for safe implementation of waste. This is a long process that despite organizational structure requires individual and professional commitment. Unacceptable, but still a fact is that medical waste from some health institutions (mostly smaller private clinics), without special labels are taken from the relevant municipal departments and with municipal waste is discharged in urban landfills without special processing.

**Keywords:**

Hazardous medical waste, Infective material, Law of waste management, Medical waste  
Municipal waste.

# Control of the psychiatric disorders in the Republic of Macedonia

*Ramov Leonid; Markovski Velo*

*Faculty of Medical Science, University of "Goce Delcev", Stip*

## **Abstract**

**Introduction:** The Psychiatric disorders are a large number of disorders which affect the mental and the behavioral function. Their etiology is rarely affiliated with some organic disorder, rather with a subjective perception or a disorder originating on a molecular level in some parts of the CNS. For their pathogenesis the key mechanisms are related with the environment and the psycho-physical development of the individual

### **Aims:**

How much are these disorders present in the republic of Macedonia?

How is the healthcare system in Macedonia handling these disorders?

**Materials and Methods:** In order to answer our aims we collected data from the institute of public health of the Republic of Macedonia, whose research from 2011 yielded some useful information about the incidence and hospitalization, which was put in a table. We confirmed the politics of the WHO on the healthcare ministry website [www.moh.gov.mk](http://www.moh.gov.mk). And in order to compare the results we used similar data from the Center of disease control from the USA

**Results and Discussion:** With the acquired data we got the number of patients being treated in the Republic of Macedonia and also that they are being treated by the standards of the WHO. We also found lack of information and public awareness of the people about these kinds of issues and also information about cases of a particular disease of this type. Compared with the data from the USA Center of disease control it had both the percentage about adults which is 18.5 of the population being affected and the population of children which is 13%. They also separated the racial groups. In our institute they only had info about patients visiting a doctor related to a mental disorder, which is 5,9% of the population and from whom 2,8 % are being hospitalized. These results are showed in the following tables and graphics.

### **Conclusions:**

-These disorders are present in Macedonia with a percentage of 5,9 % of the population in general and 2,8 of them are being hospitalized.

- The Healthcare of RM is dealing with these disorders according to the WHO and has lower incidence than USA according these results.

### **Keywords**

Healthcare; Psychiatric disorder; Psychiatry; Republic of Macedonia;

# Monitoring of the renal function in Indometacin treated patients with rheumatoid arthritis

**D. Yzeiri Havziu**<sup>1</sup>, M.Hiljadnikova-Bajro<sup>2</sup>, T. Kadifkova Panovska<sup>2</sup>

<sup>1</sup> Faculty of Medical Sciences-State University of Tetovo, Macedonia

<sup>2</sup>Faculty of Pharmacy, Ss. Cyril and Methodius University, Skopje, Macedonia

389 070771234 dritauzeiri@yahoo.com

## **Abstract**

Nonsteroidal antiinflammatory drugs (NSAIDs) are considered as one of the most nephrotoxic drugs and their use in chronic rheumatic treatment is frequently accompanied by renal impairments of various pathophysiology and severity. The aim of this study was to evaluate the kidney performance among Indometacin treated patients with rheumatoid arthritis (RA).

A total of 20 patients (14 RA<sup>sero+</sup>, 6 RA<sup>sero-</sup>) with an average age of 46,57 ±7,51, suffering from chronic rheumatic pain were evaluated quarterly for one year and once more one month after discontinuation of treatment. The results were compared to the reference interval and a control group of 80 healthy individuals. A panel of 5 urinary specific nephrotoxicity biomarkers including N-Acetyl-β-(D)-Glucosaminidase (NAG), Alanine Aminopeptidase (AAP), γ-glutamyl transferase (γ-GT), α1 Microglobulin (α1M) and microalbuminuria, was used to monitor glomerular and tubular functioning. Present or past history of kidney disease was considered an exclusion criteria for enrollment in the study.

After a 12 month treatment with Indometacin (2x25mg) a significant increase of the evaluated markers was evident among all patients, except for microalbuminuria and α1M which were insignificantly increased among RA<sup>sero-</sup> patients and did not exit the reference interval. These findings suggest a renal impairment resulting from Indometacin nephrotoxicity but might also be affected by the rheumatic complications. Fortunately, the damage is reversible at this stage and the evaluated parameters normalize within one month after the cessation of treatment indicating that the detected impairment is predominantly caused by the toxicity of Indometacin. Further studies are needed to precisely differentiate the level of impairment caused by the NSAIDs and the rheumatic pathology itself but we strongly recommend regular monitoring of the renal performance in patients undergoing continuous Indometacin treatment for rheumatic pain.

## **Keywords**

Biomarkers, Nephrotoxicity, Nonsteroidal antiinflammatory drugs, rheumatoid arthritis.

# Incidence of breast cancer in Macedonia

*Stojanova Dijana; Markovski Velo*

*Faculty of Medical Sciences, UGD - Stip*

## **Abstract**

**Introduction:** Breast cancer is an abnormal growth and uncontrolled division of cells in the breast. Breast cancer is the most common cancer among women in the country and the most common cause of cancer death in women. According to the WHO, breast cancer is the most common cancer in women worldwide, claiming the lives of hundreds of thousands of women each year.

**Purpose:** The purpose of this work is to determine the incidence of breast cancer in the Republic of Macedonia and setting relation in terms of the prevalence of this disease in the world.

**Materials and Methods:** Within this analysis, data were taken from the hospital in the region of the capital Skopje, which marks the most populated. These data represent the men and women suffering from breast cancer who were hospitalized.

The data used were obtained from the Centre for Public Health, National Institute of Statistics - MAKStat base, Institute of Public Health, data taken from the organization Borka and International Agency for research on cancer - EUCAN.

**Results:** In Macedonia, breast cancer is the first of malignant disease in women. According to the Institute of Public Health, the incidence of breast cancer is about 696 / 100,000 cases, while mortality is 240 / 100,000 that is represented by the absolute values of 147 men and 1280 women such cases in 2014, 225 men and 839 such cases in 2013 and 139 men and 2629 women such cases in 2012. Breast cancer in men is found in about 6 % of cases respectively in 2014 there were 147 infected men. Most patients are from 50-59 years of age.

**Conclusion:** In Macedonia, breast cancer is the first of malignant disease in women. The country is a country with an average incidence rate, but with higher mortality. The number of cases of breast cancer has increased in 2014. Most cases of this disease is 50-59 years. In a small percentage of breast cancer are diagnosed and men with 6%.

## **Keywords**

breast cancer, disease incidence, Macedonia.

# HPV virus as a cause of cancer of the cervix in R.Macedonia

Joveva Stefanija ; Taleski Vaso; Markovski Velo;

Faculty of Medical Sciences, UGD - Stip

## **Abstract**

**Introduction:** Approximately 130 types of HPV infections have been identified. Among them high-risk types of HPV are HPV 16, 18, 31, 45. HPV virus is 99,7 percent isolated of all cervical cancers.

**Purpose:** The purpose of this paper is to present incidence of HPV (human papillomavirus) in connection with cervical cancer during 2012, in R. Macedonia.

**Material and methods:** Data were collected from "Official Gazette of Republic of Macedonia", number 9, the 20<sup>th</sup> of January, 2012, Friday and HPV Information Centre Institut Català d'Oncologia,. Avda. Gran Via de l'Hospitalet, 199-203 08908 L'Hospitalet de Llobregat (Barcelona, Spain), November 2013.

**Results and discussion:** Cervical cancer is one of the most common chronic disease which affects the female reproductive organs. It is *the twelfth* most common cancer in frequency and the fifth leading cause of cancer death in females worldwide. The number of the cervical cancer cases in the world is 527,624 while the mortality rate is 50,3 percent or 265,563. Serbia has the highest cancer incidence and mortality rate in Europe. The high-risk HPV types may also cause an oropharyngeal cancer which is more common in males. Number of oropharyngeal cancers, linked to HPV in males (estimated incidence 26/100.000 and mortality 14/100.000) is higher than in females (estimated incidence 4/100.000, and mortality 3/100.000). *Cervical cancer* ranks as the 6<sup>th</sup> most frequent cancer among women in R. Macedonia, of all cancers cases with incidence rate of 16,6. The first place belongs to a breast cancer 111,7%/100.000, followed by corpus uteri cancer 43,1% /100.000; colorectal cancer 35,5% /100.000, lung cancer 21,7% and abdominal cancer 18,2% /100.000. Cervical cancer in Republic of Macedonia compared with other South European countries ranks the 4<sup>th</sup> place in incidence with 12.4 cases per 100,000 and the 3<sup>rd</sup> place in mortality with 5.1 deaths per 100,000.

In the Republic of Macedonia the estimated numbers of new cases of cervical cancer in 2012, were 171 and 81(47,3 %) die as a result of this disease.

**Conclusion:** The number of cases of cervical cancer in 2012 worldwide was 527,624 and the number of deaths from cervical cancer was 265,563 (50,3%). In comparison with South European countries, Republic of Macedonia ranks at 4<sup>th</sup> place with elevated rates of incidence 12,4 % and at 3<sup>rd</sup> place with elevated rates of mortality 5,1%. Cervical cancer is one of the most frequent types of cancers among women in Macedonia. The highest incidence rate in females is between 45 and 54 years of age and mortality rate in females is over 70 years of age.

## **Keywords**

cancer, cervical, incidence, mortality, oropharyngeal.

## Analysis of the Pap test results by age groups in the area of Kriva Palanka

Nikolovski R; Denchovska K; Mladenovski G; Markovski V;  
Goce Delčev University – Štip

### **Abstract**

**Introduction:** Pap test is a method of early detecting cancerous processes in the uterus. The first Pap test in Kriva Palanka was made in 1974. It was performed by doctors of General Medicine, till the opening of the Gynecological - Obstetric Department.

**Purposes:** The aim of this work is to make comparison between positive results of Pap test in different age groups.

**Materials and methods:** For this purpose it is used an epidemiological method with a retrospectively study. Two age groups are being analyzed. In the first group there are female patients at the age of 49 to 60 years and the second group is consisted of female patients at the age of 24 to 35 years. The screening of the first group was made in 2014 while the screening of the second group in 2015. The data of only first 9 months for both years are being used for the analysis because the year 2015 hasn't finished yet. The data are from Gynecological - Obstetric Department in Kriva Palanka.

**Results and discussion:** From January 1st 2014 to December 30th 2014, the total number of female patients that came for screening of detecting cancer of the uterus was 493, elder group in age of 49 to 60 from which 397 came in the first 9 months. In the second age group, 24 to 35 years, there were 418 female patients that came in the first 9 months. The study analyzed the following findings: ASC-US-atypical squamous cells of undetermined significance., ASC-H (atypical squamous cells-high grade lesion); Endo CIN1 (endocervical-cervical intra epithelial neoplasia1); endo CIN2 (endocervical-cervical intra epithelial neoplasia2); AGC (atypical glandular cells); CIN 1 (cervical intra epithelial neoplasia 1); 2 CIN (cervical intra epithelial neoplasia 2); 3 CIN (cervical intra epithelial neoplasia 3); CIS (carcinoma in situ). All mentioned findings are considered high risk and without proper treatment after a certain period will lead to development of malignant neoplasm. The samples from the patients are given to the analysis laboratory at PHI "CytoLab" - Kumanovo. The typology of confirmed HPV was made in the laboratory of MASA (Macedonian Academy of Sciences and Arts). ASC-US is found at 15 female patients in the elder group, and in 7 cases in the younger group; ASC-H is found in 2 cases in the elder group. In the younger group there were no such findings. There was 1 finding of Endo CIN 1, but in the elder group, as the case with Endo CIN 2 – only 1 finding in the elder group. In the elder group, HPV was diagnosed in 23 cases, and in the younger group it is diagnosed in 11 cases. In the elder group CIN 1 is diagnosed in 45 cases over against younger group-diagnosed in 13 cases. In the elder group CIN 2 was diagnosed in 4 cases contrasted with 1 case diagnosed in the younger group. CIN 3 was found in 1 case in each age group. In the elder group AGC was found in 8 cases unlike the younger group - only in 1 case. There were 2 cases with findings of CIS in the elder age group and none in the younger group. According to the results, the total amount of positive results in the elder group add up to 102 from among 397 examined female patients (25,7%), and in the younger group 35 from examined 418 female patients (8,4%). In the Republic of Macedonia the screening programme is established on April 1<sup>st</sup> 2012.

**Conclusion:** In accordance with the positive Pap tests, it is determined statistically significant difference between first and second age group of the patients. In the elderly group of patients there is an increased number of diagnosed high-risk premalignant lesions, unlike the younger group where this number is significantly smaller. There is significant increase in the number of patients undergoing a proven high-risk HPV in the elder population. Based on the analysis results we can conclude that it is particularly important initiation of timely screening in the younger population so early detection, timely treatment and prevention of progression to malignancy is provided.

**Keywords**

cancer, cervical cancer, HPV, Pap test.

# Giant rhinophyma treated by excision and full thickness skin grafting

**Emilija Lozanovska Doneva**

*Klinicka Bolnica Stip, R.E. Otorinolaringologija  
St. Hristijan Karpos 5/28 2000 Stip Macedonia  
+38970368608, chillamak@yahoo.com*

## **Abstract**

Rhinophyma is a slowly progressive, disfiguring disorder of the nose seen almost exclusively in men over the age of forty. It consists of large nodular masses of hypertrophic and hyperemic connective tissue and sebaceous glands. The supposed association with increased alcohol abuse often leads to psychological problems for the person concerned. Rhinophyma is the final stage in poorly controlled acne rosacea. Its etiology remains uncertain. Surgery is the most common treatment of choice. Different surgical procedures have been described, such as excision with primary suture or extirpation with plastic covering of the defect by free transplants, subcutaneous rhinophyma resection, as well as decortication with peeling off the proliferations, dermal abrasion, or dermal shaving.

We report on a 72-year-old man presented with an unusually severe case of rhinophyma. The patient presented with a seven-year history of a progressively growing mass on the nose with a history of nasal obstruction and history of alcohol abuse. On examination, there was a large pedunculated mass measuring 7,5x7x5,5cm arising from the tip to the dorsum of the nose. The pedunculated mass was widely excised and a skin graft from the medial upper leg was applied. A very satisfactory cosmetic result was obtained.

## **Keywords**

Rhinophyma, excision, skin grafting.



# Incidence of patients with chronic renal failure in Skopje

*Simona Kamcheva*, *Markovski Velo*

*Faculty of Medical Sciences, UGD– Shtip*

## **Abstract**

**Introduction:** Chronic renal failure it contains a large number of pathological processes, all of which are characterized by a gradual loss of kidney function. HBI main dysfunctions associated with decreased glomerular filtration rate <60 ml/min and loss of tubular function.

**Purpose:** The purpose of this paper is to ascertain the incidence of patients with chronic renal failure on hemodialysis for the City of Skopje (of the Republic of Macedonia), for the period from 2012 to 2014.

### **Material and methods:**

Centre for Public Health of the City of Skopje  
Institute of Public Health of the Republic of Macedonia  
University Clinic of Nephrology, Faculty of Medicine Skopje  
Macedonian Academy of Sciences and Arts, Skopje

**Results:** In 2012 in Skopje, registered 1318 cases of chronic renal failure treated with dialysis, and according to data processed 50.5% were male and 49.5% were female. While in 2013 the number of cases increased by a total of 328 infected people, whereas this year the percentage dominance belongs to the female (50.1% of the total infected people in 1646). In terms of 2013 in 2014 in Macedonia incidence of cases in which declines were registered in 1586 patients, of which 804 are males and 782 are females. Declining incidence is likely due to fewer new patients with HKD on the one hand, and dead or displaced from Skopje on the other hand.

**Conclusion:** The analyzed period, the City of Skopje in 2013 has the most registered patients on dialysis (1646) compared to 2014 and 2012.

Has the highest incidence in the age group of 55-64, more patients are female.

### **Keywords**

chronic renal failure , prevalence, infected people.

# Calculation of effective dose to family members of patients with thyroid diseases

***Marina Zdraveska Kochovska<sup>1</sup>, Emilija Janjevik Ivanovska<sup>2</sup>, Meri Angeleska<sup>1</sup>, Sasho Nikolovski<sup>3</sup>, Zlatko Filipovski<sup>3</sup>***

*<sup>1</sup>Institute of pathophysiology and nuclear medicine, Medical faculty, Vodnjanska 17, 1000 Skopje*

*<sup>2</sup>Faculty of medical science, University of Goce Delchev, Stip*

*<sup>3</sup>PET centar-proektna edinica, Skopje  
0038978517171, mzk2003@hotmail.com:*

## **Abstract**

Radioactive iodine  $^{131}\text{I}$  has been used for many years to treat benign thyroid disease. Treatment of thyroid cancer with  $^{131}\text{I}$  NaI is the most common application of radionuclide therapy in nuclear medicine and has been in use for many decades. At the Institute of pathophysiology and nuclear medicine at Skopje this kind of radiotherapy is performed since 1956y. Approximately 50 thyroid cancer patients and the same number hyperthyroid patients have been treated with radioactive iodine  $^{131}\text{I}$  every year. The patients, treated with radioactive iodine  $^{131}\text{I}$  present a radiation hazard to other individuals such as hospital staff, the patient's family and members of the public with whom a treated patient may come in close contact. This situation can be overcome by imposing restriction on the behavior of the patient, to minimize the dose to close relatives and other individuals. In 1991, the International Commission of Radiological Protection (ICRP) has recommended a radiation constraint of 1 mSv/year to the general population. According to Basic Safety Standards Directive, the dose limits to the general public are not valid for "exposure of individuals, who are knowingly and willingly helping, other than as a part of their occupation, in the support and comfort of in-patient or out-patients undergoing medical diagnosis or treatment". Proposed dose constraint from the BSS is: 0.3 mSv per episode for the public, 1 mSv for children, for the adults up to sixty years the dose constraint is 3 mSv and for adults more than 60 years old it is 15 mSv. The implementation of this guideline differs among various countries. In the Republic of Macedonia about fifty thyroid cancer patients are treated on in-patient basis and approximately fifty hyperthyroid patients is treated ambulatory on out-patient basis. According to the local hospital rule and old guidelines the maximum given activity to hyperthyroid patients, treated on out-patient basis, is 1110 MBq. The new, not yet established guidelines, proposed to reduce the maximum given activity to hyperthyroid patients, treated on out-patient basis, from 1110 – 555 MBq. This group of patient's present great radiation hazard to their family members. Upon discharge from hospital, the patients as well as their family members were given brief radiation instructions. The aim is to minimize the transfer of radioactive material to person coming in close contact with patient. There are several papers in the literature concerning the subject of doses received by family members of thyroid cancer and hyperthyroid patients. Most of the published studies agree that doses to the family members are below the proposed dose constraint of 1 mSv. There are also several papers that present cases where children or other persons have received higher radiation doses than proposed dose limit and usually it is case with hyperthyroid patients and their close relatives. This study was undertaken

to measure the effective doses to family members of patients treated with radioactive iodine  $^{131}\text{I}$  for thyroid diseases at nuclear medicine department in Skopje.

