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Vorwort

Mit dem alljährlich stattfindenden Paracelsus Science Get Together #SGT durften wir auch in diesem Jahr wieder über 100 Besucher*innen, Forscher*innen und Forschungsinteressierte an der Paracelsus Medizinischen Universität (dieses Mal in Nürnberg) begrüßen und gemeinsam einen Tag der Forschung feiern.

Forschende der PMU Salzburg und Nürnberg, des Uniklinikums Salzburg, des Klinikums Nürnberg, sowie Kooperationspartner der PMU reichten insgesamt mehr als 100 Poster ein. Sie stellten ihre aktuellen Forschungsarbeiten vor – diese sind auch beim Virtual Science Summer online über die PMU-Website <https://sgt.pmu.ac.at/> verfügbar. Die gezeigten Arbeiten umfassen eine enorme thematische Bandbreite aus den verschiedensten Wissenschaftsbereichen, darunter Medizin, Natur- und Sozialwissenschaften, von Grundlagen- bis zu klinischer Forschung.

Die eingereichten Poster wurden durch eine Fachjury bewertet und Preisträger*innen in den Kategorien „Best Poster“, „Best PhD Poster“ und „Best Student Poster“ ausgewählt.

Die ausgewählten Preisträger*innen sind:

Kategorie Best Poster: **Bernd Neumann** (Nürnberg): „WGS-based characterization of putative hypervirulent *Klebsiella pneumoniae* identified in a tertiary care hospital in Germany“

Kategorie Best PhD Poster: **Selina Ismail** (Salzburg): „Within and between effects of mothers' and fathers' attachment, mentalizing and caregiving“ und **Mahdi Safdarian** (Salzburg): „Burden of spinal cord injury, 1990 2019: a systematic analysis for the Global Burden of Disease Study 2019“

Kategorie Best Student Poster: **Melina Wirtz** (Nürnberg): „A new approach for management of aneurysmal subarachnoid hemorrhage based on Manual and Artificial Intelligence blood volume measurement in Non-Contrast Head CT scans“

Herzliche Gratulation an alle Gewinner*innen der Poster Awards! 🏆

Die Preisträger*innen stellten ihre Arbeiten am 28. Juni im Rahmen der Posterausstellung vor.

Ein herzlicher Dank gilt unseren Organisator*innen aus dem Forschungsmanagement und Services Nürnberg, sowie den zahlreichen Unterstützer*innen, die auch in diesem Jahr wieder die Durchführung des SGT mitermöglicht haben. Die fünf internationalen Sponsoren Cochlear, Terumo Aortic, Janssen, Bristol Myers Squibb und insbesondere der Hauptsponsor Der Westerhof / Berghotel Sudelfeld (Inhaber: Dr. Andreas Greither), der zum zweiten Mal die Preise der Research and Innovation Preisträger*innen gesponsert hat, ermöglichten das umfangreiche standortübergreifende Netzwerken.

Wir freuen uns, Ihnen zum Abschluss des Paracelsus Science Get Together und dem bis 15.10.2024 verfügbaren Virtual Science Summer, diesen Abstractband zum besseren Überblick und als Nachschlagewerk übermitteln zu dürfen - wiederum mit einer ISBN-Nummer versehen und damit zitierfähig.

Der besondere Dank der Universität gilt neben den Mitarbeiter*innen des Forschungsmanagement und Services Nürnberg und Forschungsmanagement Salzburg, der gesamten IT, die das virtuelle Format bestens betreute. So wurde der Netzwerkgedanke des SGT nicht nur von den Teilnehmenden, sondern auch von der Organisation gelebt – ganz im Sinne des Leitbildes der Universität.

Es ist uns ein großes Anliegen, den Vernetzungsgedanken weiter zu verankern und auch gemeinsame Forschungsprojekte zwischen den beiden Universitätsstandorten Salzburg und Nürnberg im Sinne eines Brückenschlages innerhalb der PMU weiter voranzutreiben und zu fördern und auch die Standorthochschulpartner miteinzubeziehen.

Bleiben Sie gesund und neugierig und freuen Sie sich mit uns auf den Science Get Together 2025 in Salzburg, bei dem in einem etwas anderen Format das großartige Portfolio der Forschung an der PMU präsentiert werden soll.

Es grüßen Sie herzlich

Univ.-Prof. Dr. Wolfgang Sperl
Rektor

a.o. Univ.-Prof.ⁱⁿ Mag.^a Dr.ⁱⁿ Barbara Kofler
Vizerektorin für Forschungsangelegenheiten

Inhaltsverzeichnis

Vorwort	I
----------------	----------

Sponsor*innen	IX
----------------------	-----------

Abstractsammlung

Nr. 1:	A retrospective analysis of an AI-algorithms performance compared to radiologists and the departments acceptance over time.....	S. 1
Nr. 2:	Synergistic effects of Lenvatinib and Dinaciclib combinational treatment in differentiated thyroid cancer cells.....	S. 2
Nr. 3:	Identification of patients with clinically relevant sleep disordered breathing using a contactless device in neurological rehabilitation.....	S. 3
Nr. 4:	Automated diabetic retinopathy screening in out-patient diabetes care.....	S. 4
Nr. 5:	Validation of a physiological relevant biomechanical test setup for the investigation of complex pelvic ring fractures.....	S. 5
Nr. 6:	Application of the 5th WHO guidelines for the diagnosis of small lung biopsies in a tertiary care center: is insecurity of pathologists for the right diagnosis justified?.....	S. 6
Nr. 7:	What Keeps You Up at Night? Moral Distress in Nurse Leaders in the U.S., Germany, Austria, and Switzerland.....	S. 7
Nr. 8:	Multimodal evaluation of cryotherapy to reduce incidence of chemotherapy-induced peripheral neurotoxicity in breast cancer patients.....	S. 8
Nr. 9:	Clinical and demographic factors affecting trough levels of isavuconazole in critically ill patients with or without COVID-19.....	S. 9
Nr. 10:	Procnostic scoring in Stevens-Johnson-syndrome & toxic epidermal necrolysis : A 17-year analysis at a high-volume center.....	S. 10
Nr. 11:	Demographic and morphologic factors influencing Transcranial Doppler Sonography (TCD) performance.....	S. 11
Nr. 12:	Influence of Vitamin K2 on the Response of Chondrocytes from Diabetic and Non-diabetic Rats....	S. 12
Nr. 13:	Development of a new protective solution for vein grafts in bypass surgery.....	S. 13

IV

Nr. 14:	Does vitamin K2 (MK7) influence cardiac fibrosis in diabetes mellitus type 2 (T2DM) associated cardiomyopathy progression - insights from a rat diabetes model.....	S. 14
Nr. 15:	Laboratory and Anamnestic Risk Indicator for Necrotizing Fasciitis.....	S. 15
Nr. 16:	Cost-effectiveness of Arthroscopic knee surgery in degenerative meniscal tears.....	S. 16
Nr. 17:	How do Parkinson's patients from south tyrol sleep?.....	S. 17
Nr. 18:	Generation of a Tendon-specific Knock-Out Mouse Model to Deeply Probe the Role of SPARC in Tendon Health and Disease.....	S. 18
Nr. 19:	Structural diversity and biophysical properties of voltage-gated proton channels (Hv).....	S. 19
Nr. 20:	Sodium Valproate Modulates Cortical Morphology in Juvenile Myoclonic Epilepsy.....	S. 20
Nr. 21:	Small-Molecule Library Screen Identifies Tanespimycin as a YAP-modulator in SH-SY5Y Cells.....	S. 21
Nr. 22:	Effect of Probiotic Supplementation on the Intestinal Microbiome of Preterm Infants.....	S. 22
Nr. 23:	Sunflower Syndrome – Creating Awareness & International Medication Survey.....	S. 23
Nr. 24:	Prenatal Psychosocial Risk: Association with Stress, Social Support and Resilience.....	S. 24
Nr. 25:	From laptop to top-lab: a combined in silico in vitro approach to identify novel microtubule stabilizers as potential drug candidates.....	S. 25
Nr. 26:	Safe Forests: The psychological wellbeing of harvester and forwarder drivers – a cross-sectional study.....	S. 26
Nr. 27:	A comparative study of three different bioactive glass scaffolds tailored for cartilage tissue engineering.....	S. 27
Nr. 28:	Chondrogenesis of hMSCs in 3D printed bioglass/hydrogel scaffolds for cartilage regeneration.....	S. 28
Nr. 29:	Hiatal hernia after transthoracic esophagectomy for cancer: the key role of omentectomy.....	S. 29
Nr. 30:	Impact of Anastomotic Leak vs Pneumonia on failure to rescue after transthoracic Esophagectomy for cancer.....	S. 30
Nr. 31:	Mixed Methods Evaluation of Early Home-Based Interventions for Children at Risk.....	S. 31
Nr. 32:	First insights into SESAM: „SonoElastography: Sarcopenia Associated Muscle Change“.....	S. 32
Nr. 33:	Parents Media Guide: How parental Smartphone use influences family life.....	S. 33
Nr. 34:	Role of galanin receptor 2/3 in inflammation associated with peritonitis.....	S. 34
Nr. 35:	Therapeutic Drug Monitoring in critically ill patients with urosepsis.....	S. 35

Nr. 36:	First results from a multimodal day-care psychosomatic post-COVID treatment approach.....	S. 36
Nr. 37:	The ubiquitin-proteasome system component Zbtb preferentially interacts with pathogenic variants of SLC26A4 (pendrin).....	S. 37
Nr. 38:	Comparison of image quality in CT neck imaging between different protocols with linearly reduced radiation doses and contrast agent amounts.....	S. 38
Nr. 39:	Within and between effects of mothers' and fathers' attachment, mentalizing and caregiving 🐾.....	S. 39
Nr. 40:	Deckung komplexer pararektaler Beckendefekte: Rolle der freien myokutanen Musculus vastus lateralis Lappenplastik.....	S. 40
Nr. 41:	Influencing factors on SARS-CoV-2-specific IgG antibody development following vaccination...	S. 41
Nr. 42:	Collection efficiency of mononuclear cells in offline extracorporeal photopheresis: can processing time be shortened?.....	S. 42
Nr. 43:	Characterization of patients with classical myeloproliferative neoplasms: A retrospective, single-center analysis.....	S. 43
Nr. 44:	A personalised and customisable serious gaming system for children with movement disorders....	S. 44
Nr. 45:	Relationship between Education and Steatotic liver disease.....	S. 45
Nr. 46:	Caring for a relative with dementia and the lived experiences of boundaries in caregiving – a qualitative study in a rural area of Salzburg.....	S. 46
Nr. 47:	Interatrial block improves prediction of new-onset atrial fibrillation after cardiac surgery.....	S. 47
Nr. 48:	Novel genetic variants lead to sensorineural hearing loss and Enlarged Vestibular Aqueduct (EVA).....	S. 48
Nr. 49:	Oxidative stress-related cellular aging causes dysfunction of the Kv3.1/KCNC1 channel reverted by melatonin.....	S. 49
Nr. 50:	Fructose appears to be able to influence the immune system.....	S. 50
Nr. 51:	Influence of the isolation method on the measurement of the respiratory burst.....	S. 51
Nr. 52:	Telemedicine for the management of behavioral disorders in nursing home residents with dementia.....	S. 52
Nr. 53:	Impact of sugars on reactive oxygen species production during the respiratory burst of phagocytes.....	S. 53
Nr. 54:	Embroidered silk fibroin scaffolds for ACL tissue engineering.....	S. 54
Nr. 55:	Transcriptomic analysis unveils the regulatory network of Sturge-Weber syndrome-associated Gαq protein during neural differentiation.....	S. 55