The main purpose of this study was to estimate the radiation exposure to family members of hyperthyroid and thyroid cancer patients treated with radioactive iodine  $^{131}\text{I}$  and to calculate the effective dose according given activity using Radiation Dose Assessment Resource (RADAR) software.

**Keywords**

Effective dose, iodine, thyroid.

# Contemporary Microbiological Diagnostic Tests for Rapid Identification and Detection of Resistance of *Mycobacterium tuberculosis*

Oliver Taleski<sup>1</sup>, Vaso Taleski<sup>1</sup>

<sup>1</sup>Faculty of Medical Sciences, Univ. „Goce Delchev“ Shtip, Republic of Macedonia

Presenter's phone 389 78 604 932, e-mail: oliver.111672@student.ugd.edu.mk

## **Abstract**

Tuberculosis (TB) occurs in every part of the world as a top infectious disease killer. In 2014, 9.6 million cases and 1.5 million deaths (140 000 children) from TB were registered. Over 95% of TB deaths occur in developing countries.

The Millennium Development Goal target of halting and reversing the TB epidemic by 2015 has been met globally. TB incidence has fallen since 2000 and is now 18% lower, by an average of 1.5% per year. An estimated 43 million lives were saved through TB diagnosis and treatment between 2000 and 2014. Another Goal target is ending the TB epidemic by 2030.

According WHO Director General, „Everyone with TB should have access to the innovative tools and services they need for rapid diagnosis, treatment and care. This is a matter of social justice, fundamental to our goal of universal health coverage”.

In cases of drug-susceptibility, TB is a treatable and curable disease with a standard 6 month protocol of 4 antimicrobial drugs. In some cases, extensively drug-resistant TB, XDR-TB, a form of multi-drug resistant TB with weak responds including the most effective second-line anti-TB drugs. About 480 000 people developed MDR-TB in the world in 2014.

Establishing, equipping, financing, and ensuring sustainability of appropriate laboratory networks are challenging, complex and expensive, but necessary for an effective response to the challenges of TB-HIV and drug-resistant TB (DR-TB) control.

Beside classical methods for isolation, identification and susceptibility testing, Reference laboratories introduce new, rapid methods.

New systems for isolation use selective, liquid media (BACTEC, MGIT), which enable final diagnosis in about two weeks.

In 2012, for the first time, rapid diagnostic test GeneExpert (based on molecular technics) was established in Republic of Macedonia. GeneXpert MTB/RIF is an automated, cartridge-based nucleic amplification assay for the simultaneous detection of TB and rifampicin resistance directly from sputum in under two hours.

As a result of use of contemporary standards for detection, treatment and prevention of TB included in National program for control of TB, in connection with realization of the Program for control of TB financially supported with grant of Global fund to fight against HIV/AIDS, TB and malaria, from 2002 to date number of new cases with TB in Republic of Macedonia significantly decreased.

## **Keywords**

Tuberculosis, rapid diagnostic test, GeneExpert.

## Analysis of clinical features and complications in patients with $\beta$ -thalassemia in the region of Strumica

***Sinokapovska Silvana***<sup>1</sup>, *Dimova Cena*<sup>2</sup>

<sup>1</sup> Graduate in medical laboratory diagnostics specialisation in transfusiology

<sup>2</sup> Associate Professor, Department of oral and maxillofacial surgery and dental implantology,

Faculty of Medical Science, University of "Goce Delcev", Stip

*cena.dimova@ugd.edu.mk*

### **Abstract**

Thalassemias are hemoglobinopathies and are hereditary diseases which are characterized by disturbance in synthesis of one or more polypeptide chains of globin. Thalassemias are type of anemia of quantitative nature, where synthesized chain of hemoglobin are with normal structure, but not in adequate quantities.  $\beta$ -thalassemia is a disease characterized by production of large quantities of  $\alpha$ -chains which exceeds the production of  $\beta$ -chains, whereas  $\beta$ -chains accumulate and precipitate into precursors of red blood cells and change their permeability, which leads to lysis of red blood cells. Within Research Center for Genetic Engineering and Biotechnology (RCGEB) is operating national reference laboratory for hemoglobinopathies, founded in 1970, where over the past 40 years examined more than 30,000 individuals from our country. The analysis revealed that the average frequency of beta-thalassemia in Macedonia is 2.6%, of alpha thalassemia is 1.5%, delta-beta-thalassemia is 0.2%, while the share of Swiss type of hereditary persistence of fetal hemoglobin (HPFH) is 0.3%.

**Aim of the study:** The objective of this study was to show the prevalence, or the presence, of a certain type of thalassemia in the region of Strumica, R. of Macedonia, the complications that arise in specific cases, and the diagnosis and treatment of this inherited disease, not only for successfully identifying the extent of the presence of thalassemias in this region, but also to display the patient status in this region.

**Material and methods:** The target group for this research were registered patients with thalassemia from the region of Strumica. For that purpose, we processed medical histories of 29 subjects suffering from some type of thalassemia. All subjects which entered in this study were respectively coded in order to avoid violation of their privacy and were randomly selected. As a material for the research we used data from medical histories of the subjects of interest, and subsequently analyzed those data. Of all data we selected those who are significant for our research like geographical location, sex, age, type of thalassemia, blood tests values, comorbidities and complications from the disease.

**Results and discussion:** Analysis of the available data shows that the most of the patients had or have  $\beta$ -thalassemia type minor, followed by patients with  $\beta$ -thalassemia type major, then  $\alpha$ -thalassemia, and only 2 patients with  $\beta$ -thalassemia intermedia. As far as geographical location we can conclude that the most of the patient came from the city of Strumica, while other patients are from rural suburbs of Strumica. As suspected, all significant blood parameters which are characteristic for thalassemias, such as Hgb, Er, MCV, MCH, HbF, HbA<sub>2</sub>, AST, ALT, and others, shows deviation from normal ranges.

Also we found a lot of comorbidities and complication associated with  $\beta$ -thalassemias. All patients were treated with standard therapeutically agents and procedures, such as iron chelating agents, iron supplements and therapy with washed and filtered red blood cells.

**Conclusion:** The data analysis indicates the presence of many characteristic symptoms and clinical manifestation of many features of thalassemias, which confirms the theoretical framework for this hemoglobinopathy. In many patients it is observed decline in values of hemoglobin, reduces number of red blood cells, and disruption of liver function, followed by decreased function of liver enzymes. Therapy that is administered to the patients is of basic character, a continuous blood transfusion in patients with milder form of thalassemia, and excess iron chelators, whilst in the patients with severe forms of thalassemia splenectomy was performed. The results shows that the experimental group of patients present many comorbidities and complications they complains with the medical theory about thalassemia.

### **Keywords**

Thalassemia, blood transfusion, anemia.

## Lymphoepithelioma: A case report

Vase Stojcheska<sup>1</sup>, Rade Filipovski<sup>1</sup>, Dobri Stoimenov<sup>1</sup>, Nikica Atanasova<sup>1</sup>, Goran Karaivanov<sup>1</sup>, Ana Doneva<sup>2</sup>, Irena Shulevska<sup>1</sup>, Silvana Krалеva<sup>3</sup>

<sup>1</sup>ENT department, General hospital 8 September, Skopje, Macedonia

<sup>2</sup>Neurology department, General hospital 8 September, Skopje, Macedonia

<sup>3</sup>Anesthesiology department General hospital 8 September, Skopje, Macedonia

### **Abstract**

**Introduction:** Lymphoepithelioma is a type of a poorly differentiated nasopharyngeal carcinoma characterized by prominent infiltration of lymphocytes in the area involved by the tumor. Malignant neoplasms of the nasopharynx are rare, about 2% of the head and neck tumors and to 0.25% of all tumors. They are more prevalent among males, in a 3:1 ratio when compared to females, and presents two peaks of incidence: young people under 30 years of age. There is an intermediate incidence in population in the Mediterranean basin. Available data suggests an association with genetic susceptibility, environmental factors and infection by the Epstein Barr virus (EBV).

**Case Report:** A 8 year old boy had a symptoms of nasal congestion, nasal obstruction, pain and fullness localized in the right ear, sleeping with open mouth, no history of nasal bleeding or visual disturbance, headache, tinnitus and conductive hearing loss on the both ears (in the period of 3 months). Results from tympanometry made during our examinations were: Type B on the right and type C on the left ear. Patient had complains on these symptoms about few months. Examination with rigid endoscope through left nasal cavity shows that there was enlargement, an adenoid hypertrophy in the epipharynx, macroscopically its surface was smooth and not ulcerated. But, rigid endoscopy through right nasal cavity was impossible due to excessive amounts of seromucous. Routine blood investigations were normal. According to the age and symptoms, the decision was adenoidectomy and application of the ventilation tube Grommet on the right ear. Operation procedure was performed under general anaesthesia and the specimen was sent for histopathology. Histopathology results pointed at Lymphoepithelial carcinoma. After this procedure, CT scan was performed (asymmetrically on the level of the nasopharynx, because of the presence of the tumor formation, and the reduction and obstruction of the air-space in the level of naso and oropharynx). In parapharyngeal space, bilateral enlargement of the lymph nodes are detected. After confirmation of the diagnosis, the patient was referred for radiotherapy and chemotherapy in University Hospital in Turkey. After radiation treatment, the patient is in good condition.

**Discussion:** Epithelial tumors (85% of malignant tumors of the nasopharynx) are classified by the World Health Organization (WHO) according to their differentiation and production of keratin, as: Type I – Carcinoma of Squamous Cell, Type II – nonkeratinized Carcinoma and Type III - undifferentiated carcinomas. Type II and Type III have a positive serological profile for EBV, and patients affected by the tumor Type I are characterized by the detection of viral DNA and viral antigens in tumor cells and high antibody titer. The lymphoepithelioma is classified as carcinoma Type III.

### **Keywords**

Epipharyngeal tumor, Lymphoepithelioma, radiation therapy.

## F-ra Capitulum Radii L.Dex. – A Case report

*M.Idrizovikj<sup>1</sup>, S.Jovevska<sup>2</sup>*

*<sup>1</sup>JZU GOB „8<sup>th</sup> – September”, Skopje, R. Macedonia*

*<sup>2</sup>UGD „Goce Delcev”, Stip, R. Macedonia*

### **Abstract**

**Introduction:** Fractures are common joint injuries that can occur in any age group.

**Case report:** This case report is a presentation of a mechanical injury in a bicycle fall where the fracture occurs on the head of the right radius in a male person aged 27 years. The patient was admitted to the hospital with pain, swelling and loss of function of the right hand. Reposition and operation were performed by placing osteosynthetic material and plaster immobilization. An osteosynthetic material - a pin was inserted in order to connect the radius with the ulna. The patient was treated with electrotherapy and kinesiotherapy for two months. Electrotherapy with low frequency interference currents and magnetic therapy was also applied. Kinesiotherapy with active and active assisted exercises of moderate dose were used until the metal was removed. Physical therapy continued to be used after the removal of the metal. In addition, the patient was treated with electro-ultrasound in low doses of 0.3 w in cm<sup>2</sup>, and electrophoresis (EF) with potassium iodide (KI), which is placed on a positive electrode and inserted in the skin and subcutaneous tissue using galvanic current, thus stimulating the creation of callus. The kinesiotherapy with active and active assisted exercises also continued to be used, now with increased resistance. Exercises for strengthening the muscles by using a ball, dumbbells, bands with different resistance were also introduced. The function returned to normal in two months.

**Conclusion:** Physiotherapy, especially kinesiotherapy, is of great importance in restoring the functional status of the patient.

### **Keywords**

fracture, joint, surgery, kinesiotherapy.



## **Patient with intracranial hemorrhage and arteriovenous malformation detected with transcranial color duplex sonography – case report**

**Elena Simeonovska Joveva**<sup>1</sup>, Marija Karakolevska Ilova<sup>2</sup>, Aleksandar Serafimov<sup>3</sup>, Lidija Petrovska<sup>4</sup>, prof.dr. Anita Arsovska<sup>5</sup>

<sup>1</sup>Department of neurology, Clinical Hospital Stip, Faculty of medical sciences, "ASNOM" 5 Stip

<sup>2</sup>Department of oncology and radiotherapy, Clinical Hospital Stip, Faculty of medical sciences, "General Mihajlo Apostolski 34/14" Stip

<sup>3</sup>Department of pathology, Clinical Hospital Stip, Faculty of medical sciences, Roza Petrovabr 15 1-1/3-1, Kocani

<sup>4</sup>Department of dermatology, Clinical Hospital Stip, Faculty of medical sciences, "Kozjakplanina" 2 Stip

<sup>5</sup>Department of neurology, Clinical Hospital Skopje, Faculty of medical sciences Skopje, Pavel Satev 10/32, Skopje

++389/ 78 492 921, elena.joveva@ugd.edu.mk

### **Abstract**

**Introduction:** Transcranial color duplex sonography represents a non-invasive diagnostically method which allows visualization of the brain arteries on the basis of the skull through color-coding of the flow rate. The arteries of the Willis' circle (circulus arteriosus cerebri) can be identified through their anatomic localization in relation to brain stem structures and by determining the direction of flow. During examination the ultrasound beam passes through natural cranial openings, or windows, which are areas of the cranium where the bone is the thinnest (transtemporal, tansorbital and transoccipital windows). During hemodynamic analysis on the Doppler wave, the following basic parameters are analyzed: systolic speed peak, median speed, spectral distribution of the frequencies, direction of flow, Doppler indexes (index of pulsation and index of asymmetry).

**Goal:** The goal is to show the diagnostic application of transcranial color duplex sonography in detection of morphologic and hemodynamic changes of the intracranial arteries in patients with stroke.

**Material and methods:** We represent 62-year old patient who has been hospitalized due to acute paralysis of the left limbs, slurred speech and headache. Neurological examination on admission: left-sided hemiplegia, dysarthria, headache. At admission a CT was made with finding clearly limited hyperdense change – intracerebral hemorrhage with perifocal edema without evident mass effect on the adjacent brain structures. A neurosurgeon was consulted who said that there are no indications for operation. Significant information: history of CVI before 18 years, with left limbs weaknesses (no medical documentation). Transcranial color duplex sonography was made whit detected area of mixed arterial and venous signal, with increased flow rate and turbulence through transtemporal sonographic window. Because of that a CT angiography of the intracranial blood vessels was indicated which found anpial arteriovenous malformation with big nidus and dilated and tortuous vein which flows to v. Galeni. Arteriovenous malformation receives blood through the right a. cerebri media, right a. carotis posterior and also cross-filling through the left a. carotisinterna and aa. comunicantes anterior.

**Results:** On discharge improved neurological condition, patient was with residual left sided hemiparesis and discreet dysarthria – mRS score 3.

**Discussion:** Transcranial color duplex sonography is a non invasive method of evaluation of intracranial blood flow, especially in patients with stroke. It helps if selection is made for patients that should undergo additional invasive radiological tests such as CT angiography.

**Keywords**

arteriovenous malformation, transcranial color duplex sonography.

## Hereditary supracondylar spur of the humerus: Case report

George Zafiroski<sup>1</sup>, Strahil Todorov<sup>2</sup>, Christian Lozanoski<sup>2</sup>

<sup>1</sup>Dept. for Orthopaedic Surgery and Traumatology, Special Hospital for Surgical Diseases "Filip Vtori"; Address: Boulevard Ilinden No.113 - Skopje, Republic of Macedonia

<sup>2</sup>Faculty of Medical Sciences, University "Goce Delcev"; Address: "Krste Misirkov" No.10-A - Stip, Republic of Macedonia  
+38976444137; strahil.15405@student.ugd.edu.mk

### **Abstract**

The spur or the supracondylar process variation of the humerus was first described by Struthers in 1849. The supracondylar spur has a prevalence of 0.3% - 2.7%. It is believed to represent a phylogenetic vestige of the supracondyloid foramen found in reptiles, cats and climbing animals. Three cases of supracondylar process of the humerus are presented. The main features of a supracondylar process correlated with osteochondroma are reviewed. Family relation is obvious in our case - father and two daughters. No one of them had compression symptoms or pain. They accidentally revealed the outgrowth: the father during bathing, and in two children during bathing and dressing. Radiographic findings are identical in all three cases: native radiography of the skeleton on the right elbow, on the medial side of the distal right humerus presented soft tissue shadow like the avian spur, with a broad background associated with the skeleton; suspect cartilage exostose findings. Ultrasound findings determined: ultrasonographic soft shadow, in addition to a soft tissue, suspicious for a cartilage exostosis. Also, motor and sensory functions of the nerves and muscle strength were within normal limits and Tinel and Phalen tests were negative in all three cases. No anomalies were identified on neurography and electromyography. Laboratory tests showed normal values. No one of our three patients underwent surgical interventions, because no one of them had median nerve compression or long standing pain. We suggest a follow-up of the spur's growth in both children and to re-investigate in a 6 month interval, because of the non-completion of the spatial growth. After depiction in our cases and a review of the literature available for this kind of scenario using same aiming, it is important to emphasise the characteristics of spurs as an anatomic variant. Second is to evaluate and differentiate between osteochondroma and our findings on supracondylar processes, which will give us a hint for specific treatment in both osteochondroma and spur anomalies within coherent family incidence.

### **Keywords**

Electromyography; follow-up; humerus; radiographic findings; supracondylar process.

## **Prosthetic rehabilitation in patient with advanced degree of functional disorders (case report)**

**Denkova Natasha**, Zlatanovska Katerina, Radeska – Panovska Ana, Nashkova Sanja, Kovachevska Ivona

*Faculty of medical science - dental medicine, University GoceDelchevShtip  
Natasa.denkova@ugd.edu.mk078-390 432*

### **Abstract**

**Introduce:** Loss of hard dental tissues from noncarios etiology is multifactorial irreversible process, occur as a result of chemical and physical factors. These disorders are associated with the terms of abrasion, erosion and attrition - functional disorders. The severity of the defects can significantly depending on the predominant etiologic factor.

These disorders rarely occur individually and in isolation, often in the same patient observed several forms of loss of hard dental tissues, which are mutually combined.

**Aim:** In this theme we set a purpose about solving combined functional disorders at an advanced stage.

### **Case report:**

For the realization of our purpose, we had a 43 years old patient with advanced stage of combined functional disorders.

The patient had impaired aesthetics and difficulty mastication.

At the same patient was suggested high aesthetic restauration, with porcelain crowns.

Final result is achievement of normal occlusion, articulation and satisfactory esthetics by setting porcelain crowns on teeth with combined functional impairments.

**Conclusion:** Thanks to the developed aesthetic restoration, except getting aesthetics, we prevent the deepening of the tooth defect and enabled smooth realization of the function of masticator apparatus.