Nr. 56:	EZH1 - a new therapeutic target for biliary tract cancer?.....	S. 56
Nr. 57:	Prevalence of metabolic dysfunction-associated fatty liver disease (MAFLD) and effects of glucose-lowering medications in patients with type 2 diabetes mellitus.....	S. 57
Nr. 58:	Risk of Interprosthetic Femur Fracture Is Associated with Implant Spacing - A Biomechanical Study.....	S. 58
Nr. 59:	Trauma-focused art therapy in patients with miscarriage or stillbirth: Psychometric treatment effects of the randomized controlled MALT! study.....	S. 59
Nr. 60:	The voltage-gated proton channel discovers its family and function.....	S. 60
Nr. 61:	Pathogenic Pendrin (SLC26a4) variants are functionally rescued by Carfilzomib.....	S. 61
Nr. 62:	WGS-based characterization of putative hypervirulent <i>Klebsiella pneumoniae</i> identified in a tertiary care hospital in Germany 🏰.....	S. 62
Nr. 63:	Impact of Mesenchymal Stem Cells Derived Laminin-Binding Extracellular Vesicles on Schwann Cells and in Peripheral Nerve Regeneration Processes.....	S. 63
Nr. 64:	Concentrations of antiseizure medications during pregnancy and breastfeeding in women with epilepsy: evaluation of acute side effects and systematic follow-up of development of breastfed infant. A international multicenter study.....	S. 64
Nr. 65:	Digital assessment of real-world walking activity in pulmonary hypertension: A prospective bicenter clinical trial.....	S. 65
Nr. 66:	Patient's Perspective and Expectations in Dupuytren's Disease Treatment.....	S. 66
Nr. 67:	Barrieren des Zugangs zu Palliative Care im Krankenhaus.....	S. 67
Nr. 68:	The assessment of biological maturation I academy soccer players: a comparison of two methods.....	S. 68
Nr. 69:	Minimally invasive ascending aortic surgery: operative and mid-term outcomes.....	S. 69
Nr. 70:	ATR-FTIR as tool for quality control of extracellular vesicles.....	S. 70
Nr. 71:	Ozanimod – Safety and Efficacy in a real-world-MS-cohort.....	S. 71
Nr. 72:	The Influence of Chronotype on Interictal Epileptiform Discharges and Sleep Quality in Individuals with Epilepsy: A Study of Sleep-EEG Findings.....	S. 72
Nr. 73:	Risk factors for prolonged length of stay after first single-level lumbar microdiscectomy.....	S. 73
Nr. 74:	Burden of spinal cord injury, 1990 2019: a systematic analysis for the Global Burden of Disease Study 2019 🏰.....	S. 74

Nr. 75:	Validation of the arthroplasty register of south Tyrol between 2010-2020 – data analysis of the SABES hospitals.....	S. 75
Nr. 76:	How primary care physicians deal with the climate crisis: preliminary results of a scoping review...S. 76	
Nr. 77:	Sex differences in pain courses in patients with hip or knee osteoarthritis after multimodal spa therapy in the Austrian valley of Gastein.....	S. 77
Nr. 78:	Comparison of naturally produced EVs and artificial CDVs.....	S. 78
Nr. 79:	Physicians' Perspectives, Well-being, and Fulfilment in Telemedicine.....	S. 79
Nr. 80:	Characterisation of variants in the SLC26A4 gene identified in a Slovak cohort with non-syndromic enlarged vestibular aqueduct and Pendred syndrome.....	S. 80
Nr. 81:	Prognostic and predictive factors (clinical data, histological and molecular data, laboratory values) under palliative first-line therapy for squamous cell carcinoma of the lung with chemotherapy plus immunotherapy.....	S. 81
Nr. 82:	Metabolic Footprint of Ketosis-inducing Diets in Mice.....	S. 82
Nr. 83:	Theranostic EV biomarkers from non-invasive liquid biopsies.....	S. 83
Nr. 84:	Nanoindentation on Tendon Tissue.....	S. 84
Nr. 85:	The clinical relevance of low-grade infected nonunion.....	S. 85
Nr. 86:	Bioanalytic methods in psychosomatic medicine.....	S. 86
Nr. 87:	Detecting high risk neighborhoods and socioeconomic determinants for common oral diseases in Germany with geostatistics and machine learning models.....	S. 87
Nr. 88:	The Impact of Educational Status on the Occurrence of Colonic Diverticula.....	S. 88
Nr. 89:	Optimised intraoperative radiotherapy treatment workflow using machine learning methods.....	S. 89
Nr. 90:	PKC activators orchestrate neuronal immune modulation: Unveiling microglial dynamics in NF-KB activation and phagocytosis.....	S. 90
Nr. 91:	Preliminary Data of a 3d Single-Limb-Squat Assessment of Laterality in Exercise-proficient Physiotherapists.....	S. 91
Nr. 92:	The degree of cyclic stretching influences lapine Achilles tenocytes and hMSCs in 2D culture and under 3D conditions on a Dura mater cell carrier.....	S. 92
Nr. 93:	Lessel-Kubisch syndrome as a model to decipher the Achilles heel of p53.....	S. 93
Nr. 94:	The effect of UVC irradiation on germ density on breast implants and epidermis.....	S. 94
Nr. 95:	DIAFILD – a study aiming to expedite DIAgnosis of Fibrosing Interstitial Lung Disease.....	S. 95

VIII

Nr. 96:	A new approach for management of aneurysmal subarachnoid hemorrhage based on Manual and Artificial Intelligence blood volume measurement in Non-Contrast Head CT scans 🏰.....	S. 96
Nr. 97:	Wound healing and self organization of skin cells is guided by protein corona-bearing extracellular vesicles.....	S. 97
Nr. 98:	Beyond Stress: The Role of Attachment and Mentalizing for the Well-being among Elementary Educators.....	S. 98
Nr. 99:	Short-term CD8+ T cells ablation reduces microgliosis in the hippocampus of old APP/PS1 animals	S. 99
Nr. 100:	3D Scanning and Printing Technology for Breast Reconstruction: Increased Aesthetic Outcomes and Quality of Life.....	S. 100
Nr. 101:	Impact of 2-hydroxypropyl- β -cyclodextrin inclusion complex formation on dopamine receptor-ligand interaction – a case study.....	S. 101
Nr. 102:	BEATS – MIGRAINE: Biomarker Establishment of Activated Targets in Skin for Migraine.....	S. 102

Liste der Einrichtungen (korrespondierende Autor*innen)

X

Verzeichnis aller Autor*innen

XI

Der Paracelsus Science Get Together 2024 wurde mit freundlicher Unterstützung folgender Unternehmen ermöglicht:



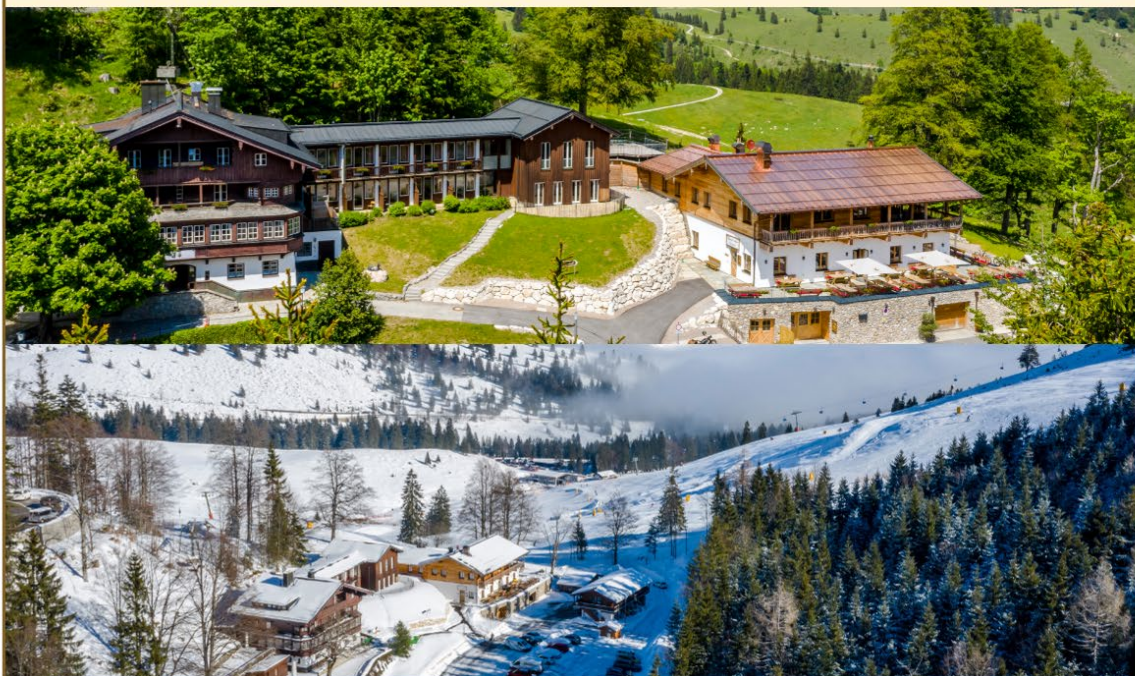
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Abstractsammlung

A retrospective analysis of an AI-algorithms performance compared to radiologists and the departments acceptance over time

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Objective

There is an increasing number of scans being done in hospitals, which is leading to an increase in workload of radiologists. In the emergency setting the detection of intracranial haemorrhage (ICH) is essential to start treatment as soon as possible. Artificial intelligence (AI) algorithms have shown use in several different medical settings, including the detection of ICHs. In our radiology department, we implemented an FDA-approved and CE-marked deep learning algorithm to aid in the detection of ICHs.

Methods

This study evaluated the performance of the algorithm compared to general radiologists, while using a board-certified neuro radiologist as "ground truth". We performed two three-week retrospective analyses six months apart. We also conducted two surveys six months apart to gauge the acceptance of the algorithm among radiologists. False negatives and false positives were defined as cases where either the original interpreting radiologist or the AI algorithm misinterpreted the presence of ICH. Discrepancies were identified when the AI algorithm flagged cases that were not initially reported as ICH by the radiologist. As stated, before the neuroradiologist served as "ground truth".

Results

Our findings demonstrate that the algorithm had a comparable performance to radiologists in detecting ICHs. The sensitivity and specificity that we calculated were in the range reported in previous studies with comparable or the same algorithm. The survey results indicated a high level of acceptance of the algorithm among radiologists, which increased slightly over time. A significant proportion of radiologists found that an additional resident post would provide more value, given they have a similar yearly cost.

Conclusions

In conclusion, the implementation of the algorithm to detect ICHs showed promising results. The algorithm performed comparable to radiologists, and its integration, especially over time, led to a high and increasing acceptance among the department's staff. The use of AI in radiology in general has the potential to reprioritise acute finding, improve workflow, reduce errors in interpretation by serving as second look, and facilitate early treatment for conditions such as ICHs, which require immediate attention. We encourage further research into the performance of AI-algorithm, their potential uses and their acceptance among medical professionals.

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Synergistic effects of Lenvatinib and Dinaciclib combinational treatment in differentiated thyroid cancer cells

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Objective

Thyroid cancer is the eighth most frequently cancer worldwide, whereas differentiated thyroid carcinomas (DTCs) represent over 90% of thyroid cancers (1). Although thyroidectomy and administration of radioactive iodine results in a good prognosis, some patients develop therapy resistance (RR-DTC) (2). In this case Lenvatinib was approved for the treatment of RR-DTC. Due to severe side effects and/or resistance to therapy, there is an urgent need to develop new treatment strategies (3). Dinaciclib, a Cdk-inhibitor, has shown promising anti-tumor effects in different tumor entities (4). Therefore, the aim of this study is to investigate potential synergistic effects of combinational treatment of Lenvatinib and Dinaciclib in DTC cell lines.

Methods

To assess the combination effects of Lenvatinib and Dinaciclib, Lenvatinib-resistant K1 and radio-iodine resistant TT2609-C02 cells were treated for 72 h and analyzed via CCK8 kit. The migratory ability of K1 was investigated via a wound healing assay and the Tecan Spark plate reader over 24 h. To elucidate colony formation, DTC cells were pre-treated for 24 h and viable cells were further re-seeded and allowed to form colonies before they were stained with crystal violet. For 3D cell culture, spheroids were treated with Dinaciclib/Lenvatinib for 96 h and spheroid viability was assessed with the CellTiter-Glo® 3D kit.

Results

The combinational treatment of Lenvatinib and Dinaciclib significantly reduces the 2D and 3D cell viability in K1 and TT2609-C02 cells either in a synergistic or additive manner. Additionally, for K1 cells, the combination treatment inhibits the migration potential, whereas monotherapies do not lead to a change in the migration behavior. We demonstrated that the simultaneous treatment synergistically decreases the colony formation capacity in both DTC cell lines, while cells receiving monotherapy are still capable of forming colonies.

Conclusions

We show that the Cdk-inhibitor Dinaciclib synergistically enhances the efficacy of Lenvatinib treatment. additional experiments will give further insight into the molecular mode of action to improve future therapy options for DTC patients.

Acknowledgements

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Identification of patients with clinically relevant sleep disordered breathing using a contactless device in neurological rehabilitation

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Objective

Stroke is one of the five leading causes of death in the Western world. Sleep disturbances are common in ischaemic stroke patients and are associated with poorer stroke outcomes. To improve the quality of medical care for post-stroke patients, we assessed neurological patients in a rehabilitation clinic simultaneously with a non-contact method (Sleepiz One, based on Doppler radar technology and advanced signal processing) and a standard diagnostic polygraphy (PG) measurement.

Methods

We studied patients who had suffered a stroke within >5 days but <180 days before inclusion, were older than 18 years, were able to give informed consent, and were able to undergo routine electrophysiological sleep measurement. Of 230 consecutive patients, we recruited 47 participants (the main reasons for exclusion were dementia, aphasia and inability to give written informed consent). We simultaneously performed a standard PG measurement (device set-up by trained carers) and a non-contact Sleepiz-One measurement; 6 measurements were excluded due to insufficient data.

Results

Data analysis was performed with 41 complete measurements, simultaneous registration of classic polygraphy and non-contact sleep diagnostics. 58% of the patients suffered from severe sleep apnoea (RDI >15), 33% from severe sleep apnoea (RDI > 25). The comparison of the raw scores showed a correlation of $r = 0.79$ between the conventional (PG) and the non-contact method (Sleepiz One). In 30 cases there was a classification (sleep apnoea (0/1)) with both variables (Respiratory Disturbance Index (per hour) RDI PG ≥ 15 and RDI Sleepiz One ≥ 15). No significant difference in the prevalences was found (McNemar test, $p = 1.0$). Both examination methods had a similar error rate.

Conclusions

In neurological care, a relevant number of patients with sleep-disordered breathing can be detected with a simple screening examination. In this study, no recognisable difference in the quality of recordings was found between conventional polygraphy (PG) and an innovative contactless device (Sleepiz). Easy-to-use technical procedures such as Sleepiz can reduce the burden on patients and staff.

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Automated diabetic retinopathy screening in out-patient diabetes care

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Objective

The aim of this study is to evaluate the performance of an autonomous screening system for diabetic retinopathy (DR) in a real-world setting at the diabetes out-patient center Nuremberg. Digital retinal photographs of the retina were taken by a mobile and a table-top non mydriatic fundus camera. The images were graded for quality and DR by an ophthalmologist and an artificial intelligence (AI) software (1,2).

Methods

This is a prospective study. From August 2023 till November 2023 one hundred fifty patients with diabetes type 1 or type 2 were included. Each patient underwent fundus photography in Miosis with a standard 45° camera NW400 (Topcon Medical Systems, Oakland, USA) and then with a hand-held 50° camera Aurora (Optomed Plc, Oulu, Finland). Two images per eye, macula and optic nerve head centered were taken (figure 1). All images were graded by an ophthalmologist and the artificial intelligence software RetCAD Version 2.2.0 (Thirona Retina, Nijmegen, Netherlands) (3). The DR was graded according to the International Clinical Diabetic Retinopathy Severity Scale (ICDR) (figure 2). More than mild DR (mtmDR) means DR grade 2 or more and was defined as referable DR. The patient was graded taking the worst of two eyes. The images were analyzed by the ophthalmologist first and then by the AI software RetCAD Version 2.2.0 (Thirona Retina, Nijmegen, Netherlands).

Results

A total of 150 participants were enrolled, of which 138 completed fundus imaging with both cameras. The average age was 56 years (range, 21-98 years). The mean HbA1c was 7,4 mmol/l (range, 4,8-12,3 mmol/l) (table 1). In 95% of patients DR screening without pupil dilation was possible. The prevalence of mtmDR was 7.3% (10/138). The AI software RetCAD Version 2.2.0 (Thirona Retina, Nijmegen, Netherlands) obtained a sensitivity of 70% and specificity of 98% for recognizing referable DR in 552 fundus images taken with the table top camera NW 400 (Topcon Medical Systems, Oakland, USA). The image quality was rated sufficient in 98%. The AI software RetCAD Version 2.2.0 (Thirona Retina, Nijmegen, Netherlands) reached a sensitivity of 90% and specificity of 100% for correctly identifying referable DR in 552 digital photographs taken with the handheld camera Aurora (Optomed Plc, Oulu, Finland). The image quality was rated sufficient in 89% (table 2). There was no significant difference in the number of mtm DR patients detected by the ophthalmologist compared to the AI independent of the camera system used.

Conclusions

The analysis of retinal images for DR by the AI software RetCAD Version 2.2.0 (Thirona Retina, Nijmegen, Netherlands) showed a high agreement to the evaluation by an ophthalmologist. The handheld fundus camera Aurora (Optomed Plc, Oulu, Finland) reached similar results compared to the table top camera NW 400 (Topcon Medical Systems, Oakland, USA) despite lower image quality scores (figure 3). The tested automated diabetic retinopathy screening system seems to be suitable for a diabetes out-patient center or primary care setting and offers patients a fast access to routine DR screening.

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Validation of a physiological relevant biomechanical test setup for the investigation of complex pelvic ring fractures

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Objective

Fractures of the human pelvis can lead to disruptions of the ring-shaped structure which results in mechanical destabilization of the pelvic ring. A variety of different methods for an osteosynthetic treatment are available, but there is still a lack of knowledge about the mechanical stability of these methods. The aim of this project is to build a test setup able to determine the stability of different fixation methods for complex pelvic ring fractures under a valid loading situation simulating human gait.

Methods

In order to be able to evaluate the force distribution on the entire pelvis for the validation of the new test setup, a 6-component load cell was mounted on an embedding pot in addition to the other load cells already installed. With an increasing load protocol, 58 load cycles were applied and the forces normalized to the resulting hip joint force were compared with data from the literature [1,2].

Results

In accordance with the literature, the largest force component at the acetabulum acts in the vertical direction at the time point of contralateral heel strike. The forces on the anterior and posterior muscle pull and the force applied to the sacrum correspond to approximately one third of the resulting hip joint force.

Conclusions

To date, biomechanical experiments on pelvises have been performed primarily on single-leg stance or double-leg stance models. Because these do not fully take into account the complex loading situation during gait, the new test setup was developed. Simplifications were made to account for the applied loads, especially the muscle forces. The new test setup can be used to evaluate the fatigue strength of osteosyntheses for complex pelvic ring fractures under dynamic and realistic loading.

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Application of the 5th WHO guidelines for the diagnosis of small lung biopsies in a tertiary care center: is insecurity of pathologists for the right diagnosis justified?

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Objective

The diagnosis of lung cancer based on small lung biopsies is part of the diagnostic routine for many pathologists. According to the recent WHO guidelines, lung cancer in small biopsies should be made by morphology when possible. If this is not possible, a limited panel of additional testing, namely PAS, TTF-1 and p40 should be performed. In daily routine, however, according to our experience numerous ancillary examinations are often conducted to further confirm the morphological diagnosis or to exclude metastases. The aim of this study was to compare the histological diagnosis made by applying the guidelines suggested by the recent WHO classification of lung cancer with the diagnosis made by an extensive use of ancillary techniques.

Methods

We have carried out a retrospective analysis of 288 lung biopsies diagnosed in the Department of Pathology, Nuremberg Hospital between September 2020 and May 2021. Two experienced pathologists re-examined all samples according to the guidelines suggested by WHO. We also compared the results of the two immunohistochemical markers used routinely for the diagnosis of squamous cell differentiation, namely p63 and p40.

Results

The histological classification was made using a mean number of 1 ancillary technique ($SD \pm 1,4$) compared with a mean number of 6 techniques ($SD \pm 3$) in the original diagnostic procedure. By comparing the diagnoses obtained, we were able to show that a comparable diagnostic certainty can be achieved by applying the WHO guidelines in the case of definite primary disease, reaching a concordance rate of 97,3% compared to the extensive use of additional testing. Only in the presence of metastases, the application of limited additional testing could lead to a diagnosis of a primary non-small cell lung carcinoma not otherwise specified (NSCLC NOS) (14/47 metastases). In this setting, clear advantage in diagnostic accuracy using more extensive immunohistochemical examinations is proven. We also found a comparable sensitivity of p40 and p63 for the diagnosis of squamous cell carcinoma, but higher expression of p63 in adenocarcinomas ($p < 0,001$) or NSCLC NOS ($p = 0,007$).

Conclusions

The uncertainty of pathologists regarding the diagnosis of lung cancer in small biopsies is justified, in cases where the diagnosis of NSCLC NOS is reached.

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What Keeps You Up at Night? Moral Distress in Nurse Leaders in the U.S., Germany, Austria, and Switzerland.

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Objective

Nurse leaders are challenged by ethical issues in today's complex health care settings. The purpose of this research was to describe and analyze key elements of moral distress identified by nurse leaders from health care systems in the U.S., Germany, Austria, and Switzerland. The aim was to develop an understanding of distressing ethical issues nurse leaders face in the U.S. and three German-speaking European countries.

Methods

This descriptive cross-sectional study surveyed a convenience sample of nurse leaders in the U.S., Germany, Austria, and Switzerland. The voluntary, anonymous survey also included qualitative questions and was distributed using the Qualtrics® platform. A thematic analysis of the qualitative data in each country was carried out and a comparative analysis identified similarities and differences between the groups of nurse leaders comparing the U.S. data to that from three German-speaking European countries.

Results

The survey was completed by 316 nurse leaders: Germany, Austria, and Switzerland (n=225) and the U.S. (n=91). Similar themes identified as causing all nurse leaders moral distress included a lack of individual and organizational integrity, hierarchical and interprofessional issues, lack of nursing professionalism, patient care/patient safety concerns, finances negatively impacting care, and issues around social justice. Within these six themes, there were also differences between the U.S. and the three German-speaking European countries.