### **Keywords**

hard dental tissues, functional disorders, aesthetic restoration.

## Marginal Implants Bone Loss – a Case Report

**Papakoca Kiro**<sup>1</sup> , Ana Radevska Panovska<sup>2</sup> , Katerina Zlatanovska<sup>2</sup>

<sup>1</sup> University “Goce Delcev” – Shtip, R. Macedonia, Faculty of medical sciences, Dental medicine, Department of oral and maxillofacial surgery and dental implantology

<sup>2</sup>University “Goce Delcev” – Shtip, R. Macedonia, Faculty of medical sciences, Dental medicine, Department of dental prosthetics.  
kiro.papakoca@ugd.edu.mk 071 332 232

### **Abstract**

The aim was to show an available treatment for preventing ridge atrophy and optimize esthetic mandibular area, whit socket preservation procedure. So many practicing took about effect of surgical trauma during implant insertion. Particular factor may trigger more rapid attachment breaking, thereby producing an environment that will harbor many putative pathogens. In our presentation we will show some x-ray from the 43 years old female patient who come in dental clinic Dent Estet – Shtip, for making prosthetic solution. After anamnesis we found about implant placement in other dental clinic past 6 months. But we must to extract implants, making bone augmentation (the extraction site was grafted with an osteoconductive bone graft) and after another 6 month making another prosthetic – implants solution. In that way, they may contribute to greater physiologic bone loss caused by the reestablishment of biologic width or due to a foreign body reaction.

### **Keywords**

Implants placement, marginal bone loss.

# Ectodermal Dysplasia, a Case Report: Challenge for Prosthodontic Solution

Emilija Bajraktarova Valjakova<sup>1</sup>, Bajevska Jagoda<sup>1</sup>, Vesna Korunoska Stevkovska<sup>1</sup>, Biljana Kapushevska<sup>1</sup>, Nikola Gigovski<sup>1</sup>, Aneta Mijoska<sup>1</sup>, **Katerina Zlatanovska**<sup>2</sup>, Cvetanka Bajraktarova Mishevaska<sup>3</sup>

<sup>1</sup>Department of Prosthodontics, Faculty of Dentistry, University "Ss. Cyril and Methodius", Skopje, Macedonia

<sup>2</sup>Department of Prosthodontics, Faculty of Dentistry, University "Goce Delchev", Shtip, Macedonia

<sup>3</sup>Department of Orthodontics, Faculty of Dentistry, University "Ss. Cyril and Methodius", Skopje, Macedonia

katerina.zlatanovska@ugd.edu.mk

## **Abstract**

**Introduction:** Ectodermal dysplasia (ED) is an inherited disruption of two or more tissues and structures of ectodermal origin during their embryonal development. Hypodontia or anodontia of the primary and permanent teeth, poorly developed alveolar ridges and inappropriate maxillo-mandibular relations are the most common oral manifestations. Management of patients with ED (depending on the phenotypic characteristics) needs a multidisciplinary team approach that involves maxillo-facial surgeon, pedodontist, orthodontist and prosthodontist.

**Case report:** A 6-year-old girl with ectodermal dysplasia having a normal intellectual development has typical facial expression: square forehead, prominent ears and supraorbital ridges, pigmented and wrinkled eyelids, nose with anteverted nostrils, thin inward lips, and pointed chin. Hypotrichosis is characterized by almost no eyebrows, eyelashes and skin hairs; the sculp is covered with a wig. The skin is dry, thin and rough as a result of decreased function of the sweat glands. Finger and toe nails are short, thick and striated. Decreased lower facial height, together with deep mentolabial and nasolabial folds contributed to an old-looking facial expression. Complete bilateral cleft palate was partially solved on 1.5 year of age, with remained oro-nasal communication and a presence of soft palate only. An alveolar ridge in the mandible is rather atrophic with deciduous canines destroyed by caries and and carious permanent molar teeth in both jaws (severe hypodontia). The gingiva is rather swollen, with dark-red color especially around the teeth.

**Treatment procedure:** Taking into consideration the patient's age and clinical findings, removable complete over-denture prosthesis was the treatment of choice. The preliminary impressions were taken with stock trays and irreversible hydrocolloid material, while the functional impressions were taken using custom trays and thermoplastic material for border molding and polyvinyl siloxane impression material. Maxillo-mandibular relations were determined using temporary bases with wax rims. The final trial with artificial teeth arranged according to a balanced occlusion was conducted to verify horizontal and vertical relations, phonetics and esthetics. The maxillar and mandibular prosthesis were produced in the heat cure acrylic resin. Disrupted functions of the oro-facial system such as mastication, swallowing and phonetics are improved significantly with complete dentures.

**Conclusion:** Correct maxillo - mandibular relations and normal function of the dento-facial system in patients with ED, can be achieved by the acrylic dentures. Prosthodontic treatment has a major impact not only on the functions and esthetics, but on the psychological development and emotional state as well.

**Keywords**

Cleft palate, Ectodermal Dysplasia, Hypodontia, Removable dentures.

# Alveolar socket preservation and shaping using temporary prosthetic construction – cases presentation

Gigovski N.<sup>1</sup>, Radeska-Panovska A.<sup>2</sup>, Korunoska Stevkovska V.<sup>3</sup>, Bajraktarova  
Valjakova E.<sup>4</sup>, Mijoska A.<sup>5</sup>, Gigovska A.<sup>6</sup>

*Affiliation and address: <sup>1,3,4,5</sup> prosthetic dentistry, Faculty of Dentistry, University St. Cyril  
and Methodius, Skopje*

*<sup>2</sup> orthodontics, University Goce Delcev, Stip*

*<sup>6</sup> general dentistry, Private dental practice Denta Nova, Skopje*

*Presenter's telephone and e-mail: 0038978214369, ana\_radeska@yahoo.com*

## **Abstract**

**Introduction** - Postextraction bone resorption usually results in reduced, deficient and sometime even defective alveolar ridge compromising the fabrication, hygiene and esthetic of the gingival part of pontic design. The deficiency of the partial ridge due to bone resorption is normal and expected, but its intensity and shape can be improved with proper planning and fabrication of immediate temporary construction prior the tooth extraction.

**Objective** - The aim of the study is to present and investigate the effect of alveolar socket preservation and partially toothless residual ridge shape using immediate fixed or removable temporary prosthetic construction in cases with single tooth extraction indication.

**Material and method** – Immediate temporary removable single tooth denture (4 cases) or temporary bridge (3 cases) were fabricated in 7 patients with indication of tooth extraction. The specific element in both prosthetic constructions is a small false root (4-5 mm) inserted in the postextraction alveolar socket. This pseudo-root was periodically corrected and decreased in height every 2 weeks.

**Results** – The prosthetic construction applied immediately after extraction protects the alveolar socket allowing undisturbed healing and ossification. The short pseudo-root inserted in the cervical part of the alveolus gives support and prevents collapse of the soft tissue. Recommended period for using temporary construction is 8-12 weeks.

**Conclusion** – The benefit of this simple procedure is to achieve faster healing of the postextraction socket and desirable shape of the toothless area. The disadvantages are necessity for proper planning prior the tooth extraction, relatively long period for shaping of the alveolar ridge and frequent adjustments of the immediate temporary construction.

## **Keywords**

alveolar ridge, alveolar socket, prosthetic rehabilitation.



## **Porcelain veneers produced by refractory die method**

***Katerina Zlatanovska, Julija Zarkova-Atanasova, Ana Radeska-Panovska,  
Natasa Denkova, Kiro Papakoca***

*Faculty of medical science – Dental medicine, University Goce Delcev - Stip  
[katerina.zlatanovska@ugd.edu.mk](mailto:katerina.zlatanovska@ugd.edu.mk) 078 211 678*

### **Abstract**

Nowadays porcelain veneers are constantly increasing in popularity among dental practitioners because of their excellent clinical performance. As materials and techniques develop they have become most utilized, high aesthetic and less invasive therapeutic possibility used for conservative restoration of unaesthetic anterior teeth. Technological advances today make it easy to obtain natural aesthetic result with conservative interventions. The many all-ceramic systems available to dentists and dental technicians today offer choices like never before. The choice of material and technique depends on the indications and clinical case. There are many ways to fabricate porcelain restorations. This study describes that a quality porcelain veneer restoration can be made by the refractory die method, which produce excellent results but requires more effort in model making.

### **Keywords**

All-ceramic systems, non-invasive, porcelain veneers, refractory die.

# Correlation of Two Different Local Hemostatic Modalities in Oral Surgery Patients with Oral Anticoagulants

*Cena Dimova*

*\*Associate Professor*

*Department of oral and maxillofacial surgery and dental implantology,*

*Faculty of Medical Science, University of "Goce Delcev", Stip*

[\*cena.dimova@ugd.edu.mk\*](mailto:cena.dimova@ugd.edu.mk)

## **Abstract**

**Introduction:** The oral surgeons are frequently asked to manage patients who are receiving oral anticoagulants. The goal of treatment is to minimize the risk of hemorrhage while continuing to protect the patient against thromboembolism formation. The ordinary treatment includes the interruption of anticoagulant therapy for oral surgery interventions to prevent hemorrhage. However, this practice may logically increase the risk of a potentially life-threatening thromboembolism. Thus, this issue is still controversial. Various protocols have been suggested for treating these patients, including substituting heparin for warfarin, decreasing the level of anticoagulation preoperatively, temporarily stopping the warfarin, and not altering the anticoagulant regimen at all. There remains, however, no standard therapeutic approach, and currently it appears that each patient's treatment plan is individually tailored by his or her attending specialist.

**Aim:** The evidence from clinical trials and focused reviews supports continuing oral anticoagulation for patients needing dentoalveolar surgery. As long as the INR is within the therapeutic range and local hemostatic measures are taken following the surgery, these patients will have little chance of developing uncontrolled bleeding following the surgery. The aim of this study was to compare the clinical hemostatic effect of tranexamic acid mouthwash and resorbable oxycellulose dressing after oral surgery interventions in patients receiving continuous oral anticoagulant therapy

**Material and method:** A first group was consisted of 25 patients with a preoperative international normalized ratio (INR) in the range of 1.8 to 3.0. After the interventions was used 5% tranexamic acid mouthwashing for 2 minutes, 4 time daily during a postoperative period of 4days. The second group of 25 patients with a comparable INR range of 1.9 to 2.9 had oral surgical interventions performed and the socket(s) dressed with a resorbable oxycellulose dressing and sutured with a resorbable suture.

**Results:** No discernible difference in the postoperative outcome with regard to hemorrhage was noted. Postoperative pain was reported more frequently in the group that used a resorbable oxycellulose dressing. Only 1 patient had significant postoperative bleeding. The risk of uncontrolled life threatening bleeding following dentoalveolar surgery is so low that it is not necessary to stop anticoagulation even for a short interval and risk thromboembolism in patients on oral anticoagulants.

**Conclusions:** Dental extractions can be performed without interruption in patients treated with oral anticoagulant. This study shows that in patients receiving oral anticoagulants whose INR is within the therapeutic range, the tranexamic acid mouthwash is as effective as the resorbable oxycellulose dressing in preventing post oral surgical hemorrhage. The results indicated that a combination of local antifibrinolytic therapy and a local hemostatic agent is effective in preventing postoperative bleeding

after oral surgery in patients treated with anticoagulants. Local hemostasis will control the bleeding in the few patients who develop postsurgical bleeding.

**Keywords**

bleeding, oral anticoagulant, oral surgery, oxycellulose dressing, tranexamic acid.

## Assessment of orthodontic treatment need among school children by using IOTN (Index of Orthodontic Treatment Need)

**Ana Radeska-Panovska**<sup>1</sup>, Kiro Papakoca, Natasa Denkova, Ivona Kovacevska, Katerina Zlatanovska

<sup>1</sup>University "Goce Delcev" – Shtip, R. Macedonia, Faculty of medical sciences, Dental medicine

[ana.radeska@ugd.edu.mk](mailto:ana.radeska@ugd.edu.mk) 078 214 369

### **Abstract**

**Introduction:** Dental treatment is carried out in order to improve dentofacial aesthetic, function and health of patient. Aesthetic is the main reason for treatment, therefore we have to decide which aesthetic norms should we follow when we are planning orthodontic treatment. Although no consensus was reached for individual and occlusal features that need to be assessed in order to ascertain the orthodontic treatment need. In modern literature are using multiple indices to improve treatment planning. One of these indices is IOTN (Index of Orthodontic treatment need), described by Brook and Shaw (1989) and amended by Richmond (1990) as a method to objectively assess the orthodontic treatment need.

**Aim:** This index is used to assess patient eligibility for orthodontic treatment.

**Material and method:** Examinees aged 12-16 years of both sexes occurred in the orthodontic practice with a desire to be treated. Each of them were given a questionnaire filled out before completing the clinical examination. Normative orthodontic treatment need was assessed clinically using IOTN index.

**Results:** 70% of examinees thought it definitely need orthodontic treatment, and 30% of them think that probably yes. In 60% of them, the irregularities of the teeth noticed parents, 40% irregularities them into notes their dentist. 60% of respondents were previously orthodontic treatment, while 40% of them never previously had orthodontic treatment.

**Conclusion:** A significant difference was found between our assessment and self-assessment of the examinees in the attractiveness of their occlusion. For effective orthodontic treatment, in addition to professional evaluate it, subjective perception must be taken into consideration when formulating a treatment plan in order to ensure a final product that will satisfy expectations of the patient.

### **Keywords**

IOTN, aesthetic, function.

# Oral Hygiene Level Maintenance among Dental Medicine Students

**Darko Kochovski**, Verica Toneva, Cena Dimova

Faculty of Medical Sciences – Dental Medicine, University Goce Delchev–Shtip

[kocovski99@gmail.com](mailto:kocovski99@gmail.com) 078646855

## **Abstract**

**Introduction:** Oral hygiene is one of the most important measures for the preservation and promotion of oral health. Not proper maintenance of oral hygiene leads to create dental plaque. Dental plaque of the teeth and gums is the major cause of diseases of the tissues such as tooth decay, sensitivity of teeth and tooth necks, sore gums, gum recession, loosening of the teeth as a result of periodontitis.

**Aim:** The aim of this study was to determine the level of maintenance of oral hygiene among students of Dental medicine.

**Material and method:** For the realization of this survey was made a questionnaire with 5 questions. In the survey were included 40 students from third year. In the same students, checks were made, where it was determined the condition of the teeth and plaque index.

**Results:** Forty-five percent of students had a plaque index less than 0.6 which means that they maintain proper oral hygiene. Fifty-two percent had plaque index of 0.6 to 1.9 which means that they maintain good oral hygiene, but they should take adequate measures to promote their oral hygiene. It was determined unsatisfied level of oral hygiene among 2.5% of the students.

**Conclusion:** As a general conclusion, the study showed that students of Dental medicine maintained good oral hygiene. Individuals who maintain proper oral hygiene have a small percentage of dental plaque and have less probability to develop diseases of the teeth and parodontium.

## **Keywords**

Oral hygiene, dental plaque, teeth, students, plaque index.

## Poor oral hygiene and show of caries in 12 year old children

**Sanja Nashkova**

*Teaching assistant at University "Goce Delcev"-Shtip  
Faculty of medical science-dental medicine  
071/210 171; sanjanashkova@ugd.edu.mk*

### **Abstract**

Poor oral hygiene leads to the presence of dental plaque which is a non-mineralized organized content of microorganisms in the organic matrix of carbohydrates located on the teeth surface. The amount of the plaque and the number of bacteria in the saliva are directly related to the threat of caries in every individual. This shell on the surface of the teeth is difficult to remove, is colorless and invisible, but with coloring it can be seen, and it can be removed only by mechanical cleaning. That, which is noted in the modern literature is increasingly considered that is more the result of the disruption of the ecological balance of the oral cavity, than the result of poor diet or lack of oral hygiene.

**Aim:** Our aim is to determine the index of the oral hygiene and its association with the show of dental caries.

**Material and method:** The study included 70 subjects (35 male, 35 female), aged 12, randomly selected. The research was realized by the recommendations for action resulting from the basic criteria for the assessment of oral and dental health that are recommended by World Health Organization (WHO). For the assessment of the oral hygiene habits and the presence of soft plaque we used the simplified method of Greene Vermillion which evaluates six surfaces of six teeth that are representative sample of the entire dentition.

**Results:** The results indicate higher values for distribution of OHI (Oral Hygiene Index)-the index distribution among male ( $0.51 \pm 0.57$ ,  $X \pm SD$ ), unlike the subjects who were female ( $0.49 \pm 0.76$ ,  $X \pm SD$ ), with significance ( $p < 0,01$ ).

**Discussion:** Our obtained results undoubtedly show in addition to numerous authors' claims that in patients with poor oral hygiene caries is more often. In children with poor oral hygiene and consumption of sweets between meals are the two most intensive risk factors for appearance of caries. As a result of poor oral hygiene higher values of plaque index in children are determined.

### **Keywords**

caries, dental plaque, oral hygiene, oral hygiene index, saliva.

## Implant-prosthetic therapy failure in smoker and nonsmoker patients

Aneta Mijoska<sup>1</sup>, Mirjana Popovska<sup>2</sup>, Nikola Gigovski<sup>3</sup>, Vesna Korunovska- Stevkoska<sup>4</sup>,  
Emilija Bajraktarova<sup>5</sup>, **Katerina Zlatanovska**<sup>6</sup>

<sup>1,2,3,4,5</sup> Faculty of Dentistry, "Ss Cyril and Methodius" University, Skopje, Macedonia

<sup>6</sup> Faculty of Medical Sciences, Goce Delcev University, Stip, Macedonia

Tel: 389 70323434, [amijoska@yahoo.com](mailto:amijoska@yahoo.com)

### **Abstract**

**Introduction:** Implant-prosthetic therapy has predictable success, and the complications are associated with a lot of factors. Smoking cigarettes is reason for different oral diseases, bone loss, loss of soft tissue and teeth, appearance of periimplantitis and implant loss. The correlation of smoking and implant-prosthetic therapy failure was examined in the clinical study.

**Materials and method:** Fifty patients with FDP on 61 implants in frontal and molar region were investigated. They were divided in two groups: smokers and nonsmokers. Thirty four patients were smokers, and sixteen didn't smoke cigarettes in the last two years. Criteria data for the success of the therapy were mobility of the implant, pain, peri-implant bone loss higher than 1.5 mm, absence of technical complications and function and aesthetics appeal. Control checkups were made after six months, one and two years. Patients had questionnaires, clinical examination and X-ray.

**Results:** There is a statistically significant difference between smokers and nonsmokers in the failure rates of dental implants. During first year 0,5 mm of bone was lost around eleven implants, and 0,05 mm next years. Total seven implants failed, five in smoker group at the beginning of the first year, and 2 in nonsmoker group during second year.