Conclusions

This study demonstrates that it is vital to develop and retain ethically competent nurse leaders in the U.S. and three German-speaking European countries where patient care, professional development, and organizational integrity are paramount. Despite the geo-political differences between these countries, there were reported similarities in the ethical issues that trouble nurse leaders. This study can be a segue into a health care organization's self-assessment to survey its nurse leaders and work collectively to develop supportive leadership development programs, both practical and theoretical, with the goal of reducing moral distress and improving the well-being of these leading employees within complex health care systems.

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Multimodal evaluation of cryotherapy to reduce incidence of chemotherapy-induced peripheral neurotoxicity in breast cancer patients

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Objective

Chemotherapy-induced peripheral neurotoxicity (CIPN) is a common side effect of the drug Paclitaxel, used as adjuvant therapy against breast cancer, which can affect the outcome of cancer therapy, reduce patients' quality of life, and has an important economic and social burden. Although many possible interventions have been proposed in this context, to date there is no standard treatment for the prevention of CIPN (1,4). Cryotherapy, which through cold-induced acromial vasoconstriction reduces the exposure of peripheral nerve fibers to the neurotoxic agent, has been proposed as a promising solution. It can be administered in various ways, including the use of refrigerated gel gloves and stockings or the use of dedicated devices. Many studies support the use of cryotherapy, but to date, there is a lack of consensus on its efficacy and how to perform it (2).

Methods

This randomized controlled trial aims to evaluate the efficacy of the two main cryotherapy methods, compared to a control group, using a multimodal assessment approach. For this purpose, 144 breast cancer patients, treated with adjuvant Paclitaxel-weekly in the day-hospitals of Brixen and Meran, will be recruited in the present study and divided into three groups of equal numbers. Group A will receive cryotherapy via a dedicated device (HilothermTM), group B via gloves and refrigerated gel stockings, and group C (control) will not receive cryotherapy. To objectively assess the effectiveness of cryotherapy, robust clinical and neurophysiological outcome measures will be used. Together with a clinical neurological evaluation, following the TNSn score as a guide, and the collection of the FACT/GOG-NTX questionnaire, nerve conduction studies of the dorsal sural nerve, nerve excitability testing of the ulnar nerve, neurological clinical evaluation and measurement of light chain neurofilaments in serum will be performed (3). These evaluation procedures will be collected prospectively during the course of Paclitaxel therapy up to 12-month follow-up.

Results

At this time no data are available.

Conclusions

Giving the scientific community solid results in favor of the efficacy of cryotherapy in preventing CIPN would encourage its more widespread use. This would ideally reduce the incidence of CIPN, decrease the rate of reduction or discontinuation of chemotherapy, increase the success rate of chemotherapy, and thus increase the life expectancy and quality of life of patients. Furthermore, the development and validation of an effective method to prevent the onset of CIPN, which constitutes a heavy socio-economic burden for patients and public health, would reduce the costs associated with CIPN and thus provide a major contribution to the efforts to build sustainable healthcare for the future.

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A new mouse model of DFNB4/Pendred syndrome: CBA/J-Slc26a4p.R409H/p.R409H

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Objective

Pendrin (SLC26A4) is an anion exchanger mainly expressed in the inner ear, kidney, and thyroid. Defects in the ion transport function consequent to genetic mutation are associated with syndromic (Pendred syndrome) and non-syndromic forms of deafness (1). The generation of a consistent animal model would help in understanding the pathophysiology of pendrin-related hearing loss and the investigation of potential therapeutic approaches.

Methods

A mouse model expressing the pendrin protein variant p.R409H has been produced by CRISPR-Cas with Cyagen-Taconic (Santa Clara, CA, USA). For fast genotyping, a silent mutation resulting in a restriction site for BsrGI has also been introduced. After gDNA extraction and amplification of a 500bp fragment, the presence of the mutation is identified by enzymatic digestion. A homozygous WT produces only a 500bp band on an agarose gel, a heterozygous a 500bp band and a 250bp band, and a homozygous mutant only a 250bp band. To investigate the hearing and vestibular function of the mice, open-field and startle reflex tests were performed. The mice were placed individually in an empty box and their movements were recorded for 15 minutes with a camera and analyzed with Ethovision XT (Noldus, NL).

Results

F1 heterozygous mice have been mated in our facility and produced the first F2 litter of 8 pups, 7 males and 1 female. The pups were genotyped with tissue samples from the ear punch. From the restriction analysis, 3 mice were homozygous WT, 3 homozygous mutant, and 2 heterozygous. The vestibular function test was performed at P30 with all 8 mice from the first litter. Several parameters have been evaluated, including the total distance, the velocity, the area occupied, and the rotational movements of the mice. Mouse #7 (MUT) behaved anomalously, remaining the whole time of the experiment in one corner, showing a very agitated state and it was therefore excluded from the analysis.

Conclusions

We could successfully produce and mate mice carrying a pathogenic variant in the pendrin gene. From a pilot experiment investigating the vestibular function of the first litter, we could observe that the homozygous mutant mice behaved differently from the WT and heterozygous mice and displayed the typical hallmarks of vestibular dysfunction. Even with the limited number of animals, we could show a significant difference in most of the observed parameters (distance moved, velocity, rotations). Hearing measurements have not been performed yet, but we could observe a lack of startle reflex to a loud clap in all three mutant mice, denoting hearing loss.

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PROGNOSTIC SCORING IN STEVENS-JOHNSON-SYNDROME & TOXIC EPIDERMAL NECROLYSIS : A 17-YEAR ANALYSIS AT A HIGH-VOLUME CENTER

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Objective

Toxic Epidermal Necrolysis (TEN) and Stevens-Johnson Syndrome (SJS) are rare yet severe dermatologic conditions with potentially life-threatening consequences due to extensive skin and mucous membrane involvement. Despite their low incidence, they pose significant challenges in clinical management and carry high mortality rates. This retrospective study aimed to characterize SJS/TEN cases and evaluate the clinical applicability of existing prognostic scoring systems to predict patient outcomes.

Methods

Data from 68 SJS/TEN patients treated over a 17-year period at a specialized burn center were meticulously analyzed. Demographic, clinical, and laboratory information, alongside prognostic scores (SCORTEN, Re-SCORTEN, ABCD-10), and the newly devised Nuremberg Classification Tree for Stevens-Johnson Syndrome and Toxic Epidermal Necrolysis (NCT-SJS/TEN), underwent thorough evaluation regarding their ability to predict mortality.

Results

The study identified metamizole as the most frequently associated trigger for SJS/TEN. The overall mortality rate was 51%. Survivors exhibited significantly lower body surface area involvement, platelet counts, and serum blood urea nitrogen levels compared to non-survivors. Among the prognostic scoring systems, only Re-SCORTEN demonstrated significant differentiation between survivors and non-survivors. Notably, the newly developed NCT-SJS/TEN model exhibited a remarkable 89% accuracy in predicting mortality risk.

Conclusions

This study underscores the limitations of current prognostic scoring systems in effectively predicting mortality in SJS/TEN cases. The parameters identified of the NCT-SJS/TEN model may offer a potential avenue for enhanced risk stratification and clinical decision-making in managing these complex conditions. However, further validation through larger-scale studies is essential to enhance the reliability and generalizability of predictive models for SJS/TEN. Such advancements hold potential to significantly improve patient outcomes and optimize therapeutic strategies in the clinical management of SJS/TEN.

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Demographic and morphologic factors influencing Transcranial Doppler Sonography (TCD) performance.

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Objective

Transcranial Doppler sonography (TCD) is a cost-effective examination that can be performed bedside on the patient to assess the presence of different intracranial pathologies, from brain edema to subdural hemorrhage. TCD can also be used to visualize the middle cerebral artery (MCA) and its pathological changes due mainly to atherosclerosis or vasospasm, the latter being a frequent complication after subarachnoid hemorrhage. The aim of this study was to evaluate the performance of TCD in patients with acute neurological symptoms by testing its efficacy in assessing the MCA as well as three other structures, including the contralateral temporal bone, the mesencephalon, and the ipsilateral sphenoid bone.

Methods

Patients who referred to the emergency room of the Klinikum Nürnberg Süd (Nürnberg, Germany) after the onset of acute neurological symptoms between September and November 2021 were eligible for enrollment. Each patient received a computed tomography (CT) scan of the skull and brain to rule out acute intracranial pathologies such as stroke or bleeding. TCD was later performed with a linear array transducer by a trained neurologist as a follow-up examination and to rule out vasospasm. The ultrasound was performed on the temporal bone on both sides of the head. One score was used to evaluate the MCA (0= no visible, 1= poorly visible, 2= visible in its vast majority, and 3= completely visible). Another score, the Transcranial color-coded duplex sonography (Tccs) score was used to assess the visibility of the contralateral temporal bone, the mesencephalon, and the ipsilateral sphenoid bone (0= none of the above-mentioned structures is visible, 1= one structure is visible, 2= two structures are visible, 3= all three of the structures are visible). Furthermore, the area on the temporal bone where the transducer was placed during the TCD was divided into 9 portions and temporal bone thickness (TBT) was measured in millimeters (mm) in 9 different points per side using imaging data from the CT-scans. The two scores were then correlated to age, sex, side and skull thickness and the Pearson coefficient (r) was calculated. Linear regression was used to assess whether TBT significantly predicted the outcome of the MCA and Tccs scores and the R² coefficient was calculated.

Conclusions

This study shows that the visibility of the intracranial structures at TCD is correlated to age and sex, and particularly that poor diagnostic performance and lower MCA and Tccs scores can be more frequently associated with female sex and older age. Furthermore, a moderate negative correlation between skull thickness and MCA and Tccs scores was found, and regression analyses suggested that with increasing TBT the visibility of intracranial structures decreases substantially. These findings are in agreement with previous literature showing that TCD performance is influenced by sex and age, thus strongly corroborating these notions with data from a vast unselected cohort of patients. Adding to this, we also identified TBT as a further relevant parameter to determine the performance of TCD, suggesting that patient-specific characteristics also influence the visibility of intracranial structures by TCD. Whether this is due to bone thickness alone or even to the mineral density of the bone remains to be determined and has not been assessed during this study. Thus, further validation studies are needed to further define the field of application of TCD.

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Influence of Vitamin K2 on the Response of Chondrocytes from Diabetic and Non-diabetic Rats

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Objective

Osteoarthritis (OA) is a chronic inflammatory joint disease and often coexists with type 2 diabetes mellitus (T2DM)[1,2]. The chronic state of hyperglycemia and inflammation in the context of T2DM is believed to play a crucial role in the onset and progression of OA, yet the complex pathogenetic connections are not fully understood [3]. Due to its anti-inflammatory and antioxidative properties, Vitamin K2 (Vit.K2) appears to counteract chronic inflammatory diseases [4], but there is still limited research regarding OA. Therefore, this study aims to investigate the interplay between OA and T2DM, as well as the potentially protective influence of Vit.K2 on articular chondrocytes.

Methods

Chondrocytes were isolated from the knee joints of non-diabetic and diabetic rats (Zucker Diabetic Fatty Leptfa/Crl rats), some of which were supplemented with Vit.K2 (Menaquinone-7, 100 mg/kg per day, Kappa Bioscience AS), resulting in four experimental groups: control without (Ctrl w/o Vit.K2) or with Vit.K2 supplementation (Ctrl w/ Vit.K2), and diabetic without (T2DM w/o Vit.K2) or with Vit.K2 supplementation (T2DM w/ Vit.K2). After additional stimulation with tumor necrosis factor α (TNF α , 10 ng/ml) and anaphylatoxin C5a (25 ng/ml) to induce an inflammatory milieu, as well as culturing in normo- (NG, 1.0 g/l) or hyperglycemic (HG, 4.5 g/l) medium to mimic advanced T2DM conditions, chondrocytes were examined in various assays. In addition to assessing metabolic and proliferative activity, the directed migration/wound healing capacity, as well as undirected motility of chondrocytes, were determined. Furthermore, gene expression analyses were conducted for the cytokine feedback inhibitors 1 and 3 (Socs1 and Socs3) and the stress response gene Heme Oxygenase 1 (Hmox1) using Real-Time detection PCR.