**Conclusion:** Results showed that smoking habit can increase the risk of *early* implants loss two times more often in smokers. For some complications like periimplantitis, local factors have greater influence. Smoking does not increase the risk of *late* implant loss, but the implants at patients with smoking habit, in correlation with several different local risk factors, is contraindicated. Early complications are results of smoking, while quality and quantity of surrounding bone are responsible for late complications. The results from the investigation, also give informations for proper treatment planning, and patient education for quitting their harmful habit.

### **Keywords**

Implants, therapy failure, smoking, periimplantitis.

## Oral surgery treatment in the patients with combination syndrome

*Korunoska-Stevkova V., **Zlatanovska K.** Gigovski N., Menceva Ž., Nikolovska J., Bajraktarova-Valjakova E., Mijoska A.*

### **Abstract**

**Introduction:** Combination syndrome is periodically associated in wearers with removable dentures, where upper is complete denture and lower is partial denture with some of the anterior natural teeth still in the mouth.

**Material and method:** The study was provided on five patients with removable dentures at the Department of prosthodontics in the period of last three years. Three of them have worn the dentures more than ten years, and came to the clinic for a new one. Another two patients have worn removable dentures between two and four years, and came because in the frontal part of the upper jaw appeared swollen. By clinical examination in all patients we noticed: hyperplastic tissue in the pre-maxillary region, reduction of the residual ridge on the frontal part of the maxilla as a result of the increasing pressure from the anterior teeth of the lower jaw. This tissue was removed by oral surgery (laser removing of hyperplastic tissue). Also we noticed periodontal changes and extrusion of natural lower frontal teeth and increased reduction of mandibular residual ridge.

**Results and conclusion:** After the healing period we made: new dentures in the three patients which were covered by the HIFM and in another two patients we made indirect relining on the upper denture, re-occlusion and re-articulation achieving weak contacts between the lower natural teeth and upper teeth of the complete denture. We cautioned the patients not to bite food with anterior teeth and to avoid chewing very hard food which tends to imprint and displace dentures and of course to come to regular controls.

### **Keywords**

removable dentures, combination syndrome, hyperplastic tissue, oral surgery treatment.



# Iatrogenic mistakes, cause for a failure at surgical treatment of a chronic periapical processes

**Dr. Sarita Kadrova**<sup>1</sup>, Professor Dr. Cena Dimova

<sup>1</sup>``Blazho Aleksov`` 54, Kavadarci, Macedonia  
Telephone 071 390 428, 043/410-717,  
email: kadrovasarita@yahoo.com

## **Abstract:**

**Introduction:** The chronic periapical processes are common changes that can be located in the oral cavity. One of the main reasons for their occurrence are untreated infected teeth, usually infected by caries, but also bad, late or incompletreatment of the root canals. According to numerous researches over 60% of all the surgical interventions are the surgical treatments of a chronic periapical processes and their consequences. The failure at the surgical treatment of the chronic periapical processes can show up as a result of iatrogenic mistakes, and sometimes the causes are some general or local factors.

**Aim:** The aim of this research was to present some of the iatrogenic mistakes as a rear reason for the failure of the surgical treatment of the chronic periapical processes.

**Material, methods and results:** In a 12 months period from August 2014 to July 2015, the surgical treatment of a chronic periapical processes was applied to 20 patients in different dental offices.

**Results:** After a period of three months in 10 % of the cases (two patients) a failure of the treatment was found which led to an extraction of the apicoectomied teeth.

**Conclusion:** The cause of the failure in these cases is the iatrogenic mistake which can be seen on the RTG that was made after the intervention.

## **Keywords**

iatrogenic, periapical.

# Evaluation of Different Preparation of Artificial Teeth and Acrylate Prosthetic Base

Apostoloski Pavle<sup>1</sup>, Dimova Cena<sup>2</sup>, Katerina Zlatanovska<sup>3</sup>, Zarkova Julija<sup>3</sup>

<sup>1</sup> professional dental technician

<sup>2</sup> associate professor

<sup>3</sup> assistant professor

Faculty of Medical Science, "Goce Delcev" University, Stip

## **Abstract**

Preparation of the basal area in acrylate artificial teeth is a very important factor in the quality of a dental prosthesis. It refers to the link between artificial teeth and acrylic denture base made of heat polymerized acrylic.

The most common reason for failure of mobile prosthetic works is falling artificial teeth acrylate prosthetic base. The failure is due to the manner of connection between the base and artificial teeth. As the main factor which affects the level of retention is mechanical preparation of the basal area in acrylate teeth.

For the realization of the set targets were tested 10 acrylic models. The theme was designed to show the justification for the mechanical preparation of the basal area in acrylate artificial teeth, then using a light microscope to measure the size of the crack between acrylic artificial teeth and acrylic denture base. The paper described two techniques, without preparation and separation technique, which justify the best technique of preparation.

The results can be analyzed that the maximum distance to the interspace occurs models from the A group. As for the models of group B interspace between artificial teeth and acrylic base with smaller values as opposed to models of A group.

Mechanical preparation of artificial teeth significantly affect the degree of physical connection and also provides greater contact surface with acrylate prosthetic base.

## **Keywords**

Connection acrylic pedestals, heat polymerized acrylic, mechanical preparation, separation.

# **Analysis of the dimensional stability of elastomeric silicone impression materials**

**Galaba Veresa-Dimova**, *Cena Dimova, Julijana Miloseva*

*Dental lab technician, 078-473 263, gveresa@yahoo.com*  
*Associate professor*  
*Doctor of dental medicine*

## **Abstract**

Taking an imprint is the first stage of indirect fix prosthetics restoration and preparation and choosing impression material that fulfils the requirements for accurate and precise printing is of great importance.

The aim of this research is to responds to the measure and compare the dimensional stability of the additional and condensational elastomeric silicon's impression materials in a different time sequence and to highlight the importance of the outpouring of print within 2 hours, after taking the print.

For the analysis of dimensional stability are used most commonly used silicone impression elastomeric materials that takes an imprint in the production of restorations fix prosthetics condensational silicone (Xantopren Comfort Heraeus Kulzer) and an additional silicone (Variotime Easy Putty Heraeus Kulzer). During the research materials were placed in the same room with a stable temperature of 21-23<sup>o</sup>. Both impression materials was prepared according to the manufacturer's instructions.

The sample is phantom model of an upper jaw with stuffed first premolar and first molar. Stuffed dental nog are marked cervical border, in the longest distance in two directions buccal-oral and distal-mesial. With standard No. 3 spoons taken by an imprint of both types of silicone condensational silicone (Xantopren Comfort Heraeus Kulzer) and an additional silicone (Variotime Easy Putty Heraeus Kulzer). Imprints are poured with a super hard, yellow plaster (Hera Moldastone tipe IV, Heraeus) at different time's sequence.

They were made of 8 patterns at different time period: immediately after 4 hours, 12 hours and 48 hours. Received 4 models print from condensational silicone and 4 models print from an additional silicone. Were measuring 16 stuffed dental nog in 32 measuring points.

The obtained model was conducted measuring the previously marked areas of the prepared tooth nog using a screw micrometers (MEBA) with a measurement accuracy of 0,01 mm.

The methodological tools that is used is based on the finding of the impact of the time factor on the dimensional stability of prints from two different impression materials and mutual comparing the results obtained with manual survey of replica models printout of an additional and condensational silicone and comparing them with the control model. The results are expressed in millimeters and percentages.

Dimensional changes between model and its reproductions occurred as a consequence of dimensional instability impression material. The results indicate that in both directions, with each successive measurement was continuously increasing dimensional change. In measuring replica models derived from the print of an additional impression silicone material can be noted that the dimensional changes occurring are much smaller than the dimensional changes that occurred in replica models derived from the prints of condensational silicon, indicating that the additional of silicon was dimensionally stable than condensational.

Dimensional changes between the model and its reproductions resulted from the dimensional instability impression material. The difference was greater in print taken with condensation silicone (0.78%), compared to the imprint taken with an additional silicone (0.30%).

Both impression materials showed satisfactory results in terms of dimensional stability and did not change more than 1.08%.

**Keywords**

dimensional changes, impression material, print, phantom model restoration.

# Use of Gypsum Into Working Everyday in Dental Technician

*Hadis Arslanov, Cena Dimova, Julija Vladikova, Pavle Apostolski*

*Faculty of medical science, University "Goce Delcev" Stip*

## **Abstract**

**Introduction:** Gypsum is a mineral consisting of compounds of the crystal structure. Composition is calcium sulfate dihydrate ( $\text{CaSO}_4 \cdot 2\text{H}_2\text{O}$ ). In dental laboratory the cast is of great importance and it is used for each prosthetic manufacture, or most exploited material in dental laboratory. White the overflow gypsum obtained a copy of the negative (imprint), on which the spill gets positive or model in the same subject, which according to the size and shape of fully reproduce the original, we get a clear and precise situation of the teeth and around structures.

**Purpose:** The purpose of this study is exploring the kinds of gypsum in chemical composition, alabaster gypsum, blue or hard gypsum, yellow or superhard gypsum and their proper use in spills manufacture to obtain anatomical studio and working model.

**Materials and Methods:** For the realization, we made research in PubMed from 1940 to till today. In dentistry are used white gypsum, hard and super hard gypsum. With the overflow of the negative in alabaster gypsum, we received studio models and anatomical models. White gypsum are also used for fixing models in articulator. Hard and super hard gypsum are used for models which is needed to serve for the preparation of dental construction with great precision. Super hard gypsum is used for working models and mobile dental nogs. The working model presents field- (exactly and precisely all parameters of prosthetic), (teeth, alveolar ridges), occlusion-articulation relations between the jaws and teeth. The main features that should have been cast are: easy to mix, no porosity in model, the expansion of the gypsum binding is accompanied by a heat release.

**Results:** Right and wrong manufacture of prosthetic devices in the manipulation of the gypsum. Alabaster gypsum was used for the outpouring of anatomical prints and obtaining anatomical and working patterns, to the articulator models and others. Hard gypsum was used for the outpouring of prints to obtain work and all kinds of precise models. Super hard gypsum was used for the outpouring of prints and acquiring operational models, for dental construction and others.

**Conclusion:** Obtained data from a lengthy application and work with different types of gypsum, of which we could conclude that manipulation with the gypsum should be according to rules prescribed by the manufacturer.

## **Keywords**

gypsum, prints, model, prosthetic devices.

## Mobile dental NOG types used in working dental models

Julija Vladikova<sup>1</sup>, Cena Dimova<sup>2</sup>, Hadis Arslanov<sup>1</sup>, Pavle Apostolski<sup>1</sup>

Faculty of Medical Science, University of "Goce Delcev"- Stip,

1- Professional dental prosthodontics

2- Associate professor

Julija Vladikova - 078/394-285, [jvladikova@yahoo.com](mailto:jvladikova@yahoo.com)

### **Abstract**

A working dental model is a model made from the mold taken from an intervention in the mouth (in the fixed prosthetic that is preparation of the teeth) and on which it is directly modeled and a fixed prosthetic construction is made. We pour a hard or super hard plaster. The mold is made first by mixing the super hard plaster, a small quantity is poured on the protruding part of the mold (distal part of the palate) by tapping in slowly it slides in the lumen of all the molded teeth. In this way the water and air are squeezed out so there aren't any defects or porosity on the molded movable dental nog.

Today the dental model making is imperative, and the whole laboratory making of the artificial dental crowns taken from the working models (known as "master" models) are mobile nogs that can be taken out of the rest of the mold multiple times and again put back in the completely same position. The reason is that, the removed nogs very easy to approach, model and control the precision of the gingival edge of the artificial crown, especially from the mesial and distal side where there is a chance of a small gap. The second reason is that some particular widely accepted models for making an envelope as the first phase of the modeling of the crown (for example: making an envelope by wrapping it in plastic foil also known as the Adapta-system or a model made by dipping in melted wax) they can be made only if the working nog is not mobile. In a working dental model is made with a mobile nog, there are a number of ways of making that: with Ney metal stakes, Trey- model- system with tray leading grooves and with separation, with root continuance from plaster or peg, with galvanization, with a mobile periodontium (his regards the surrounding gingival, and not directly on the movable working log.)

The goal of the study is to explore methods and apparatus for making models with movable dental nogs and their use in today's modern practice.

For realization of the set goal a research was made and information was gathered from different manufacturers of apparatus and methods for making models with movable dental nogs. By using the Pindex apparatus we can drill channels in the plaster for placing double (Duplex) stakes, by using the Top Spin (automatic laser drill) a laser drill is made and placement of the stakes for making movable dental nogs in the dental practice. By using different methods and apparatus in the dental practice we get working models with movable dental nogs which secure better retention, stabilization and orientation for rightful acting.

### **Keywords**

Apparatus, dental nog, dental prosthetics, models, modern methods.

## Determining normal tissue toxicity of non-radioactively Lu/Y-labeled rituximab-conjugates in rat animal model

**Darinka Gjorgieva Ackova**<sup>1</sup>, Katarina Smilkov<sup>1</sup>, Icko Gjorgoski<sup>2</sup>, Emilija Janevik-Ivanovska<sup>1</sup>

<sup>1</sup>Department of Pharmacy, Faculty of Medical Sciences, University Goce Delcev – Štip, R. Macedonia, str. “Krstе Misirkov” no.10-A, 2000 Stip, R. Macedonia, tel: +389 75 499 809, [darinka.gjorgieva@ugd.edu.mk](mailto:darinka.gjorgieva@ugd.edu.mk)

<sup>2</sup>Institute of Biology, Faculty of Natural Sciences and Mathematics, University “Ss. Cyril and Methodius”- Skopje, R. Macedonia

### **Abstract**

Antibodies are slowly eliminated by the reticuloendothelial system where the resulting effect on toxicity towards healthy tissue during treatment with preparations containing them arises. Radiolanthanides that dissociate from the conjugate *in vivo*, can form colloids in the blood stream, increasing the uptake in the liver, or can accumulate in bones due to high affinity of the metal ions to the phosphate anion which results in myelotoxicity. Radiolabeled monoclonal antibodies (mAbs) intended for radioimmunotherapy (RIT) of cancers in humans should first be evaluated by preclinical toxicological studies in animal models. Kinetics, distribution and induced effects in healthy mice/rats for normal tissue toxicity and in animals with implanted tumor are followed.

Generalized and gastrointestinal toxicity, liver toxicity and haemopoietic toxicity are followed. Haemopoietic toxicity, if present, is usually seen within 2-3 weeks after injection of the radiopharmaceutical and resolves within 6-8 weeks, while liver and renal toxicity may require a longer period of observation (4 - 8 weeks). Ideal radiotherapeutic agent would demonstrate specific anti-tumor effects with minimal to moderate toxicity to normal tissues.

Concerning these facts, *in vivo* examination of the behavior of Lu- and Y-rituximab-conjugates in healthy animal models (rats) with particular reference to haematotoxicity was performed. The results from blood analysis showed decrease in value for RBC in all samples from all groups (without exception) where the lowest value detected was RBC value determined in the group treated with Y-*p*-SCN-Bn-DOTA-rituximab. This result is in consistence with the confirmed myelosuppressive activity of rituximab itself and the affinity of the yttrium to the bone marrow. On average, in half of the tested samples thrombocythemia (thrombocytosis) was also observed. It is important to note that after the completion of treatment (4 weeks after administration of the last dose) results showed normalization of blood parameters, i.e. RBC values approaching almost normal values. Additional *in vivo* tests for evaluation of rituximab-conjugates in tumor-bearing animal model are required in order to make a final characterization for qualification of this formulation for possible use in RIT for Non-Hodgkin's lymphoma.

### **Keywords**

antibodies, conjugates, rat animal model, toxicity.

# Genetically Engineered Mouse Models For Human Pancreatic Cancer: A Review Of The KC, KPC And iKras\*P53\* Models

David Mwanza Wanjeh.<sup>1,3</sup>; Joel Munene Muchira.<sup>1,3</sup>; Aschalew Alemu.<sup>2,3</sup> Darko Bosnakovski<sup>3</sup>

1. Ministry of Health, Kenya. P.O. Box: 30016–00100, Cathedral Rd, Nairobi, Kenya.
2. Faculty of Medicine, Addis Ababa University. King George VI St., Addis Ababa 1000, Ethiopia.
3. Faculty of Medical Sciences, University “Goce Delcev”; Address: “Krste Misirkov” No.10-A - Stip, Republic of Macedonia.  
Email: dmwanza15@yahoo.com

## **Abstract**

Pancreatic cancer is almost always a ductal adenocarcinoma of the exocrine pancreas, called pancreatic ductal adenocarcinoma (PDAC). Over 80% of PDAC cases show oncogenic Kras activation, mostly co-occurring with p53 gene mutation. Pancreatic intraepithelial neoplasms (PanIN) are the precancerous lesions that usually precede PDAC. Desirable mouse models for PDAC must be able to reliably and predictably recapitulate the human disease. The choice of a mouse model for a particular research study requires careful evaluation of all the available models with respect to their characteristics and the research question.

The aim of this paper is to review and compare the characteristics of the conditional **KC** (Pdx1 Cre; LSL-Kras<sup>G12D</sup>), **KPC** (Pdx1 Cre; LSL-Kras<sup>G12D</sup>; LSL-P53<sup>R172H</sup>) mouse models and the newer inducible **iKras\*p53\*** (Ptf1a Cre; LSL-rtTa; LSL-P53<sup>R172H</sup>; tetO-Kras<sup>G12D</sup>) mouse model and to make an opinion about their suitability to use in oncogenic Kras-targeting translational research for PDAC.

The KC mouse model, developed in 2003, was the proof of principle. It shows a PanIN penetrance of 100% starting prenatally, PDAC penetrance of less than 10% in its first year of life and a transgene expression that is targeted to its usual Kras genomic locus. However, it lacks pancreas-specificity in its transgene expression. The KPC mouse model, developed in 2005, demonstrates 100% PanIN penetrance starting prenatally, 100% PDAC penetrance, a transgene that is targeted to its usual genomic locus and 5months mean survival. Like the KC mouse model, it lacks pancreas-specificity in its transgene expression. The iKras\*p53\* mouse model was developed in 2012. Unlike the other models above, its oncogenic KRas transgene expression is inducible and more pancreas-specific. It has about 7months mean survival, more rapid formation of PDAC and metastases with larger tumor masses than the KPC model. Its oncogenic Kras transgene expression, is however targeted to a different locus than the usual Ras locus of the mouse genome.

Our current opinion is that each of the above models has a unique place in pancreatic cancer research. The KC model (especially its Ptf1a-Cre analog) is more suited for preclinical evaluation of diagnostic agents and the others are useful for evaluating therapies. The iKras\*p53\* mouse is more suitable for studying oncogenic Kras pathway inhibitors but generally, the KPC mouse is still a reasonable choice since it has been studied for longer and researchers have had more years experience with it.

## **Keywords**

GEMMs, oncogenic Kras, pancreatic cancer.