Results

In the comparison between chondrocytes from non-diabetic and diabetic rats, no differences were observed in terms of metabolic activity, while higher DNA quantities were detected in chondrocytes from animals with T2DM in terms of cell proliferation. The supplementation of rats with Vit.K2 tended to increase metabolic activity and significantly enhance chondrocyte proliferation. T2DM tended to increase the undirected motility of chondrocytes but significantly decreased directed migration/wound healing capacity. Chondrocytes from rats supplemented with Vit.K2 showed a trend towards higher motility and migration. No differences were found in the gene expression of Socs1, Socs3, and Hmox1 between chondrocytes from non-diabetic and diabetic rats. Supplementation with Vit.K2 tended to decrease the gene expression of Socs1, Socs3, and Hmox1 in chondrocytes.

Conclusions

The increase in cell proliferation and undirected motility of chondrocytes induced by T2DM, coupled with a decrease in wound healing capacity, suggests a loss of cell quality that may potentially predispose to OA development. Elevated metabolic and proliferative activity, as well as increased motility and wound healing capacity, indicate a general anabolic effect of Vit.K2 on chondrocytes. The lower expression of Hmox1, Socs1, and Socs3 suggests the anti-inflammatory and antioxidative properties of the vitamin within the joint. The anabolic effects and protective properties support the potential preventive role of Vit.K2 in OA

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Development of a new protective solution for vein grafts in bypass surgery

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Objective

Bypass operations are often the only treatment option for atherosclerosis [1]. However, saphenous vein grafts (SVGs) frequently fail shortly after surgery. SVGs are stored in preservative solutions, which can lead to functional decline due to the type of preservation solution used [2, 3], surgical trauma, and other factors. Research has shown that saline, the most common solution, is inadequate for storing blood vessels, causing partial detachment of the endothelium [2]. This damage makes the graft more prone to platelet adhesion, macrophage infiltration, plaque development, and intimal hyperplasia, resulting in graft failure [5].

Methods

The aim is to develop a preservation solution that protects endothelial cells (ECs) from cellular stress during bypass grafting. In our previous study, we compared several commonly used solutions. Our goal is to further optimize these solutions to protect endothelial integrity better than standard solutions. Remnants of SVGs were used for (immuno-)histological staining to detect endothelial detachment or to isolate ECs for in vitro experiments (e.g., cell viability assays, metabolic activity measurements, migration capability tests, and activity assessments of endothelium-specific genes). Additionally, ex vivo experiments with the vein remnants are planned.

Results

Our findings indicate that full electrolyte solutions with an extracellular composition are more suitable for preserving SVGs compared to saline solution (that showed the overall lowest protection) or solutions with a low sodium content. Additionally, metabolizable buffer substances like lactate show potential in maintaining endothelial integrity by serving as an energy source and increasing migration capabilities.

Conclusions

The research aims to create a perfusion solution that meets the stringent requirements of cardiac and vascular surgery, improving long-term graft patency and patient outcomes. Such a solution could significantly reduce the failure rate of SVGs and enhance the success of bypass operations.

Acknowledgements

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Does vitamin K2 (MK7) influence cardiac fibrosis in diabetes mellitus type 2 (T2DM) associated cardiomyopathy progression - insights from a rat diabetes model

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Objective

Diabetic cardiomyopathy is a severe impairment in chronic diabetes mellitus type 2 (T2DM). Vitamin K2 (Vit.K2) is commonly known to provide vasculo-protective effects, but its impact on diabetic cardiomyopathy is unknown. The homozygous Zucker Diabetes Fatty (ZDF fa/fa) rats develop T2DM and cardiomyopathy under diabetogenic high protein diet (Purina 5008), whereas heterozygous rats (ZDF fa/+) can be used under similar conditions as non-diabetic controls. Cardiomyopathy is associated with cardiac fibrosis. Factors contributing to cardiac fibrosis are increased transforming growth factor (TGF)β1 expression, collagen deposition, elevated numbers of myofibroblasts, expressing smooth muscle actin (ACTA2) and upregulated inflammatory mediators (1). This project aims to get a deeper understanding of the pathogenesis of cardiac fibrosis in the T2DM ZDF rat model and to define the influence of Vit.K2 on the heart.

Methods

Following sacrifice, rat hearts were explanted and a part of the left ventricle was shock frozen to be used for RNA isolation and Real time PCR analysis. The mid third of the remaining heart was fixed and transverse sections were prepared for histopathological analyses (hematoxylin Eosin, HE stain) or immunostained for collagen type 1 and alpha smooth muscle actin. Morphometric analysis was done using Precipoint software. Picrosirius red stain (SR) combined with imageJ based analyses reflected the total collagen content.

Results

T2DM manifestation was proven by significantly elevated blood glucose levels. Vit.K2 supplemented rats showed a trend of higher body weights and left ventricle wall thicknesses. Histopathological features of cardiomyopathy could be demonstrated in T2DM rats. The total collagen deposition was in mean higher in diabetic rats and lower in those with Vit.K2 supplementation. Fibronectin gene expression was significantly increased in the left ventricles of T2DM rats with no influence of Vit.K2 supplementation. In addition, a trend of more total collagen in hearts of T2DM rats compared to those of healthy controls became evident. This collagen deposition was lesser, if the rats were fed with Vit.K2 in both, T2DM and non T2DM rats. The collagen type 3 gene expression followed this trend of being higher in T2DM hearts but not the collagen type 1 immunoreactivity. The cytokine regulator gene suppressor of cytokine signaling (Socs) showed also elevated activity in left ventricles of T2DM compared to those of non T2DM rats.

Conclusions

The results suggest degenerative and early fibrotic changes in T2DM hearts but Vit.K2 supplementation did not significantly regulate the investigated molecular markers.

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Laboratory and Anamnestic Risk Indicator for Necrotizing Fasciitis

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Objective

Necrotizing fasciitis is a life-threatening soft tissue infection where the timing of surgical intervention significantly impacts clinical outcomes. The Laboratory Risk Indicator for Necrotizing Fasciitis (LRINEC) score, the Site other than the lower limb, Immunosuppression, Age <60 years, Renal impairment (creatinine >141), and Inflammatory markers (CRP ≥150, WCC >25) (SIARI) score, and procalcitonin levels are intended to assist in differentiating between necrotizing fasciitis and soft tissue infections.

Methods

A retrospective analysis of cases treated at Klinikum Nürnberg was conducted to evaluate necrotizing fasciitis and soft tissue infections. The diagnostic value of the two scores and procalcitonin levels was assessed, leading to the creation of a new score, the Laboratory and Anamnestic Risk Indicator for Necrotizing Fasciitis (LARINF), based on the findings.

Results

Procalcitonin, LRINEC score, and SIARI score exhibited inadequate discriminatory ability in our study. The newly devised LARINF score integrated laboratory parameters of the LRINEC score (hemoglobin and C-reactive protein) with procalcitonin and three comorbidities, resulting in a sensitivity of 84% and a specificity of 75%, with the highest area under the receiver operating characteristic (ROC) curve of 0.83.

Conclusions

The LARINF score presents a novel decision-supporting tool. The determination of when to initiate surgical exploration remains a clinical one. However, the score appears to offer an improved foundation for identifying this rare clinical condition.

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COST-EFFECTIVENESS OF ARTHROSCOPIC KNEE SURGERY IN DEGENERATIVE MENISCAL TEARS

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Objective

Osteoarthritis [OA] of the knee is one of the most common orthopedic diagnoses in patients over the age of 40 years and represents a substantial burden of disease with clinical implications and accumulation of costs in the health care sector. Degenerative tears of the meniscus of the knee in these patients is a very common occurrence and should be treated conservatively or if this treatment plan fails with full or partial arthroplasty of the knee. Recent opposing studies show that knee arthroscopy can ease the pain for patients that fail to improve after conservative treatment and find relief when undergoing surgery (1). Therefore, knee arthroscopy might be more cost-efficient than conservative therapy in working adults with degenerative meniscus lesions.

Methods

A cohort of patients over the age of 40 years, who presented to the orthopedic clinic in Salzburg from 2010 to 2022 with degenerative meniscal tear undergoing either conservative or surgical treatment was modeled from clinical records. According administrative databases allowed the calculation of costs with exhaustive time-driven activity-based costing and a decision-analytic Markov disease progression model was constructed, using strategy-specific failure rates and treatment-specific probabilities for subsequent partial or total knee replacement to run a validated Monte Carlo simulation with a 5-year time horizon with a common endpoint of total or partial knee replacement surgery.

Results

Relative to conservative therapy, arthroscopic surgery is expected to show cost-effectiveness in more than 65% of simulations at willingness-to-pay thresholds of both € 50,000 per QALY and € 100,000 per QALY in sensitivity analysis. Arthroscopic surgery could be associated with an increased failure rate, but meaningful reductions in total or partial knee replacement therapy in the model-based analysis. Over a 10- year horizon, arthroscopic surgery is expected to show savings of up to € 3000 per patient, making it the dominant index procedure strategy.

Conclusions

Both interventions are associated with a clinically meaningful improvement regarding patients' most important functional limitations. Although arthroscopic surgery is associated with a statistically larger improvement, the difference compared with conservative therapy is small and clinically not meaningful in other clinical trials and studies. Other cost-effectiveness analysis suggest that arthroscopic surgery, despite substantially higher failure rates, is associated with improved long-term outcomes and cost savings relative to conservative treatment in the majority of patients, making it the dominant treatment strategy.

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HOW DO PARKINSON'S PATIENTS FROM SOUTH TYROL SLEEP?

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Objective

Sleep disturbances (SDs) are among the most common non-motor symptoms in patients with Parkinson's disease (PD).¹ The aim of the present study was to describe daytime sleepiness and sleep quality in a small cohort of South Tyrolean Parkinson's patients. This investigation is part of a large descriptive study aimed at characterizing parkinsonian patients living in South Tyrol.

Methods

So far, a total of 22 Parkinson's patients (10 females and 12 males; Hoehn&Yahr (H&Y) stages 1-4; age 52-83 years) of the approximately 400 planned participants (recruitment until summer 2025) have completed the Epworth Sleepiness Scale (ESS) questionnaire, which assesses daytime sleepiness, and the Parkinson's Disease Sleep Scale (PDSS-2), which measures specific parkinsonian sleep problems.^{2,3}

Results

The mean ESS score was 8.14 (range 3-14), indicating a "higher normal daytime sleepiness"; there was no statistically significant difference between women and men ($p=0.067$). The highest probability of falling asleep was in the afternoon when patients lay down to rest. The mean PDSS-2 score was 16.18 (range 0-44), indicating a fairly good sleep quality, again with no significant difference between male and female patients ($p=0.378$). The most common nocturnal problems were sleeping through the night and getting up to urinate. Only seven patients (4 women with a mean age of 70.5 years and a mean H&Y stage of 2.37 and 3 men with a mean age of 74 years and a mean H&Y stage of 2.16) had a PDSS-2 score ≥ 18 , indicating poor sleep quality; only two of them (one man and one woman) were taking melatonin. Only one other patient (a 74-year-old man with a H&Y stage of 3) was on specific sleep medication, namely with triazolam, which had resulted in an ESS score of 4 and a PDSS-2 score of 10.