# Mouse Models For Human Prostate Cancer: Xenograft Vs Genetically Engineered Mouse Model

**Aschalew Alemu**<sup>1, 3</sup>, Joel Munene Muchira<sup>2, 3</sup>, David Mwanza Wanjeh<sup>2, 3</sup>, Darko Bosnakovski<sup>3</sup>

1. Faculty of Medicine , Addis Ababa University ,King George VI St, Addis Ababa 1000, Ethiopia

2. Ministry of Health, P.O. Box. :30016-00100, Cathedral Rd, Nairobi ,Kenya

3. Faculty of Medical Sciences, University “GoceDelcev”; Address: “KrsteMisirkov” No.10-A - Stip, Republic of Macedonia

Email Address: [aschuradio@yahoo.com](mailto:aschuradio@yahoo.com)

## **Abstract**

Prostate cancer is among the commonest cancers in men with high mortality. It is thought to arise from accumulated genetic mutations that may transform benign prostatic epithelium to prostatic intraepithelial neoplasia (PIN). With additional genetic alterations, PIN progresses to invasive cancer, and finally to metastatic disease. Metastatic prostate cancer is generally accompanied by emergence of androgen-independent cancer. About 70% of primary prostate cancers exhibit a loss of at least one PTEN allele and loss of both alleles is associated with advanced disease. PTEN is tumoursuppressor gene that works by suppressing the activity of Akt /PKB pathway. Over expression of many oncogenes has also been observed in many human prostate cancers. Animal models are crucial to understand the underlying biology and to test novel prevention and treatment strategies for prostate cancer. Appropriate animal models should recapitulate genetic alterations and clinical courses of human prostate cancer. The following paper describes important characteristics of genetically modified mouse model and xenograft mouse model. We performed recent literature search for human prostate cancer mouse models.

Numerous mouse models of human prostate cancer have been generated and exhibit common characteristics of human prostate cancer. Initially, the immunocompromised mouse was used as a xenograft model for in vivo analyses of human prostate cell lines. This approach does not however consider the heterogenous nature of prostate cancer as a disease with complex interactions between the transformed cells, the resident cells, the stromal cells, the endothelial cells and the immune cells all which participate in the disease pathogenesis. One of the genetically engineered mouse models is the prostate specific Cre-mediated conditional expression of Myc oncogene by removal of a conditional STOP sequence (PB-c-Myc,). This model progresses to invasive carcinoma without metastasis. The other is a conditional PTEN Knockout model using Cre recombinase targeted to the prostate specific probasin promoter. This model recapitulates the human prostate cancer to metastasis carcinoma.

Genetically engineered mouse models are more able to recapitulate the human prostate cancer compare to the xenograft. The PTEN knock out mouse is suitable for understanding molecular basis of the disease. Xenograft will remain more useful testing of therapy. In the future more sophisticated prostate animal model should be available so as to recapitulate the heterogeneity of the disease

## **Keywords**

Knockout, Mouse model, Oncogene, prostate cancer, Xenograft;

# HER2 Transgenic Mouse Models: A Way To HER2+ Breast Cancer Targeted Therapy

**Joel Munene Muchira**<sup>1,3</sup>, David Mwanza Wanjeh<sup>1,3</sup>, Aschalew Alemu<sup>2,3</sup>, Darko Bosnakovski<sup>3</sup>

<sup>1</sup> Ministry of Health, Kenya P.O Box 30016-00100, Cathedral Rd Nairobi.

<sup>2</sup> Faculty of Medical Sciences, Addis Ababa University-King George VI St, Addis Ababa 1000, Ethiopia

<sup>3</sup> Faculty of Medical Sciences, University "Goce Delcev"; Address: "Krste Misirkov" No.10-A - Stip, Republic of Macedonia  
Email address: joelmunesh@gmail.com

## **Abstract**

Breast cancer remains the second leading cause of cancer mortality in women worldwide despite major advances made in the recent years. About 20-30% of breast cancers cases show HER2 over expression and amplification which predicts poor prognosis. Though HER2 has been successfully targeted with anti-HER2 therapies including mAbs such as trastuzumab and tyrosine kinase inhibitors, resistance to trastuzumab is a major setback. Resistance is proposed to occur by steric hindrance of antibody binding to HER2, expression of mutant HER2 as well as increased PI3K/Akt pathway activation. Since there is need to develop better therapies, HER2 transgenic mouse models will contribute greatly to the search for these therapies.

The aim of this review is to analyse HER2 transgenic mouse models and demonstrate their potential towards development of new targeted therapy. The first model evaluated was generated in 2003 using wild-type HER2 and the whey acidic promoter (WAP) under the C57BL/6 background. The mouse was injected with ID8/E2, ovarian tumor cells and there was no tumor rejection in the transgenic mice which indicated tolerance to HER2. On vaccination with five cycles of a robust HER2 DNA based vaccine, there was induction of the immune system in the transgenic mice which was shown by anti-HER2 antibodies and 33% of the transgenic mice were protected from tumor growth. Consistent findings were obtained using the FVB-huHER2 mouse model which uses the MMTV promoter. In both models tolerance was broken by DNA vaccination hence offering protection.

A newer HER2+/PIK3CA mutant transgenic mouse using a Tet-inducible system for gene expression was described in 2013. It was shown that HER2+/PIK3CA expressing mice developed tumors with shorter latency compared to mice expressing HER2 or PIK3CA mutant oncogene alone. Cells from HER2+/PIK3CA tumors showed more lung metastases in the nude mice and the tumors were resistant to trastuzumab alone or in combination with lapatinib. Resistance was reversed by a PI3K inhibitor. This shows that increased PI3K activation has a role in trastuzumab resistance.

The transgenic mouse models expressing human wild-type HER2 oncogene only is suitable for testing of vaccines while the HER2+/PIK3CA mutant transgenic mouse model is suitable for studying trastuzumab resistance and testing of PI3K inhibitors. HER2 transgenic mouse models therefore have great potential towards development of better targeted therapy. If new drug targets are to be identified, new HER2 transgenic mouse models will need to be developed.

## **Keywords**

HER2, HER2 transgenic mouse, PI3K, targeted therapy, trastuzumab.

# Types of scaffolds and their application in bone tissue engineering

**Milena Volcheva**<sup>1</sup>, Darko Bosnakovski<sup>2</sup>

<sup>1</sup>Faculty of Medical Sciences, University Goce Delcev, Stip, R. Macedonia 'Krste Misirkov' No.10-A P.O 201, 2000 Stip

<sup>2</sup>Faculty of Medical Sciences, University Goce Delcev, Stip, R. Macedonia 'Krste Misirkov' No.10-A P.O 201, 2000 Stip  
071/272-355, milenavolcheva@yahoo.com

## **Abstract**

Bone tissue engineering is founded on the conception of bone structure, bone mechanics and tissue creature as it aims to restore, maintain, or improve tissue functions that are defective or have been lost by different pathological conditions. Functional bone tissue-engineering exact the newly reconstruct bone to be completely integrated with the host bone. Compared with small bone defects, for successful regeneration of large bone defects is necessary implantation of bone replacement in a critical defect.

In recent years, the research has been focused on the producing of biomaterials, scaffolds, which are defined as three-dimension porous solid biomaterials designed for differnet applications. Materials have been developed for tissue engineering approaches and currently proposed types of scaffolds made of inorganic materials, organic or synthetic polymers, or of mixed materials (composite scaffolds). The concept of tissue engineering is being applied for treatment of salivary gland disorders, regeneration of craniofacial tissues, oral mucose, periodontium, dentin and dental pulp. Further, we review current patents on scaffold for bone regeneration and their classification, as well as biocompatibility of scaffolds and cells.

Preoperative and perioperative contamination and biomaterial-associated infections pose a serious problem in tissue engineering. In order to prevent and treat bone infections, antibiotics could be incorporated into scaffold and those scaffolds could be utilized for tissue engineering.

## **Keywords**

scaffold, bone regeneration, tissue engineering, patents, antibacterial effect.

# Significance of preparation of tissue samples for electron microscopy for observation and diagnosis

Jovanka Laskova<sup>1</sup>, Darko Bosnakovski<sup>2</sup>, Gordana Petrusavska<sup>1</sup>

<sup>1</sup> Institute of Pathology, Medical Faculty, University "Ss Cyril and Methodius"-Skopje, 50-ta Divizija br.6 1000 Skopje, R.Macedonia

<sup>2</sup> Faculty of Medical Sciences, University Goce Delcev-Stip, Krste Misirkov b.b, 2000 Stip, R.Macedonia

+38978 30 55 88, laskova87@gmail.com

## **Abstract**

Transmission Electron Microscopy (TEM) is used to provide descriptive, morphological information and plays important role in cell biology for the visualization of intracellular organelles. It uses a beam of electrons which passes through the specimen and provides an image of objects 1 nm in size. The aim of this study is to compare the varies of techniques that have been developed to prepare TEM specimen ready for observation and diagnosis.

Significance of preparation of the samples for EM requires precise execution of each step in the entire procedure. The standard procedure for sample preparation is described in the following steps: extraction of tissue, fixation and dehydration with different percentages of acetones, resin infiltration, followed by embedding and polymerization and ultramicrotomy. Following steps are crucial in sample preparations. Generally, formaldehyde as a fixative penetrates better into the tissue, but glutaraldehyde better preserves the structure. After initial fixation, we used osmium tetroxide as a second fixative for lipid preservation. During the dehydration step, water from the samples is removed by solvents such as ethanol or acetone, this prevents holes-artifacts in the sections. Infiltration and embedding in resin provides stability of the tissue sample and formation of indestructible and insoluble block, suitable for section on ultramicrotome. Finally ultramicrotomy produce semi-thin and ultrathin sections which contrast can be introduced using heavy metals such as uranyl acetate and lead citrate. The alternative procedure for sample preparation is from an already paraffin-embedded tissue previously treated by the method of histopathological analysis. The procedure is very similar and differs only initial but contributes to significant differences in the final quality of the specimen.

Tissue must be first deparaffinized in xylol, processed in serial diluents of ethanol in order, and then washed in PBS to remove residue xylol, continues with following steps of the standard procedure, starting with the glutaraldehyde fixation shortly, then with osmium tetroxide, dehydration with acetone, resin infiltration, embedding and polymerization. Modification in procedure is mostly emphasized during the ultramicrotomy.

Every step of the sample preparation is important for having a valid electron-microscopic image, and every modification can result in an inadequate results. The aim of this study was to compare alternative procedures, and we found that the method based on paraffin embedded samples has several disadvantages, including disruption of continuity of the tissue and low quality of the electron micrographs. But tissue already embedded in

paraffin still can be used for TEM although initially it was not intended to be analyzed by a transmission electron microscope. However, this method can be useful for diagnostic purposes.

**Keywords**

Sample preparation, TEM, paraffin embedding.

# Design and characterization of nanoparticles as platforms for delivery of curcumin

**Elena Drakalska**<sup>1,2</sup>, Denitsa Momekova<sup>2</sup>, Stanislav Rangelov<sup>3</sup>, Nikolay Lambov<sup>2</sup>

<sup>1</sup> University "Goce Delchev"- Stip, Faculty of medical sciences

<sup>2</sup> Faculty of Pharmacy, Medical University of Sofia, 2 Dunav St., 1000 Sofia, Bulgaria

<sup>3</sup>Institute of Polymers, Bulgarian Academy of Sciences, 103 Acad. Georgi Bonchev St., 1113 Sofia, Bulgaria

E-mail: elena.drakalska@ugd.edu.mk

## **Abstract**

Curcumin, the yellow powder derived from the plant *Curcuma Longa*, exhibited numerous therapeutic applications against wide range of chronic diseases such as diabetes, pancreatitis, arthritis, neurodegenerative diseases and various types of cancer. The mechanism of antineoplastic activity of curcumin is through modulation of cell signaling pathways, mainly blockage of nuclear factor kappa B (NF-κB) activation and induction of apoptosis in different types of human cancer cell lines, associated with excellent safety profile. Despite the numerous advantages, the clinical realization of curcumin potential is limited because of its extremely low aqueous solubility and bioavailability after oral administration. An intriguing strategy to overcome these limitations is the design of nanosized vehicles for efficient delivery of curcumin. The present contribution is focused on newly-synthesized PEGylated tert-butylcalix[4]arene, used for preparation of various platforms for delivery of curcumin, such as inclusion complexes, supramolecular aggregates and hybrid liposomal systems. Curcumin:CX[4]PEG inclusion complexes as well as curcumin loaded polyoxyethylatedtert-butylcalix[4]arene supramolecular aggregates were prepared using two methods: heating method and solvent-evaporation method. Free and formulated curcumin were additionally investigated for apoptogenic activity and cytotoxicity against human tumor cell lines.

## **Keywords**

Cancer, curcumin, NF-κB, polyoxyethylatedtert-butylcalix[4]arene.

## Freeze-drying approach to enhance antibody stability

**Katarina Smilkov**<sup>1</sup>, Darinka Gjorgieva Ackova<sup>1</sup>, Emilija Janevik-Ivanovska<sup>1</sup>

<sup>1</sup>Department of Pharmacy, Faculty of Medical Sciences, Goce Delcev University,  
str. "Krstev Misirkov" no.10-A, 2000 Shtip, Republic of Macedonia  
+389 70 322 842, katarina.smilkov@ugd.edu.mk

### **Abstract**

Preparations containing antibodies are more easily formulated in solution, but their stability is often impaired, concerning the fact that aqueous solutions are prone to numerous physical and chemical changes, such as denaturation, aggregation, adsorption, hydrolysis, deamidation, nonreducible cross-linking, formation/exchange of disulfide bonds, isomerization, fragmentation, Maillard-reaction, etc. Freeze-drying is often used process in biopharmaceutical production, because the chemical and physical degradation rate can be significantly reduced in dry state. This process enables preservation of the desired characteristics of the product for a longer period of time, thus increasing its shelf life. Part of the challenges associated with the first phase of the freeze-drying process can be addressed with its' corresponding design, i.e. defining the freezing rate, but also addition of bulking crystalline agents as mannitol, glycine or disaccharides (sucrose, trehalose), that can provide fine, microporous structure. Recent research had shown that slow freezing, which includes gradual cooling of the sample to a given temperature with a certain rate, and fast freezing, including direct introduction of the sample to a previously cooled freeze-dryer, are the most favored.

Our experience was in designing a freeze-drying process in order to formulate freeze-dried kit, containing conjugated Anti-CD-20 antibody, ready-to label with radioactive isotopes. Using freeze-dryer able to controll process parameters, (Labconco Free Zone Stoppering Tray Dryer, USA), two types of freeze-drying protocols were applied, a protocol with direct freezing to the initial temperature of -40 °C and a protocol with gradual freezing from 5 °C to -40 °C, at a rate of 0,40 °C/min. Appearance after reconstitution of the finished product and presence of aggregates were evaluated, as well as the IR and Raman spectra.

Results have shown that the protocol using gradual freezing from 5 °C to -40 °C, at a rate of 0,40 °C/min was more successful in maintaining the stability of the antibody during freeze-drying, giving clear solution after reconstitution, no presence of aggregates and IR and Raman spectra most similar to the spectra of the native conjugated form.

The research performed, enabled formulation of ready-to label anti-CD-20 antibody, intended for preclinical research for Non-Hodgkin's lymphoma therapy.

### **Keywords**

antibodies, lyophilization, stability.

## **An overview of phytosomes as a novel herbal drug delivery system**

**Emilija Apostolova**<sup>1</sup>, Brankica Spaseska<sup>2</sup>, Maja Simonoska Crcarevska<sup>3</sup>, Maja Glavash Dodov<sup>4</sup> and Renata Slaveska Raichki<sup>5</sup>

<sup>1</sup> High school "Jane Sandanski", Shtip, Republic of Macedonia

<sup>2</sup> Pharmacy "PZU Apteka Orhis farmacija br.9", Skopje, Republic of Macedonia

<sup>3</sup> Institute of Pharmaceutical Technology, Faculty of Pharmacy, University Ss Cyril and Methodius, Skopje, Republic of Macedonia

<sup>4</sup> Institute of Pharmaceutical Technology, Faculty of Pharmacy, University Ss Cyril and Methodius, Skopje, Republic of Macedonia

<sup>5</sup> Institute of Pharmaceutical Technology, Faculty of Pharmacy, University Ss Cyril and Methodius, Skopje, Republic of Macedonia

Telephone: (+389-78) 473 277; E-mail address: [puzderliska2000@yahoo.com](mailto:puzderliska2000@yahoo.com)

### **Abstract**

Many polyphenolic constituents of plants possess valuable therapeutic potential with a good safety profile. On the one hand, their phenolic nature renders them polar molecules but on the other hand, many water soluble glycosylated polyphenolics are nevertheless, poorly absorbed with resulting erratic or poor bioavailability which has been experienced in conventional herbal formulations. As a consequence, these features considerably add to the complexity of herbal formulation development and the therapeutic outcomes are still dependent by the improvement of the pharmacokinetic profile of these compounds after oral or topical administration.

The new development strategy in the field of drug delivery systems for plant derived active constituents and extracts is focused on vesicular formulations like polymeric nanoparticles, microsphere, liposomes, phytosomes, transferosomes, ethosomes etc. The aim of this overview was to illustrate the phytosomes and to summarize their characteristics as novel herbal drug delivery system for polyphenolics and extracts and in addition, to highlight some key findings and recent development.

In general, phytosomes constitute complexes between a herbal active constituent and natural phospholipid. As acknowledge, plant polyphenolics exhibit a marked affinity for phospholipids via hydrogen bondings and dipolar interactions with the charged phosphates groups of phospholipids which make them ideal candidate for phytosome formulation. These advanced and novel systems are described to have noticeable advantages over conventional herbal formulation which include improved solubility, bioavailability, biological activity, and stability of plant polyphenolics. It has also been revealed that phytosomes have successfully improved the oral bioavailability of different flavonoids. Several herbal extracts or single constituents from the diverse classes of polyphenols and terpenoids are marketed in the form of phytosome.

Many studies have emphasized the additional advantages of successfully developed phytosomes with potential to overcome the delivery challenges of polyphenolics from plant origin. Phytosomes have the capacity to deliver the standardized plant extracts as well as polyphenolics through several routes of drug administration. In addition, phytosome technology substantially improves the clinical applicability of polyphenols.



With wide range of applications of phytosomes numerous studies are undergoing and lots more is expected in the forthcoming years. The techniques used for phytosome formulations are patentable and highly profitable.

**Keywords**

Delivery, Plant, polyphenolics, phytosome, system.

# Determination of active pharmaceutical ingredient – chloropyramine in *dragées*

**Vesna Kostik**<sup>1</sup>, Biljana Gjorgjeska<sup>1</sup>, Sofija Petkovska<sup>1</sup>

<sup>1</sup> Medical Faculty, Department of Pharmacy, University Goce Delčev, Štip, Republic of Macedonia

## **Abstract**

Chloropyramine is a first generation antihistamine drug approved in some Eastern European countries for the treatment of allergic conjunctivitis, allergic rhinitis, bronchial asthma, and other allergic conditions. Chloropyramine is known as a competitive reversible H<sub>1</sub>-receptor antagonist. By blocking the effects of histamine, the drug inhibits the vasodilatation, increased vascular permeability, and tissue oedema associated with histamine release in the tissue.

A simple gas chromatography method based on gas chromatography - mass detection technique (GC-MS) for the determination of chloropyramine active pharmaceutical ingredient (API) in *dragées* was developed and validated. Chromatographic separation was achieved on a fused silica ZB-5 capillary column (30 m x 0.25 mm i.d. x 0.25 μm film thickness). Acquisition was performed in selected ion monitoring mode (SIM) with target ion (58 m/z) and reference ions (71 m/z, 125 m/z). The method was validated in respect system suitability, specificity, linearity, range accuracy and precision, limit of detection (LOD), limit of quantification (LOQ), specificity, robustness and stability. The advantages of this method include simple sample treatment, short elution time (less than 15 min) and short analysis time (less than 25 min). The proposed method could be applicable for routine analysis in pharmaceutical analytical laboratories.

## **Keywords**

Active pharmaceutical ingredient, chloropyramine, gas chromatography-mass detection, *dragées*.

# Compariton of volatile aroma compounds between cultivated and spontaneous flowering stems of *Sideritis scardica* Griseb. from R. Macedonia

**Bujar Qazimi**, Gjoshe Stefkov, Marija Karapandzova, Ivana Cvetkovikj, Svetlana Kulevanova

Institute of Pharmacognosy, Faculty of Pharmacy, University SS Cyril and Methodius, Skopje, Republic of Macedonia

Telephone: 070 321 828, e mail: [bqazimi2003@yahoo.com](mailto:bqazimi2003@yahoo.com)

## **Abstract**

The specific and particular aroma of montain tea (*Sideritis scardica* Griseb.) is maybe the most important reason of its wide use by the Balkan peoples. The composition of the volatile aroma components was defined in the dried spontaneous (S-S) and cultivated (S-C) flowering stems (homogenized samples from flower, leaf and stem) of *S. scardica*, collected from 4 different localities in R. Macedonia in 2013. The analyses were made by gas chromatography – mass spectrometry (GC/FID/MS) on HP5-ms column and equipped with automated headspace system with heated syringe (HS) sampler. Thirteen individual components (8 monoterpenes representing 71.91-90.21% and 5 sesquiterpenes representing 2.52-23.69% of the entire volatiles) were identified as aroma components in S-S samples. The major components in all S-S samples were  $\beta$ -pinene (31.85-45.35%),  $\alpha$ -pinene (20.68-41.75%), *trans*-caryophyllene (1.65-21.73%) and limonene (1.21-8.40%). In the S-C sample of *S. scardica*, twelve individual components were identified, 7 monoterpenes (88.10%) and 5 sesquiterpenes (9.18%). Prevailing components in tested S-C sample were  $\beta$ -pinene (44.39%),  $\alpha$ -pinene (32.21%), limonene (8.77%) and *trans*-caryophyllene (7.39%). There was almost no difference in the chemical profiles of the volatile aroma compounds between S-S and S-C samples. Cultivated sample exhibit very similar aroma compounds profile with the spontaneous flowering stems of *S. scardica*.

## **Keywords**

*Sideritis scardica*, aroma compounds, headspace, GC/MS-FID.

# Bioactive compounds of cold-pressed oil from the seeds of Goji Berry (*Lycium barbarum*)

**Sanja Kostadinović Veličkova**

Faculty of Agriculture, University "Goce Delčev", Štip, Macedonia

Presenter's telephone and e-mail address: +38975390707

sanja.kostadinovik@ugd.edu.mk

## **Abstract**

Wolfberry (*L. barbarum*) in the family *Solanaceae* is famous as functional food as well as traditional cure in Chinese herbal medicine. There is positive relation between daily intake of this fruit and hypoglycemic, immunomodulation, anti-hypertension, lipotropic, protecting hepatic function, anti-ageing, anti-fatigue and antioxidant activity.

The object of this study is determination of bioactive compounds in cold-pressed oil from the seeds of Goji Berry, including determination of fatty acid composition, vitamin-E-active compounds and phytosterols.

Cold-pressed oil obtained from the seeds of Goji Berry is valuable source of unsaturated fatty acids, vitamin-E-active compounds and phytosterols.

Fatty acid composition indicated monounsaturated oleic acid and polyunsaturated linoleic acid as the most abundant with  $17.33 \pm 0.01$  and  $66.97 \pm 0.02\%$  respectively.  $\alpha$ -linolenic acid was detected only in quantity less than 2%.

Significant amount of  $\alpha$  and  $\gamma$ -tocopherol ( $34.43 \pm 0.05$  and  $65.57 \pm 1.02$  mg/100 g oil) was identified and quantified by HPLC and fluorescence detector.  $\beta$ -tocopherol,  $\delta$ -tocopherol and  $\beta$ -tocotrienol were abundant in quantity less than 0.6%.

Phytosterols are plant sterols with structure similar to cholesterol. They are minor constituents in oils and normal constituents of human diet. Phytosterols, primarily  $\beta$ -sitosterol, campesterol, and stigmasterol are membrane constituents of plants that effectively reduce serum LDL cholesterol and atherosclerotic risk. The most dominant phytosterol in Goji berry seed oil was  $\beta$ -sitosterol with abundance of  $2183.46 \pm 111.26$  mg/kg oil. Stigmasterol was quantified in the level of  $521.58 \pm 21.77$  mg/kg oil. Significant amount of brassicasterol ( $480.45 \pm 12.28$  mg/kg) and other identified and quantified phytosterols in levels below 200 mg/kg makes this oil interesting for further examination.

In conclusion, cold-pressed oil from Goji Berry is valuable product which can have significant effect on human health. High level of oleic and linoleic acid, as well as high amount of  $\alpha$  and  $\gamma$ -tocopherols makes this oil suitable for further in-vitro and in-vivo examinations. Furthermore, the phytosterols can be useful as markers for the purity of oil and possible contribution in the overall antioxidant potential of the oil.

## **Keywords**

Bioactive compounds, Cold-pressed oil, Fatty acid composition, Seeds from *Lycium barbarum*, Vitamin – E – active compounds.

# Development and validation of HPLC method for determination of flavonoids in herbal preparations

Tanja Janeva<sup>1</sup>, Zorica Arsova – Sarafinavska<sup>1,2</sup>

<sup>1</sup> University Goce Delcev – Stip, Faculty of Medical Sciences, Krste Misirkov 10-A, Stip, 2000, R. Macedonia

<sup>2</sup> Institute of Public Health of the Republic of Macedonia, 50 Divizija 6, 1000 Skopje, Republic of Macedonia

Telephone: (+389-78) 660 726; E-mail address: tanja.15549@student.ugd.edu.mk

## Abstract

**Introduction** - Flavonoids are a large group of polyphenolic components possessing benzo- $\gamma$ -pyronic structure and widely distributed in plants. The chemical nature and the biological activity of flavonoids depends on the structural class to which they belong, the degree of hydroxylation, the degree of polymerization, and the presence of other substituents and bonds. Today, there are large number of herbal preparations containing plant extracts rich in flavonoids used as OTC drugs, and therefore it is necessary to develop methods for controlling and monitoring their quality.

**Aim** - Development and validation of HPLC method for determination of rutin and quercetin in tablets containing 1200 mg dry leaf of *Ginkgo biloba*.

**Method** - Simple HPLC method with gradient elution (acetonitrile: 0.3% phosphoric acid), flow rate of 1,2 mL/min, column temperature of 25°C and UV detection (rutin at 255 nm, quercetin at 375 nm) of rutin and quercetin in herbal preparation containing dry leaf of *Ginkgo biloba*.

**Results** - The method showed high specificity, excellent linearity for the concentration in the range of 0.01-0.08 mg/ml. Correlation coefficient ( $R^2$ ) for rutin is 1, while for the quercetin is 0.999. Precision, which was determined by six repetitions of the analysis of 0.05 mg/mL standard solution, showed a relative standard deviation of less than 1% for both rutin and quercetin.

**Conclusion** - The method is simple, easy to perform and specific for determination of rutin and quercetin in herbal preparations containing dry leaf of *Ginkgo biloba*, and additionally, can be used for routine analysis.

## **Keywords**

*Ginkgo biloba*, HPLC, quercetin, rutin, validation.

## Atomic emission spectrometry with inductively coupled plasma (ICP-AES) analysis of trace elements in *Camellia sinensis* teas

**Dragica Doneva**<sup>1</sup>, Trajce Stafilov<sup>2</sup>, Zorica Arsova-Sarafinovska<sup>1</sup>, Katerina Starkoska<sup>1</sup>, Maja Shishovska<sup>1</sup>

<sup>1</sup>Institute for Public Health, Medicines Quality Control Department, 50 Divizija, No. 6, 1000 Skopje, Republic of Macedonia

<sup>2</sup>Institute of Chemistry, Faculty of Science, Ss. Cyril and Methodius University, Skopje, Republic of Macedonia

e-mail: [donevadaci@gmail.com](mailto:donevadaci@gmail.com)

### **Abstract**

The atomic emission spectrometry with inductively coupled plasma (ICP-AES) technique was used for determination of trace elements presence and their contents in *Camellia sinensis* teas and its tea mixtures. Samples were collected from macedonian market originating from Macedonia, Serbia and Poland. For sample preparation microwave digestion system using HNO<sub>3</sub> and H<sub>2</sub>O<sub>2</sub> was applied. The following trace elements: Al, Ba, Ca, Cd, Cr, Cu, Mn, Fe, K, Li, Mg, Mn, Mo, Na, Ni, P, Pb, Sr, V and Zn were determined in several types of tea products. The results showed that K, Ca and Mg were the most abundant elements (10287 mg/kg, 6072 mg/kg, 3072 mg/kg, respectively) and Mo and V were not detected. The elements: Na and Li were detected at the widest ranges. As, Cd and Pb were detected at allowed quantities. The results for the content of all analyzed elements showed the expected variation among sampled teas and therefore these tea products may not produce any health risks for human consumption as sources of toxic metals.

### **Keywords**

Atomic spectrometry; ICP-MS; *Camellia sinensis*; trace elements; tea.

# Determination of trace elements analyzed by atomic emission spectrometry with inductively coupled plasma (ICP-AES) in *Matricaria chamomilla* L. teas present on macedonian market

**Dragica Doneva**<sup>1</sup>, Trajce Stafilov<sup>2</sup>

<sup>1</sup>*Institute for Public Health, Medicines Quality Control Department, 50 Divizija, No. 6, 1000 Skopje, Republic of Macedonia*

<sup>2</sup>*Institute of Chemistry, Faculty of Science, Ss. Cyril and Methodius University, Skopje, Republic of Macedonia*

e-mail: [donevadaci@gmail.com](mailto:donevadaci@gmail.com)

## **Abstract**

This study was conducted to determine trace metals presence and their content in *Matricaria chamomilla* L. teas. Samples were collected from macedonian market originating from Macedonia, Serbia and Croatia. The twenty trace elements: Al, Ba, Ca, Cd, Cr, Cu, Mn, Fe, K, Li, Mg, Mo, Na, Ni, P, Pb, Sr, V and Zn were determined in several types of tea products. The samples were prepared by microwave digestion system using HNO<sub>3</sub> and H<sub>2</sub>O<sub>2</sub>. The atomic emission spectrometry with inductively coupled plasma (ICP-AES) was used for determination of contents of elements. The obtained results showed that K, Ca and Mg were the most abundant elements (19529 mg/kg, 7690 mg/kg, 3292 mg/kg, respectively), Mo was not detected, and the elements: Al, Cr and Ba were detected at the widest ranges. As, Cd and Pb were detected at allowed quantities. The analysis of data from this study should provide guidance for quality control of teas.

## **Keywords**

Atomic spectrometry; ICP-MS; *Matricaria chamomilla* L.; tea; trace elements.

# Human health risks from heavy metals via consumption of contaminated food

***Biljana Balabanova***<sup>1</sup>, *Rubin Gulaboski*<sup>1,2</sup>,

<sup>1</sup>*Faculty of agriculture, "Goce Delčev" University, "Krstе Misirkov" No.10-A,  
P.O 201, Stip - 2000, R.Macedonia*

<sup>2</sup>*Faculty of medical sciences, "Goce Delčev" University, "Krstе Misirkov" No.10-A,  
P.O 201, Stip - 2000, R.Macedonia*

[biljana.balabanova@ugd.edu.mk](mailto:biljana.balabanova@ugd.edu.mk)

## **Abstract**

Mining and processing metal ore can be a significant source of heavy metal contamination of the environment. The environmental concern in mining areas is primarily related to physical disturbance of the surrounding landscape, spilled mine tailings, emitted dust and acid mine drainage transported into rivers. Excessive accumulation of heavy metals in agricultural soils around mining areas, resulting in elevated heavy metal uptake by plant food, is of great concern because of potential health risk to the local population. The consumption of plants produced in contaminated areas, as well as ingestion or inhalation of contaminated particles is two principal factors contributing to human exposure to metals. Cultivation of crops for human or livestock consumption on contaminated soil can potentially lead to the uptake and accumulation of trace metals in the edible plant parts with a resulting risk to human health. Increasing evidence shows that heavy metal pollution of mined areas caused health damage to the local inhabitants. Serious systemic health problems can develop as a result of excessive dietary accumulation of heavy metals such as Cd, and Pb in the human body. Although Zn and Cu are essential elements, their excessive concentration in food and feed plants are of great concern because of their toxicity to humans and animals. Lead and Cd are considered potential carcinogens and are associated with etiology of a number of diseases, especially cardiovascular, kidney, nervous system, blood as well as bone diseases. Dietary intake is the main route of exposure for most people, although inhalation can play an important role in very contaminated sites. Thus information about heavy metal concentrations in food products and their dietary intake is very important for assessing their risk to human health.

## **Keywords**

Heavy metals, food, dietary intake, health risk.



# Development of an ultrasonic method for effective extraction of capsaicin as a potent bioactive compound

**Viktorija Maksimova**<sup>1</sup>, Liljana Koleva Gudeva<sup>2</sup>, Blaga Radovanovic<sup>3</sup>, Rubin Gulaboski<sup>1</sup>

<sup>1</sup> Faculty of Medical Sciences, "Goce Delcev" University, Krste Misirkov bb, 2000, Stip, R. of Macedonia

<sup>2</sup> Agricultural faculty, "Goce Delcev" University, Krste Misirkov bb, 2000, Stip, R. of Macedonia

<sup>3</sup>, Faculty of Sciences and Mathematics, Institute of chemistry, University of Nis, Višegradska 33, 18000 Niš, Serbia

*viktorija.maksimova@ugd.edu.mk*

## **Abstract**

Many recent studies concerning the medicinal use of capsaicin as a bioactive compound, justify the demands for new and effective methods of its extraction. Its pharmacological activity includes antihyperlipidemic, antiglycemic, anti-oxidative, antitumor properties. The majority of basic research studies suggest that capsaicin induces cell-cycle arrest or apoptosis or inhibits proliferation in different malignant cells including lung cancer, adeno carcinoma, pancreatic cancer, breast cancer. In many cases this activity of capsaicin is concentration dependent and that is one of the reasons for establishing a method for more effective extraction of capsaicin from hot peppers. Moreover synergistic effect of capsaicin with the effects of the other bioactive compounds of the peppers (vitamin C, vitamin E, quercetin, luteolin, carotene), makes these extracts more effective in potential antitumor therapy.

This method for capsaicin extraction was performed by using an ultrasonic bath with frequency of 35 kHz. We have used three different ratios of solid/liquid phase, different extraction times (20 to 60 min), and different temperatures (45 to 60°C). Concentration of capsaicin in the extracts was measured by HPLC-DAD.

Results obtained from liquid chromatography showed that capsaicin concentration was highest in the extract obtained with 1:25 (solid/liquid ratio), with ethanol (96% V/V). Results for time and temperature dependency on the efficiency of extraction of capsaicin showed that concentration of capsaicin in extracts from 50 and 60°C, is 0.406 mg/ml and 0.726 mg/ml, successively, and for the time of 60 minutes the highest concentration of capsaicin was obtained 0.685 mg/ml.

As a conclusion of this study we can propose that extraction time of 60 min on temperature of 60°C for 1/25 (solid/liquid ratio), gives the most efficient extraction of capsaicin. Optimization of the conditions for ultrasonic method of extraction is one of the key factors for obtaining an extract with high concentration of capsaicin, and protected pharmacological activity.

## **Keywords**

capsaicin, chromatography, extraction, ultrasonic bath.

# Electrochemical analysis of the properties of benzene-1,2,4-triol

Milkica Janeva<sup>1</sup>, Rubin Gulaboski<sup>1</sup>,

<sup>1</sup>Faculty of Medical Sciences, "Goce Delcev" University, Stip, Macedonia

E-mail address: milkica.15548@student.ugd.edu.mk

## **Abstract**

1,2,4-benzenetriol is an aromatic chemical compound used in direct hair colouring products at a maximum use concentration of 3.0%. In plants it can be found as a product of the degradation of some organic compounds, while in humans it can be detected after poisoning with benzene because it is a metabolite of the biotransformation of benzene. In the human organism, 1,2,4-benzenetriol causes harmful effects such as DNA damage and there is possibility that 1,2,4-benzenetriol-induced DNA damage is one of the primary reactions in carcinogenesis induced by benzene. In nature, this compound is found in coffee extracts inhibiting the anti-hypertensive effect of chlorogenic acid. Hydroxyhydroquinone or 1,2,4-benzenetriol (BT) detected in the beverages has a structure that coincides with the water-soluble form of a sesame lignan, sesamol and further studies are required to confirm the importance of the cellular antioxidant activity of BT.

**Materials and methods:** In this study we examined the electrochemical properties of 1,2,4-benzenetriol by using cyclic voltammetry and square-wave voltammetry. Cyclic voltammetry (CV) is widely used for the study of redox processes, for understanding the reaction mechanisms, and for obtaining stability of reaction products.

To perform this study, we used a three-electrode system, graphite rod was used as a working electrode, the reference electrode was silver / silver chloride (Ag / AgCl), while the auxiliary electrode was Pt-electrode.

**Results:** The electrochemical response of the aqueous solution of 1,2,4-benzenetriol at different pH (3 to 9) depends mainly on pH. The calculated diffusion coefficient indicates that the process of diffusion of this substance is relatively low. The complexes between benzenetriol the Fe<sup>2+</sup> and Mg<sup>2+</sup> ions are the type 1:1 (one ligand and one metal ion are complexed). The values of the stability constants show that the complex of magnesium ions and benzenetriol is weak, while the complex with iron ions is moderately stable complex. In strong alkaline environment there is a chemical transformation and it is assumed that the new compound has four OH groups. For examination of the anti-oxidative potential we compared the native 1,2,4-benzenetriol, re-titrated benzenetriol and vitamin C using ABTS. It has been confirmed that the tetra-hydroxy compound has the highest antioxidant potential.