Conclusions

Preliminary findings indicate that no severe SDs were detected in the enrolled PD patients, regardless of gender. Overall, there was no evidence of excessive daytime sleepiness and only a few patients suffered from poor sleep quality, which did not clearly correlate with the PD's stage. Only three patients in total (13.64%) were taking sleeping pills, two of them with a PDSS-2 score above 18; both were taking melatonin. A comprehensive understanding, and a more robust picture of daytime sleepiness, sleep quality and therapy behaviour of the parkinsonian patients living in South Tyrol will only emerge once all 400 planned participants have been surveyed. In a second step, the final results will be compared with data from similar studies of other PD populations to assess the influence of geographical and cultural factors on sleep.

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Generation of a Tendon-specific Knock-Out Mouse Model to Deeply Probe the Role of SPARC in Tendon Health and Disease

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Objective

Injured tendons mostly heal inadequately, leading to the formation of a stiff scar tissue with an altered extracellular matrix (ECM). These changes trigger degenerative cellular responses, ultimately driving tendon disease. Recently, the critical role of the ECM protein Sparc (Secreted protein acidic and rich in cysteine; BM-40 or osteonectin) in tendons has been described by our group (1,2). Sparc-null mice exhibit severely hypotrophic tendons, resulting in significantly reduced biomechanical strength and a higher incidence of spontaneous Achilles tendon rupture. Overall, our studies demonstrate that loss of Sparc results in a deteriorated, catabolic tendon phenotype, with altered sensitivity to mechanical stress and an impaired ECM. However, as these studies were conducted using a global Sparc KO model we cannot fully exclude, that the functional impairment is in part caused by loss of Sparc in e.g. bone or muscle in the tendon unit. Further, we are currently deciphering the potential role of Sparc during metabolic re-wiring in tendon degeneration. Therefore, we generated tendon-specific Sparc-null mice using the constitutive Scleraxis-Cre mouse line (Sparcfl/fl:Scx-Cre+).

Methods

The successful loss of Sparc in tendons was examined by genotyping, gene expression analysis and Western blotting. Tendon phenotype was examined by gross morphology (e.g. Achilles length and width, tail tendon diameter), descriptive histology (e.g. Herovici's and Alcian blue staining), immunohistological stainings (e.g. Sparc, collagens) and biomechanical testing (e.g. tendon stiffness, maximal load).

Results

We could confirm a significant reduction of Sparc in tendon tissues, both on the transcriptional and protein level. Additionally, Achilles tendon width is significantly smaller in Sparcfl/fl:Scx-Cre+ animals when compared to age-matched controls, whereas the tendon length remains unchanged. In addition, Sparcfl/fl:Scx-Cre+ load-bearing tendons display a severe hypoblastic phenotype, similar to Sparc^{-/-} mice (1,2).

Conclusions

In conclusion, Sparcfl/fl:Scx-Cre+mice are a valuable novel tendinopathy mouse model, avoiding the need for inducing tendon degeneration through ECM-degrading enzymes or subjecting mice to sustained mechanical overload. Therefore, this mouse model is an essential tool for investigating the cellular, molecular, and metabolic changes underlying degenerative tendon diseases and to further investigate the central role of Sparc in tendon biology.

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Structural diversity and biophysical properties of voltage-gated proton channels (Hv)

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Objective

The main objective of this study was to investigate the structural diversity and functional properties of voltage-gated proton channels (Hv) within a single species, challenging the conventional dogma of a single Hv channel gene per species.

Methods

GenBank (nr), transcriptional survey sequences (TSA), and expressed sequence tags (EST) databases were screened with the TBLASTN algorithm for mollusc sequences with significant homology to known Hv1 sequences. Homology models for each paralog were constructed by homology modelling of the transmembrane domain of Ciona VSP. Molecular dynamics simulations for AcHv3 paralog were done. Hv gene paralogs were synthesized, cloned and heterologously expressed in tsA201 cells to further electrophysiological characterization.

Results

Our study revealed the presence of novel paralogs of the typical Hv1 channel within a single species, indicating previously unrecognized diversity of a Hv family. These newly discovered Hv channels exhibit typical biophysical characteristics but also display subtle differences in functioning, potentially attributed to small but significant structural components. Structural analysis highlighted notable examples such as Hv2, which activates negatively to the Nernst potential for protons, enabling proton influx into the cell and membrane depolarization. Additionally, Hv3 and Hv4 paralogs exhibited distinct structural features compared to Hv1 or Hv2, such as variations in the voltage-sensing motif and disrupted channel behavior.

Conclusions

1. The discovery of novel paralogs within the Hv channels challenges the traditional view of a unique Hv-channel gene per species, highlighting for the first time the existence of a voltage-gated proton channels family.
2. Structural analysis of these newly discovered paralogs, such as Hv2, Hv3, and Hv4, revealed distinct features and functional properties, including variations in gating charge carriers and altered voltage dependence, expanding our understanding of Hv channel diversity and function.
3. The findings provide valuable insights into the structural determinants underlying the functional diversity of Hv molecules, shedding light on their roles in various physiological processes and potentially informing future research and therapeutic strategies targeting Hv channels.

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Sodium Valproate Modulates Cortical Morphology in Juvenile Myoclonic Epilepsy

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Objective

Juvenile myoclonic epilepsy (JME) is associated with cortical thinning of the motor areas (1). The relative contribution of anti-seizure medication to cortical thickness is unknown. We aimed to investigate how valproate influences cortical morphology of JME.

Methods

In this cross-sectional study, individuals with JME with and without valproate, temporal lobe epilepsy (TLE) with valproate and controls were selected through propensity score matching. Participants underwent T1-weighted brain imaging and vertex-wise calculation of cortical thickness.

Conclusions

Valproate was associated with JME-specific and dose-dependent thinning of the motor regions. This suggests that valproate may be a key modulator of cortical morphology in JME, on the mechanisms behind valproate's high efficacy in this syndrome.

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Small-Molecule Library Screen Identifies Tanespimycin as a YAP-modulator in SH-SY5Y Cells

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Objective

Neuroblastoma (NB), the most common extra-cranial solid tumor in children, displays a heterogeneous clinical spectrum due to its diverse cellular composition. Because of the phenotypic variability presented by this disease, timely diagnosis, accurate prognosis and choice of treatment remain challenging. Despite recent advances in treatment approaches, current therapies often fall short of achieving complete tumor eradication, highlighting the urgent need for novel therapeutic approaches that target high-risk therapy-resistant NB, and selectively modulate tumor behavior. A preliminary study conducted by Ferlemann et al. provided the first comprehensive flow cytometric characterization of surface molecule expression in NB cell lines, and employed an unbiased clustering algorithm (SPADE) to resolve cellular heterogeneity and identify distinct neuroblastoma subsets based on combinatorial expression of CD15, CD24, CD44, CD57, CD184, and TrkA [1]. Building on that study, we screened a small-molecule library consisting of protein-protein interaction inhibitors, using the same methodology as the preliminary investigation. The goal of the screen was to identify drug candidates capable of modulating NB surface marker expression profiles.

Methods

SH-SY5Y NB cells were pre-cultured in DMEM/F12 supplemented with 10% FBS and 1% Pen/Strep until reaching 85% confluence. Cells were harvested with TrypLE and used to seed 6-well plates. After 24 hours, medium was exchanged for DMEM/F12 supplemented with 10% KnockOut Serum Replacement. Tanespimycin was added to a 1µM final concentration. DMSO served as the vehicle control, at a final concentration of 0.01%. Medium was changed after 24 hours and fresh treatment compounds were added. After 48 hours of treatment, cells were harvested, labeled with fluorescent antibodies and analyzed by flow cytometry.

Results

Among the potential therapeutic candidates, we identified tanespimycin (17-AAG), as a modulator of the YAP-positive phenotype in SH-SY5Y cells. Tanespimycin significantly altered the composition of specific NB subpopulations in-vitro, as evidenced by downregulation of CD44 and CD49d (markers associated with a YAP-positive phenotype [2]). Upregulation of CD184 and CD24 was also observed. The selective regulation of YAP-positive subpopulations by tanespimycin expands our understanding of this drug's mechanism of action in NB cells.

Conclusions

This study builds upon the groundwork laid by the preliminary investigation [1], advances our insights into NB cellular heterogeneity, and corroborates the potential of tanespimycin as a selective modulator of surface marker expression and the YAP pathway. These findings highlight the significance of tanespimycin as a promising addition to our therapeutic arsenal for combating this challenging pediatric malignancy.

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Effect of Probiotic Supplementation on the Intestinal Microbiome of Preterm Infants

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Objective

In the current study, 30 preterm infants (mean gestational age 205 d) received the probiotic ProPrems (1) containing *Bifidobacterium longum* subsp. *infantis*, *Streptococcus thermophilus* and *Bifidobacterium animalis* subsp. *lactis*. 14 Patients without supplementation (mean gest. age 237 d) served as control.

Methods

Longitudinal stool samples were collected: 28 samples before, 118 during and 69 after supplementation and 44 of the control group. Bacteria were identified by Nanopore sequencing of the complete 16S gene. Sequence analysis was performed by a workflow based on QIIME 2.

Results

PCoA based on Bray-Curtis distances, PERMANOVA and ANCOM analysis show significantly higher abundances of the ProPrems species "During" supplementation compared to "Before". Unexpectedly, both *S. thermophilus* and *B. animalis* are strongly reduced in "After" samples compared to "During".

Conclusions

All three probiotic strains are found during supplementation, but apparently only *B. longum* subsp. *infantis* successfully colonizes the preterm gut.

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Sunflower Syndrome – Creating Awareness & International Medication Survey

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Objective

Sunflower syndrome (SFS) is a rare epileptic disorder characterized by pronounced stereotyped seizures. People with SFS look at a light source, usually the sun, and wave a hand in front of their eyes. In connection with these hand-waving episodes (HWE) eyelid myoclonus can occur. In addition to HWE, other forms of seizures such as forms such as absences and generalized tonic-clonic seizures. A genetic cause is suspected, but has not yet been clarified. Objectives of our study: 1. Awareness SFS is insufficiently recognized and is not described in detail in the literature. HWE is often incorrectly classified as a tic disorder or obsessive-compulsive disorder. This lack of awareness and understanding, both among healthcare professionals and the general public, has led to many patients developing a false self-perception and therefore poor self-esteem. With our survey, we would like to raise awareness of the condition among both the treating physicians and the patients' social environment. 2. Effectiveness of medication Unfortunately, SFS often proves to be resistant to treatment to the currently available anticonvulsant treatments. Non-pharmacological stimulus avoidance measures such as wearing hats and sunglasses can be beneficial, but these strategies alone do not lead to seizure freedom. Our platform PATRE (PATient based phenotyping and evaluation of therapy in Rare Epilepsies; www.patre.info) provides a standardized procedure for researching therapies for rare epilepsies based on information provided by patients and their parents.

Methods

The PATRE project for the SFS is a cooperation between the University of Leuven, the University of Genoa, Harvard University and the PMU Salzburg. For our electronic questionnaires, we use our PATRE server with REDCap for secure data collection. In an initial survey, we asked patients and their parents about their subjective assessment of the effect of medication on SFS. The effect on seizures and behavior was measured on a scale of -50 to +50.

Results

So far, 14 patients have taken part in the study. Medications for which at least two patients had provided information were evaluated. Treatment effects on seizures with valproic acid and levetiracetam have been described in the literature. For this reason, the poor performance of levetiracetam in our group is particularly surprising. According to our survey, ethosuximide and lamotrigine appear to achieve good anticonvulsant results. The positive anticonvulsant effect of valproic acid was confirmed. Lamotrigine and valproic acid also had a good effect on behavior, as did clobazam.

Conclusions

These results are only based on data from a small number of patients and are therefore only of limited value. We are continuing the survey and would be very pleased if you would contact us at sunflower@patre.info if you care for patients with Sunflower syndrome.

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Prenatal Psychosocial Risk: Association with Stress, Social Support and Resilience

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Objective

Psychosocial stress in parents is an important risk factor for child development. Already prenatal maternal stress can affect fetal brain development (1). In addition, postpartum psychosocial stress can negatively affect caregiving behavior toward the infant, which can, in turn, lead to impairments in child development. Despite these serious and long-term effects, the risk factor of psychosocial stress in parents remains widely neglected in primary care and no screening instruments are available that could assess psychosocial stress quickly and resource-effectively. The aim of the study is to validate a short screening, consisting of seven evidence-based questions, can accurately assess psychosocial stress among expectant mothers.

Methods

The study sample is part of a research project "Validierung von Screening-Fragen zur Erfassung von Psychosozialen Risikofaktoren" at the Early Life Care Institute, PMU. We recruited 80 pregnant women in the 37th-39th week of pregnancy during birth registration at the University Hospital Salzburg. Participating women were on average 33.4 (SD = 1.59) years old and in the 38th (SD = 4.22) gestation week. At time of recruitment, participants filled out online questionnaires to assess their psychosocial risks, perceived stress, social support and resilience.

Results

Correlation analysis showed that higher psychosocial risk was associated with higher perceived stress ($\beta=.673$; $t=7.117$; $p<.001$), lowered perceived social support ($\beta=-.247$; $t=-2.915$, $p=.005$) and higher resilience ($\beta=.223$; $t=2.578$, $p=.012$). Perceived stress, social support and resilience together explained 54.6% of the variance in psychosocial risk ($R^2 = .546$; $F=31.253$; $p<.001$).

Conclusions

Our findings indicate that a very short screening instrument may be suitable to assess psychosocial risk in expectant mothers. The use of universal screening in primary care practice can remove the stigma of screening selected families and reduce the likelihood of overlooking at-risk families.

Acknowledgements

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FROM LAPTOP TO TOP-LAB: A COMBINED IN SILICO IN VITRO APPROACH TO IDENTIFY NOVEL MICROTUBULE STABILIZERS AS POTENTIAL DRUG CANDIDATES

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Objective

Microtubules are integral components of eukaryotic cell structures, providing essential support and facilitating various cellular processes. Composed of α - and β -tubulin subunits, they form dynamic filaments crucial for structural integrity, intracellular transport, and cell division. Through dynamic polymerization and depolymerisation of these tube-like aggregates, these proteins represent an important element in the life cycle of eukaryotic cells. Disruption of microtubule dynamics can induce cell death, particularly in rapidly dividing cells like cancer or immune cells, by promoting apoptosis. One strategy involves inhibiting continuous depolymerization using microtubule stabilizers from the taxane family, such as paclitaxel and docetaxel. However, resistance to these potent chemotherapeutics can develop in cancer cells. Consequently, there is considerable scientific interest in identifying new compound classes and scaffolds with potential antitumor activity through microtubule stabilization, offering promising avenues for cancer therapeutics.[1, 2]

Methods

Our approach combines innovative in silico techniques such as pharmacophore modeling with in vitro studies to discover new enhancers for the β -tubulin subunit. High-quality pharmacophore models were generated using LigandScout version 4.4.5 [3]. Pharmacophore modeling identifies key physicochemical features of protein-ligand interactions, facilitating the screening of molecules with similar interaction patterns. In this study, a combination of structure- and ligand-based modeling was employed. Structure-based models utilized 3D crystal structures, while ligand-based pharmacophore models were developed by aligning active molecules from the literature. The optimized and theoretically validated pharmacophore models were used to screen the SPECS database, which contains > 200,000 commercially available compounds (april2023). Selected Hits identified by our models were further investigated in vitro using a fluorescence-based tubulin polymerization assay kit (Cytoskeleton, BK011P).

Results

A comprehensive literature search was conducted to compile microtubule stabilizers targeting the taxane binding site of the beta-tubulin subunit, resulting in a curated set of 56 active compounds. Additionally, a decoy set of 1907 compounds was generated for comparison. Using LigandScout 4.4.5, databases were converted into multi-conformational screening datasets, facilitating the training of pharmacophore models. A dataset consisting of 56 biologically tested microtubule stabilizers (MSTs) and 1907 decoy compounds was transformed into a 3D dataset. One structure-based (SB) and three ligand-based (LB) pharmacophore models were utilized to identify active substances from the SPECS database. Among 3616 candidates, 22 were screened in vitro at a concentration of 30 μ M, with 8 exhibiting significantly higher polymerization rates compared to the blank. This integrated in silico and in vitro approach led to the discovery of novel microtubule stabilizers, which will undergo further investigation using cancer cell models

Conclusions

Our highly optimized structure-based and ligand-based pharmacophore models have the capability to predict substances that also exhibit the desired activity in an in vitro assay with a success rate of 36%. To demonstrate the potency of the top-ranked biologically tested compounds, further concentration-dependent screenings are now required.

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Safe Forests: The psychological wellbeing of harvester and forwarder drivers – a cross-sectional study

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Objective

The use of fully mechanized wood harvesting systems allows forwarder and harvester machines to operate in steep terrain, thereby reducing harvesting costs and rising work safety for the operators. But working in such challenging conditions poses hazards and stressors for the drivers, such as high levels of mental stress and strain. We focused on the subjective wellbeing, stress, and strain the drivers are facing during their work and compared them to the average population. Aiming to provide a better understanding of their psychological wellbeing and providing better work-time-organisation.

Methods

Online-Questionnaire: SF-12 [1] to measure physical and mental health, RESTQ-work 27 [2] to record recovery and strain at work, OrgFit [3] for risk assessment of mental stress and work-related strain, and environmental factors, such as steepness of the terrain. Setting: recruitment by calling companies, link on webpage. Participants: mainly male healthy forestry workers in Austria, using a) harvester and b) forwarder machines with an age between 18-55 years. Analyses: parametric (unpaired t-test ($\alpha = 0.05$, 95% CI)) and non-parametric (Spearman correlation) tests.

Results

Population: 42 forestry workers (one women) with an average age of 32.2 years (SD 9.26), 88.62 kg (SD 16.44), and 27.11 BMI (SD 4.28) participated. Comparison to norm samples: participants ($M = 53.94$; $SD = 3.39$) reported a significantly higher ($t(2845) = 3.39$; $df = 2845$; $p < 0.001$; $d = 0.69$) physical health (SF-12) compared to the norm sample ($M = 49.03$; $SD = 9.35$), comprising of a representative German general population ($n = 2524$). According to Cohen (1992), this is a medium to high difference. Other factors: Environmental factors have no effect on the driver's wellbeing. The higher the assessed difficulty of the last operation, the steeper the terrain ($r = 0.6757$; $p < 0.001$) (Fig. 1). And the better their social and organisational climate (OrgFit), the higher their recovery from stress and strain (RESTQ-work 27) ($r = 0.6484$, $p < 0.001$) (Fig. 2). According to Cohen (1992), both are strong correlations.

Conclusions

being or working in nature benefits human health: shown by higher subjective physical health and recovery from stress. Social interactions of importance for psychological wellbeing: most participants work in small, family-like companies; they showed better social and organisational climate, which was also associated with higher recovery. Further analysis with higher number of participants is of need.

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A comparative study of three different bioactive glass scaffolds tailored for cartilage tissue engineering

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Objective

The hyaline cartilage has a reduced regenerative capacity. In order to prevent the progression of osteoarthritis, cartilage defects should be treated. Cartilage tissue engineering using bioactive glass (BG) is a promising approach. Until now, conventional BG (45S5, 60S5, BG1393) has been used for bone regeneration due to the formation of hydroxyapatite. The aim of this in vitro study is to compare two BGs with a novel ionic composition, specifically developed for cartilage tissue with the conventional BG1393.

Methods

The novel BG CAR12N (1) variants were activated by leaching with HCl. The highly porous and 100% bioglass scaffolds (CAR12N, CAR12 + Ca²⁺/Mg²⁺, BG1393) with the same topology) were seeded with either primary porcine articular chondrocytes (pACs) or human mesenchymal stem cells (hMSCs) and cultured dynamically for 21 days. Subsequently, the sulfated glycosaminoglycan (sGAG) content per cell was determined quantitatively, the vitality assay was performed qualitatively and quantitatively, and scanning electron micrographs (SEM) were taken. Cartilage-specific protein expressions (collagen type II, proteoglycans, SOX9 and collagen type I) were visualized by immunocytochemistry.

Results

Macro- and microscopic images showed that the leaching did not lead to any structural changes in the scaffold and that the porosity was above 75%. During leaching, the pH value changed in both HCl and water. The viability assay showed that both pACs and hMSCs can survive on all three scaffold variants. The sGAG expression of pACs increased in trend on all glass variants. After 21 days, expression is highest on the BG1393 scaffolds colonized with pACs. A significant increase was shown in the BG1393 glass at this time. The sGAG expression of the hMSCs is significantly reduced compared to the pACs. The SEM showed deep insights into the cell-material interaction as well as the surface morphology of the scaffolds. The expression of collagen type II, cartilage-specific proteoglycans and the transcription factor SOX9 was detected in pACs and hMSCs colonized CAR12N scaffolds.

Conclusions

Highly porous bioactive glass scaffolds with a comparable morphology could be produced and cultured with mesenchymal cells for several weeks. Although the BG1393 scaffolds showed the densest cell growth, it was shown that the expression of cartilage markers and therefore the onset of successful chondrogenese, was highest on pACs CAR12N scaffolds but was also seen in hMSCs. This is currently being confirmed by gene expression analysis.

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Chondrogenesis of hMSCs in 3D printed bioglass/hydrogel scaffolds for cartilage regeneration

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Objective

The self-healing capacity of cartilage tissue is low after injury. For this reason, there is still an urgent need to develop a new, cost-effective, implantable and chondroinductive matrix with mesenchymal stem cells (hMSCs) that induces cartilage formation. In contrast to conventional bioglasses, which are designed for bone regeneration our glass (CAR12N) (1) has a faster degradation rate and no hydroxyapatite deposition. This basic research project focuses on cartilage formation (chondrogenesis) in 3D printed bioglass/hydrogel scaffolds for the precise and personalized regeneration of cartilage defects.

Methods

The grid-like scaffolds (7 x 7 x 1.5 mm), consisting of a hydrogel (1.3% alginate with methyl cellulose without/with CAR12N glass spheres (25-40 µm)) and hMSCs, are produced using a "layer-to-layer" process with the 3D printer and have a porosity of 70%. After scaffold printing, they are cross-linked and then cultivated statically in different culture media. In order to determine the influence of the ions on the MSCs, the scaffolds are cultured either: in isolation medium, in chondrogenic differentiation medium. After long-term cultivation of up to 21 days, extensive analyses (morphological examinations, vitality assay, metabolic activity assay, DNA and sulfated glycosaminoglycan (sGAG) content, chondrogenic matrix components at protein and gene level) were carried out in order to be able to adequately assess the progress of chondrogenesis.