**Conclusion:** The results obtained of the study will help in further investigations of antioxidant properties of 1,2,4-benzenetriol and the potential use of this compound as an antioxidant.

## **Keywords**

1,2,4-benzenetriol, Anti-oxidative potential, Cyclic voltammetry, Complexes with metal ions.

# Comparison of the procedure for registration of medicines in the European Union and the Republic of Macedonia

Danica Zahkova<sup>1</sup>, **Sofija Petkovska**<sup>2</sup>, Biljana Gjorgjeska<sup>3</sup>

<sup>1</sup> UniversityGoceDelchev -Stip, Faculty of Medical Sciences

<sup>2</sup> UniversityGoceDelchev -Stip, Faculty of Medical Sciences

<sup>3</sup> UniversityGoceDelchev -Stip, Faculty of Medical Sciences

++ 389 75 499 912 [biljana.gorgeska@ugd.edu.mk](mailto:biljana.gorgeska@ugd.edu.mk)

## **Abstract**

Registration is a necessary step which follows every pharmaceutical preparation before being sent to the market and becoming available to patients. The approval follows two stages, the first clinical stage which provides security, safety and optimization of dosage integratively used in the four steps of clinical trials, and the second phase that provides marketing authorization. There are four agencies which operate with the procedure for approval and regulation of drugs: EU Legislation - Eudralex, European Directorate for the Quality of Medicines and Healthcare (EDQM), European Medicines Agency (EMA), Heads of Medicines Agencies (HMA) in the European Union.

Objectives – Literature review of drugs registration procedure in our country and its connection to the form and content in the available literature documentation for the medicines registration in the European Union.

Materials and methods - Comparative methods are used to compare the available literature data on the registration of medicines. Used data is from the guide on the form and content of the common technical document (Presentation and format of the dossier Common Technical Document (CTD) Volume 2B) and the Law on medicines and medical devices in the Republic of Macedonia.

Results - The main difference between the European and Macedonian legislation for the registration of medicines is that the European legislation through extensive guides, closely defines every part of the documentation. The entire documentation should be submitted in the format designated as common technical document, whose form and content is on the EMA website with a guide of 303 pages. Here, we explain each module in a detailed manner, ranging from font, text size, the length of the text, to the content of each section. Thus, each application takes the form of a standardized and uniform document. On the other hand, in the Republic of Macedonia there are no such guides, so the applications can exhibit significant variations in form and content.

Conclusion - Registered drugs in the country are registered under the national procedure for the registration of medicines in the country, according to the Law on medicines and medical devices. The national procedure is controlled by the Drug Bureau. The Republic of Macedonia needs to adopt guidelines as bylaws with exactly defined form and content of each part of the documentation.

## **Keywords**

Eudralex, EDQM, EMA, law, registration, drugs.

# Pharmacoeconomic evaluation of the antibiotic prophylaxis in orthopedic surgeries

**Dijana Atanasova**<sup>1</sup>, *Bistra Angelovska*<sup>1</sup>, *Biljana Lazarova*<sup>2</sup>

<sup>1</sup>*Faculty of medical sciences, University "Goce Delcev"- Stip, R. Macedonia*

<sup>2</sup>*Public hospital Stip R. Macedonia*

+38977 530031, [dijana.15623@student.ugd.edu.mk](mailto:dijana.15623@student.ugd.edu.mk)

## **Abstract**

Infections in orthopedic surgery are large problem in the medicine and are present all around the world. The main objective of the antibiotic prophylaxis in orthopedic surgeries is to prevent infection during the surgical intervention with antimicrobial agent that is safe, effective, and has a spectrum of activity that covers the most common pathogens that may occur during surgical procedures. Rational use of antibiotic prophylaxis in orthopedic surgeries has an important role in the prevention of the surgical infection.

Patients who have undergone orthopedic surgery represent a high-risk group for postoperative infection.

The aim of this study was to estimate the consumption and cost of antibiotics at Public Hospital – Orthopedic – Shtip in comparison with antibiotic therapy for orthopedic prophylaxis recommended by The Guides for Evidence-Based Medicine published by Ministry of health – Republic of Macedonia.

Retrospective pharmacoeconomic study has been carry out in orthopedic patients. For evaluation of rationale use and cost of antibiotics for surgery prophylaxis are used relevant literature data and recommendations: guidelines for evidence-based medicine issued by the Ministry of Health of RM, guides from European and American associations and recent published research.

Statistically used data have shown significantly higher cost in Public Hospital – Orthopedic – Shtip than the cost for antibiotic therapy recommended by Medicine Based Data, almost fourfold higher amount. This not rational use of antibiotics at Orthopedic – Shtip leads to more expensive and less effective therapy in response to recommendations from MBD.

Our recommendation is to follow the guide from MBD for rational use of antibiotics to achieve better and cheapest treatment

## **Keywords**

Infections, MBD, orthopedic surgery.

# **Therapeutic approach in the treatment of benign prostatic hyperplasia**

**Rozeta Aceva, Zorica Arsova – Sarafinovska**

*Faculty of Medical Science, University „Goce Delcev” – Štip, R. Macedonia*

*rozeta.aceva@yahoo.com*

## **Abstract**

Prostate (*glandulae prostatae*) is a small gland, part of the reproductive system in males, shaped like a chestnut or pyramid little flat front to back. The dimensions of the prostate gland show an age and individual differences. By the age of puberty, the prostate develops slowly and has a small footprint. At puberty it began to grow rapidly to 17 years and reaches its final shape and size with weight around 20 gr.

Benign prostatic hyperplasia (BPH) or even also called nodular or stromal hyperplasia, is very common abnormality of the prostate. It is present in a significant number of men around 40 years of age, and its incidence increasing with age. Prostatic hyperplasia is characterized by proliferation of the stromal and epithelial elements leading to an increasing of the gland and, in some cases, to urinary obstruction. Significant clinical features are associated with BPH symptoms in the lower urinary tract (LUTS).

In patients, diagnosed with benign prostate hyperplasia, depending on the severity of symptoms, the risk of progression and morbidity determination and type of the therapy prescribed (monitoring, drug treatment or surgical intervention ) is important next step after diagnosis. In individuals with mild to moderate uncomplicated symptoms of BPH only drug therapy can be applied. The most commonly used are alpha - 1 - blockers and inhibitors of 5 - alpha reductase. Combination of these drugs reduces the symptoms of BPH better and faster than these two drugs applied individually. Herbal preparations can be used as a supplementary therapy.

## **Keywords**

alpha – 1 – blockers, 5- alpha reductase, herbal drugs, prostate.

## **Oxidative stress, aging and antioxidants**

**Viktorija Trajkoska**<sup>1</sup>, Zorica Arsova-Sarafinovska<sup>1,2</sup>

<sup>1</sup>University Goce Delcev – Stip, Faculty of Medical Sciences, Krste Misirkov 10-A, Stip, 2000, Republic of Macedonia

<sup>2</sup>Institute of Public Health of the Republic of Macedonia, 50 Divizija 6, 1000 Skopje, Republic of Macedonia

Telephone: (+389-70) 962-738; E-mail address: viktorija.15542@student.ugd.edu.mk

### **Abstract**

The term oxidative stress is defined as a direct consequence of the increased production of the so-called free radicals accompanied with the decreased activity of the antioxidant defense system against them. The “free radicals theory of aging” was firstly proposed by Denham Harman in 1950. According to this concept, free radicals attack the susceptible cell structures continuously over the life, thus impairing their physiological functions. Moreover, it was suggested that the increased oxidative stress plays a crucial role in the pathogenesis of various chronic diseases associated with aging, such as cancer, neurodegenerative diseases, atherosclerosis, etc. Later, in 1970, Harman expanded the previous concept introducing the role of the endogenously generated reactive species in mitochondria in the oxidative stress phenomena. The findings that the mitochondrial DNA damage in mammals increases with age further supported the mitochondrial theory of aging. Therefore, it was concluded that the intrinsic generation of free radicals is an inevitable consequence of the consumption of oxygen and ATP production by mitochondria. Later on, Halliwell and Gutteridge renamed this theory in “oxidative stress theory of aging”, suggesting that aging and age-related diseases are not only caused by free radicals, but also by other reactive oxygen species. According to their theory, organisms age because of an accumulation of oxidative damage to the critical cellular components. For example, the DNA is continuously exposed to the oxidative modification. Consequently, reactive species may form a variety of DNA adducts via direct attacks or indirectly by initiating autocatalytic lipid peroxidation. The situation is further complicated knowing that the moderate levels of radicals are not only beneficial, but also essential, for exerting their functions in signaling pathways, inflammation, or immune response to pathogens. There are various enzyme systems whose functions are to remove and/ or repair DNA modifications in order for cells to maintain the necessary level of oxidative stress. Moreover, the oxidative damage can be worsened by a decreased efficiency of antioxidant defense mechanisms. The first line of endogenous defenses against reactive oxygen species includes antioxidant enzymes. The most significant ones are glutathione peroxidase (GPX), catalase (CAT), and superoxide dismutase (SOD). Genetic factors may affect about 25% of the variation in human life span. Among the antioxidant enzymes, the biggest role in longevity can be attributed to SOD2 and GPX genes. Up to date, there are more than 80 publications supporting the role of genetic variations in the regulation of the response to the oxidative stress. Finally, nowadays, in addition to the natural defense systems, it is generally believed that dietary antioxidants are able to increase the antioxidant protection, thus improving health and increasing cellular resistance to stress. While, there is growing evidence that changes in lifestyle (such as, moderate exercise, increased intake of dietary antioxidants, and

reduced calorie intake) could improve health and increase longevity, the role of the synthetic antioxidant supplements in controlling optimal levels of oxidative stress remains still controversial.

**Keywords**

Aging; Antioxidant enzymes; Free radicals; Oxidative stress.

# **Oxidative stress, oxidative DNA damage and prostate cancer**

***Evgenija Nedelkoska<sup>1</sup>, Zorica Arsova - Sarafinavska<sup>2, 3</sup>***

*<sup>1</sup> University Goce Delcev – Stip, Faculty of Medical Sciences, Krste Misirkov 10-A, Stip, 2000, R. Macedonia*

*<sup>2</sup> Institute of Public Health of the Republic of Macedonia, 50 Divizija 6, 1000 Skopje, Republic of Macedonia*

*<sup>3</sup> University Goce Delcev – Stip, Faculty of Medical Sciences, Krste Misirkov 10-A, Stip, 2000, R. Macedonia*

*Telephone: (+389-77) 923 791; E-mail address: [evgenija.15541@student.ugd.edu.mk](mailto:evgenija.15541@student.ugd.edu.mk)*

## **Abstract**

Production of reactive oxygen species (ROS) is an element of normal cellular metabolism, which have their physiological functions. The problem occurs when the balance is disturbed and the body enters the zone of increased oxidative stress. The state of increased reactive oxygen species (ROS) is a result of either increased ROS generation or a loss of antioxidant defense mechanisms. A growing body of evidence suggests that the increased production of ROS is linked to the aging process and the etiopathogenesis of age-related diseases, such as cancer, heart disease, atherosclerosis and other cardiovascular diseases, degenerative brain damage (e.g. Parkinson's and Alzheimer's disease). Excess ROS is harmful to normal cells.

The purpose is to show the relationship between the oxidative stress, oxidative DNA damage and the development of prostate cancer. In prostate cancer (PC), oxidative stress, natural key event characterized by supraphysiological ROS concentrations, has been identified as one of the pillars/basis of the phenotype of aggressive disease. Specifically, oxidative stress is connected to PC development, progress and response to therapy. Prostate cancer is mainly a disease of aging, with in most cases, occurs in men over the age of 55. Therefore, progressive inherent or acquired changes in cellular metabolism occurring over the years may play a very important role in the development of this disease. Many factors like diet, environmental carcinogens, and other inflammatory diseases have been linked to an increased risk of prostate cancer. The main focus is on the free radicals, their endogenous and exogenous sources, DNA damage (both nuclear and mitochondrial), damage to lipids and proteins by free radicals, the oxidative stress phenomenon, cancer, and the mechanisms of carcinogenesis.

The potential role of ROS in the regulation of cellular processes, controlling the malignant transformation suggests understanding of the etiology and progression of cancer in general and prostate cancer in particular. It can open the door for development of new treatments for prevention and cure of cancer. Because of the fact that the cells of prostate cancer are undergoing oxidative stress, strategies that can take advantage of this increased oxidative stress may also provide improvements in therapies. Measurements of oxidative stress stand a challenge, due to the instability of the



compounds and the variability of the mechanisms involved. Thus, although there is a strong correlation between oxidative stress and PC, clinical data are lacking.

**Keywords**

Cancer, DNA damage, oxidative stress, prostate, reactive oxygen species.

# RNA interference (RNAi) mechanism as a basis for future successful treatment of chronic hepatitis B infection

Ana Nikolova<sup>1</sup>, Darko Boshnakovski<sup>2</sup>

<sup>1</sup>Ana Nikolova, University of Goce Delcev, Krste Misirkov bb, 2000 Shtip, Republic of Macedonia, Tel: +38977 832 881, email: ana\_nikolova@hotmail.com

<sup>2</sup>Darko Boshnakovski, University of Goce Delcev, Krste Misirkov bb, 2000 Shtip, Republic of Macedonia, Tel: +38970 516 649, email: darko.bosnakovski@ugd.edu.mk

## **Abstract**

RNAi - RNA interference is a regulatory mechanism which is found in most eukaryotic and prokaryotic cells. This mechanism can directly cause blockage of gene activity through double stranded siRNAs homologous sequences. Edru Fire and Craig Mello's discovery of RNAi in the 90s refers to the presence of double stranded micro molecules within the eukaryotic cells named siRNAs. The RNAi mechanism is led by basic dsRNA. In the cytoplasm, this dsRNA is recognized by Dicer protein, through which dsRNA is transferred into smaller micro siRNAs carrying the main inhibitory role. Furthermore, this siRNAs, found within the RISC system, with the participation of Ago2 enzymes associates with the previously recognized target iRNA and blocks the activity of their genes. Pharmaceutical companies are developing strategies for the formulation of therapeutics that have the basis of a RNAi mechanism.

About 360 million of the Earth's population are infected with chronic hepatitis B virus. Due to its high specificity and risk of death, numerous *in vitro* and *in vivo* clinical methods are researched to find out possibilities of treatment for the chronic hepatitis B with RNAi.

According to this, the main purpose of this project would be to thoroughly examine the molecular way of RNAi, as well as to explore the opportunities for its therapeutic application in chronic hepatitis B. With the investigated *in vitro* and *in vivo* RNAi studies in chronic hepatitis B, it is perceived that the success of the treatment requires a combination of siRNA or shRNA sequences. In order to achieve a greater efficiency, reliability and duration of treatment, it is eminently important to develop an appropriate distributive pattern of these micro molecules to the liver cells. Studies of Arrowhead Research Corporation and Nucleonics Biotechnology confirm that the treatment based on RNAi for chronic hepatitis successfully allows a virus reduction in serum.

From the research we can deduce that the general reduction of the virus is performed with suppression of the genes which are responsible for DNA replication, as well as suppression of the genes which are responsible for encoding HbsAg and HbeAg. If these therapies are used appropriately with the prescribed therapeutic doses, the effect will be visible after a month-long therapy and with long-lasting effect. RNAi therapeutics are expected to appear on the market in 2018.

### **Keywords**

RNA interference (RNAi), siRNAs, chronic hepatitis B virus, gene- therapy, DPC delivery model, LNP delivery model.

# Anti-cancer target therapy based on drugs conjugated to hyaluronic acid

**Marija Zafirova**<sup>1</sup>, Darko Bosnakovski<sup>1</sup>

<sup>1</sup>Faculty of Medical Sciences, University "Goce Delcev"; Address: "Krste Misirkov" No. 10-A - Stip, Republic of Macedonia

E-mail address: marija.15585@student.ugd.edu.mk

## **Abstract**

The number of cancer patients is constantly growing, and there is a need for novel more successful therapy. Understanding the difference between healthy and cancer cells is necessary for developing a new target therapy. A possible approach is the use of hyaluronic acid (HA, hyaluronan) that has an important role in the physiology and pathology of cancer cells. By bounding to CD44 and RHAMM receptors this acid participates in the signaling pathways that are involved in the pathogenesis and progression of cancer. Normal and malignant cells differ among themselves by the number of receptors expressed on the cell surface. Cancer cells have increased number of CD44 and RHAMM receptors in contrast to normal cells. HA is biocompatible, biodegradable, nontoxic, nonimmunogenic, can be easily chemically modified and used as a carrier for drugs and genes. Hyaluronic acid can be used in therapy creation in three different ways: 1.Targeting hyaluronan metabolism; 2.Targeting hyaladherins and 3. HA-based drug delivery systems. Hyaluronan is conjugated to paclitaxel, irinotecan, bisphosphonates, doxorubicin and cisplatin and conjugates designed for target therapy are obtained. Conjugates are intended for treatment when the drug alone does not show positive results, the cancer becomes resistant to the drug and the metastasizing cancer is accelerated. Conjugation of the drug with hyaluronan can be performed in different ways and each way has its positive sides, which improves the action of the drug in cancer cells. Conjugates are specifically linked only to CD44 receptors which are found in many cancer cells and allow normal cells to remain free without being affected. Through the corresponding receptors, the drugs conjugated with hyaluronan enter in the cells and exhibit its' effect. Similar to drugs, nucleic acid can be conjugated and used for inactivation of cancer related genes. However, further researcher in these promising field is necessary.

## **Keywords**

anti-cancer target therapy, hyaluronic acid, CD44, RHAMM, HA-drug.

# Cancer-specific conjugated monoclonal antibodies for anticancer therapy

*Daniela Todosieva, Emilija Janevik-Ivanovska, Darko Bosnakovski*

*Faculty of Medical Sciences, University "Goce Delcev"; Address: "Krstev Misirkov" No.10-  
A - Štip, Republic of Macedonia*

## **Abstract**

In the last two decades there is substantial development in the diagnostic and therapy of many types of cancers by using monoclonal antibodies. Efficient treatment can be achieved due to ability of antibody to recognize specific antigen expressed on the surface of the tumor cell. Even more significant improvement can be done with conjugation of the antibodies by certain molecules with pharmacological potential.

Cancer-specific monoclonal antibodies are synthesized proteins designed to recognize specific antigens on the surface on the cancer cells. They have ability to activate humoral and cellular immune mechanisms that can modulate tumor growth and metastasis. In addition, specific conjugated monoclonal antibodies can provide selective delivery of cytotoxic substance or radioactive isotope directly to the cancer cell.

In the design of the therapeutic monoclonal antibody several factors have to be considered: specificity of antibody, selection of adequate cytotoxic substance or radioactive isotope, and conjugation method. Optimizing those factors increase potency, specificity, safety and stability of the therapeutic and increase therapeutic index (relationship between the minimal effective dosage and maximal toxic dosage). Additional factor that affects the efficiency of the therapy is the mechanism of releasing of cytotoxic molecule from the antibody into the cytosol of the cancer cell. Upon intravenous administration, Antibody Drug Conjugates (ADC) bind to their target antigens and are internalized through receptor-mediated endocytosis. This facilitates the subsequent release of the cytotoxin, which eventually leads to apoptosis of the cancer cell. Approved ADCs, brentuximab vedotin and trastuzumab emtansine, have demonstrated their effect against haematological and solid malignancies. Antibody-based therapies, both unconjugated antibodies and radioimmunotherapy, have had a significant impact on the treatment of non-Hodgkin lymphoma. The approved anti-CD20 radioimmunoconjugates (90-Y-ibritumomab tiuxetan or 131-I-tositumomab) have encouraging results, with new ongoing efforts for incorporation of radioimmunoconjugates in various settings.

Conjugated monoclonal antibodies are superior to the conventional approach of cancer treatment regarding to the safety and efficiency. This was confirmed with preclinical and clinical examinations. FDA approves several monoclonal antibodies based on the data of preclinical and clinical examinations and treatment of hematological cancers. In addition, significant numbers of ongoing trials are in phase of clinical examinations.

Generation of more specific antibodies, developing advanced methods of conjugation and explorations of novel anticancer molecules should be the future in therapy of other types of cancer. Improvement of target selection and development of new linkers will be great success of ADCs in strategy for overcoming drug resistance in

cancer cells. Concerning this issues, ADCs are likely to be future of targeted anticancer therapy.

**Keywords**

anticancer therapy, anti-CD20 antibody, cytotoxic drug, monoclonal antibody, radioimmunoconjugates.

## **Accreditation of the Laboratory of Radiopharmacy – requested requirements or need of challenge**

**Apostolova Paulina**, Delipetrevva Katarina, Smilkov Katarina, Gjorgieva Ackova Darinka, Sterjova Marija, Janevik Ivanovska Emilija

*Faculty of Medical Sciences, Goce Delcev University – Štip, Republic of Macedonia*

### **Abstract**

Laboratory of Radiopharmacy is a part the Faculty of Medical Sciences, Department of Pharmacy in the Goce Delcev University in Stip and was granted by the Government of Republic of Macedonia as a part of the project for improvement of the laboratories in the country. The main field in which the Laboratory of Radiopharmacy has focused after the establishment in 2011 is to introduce a new molecules as a potential radiofarmaceuticals, labeling with radioactive and not radioactive isotopes, defining their structure and especially chemical and radiochemical identification of potential impurities. In the same time carefully implementing radiation safety program for controlling laboratory environment. The Laboratory is deeply involved in the educational program in all cycles of academic degrees following a few international and local research projects. The laboratory staff is educated and trained in the national and international programs in the field of Radiopharmacy and Radiochemistry, as well included in the training courses dedicated to the implementation the standards and quality assurance providing additional effectiveness in the work.

All that activities including the requested requirements from the Ministry of Education and Sciences were enough strong reason to start the process of accreditation of the Laboratory of Radiopharmacy and to focus on that all our activities in the next period. The aim of our study is to introduce, to validate and to accreditate the procedures for quality control of radiopharmaceuticals for clinical and research purpose according regulatory standards. At that stage we have in progress the process of Accreditation with implementation of Standard MKC EN ISO/IEC 17025 - General requirements for the competence of testing and calibration laboratories. International Standard ISO/IEC 17025 specifies the general requirements for the competence of testing and calibration laboratories if they wish to demonstrate that they operate a quality system, are technically competent and are able to generate technically and scientifically valid results. The compliance these requirements enables the acceptance of testing and calibration results also between laboratories and countries.

Our Laboratory of Radiopharmacy currently is in the phase of implementation of the General requirements for the competence of testing and calibration laboratories of the Standard MKC EN ISO/IEC 17025. This standard holds five clauses, two annexes, and one bibliography section, out of which, the most important are Clause 4, that specifies the management requirements, and Clause 5, that specifies the requirements for technical competence for the type of tests the laboratory undertakes.

In the same time we are preparing the first method that will be applied to as ISO recognized. The process of accreditation is a long process of implementation of the standards and require continuous engagement of all staff and persons included in whole activities of the Laboratory.

After the establishment in the current location and have sufficient and competent staff that was necessary required we started with the initiative of accreditation. We are expecting that the implementation of ISO/IEC 17025 as part of laboratory quality initiatives will provide both, recognized laboratory in a medical and clinical application including professional benefits, and have important rule in the research and educational field, have an access to more agreements for testing and improved national and global reputation. In the same time constantly to expand data quality and laboratory effectiveness. This will also permit to reach the agreement of the trends of implementation good laboratory under umbrella of international standards like ISO 17025 in radiopharmaceutical and radiochemical laboratories explained as a need of expanding of "good scientific practice".

The accreditation process of the laboratories according Standard MKC EN ISO/IEC 17025 is also applied for Radiopharmacy and Radiochemistry. We are expecting that our Laboratory of Radiopharmacy will finish the first step of accreditation until June 2016 and be able to continue on the same road of good recognized work following already accepted standards and to have full access and confidentiality to the national and international research and clinical activities.

**Keywords**

Accreditation, Laboratory of Radiopharmacy, MKC EN ISO/IEC 17025.



# Quality control of PET radiopharmaceuticals, with reference to its specifics vs quality control of conventional pharmaceuticals

<sup>1</sup>Filip Jolevski, <sup>2</sup>Maja Velickovska, <sup>1</sup>Maja Chochevska, <sup>1</sup>Marija Atanasova, <sup>1</sup>Katerina Kolevska, <sup>1</sup>Emilija Janevik-Ivanovska

<sup>1</sup>Faculty of Medical Sciences, University Goce Delčev Stip,

<sup>2</sup>Project Unit for implementation of Positron Emission Tomography - PET Center Skopje, Ministry of Health

## **Abstract**

Radiopharmaceutical preparations or radiopharmaceuticals are medicinal products which, when ready for use, contain one or more radionuclides (radioactive isotopes) included for a medicinal purpose. As well as pharmaceuticals, they undergo strict quality control (QC) tests and procedures before release for use in patients. PET radiopharmaceuticals are usually formulated as sterile, apyrogenic injections, so they have to fulfill requirements for quality, efficacy and safety of conventional parenteral preparations.

The specifics of QC of the radiopharmaceuticals arise from the very nature and the short half-life of the radioisotopes. The presence of radioisotope require introducing tests for radionuclidic and radiochemical identity and purity which are unique for radiopharmaceuticals. The presence of undesirable, extraneous radionuclides increases the undue radiation dose to the patient and may also degrade the scintigraphic images.

Radionuclidic purity (RNP) is defined as the fraction of the total radioactivity in the form of the desired radionuclide present in a radiopharmaceutical, usually expressed as a percentage. RNP is determined by measuring the half-lives and emitted gamma radiation (gamma spectroscopy method).

Radiochemical purity (RCP) is the fraction of the total radioactivity in the desired chemical form in the radiopharmaceutical. For most radiopharmaceuticals, radiochemical purity above 95 % is desirable, since the impurities will almost certainly have a different biodistribution which can distort the image and interfere with the interpretation of the scan. Determination of the radiochemical purity can be carried out by a variety of chromatographic methods like TLC, HPLC.

Unlike conventional pharmaceuticals, radiopharmaceuticals cannot be manufactured, then tested and left in quarantine until the results of all tests are available, as most (if not all) of the radioactivity will decay to a level when this radiopharmaceutical will become useless. The radiopharmaceuticals have to be manufactured, tested for quality and then administered to the patient within a short period of time. Since the execution of some of the tests takes more time, it is not mandatory these tests to be completed before release for use. These tests are strictly defined in the individual pharmacopeia monographs.

In addition, due to the presence of source of radiation, all aspects of radiation protection should be retained while doing the tests for quality control of radiopharmaceuticals.

## **Keywords**

radiopharmaceuticals, QC control, radioisotope, radionuclide impurity, radiochemical impurity, radiation protection;

## Production of [<sup>11</sup>C]Choline in The University Institute for PET – new perspective in diagnostics of prostate malignancy in R. of Macedonia

**Katerina Kolevska**<sup>1</sup>, Maja Chochevska<sup>1</sup>, Marija Atanasova<sup>1</sup>, Maja Velickovska<sup>2</sup>, Filip Jolevski<sup>1</sup>, Emilija Janevik-Ivanovska<sup>1</sup>

<sup>1</sup>Faculty of Medical Sciences, Goce Delcev University Stip, Republic of Macedonia

<sup>2</sup>Project Unit for implementation of Positron Emission Tomography - PET Center Skopje in RM, Ministry of Health of the Republic of Macedonia

[katerina.kolevska@ugd.edu.mk](mailto:katerina.kolevska@ugd.edu.mk) +38977701001

### **Abstract**

[<sup>11</sup>C] Choline injection is radiopharmaceutical for oncological PET imaging of tumors which overexpress choline kinase. The most important clinical application of this PET radiopharmaceutical is in prostate cancer that can be visualized precisely, having differentiated localization located in comparison with benign tissue. The uptake of specific radiopharmaceutical remains constant thereafter, allowing better visualization of this kind of tumor. [<sup>11</sup>C]Choline PET/CT could represent an important imaging modality also in the detection of distant relapses in prostate cancer patients with biochemical recurrence.

The reason to have [<sup>11</sup>C] Choline in a first line of production is the evidence-based indications including also in a clinical guides:

- Evaluation of equivocal findings on conventional imaging such as possible nodal or metastatic disease in patients with prostate cancer where confirmation or exclusion of distant disease would directly influence patient management
- Suspected recurrence in patients with a rapidly rising prostate-specific antigen (PSA) and indeterminate or equivocal conventional imaging where the results would directly influence patient management.

According to the short half-life of <sup>11</sup>C radionuclide ( $t_{1/2}=20.4$  min), the production of [<sup>11</sup>C] Choline must be performed in PET facilities with on-site cyclotrons and should be as fast as possible to reduce the loss of activity due to decay.

The University Institute for Positron Emission Tomography in Skopje is equipped with a cyclotron GE PETtrace 800 for production of <sup>18</sup>F, <sup>11</sup>C, <sup>13</sup>N and option for solid targets. <sup>11</sup>C that we are planned to use for [<sup>11</sup>C] Choline is produced by cyclotron as [<sup>11</sup>C]CO<sub>2</sub> or [<sup>11</sup>C]CH<sub>4</sub>. <sup>11</sup>C radionuclide, produced as a gas in one of these chemical forms, is being transported through stainless steel tube to the GMP production laboratory, where a hot cell for synthesis of [<sup>11</sup>C] Choline and a hot cell for dispensing are installed. MIP is shielded cell where the methylator and the module for carbon labelling CarbonSynton are placed in. BBST-PC Laminar Flow Hot Cell is equipped with Clio-volumetric dispenser which is designed to dispense both vials and syringes. The automatic compact injector system allows automatic intravenous infusion of radiopharmaceuticals in a radiologically safe manner and with maximum control of all critical parameters such as the flow, the amount and the injection time.

The UI PET Skopje is the first center with all these opportunity in the Balkan region which has full equipment for production of [<sup>11</sup>C]Choline radiopharmaceutical. In our country where improving the health care system is one of the national imperatives, introducing [<sup>11</sup>C]Choline PET/CT as diagnostic procedure, will contribute to the strategy for better management of patients with prostate malignancy.

**Keywords**

[<sup>11</sup>C] Choline, cyclotron produced radiopharmaceuticals, PET/CT, PET radiopharmaceuticals, prostate cancer.

# PET radiopharmaceuticals in the diagnosis of neurological diseases

***Marija Pandeva**, Emilija Janevik-Ivanovska*

*Faculty of Medical Sciences, University Goce Delcev - Stip, Republic of Macedonia*

## **Abstract**

**The aim** of our study is to evaluate published data for use of PET radiopharmaceuticals in neurological diseases in particular for Alzheimer's disease (AD).

**Introduction:** PET (Positron Emission Tomography) is highly specific and sensitive technique of detecting critical information with regards to the alterations in the brain's anatomy and physiology observed in many neurological diseases.

Several clinical studies in last year's strongly recommended use of [<sup>18</sup>F] FDG (2-fluoro-2-deoxy-D-glucose), which is an analogue molecule of glucose normally consumed by the brain, in detecting the presence of hypometabolism several years before the onset of AD symptoms and as the only commercially available PET radiopharmaceutical.

**Results and discussion up to reviewed literature:** From the reviewed literature we can note that the application of imaging techniques which provides the information about the causes of AD such as loss of synaptic activity, gliosis and deposits of amyloid plaques, is very important. For that reason, PET imaging is very crucial to improve the specificity and accuracy of the diagnosis of AD and predementia states.

The typical radiopharmaceuticals (mostly [<sup>18</sup>F] FDG) are designed to image specific aspects of AD and other neurological diseases. They allow early interventions with disease – modifying therapies which aim to delay the onset and progression of detected disease.

The clinical development of the newly designed novel neuroimaging radiopharmaceuticals is mostly related to the detection of functional and metabolic abnormalities. Detection of disease-specific markers, such as amyloid ligands, is leading new application of PET in the area of neuro-degenerative diseases that are prevalent in aging societies. For that reason, the translation of molecular imaging to clinical applications require combination of specific radiopharmaceutical approaches with that of targeted therapy for the realization of personalized medicine.

**Conclusion:** This work was performed as a part of the Diploma Thesis of Pharmacy "PET radiopharmaceuticals in the diagnosis of neurological diseases", that will be defended in the Faculty of Medical Sciences, Goce Delcev University in Stip.

Current literature indicates that even only [<sup>18</sup>F]FDG is commercially available PET radiopharmaceutical with clinical relevance in the early and differential diagnosis of AD, in the last years the number of new PET radiopharmaceuticals (labelled with <sup>18</sup>F, <sup>11</sup>C, <sup>68</sup>Ga, <sup>64</sup>Cu) are under investigation in different stages of clinical trials. The future of all of them will be translated into benefits for patients living with AD.

## **Keywords**

Positron Emission Tomography, radiopharmaceuticals, Alzheimer's disease.

# Achievements and perspectives in formulation of stable immunoconjugate of the HER2-targeting trastuzumab – potential for rapid labelling with Gallium-68

Marija Sterjova<sup>1</sup>, Predrag Dzodic<sup>2</sup>, Katarina Smilkov<sup>1</sup>, Darinka Gorgieva-Ackova<sup>1</sup>,  
Emilija Janevik-Ivanovska<sup>1</sup>

<sup>1</sup> University 'Goce Delcev', Faculty of Medical Sciences – Stip, R. Macedonia,

<sup>2</sup> University of Nis, Faculty of Medicine, Department of Pharmacy – Nis, Serbia

## **Abstract**

**Objectives:** To synthesize and evaluate the immunoconjugate of the HER2-targeting trastuzumab with Gallium – 68 using already established method of freeze dried kit formulation.

**Introduction:** Trastuzumab (Herceptin®) is a humanized IgG1 monoclonal antibody which is approved for therapy of HER2 positive breast cancer. Good clinical results and improvement of the patient's general condition makes it interesting for further conjugation, in order to increase the therapeutic effect of trastuzumab.

With the development of radiopharmacy many efforts are made for formulation of stable conjugates with various bifunctional chelators, further labelled with radioisotopes ( $\alpha$ ,  $\beta$  and  $\gamma$  emitters). According to the literature, successful conjugation of trastuzumab is achieved with DOTA (1,4,7,10-tetraazacyclododecane-1,4,7,10-tetraacetic acid), DTPA (diethylenetriaminepentaacetic acid), TCMC (1,4,7,10-tetra-(2-carbamoyl methyl)-cyclododecane), HYNIC (succinimidyl-6-hydrazino-nicotinamide) and DTPA derivate 1B4M-DTPA (2-(4-isothiocyanatobenzyl)-6-methyl-diethylene-triaminepentaacetic acid).

Significant radiopharmaceuticals based on peptide and antibody for diagnostic and therapeutical purpose used different radioisotopes (<sup>99m</sup>Tc/<sup>188</sup>Re, <sup>67</sup>Ga, <sup>177</sup>Lu, <sup>90</sup>Y, <sup>131</sup>I).

Several studies have shown that already existing radiolabeled formulations, using beta and alfa emitters (<sup>90</sup>Y-DTPA-trastuzumab, <sup>86</sup>Y-DTPA-trastuzumab, <sup>177</sup>Lu-DOTA-trastuzumab, <sup>227</sup>Th-DOTA-p-benzil-trastuzumab, <sup>225</sup>Ac-trastuzumab) are potent against HER2 positive breast cancer.

Our already **obtained and published results** related to the method for ready to use production of freeze dried kit formulation of Rituximab immunoconjugates for labeling with Lu-177 and Y-90 including preclinical assessment of three immunoconjugates (p-SCN-Bn-DOTA, p-SCN-Bn-DTPA and 1B4M-DTPA ) including chemical characterization, animal imaging, biodistribution and toxicological studies, were good reason to have an indication to introduce the same approach for labeling HER2-targeting trastuzumab using <sup>68</sup>Ga<sup>3+</sup> under mild conditions without subsequent purification for PET imaging.

## **Work progress towards objectives and achievements**

Progress results and research outcomes critical to work progress and achievements are listed under our project milestones, and referenced to project aims.

**Milestone 1:** Standardize previously established method used for freeze dried kit formulation of Rituximab immunoconjugates for HER2-targeting trastuzumab immunoconjugates.

**Milestone 2:** Conjugation of bifunctional chelators to targeting for HER2-targeting trastuzumab, and radiolabeling with Ga-68 (define the most appropriate immunoconjugate).

**Milestone 3:** In vitro characterization and in vivo biodistribution of  $^{68}\text{Ga}$ -labeled conjugates.

**Significance:** Already established method for freeze dried kit formulation of conjugated Rituximab antibody ready for labeling with Lutetium-177, Yttrium-90 for therapeutical purpose that is under the final phase of the evaluation provide good information to introduce the same method for labeling of for HER2-targeting trastuzumab.

The simplicity and efficiency of labelling and the possibility of kit-based  $^{68}\text{Ga}$  tracer production without complex automated synthesis typical of multistep PET radiochemistry will greatly increase  $^{68}\text{Ga}$  PET access to hospitals, expanding the use of the  $^{68}\text{Ga}$  generator.

In the same time give opportunity to work on the same or similar kit formulation using with Lu-177 for therapy.

### **Keywords**

bifunctional chelators, breast cancer, immunoconjugates, radioisotopes, trastuzumab.