Results

Extensive morphological studies have shown that the hMSC-colonized scaffolds remain dimensionally stable even after 21 days in the different media. In general, significantly more hMSCs survived over time in the isolation medium than in the chondrogenic differentiation medium. The bioactive glass spheres influence cell viability. However, the glass spheres do apparently influence proliferation and sGAG synthesis as these were always higher in the presence of the spheres compared to the control groups. Increased relative gene expression of cartilage-specific matrix components, such as aggrecan and collagen type II, was detected in hydrogel scaffolds cultured in chondrogenic differentiation medium compared to the isolation medium.

Conclusions

A printed 3D hydrogel model made of bioink alginate/methylcellulose was established for the investigation of MSC chondrogenesis. The functionalization with bioactive glass spheres enhances the effect on vitality, proliferation and sGAG synthesis of primary hMSCs. In the future, the quantity ratio and the printing pressure parameters are to be coordinated even more precisely in order to achieve faster chondrogenic differentiation.

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Hiatal hernia after transthoracic esophagectomy for cancer: the key role of omentectomy

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Objective

Hiatal Hernia after esophagectomy for cancer represents a potentially life-threatening long-term complication of which pathogenesis is unclear. However, it is well-known that its incidence is higher after minimally-invasive procedures. Aim of this single-center controlled cohort-study was to compare the incidence of hiatal hernia after open vs minimally-invasive esophagectomy (MIE), and to identify specific risk factors associated with its occurrence. Furthermore, the objective was to validate our hypothesis that the remaining omentum after MIE has a key role in the development of a post-esophagectomy hiatal hernia.

Methods

Our prospectively maintained database was retrospectively queried for patients who underwent transthoracic esophagectomy (Ivor Lewis or McKeown) for cancer over a 15 years period. Groups were defined according to the procedure (open = omentectomy vs. minimally-invasive = non-omentectomy). Minimally-invasive procedures were performed both laparoscopic and robotically- assisted. In case of a conversion to laparotomy the patient was included in the open group. The 2 groups were compared according to demographics, operative, histologic and postoperative parameters. Risk factors for hiatal hernia after esophagectomy were analyzed.

Results

A total of 897 patients were included. A hiatal hernia was registered in 1/490 (0.2%) in the open and in 21/407 (5.16%) of the minimally-invasive treated patients [Odds ratio = 26.6 (95% CI: 3.56-198.7), $p = 0.0001$]. Otherwise, significant differences (two-tailed $p < 0.05$) between the two groups were noted only in 8 out of further 31 investigated variables, as a parameter of homogeneity between the groups. Within the minimally-invasive group, patients with ASA Score of 2 and 3 had significantly lower risk to develop a hiatal hernia when compared to ASA 1 subjects (Odds ratio 0.18, 95% CI 0.06 – 0.55, $p = 0.002$ and 0.11, 95% CI 0.03 – 0.39, $p = 0.0007$ respectively). No further risk factors were identified. All patients underwent an omentectomy in the open, and none in the minimally-invasive group.

Conclusions

In our cohort, hiatal hernia was significantly lower in patients who underwent open esophagectomy compared to MIE. Omentectomy might play a key role in the prevention of post-esophagectomy hiatal hernia and should thus be considered also during minimally-invasive procedures. However, further multicentric and randomized studies are needed.

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IMPACT OF ANASTOMOTIC LEAK VS PNEUMONIA ON FAILURE TO RESCUE AFTER TRANSTHORACIC ESOPHAGECTOMY FOR CANCER

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Objectives

Data about failure-to-rescue (FTR) after oesophagectomy for cancer and its association with patient and procedure-related risk factors are sparse. Aim of this study was to analyze such aspects, particularly focusing on the impact of pneumonia and anastomotic leak on FTR.

Methods

Patients who underwent an Ivor Lewis oesophagectomy for cancer between 2008 and 2022 in two tertiary European centers were prospectively identified. Patients were classified and compared according to the type of operation (open, hybrid-laparoscopic, hybrid-robotic, minimally-invasive or robotic minimally-invasive). FTR was defined as in-hospital death following a major complication. Risk factors for FTR were identified with a univariable model. Mortality after pneumonia and anastomotic leak were calculated and compared across the groups.

Results

Sevenhundred-and-eight patients were included. There were 355 (50.1%) open, 204 (28.8%) hybrid-laparoscopic, 121 (17.1%) hybrid-robotic, 15 (2.1%) standard minimally-invasive and 11 (1.6%) robotic minimally-invasive procedures. Overall morbidity was 60%, and failure-to-rescue rate 4.5%. Anastomotic leak, pneumonia, postoperative bleeding, sepsis, pulmonary embolism, arrhythmia and need for blood transfusion were the risk factors significantly associated with in-hospital mortality ($p < 0.05$). There was no particular type of operation significantly associated with mortality ($p = 0.42$). Pneumonia and leak associated FTR rates did not significantly differ among the groups ($p = 0.99$).

Conclusions

Anastomotic leak and pneumonia are equally dangerous complications after oesophagectomy for cancer. Hybrid or minimally-invasive methods do not seem to negatively affect the FTR rates. However, implementation of minimally-invasive oesophagectomy should be considered carefully and only in high-volume centers, whereas efforts should be made to improve both tailored-approach and postoperative care.

Mixed Methods Evaluation of Early Home-Based Interventions for Children at Risk

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Objective

In early childhood, the brain is especially malleable, making early experiences crucial for later development (1). For example, the lack of appropriate treatment for visual disorders in a very limited time period in infancy can affect the entire life course, compromising the development of the visual system as well as motor, cognitive and emotional development (2), highlighting the need for early intervention. Several organizations in Vienna, funded by the Vienna Social Fund, provide early childhood interventions for children with a variety of disabilities or developmental risks and their families. These home-based interventions, delivered by trained facilitators, include not only targeted exercises with the children, but also support and guidance for parents in dealing with their child's impairment. The facilitators assist parents in handling bureaucratic barriers and societal reactions to the impairment, which parents of disabled children have identified as major obstacles (3). The aim of this study is to assess the impact of these interventions on the family system and its sustainability as well as to determine the extent to which the families' needs are met.

Methods

To review theoretical assumptions and clarify the research questions, we are currently conducting a qualitative pre-study. This explorative study includes expert interviews with early intervention facilitators as well as a focus group with eight parents of children receiving the intervention. Based on the results, we design a quantitative longitudinal study and a qualitative case study to be conducted from 2024 to 2029. The quantitative study employs a panel design, with each family being assessed three times: at the start of the intervention (T1), at the end of the intervention (T2), and one year later (T3). At each time point, the parents evaluate their parenting sense of competence, their quality of life, the child's abilities and participation, and the family's network with other supporting institutions. In addition, we will survey the parents' expectations at T1, the fulfillment of expectations and effectiveness of the intervention at T2, and long-term effects at T3. The qualitative case study will compare five cases to reconstruct the course of family histories and individual family support. We estimate 200 families to participate in the evaluation each year between 2024 and 2028.

Results

We anticipate the family system to undergo sustainable improvements including enhanced quality of life and sense of competence among parents, as well as increased levels of participation among children.

Conclusions

With regard to other studies indicating the positive impact of early childhood interventions (4), this study aims to ascertain the value and sustainability of these interventions from the parents' perspective and to contribute to optimizing care for children at risk in Austria.

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First insights into SESAM: „SonoElastography: Sarcopenia Associated Muscle Change“

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Objective

Sarcopenia poses a growing global health concern and is associated with an increase in negative health outcomes. Shear wave elastography (SWE) and B-mode ultrasound are two promising techniques for detection of muscle mass loss.

Methods

This diagnostic cross-sectional study with two control groups has 66 mobile participants assigned equally into three groups: sarcopenic older adults (65+), non-sarcopenic older adults (65+) and younger adults (≤ 30). The rectus femoris (RF) muscle of the dominant limb is examined using standardized protocols. The main outcome — RF muscle stiffness in resting position — is measured using SWE. Secondary outcomes include muscle stiffness in passively stretched position alongside conventional B-Mode measurements of the RF muscle thickness, cross-sectional area and pennation angle. Muscle stiffness is compared in resting position between the three groups. Diagnostic performance of the outcomes and their correlation with appendicular skeletal muscle mass (ASM) measured using bioelectrical impedance analysis are examined.

Results

The current sample ($n = 34$, ongoing inclusion) shows a RF stiffness in resting position in sarcopenic individuals of mean 24.7 kPa (SD 11.4) compared to 19.5 kPa (7.2) in non-sarcopenic older adults and 19.8 (5) among younger adults. The Spearman correlation coefficient between muscle stiffness in resting position and ASM is 0.35, compared to -0.17 in the passively stretched position. B-Mode measurements correlations with ASM are: muscle thickness 0.68, cross-sectional area 0.73 and pennation angle 0.34.

Conclusions

SESAM preliminary results show slightly higher RF stiffness in sarcopenic adults, which seems an interesting feature in sarcopenia detection. Also, B-Mode measurements seem to correlate closely with muscle mass.

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Parents Media Guide: How parental Smartphone use influences family life

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Objective

Scientific studies report that the mere presence of a smartphone reduces the quality and enjoyment of the interaction between conversation partners, e.g., when a phone is used / is present during meal (1,2). It appears that the ability of adults to interact closely with their babies and young children is influenced by smartphone use. In addition, mothers who report that they use their smartphone more often, are less able to calm their child down after a stressful situation (3). Constant interruptions also influence the relationship between mother and child. For example, mothers - depending on their spontaneous smartphone use while eating - show less verbal and non-verbal contact with their children (4).

Methods

The present empirical work investigates the influence of parental smartphone-use on the quality of family life e.g., infants' behavioral and physiological stress responses due to parental smartphone use and sums up several disadvantages of parental smartphone use next to their children. In the prospective follow-up interview study, parents are asked whether there has been a change in their behavior as a result of participation in the Smart Baby study. The aim of the work is to develop recommendations for parents and professionals working with parents or parents-to-be.

Results

The results of the Smart Baby Study show a correlation between the interaction interruptions and the heart rate of the children, shown as a statistically significant increase in heart rate (HR) and thus a physiological stress response in the children. These findings will be discussed in the light of current knowledge based on further related empirical data. Together with the findings of the interviews, valuable statements can be made about appropriate smartphone use of parents.

Conclusions

For creating the new parental smartphone guidebook "Parents Media Guide", we concentrate on the main influence factors of parental smartphone use, based on empirical data. Each chapter is devoted to a different topic, from the possible negative effects of smartphone use on family life to the testimonials and finally the summary of the findings. The results of the Smart Baby Study will be included in the evaluation.

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Role of galanin receptor 2/3 in inflammation associated with peritonitis

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Objective

Peritonitis poses a serious medical challenge due to abdominal wall inflammation, often triggered by infectious agents. If not medicated timely, it can lead to life-threatening conditions. Therefore, understanding its immunological mechanisms is crucial for innovative therapies. The regulatory peptide galanin and its receptors (GAL1-3-R) are expressed on various immune cells and play pivotal roles in diverse immunoregulatory mechanisms and inflammation (1) upon mediation of the cross-communication between the nervous- and immune system. Thus, we aimed to explore the impact of GAL2/3-R knockout (KO) in a preclinical model of peritonitis.

Methods

The impact of GAL2/3-R knockout (KO) was assessed in a preclinical peritonitis model, using aged 4% thioglycollate medium (TGM) injected intraperitoneal in GAL2/3-R KO and corresponding WT mice. Comparison to vehicle controls (0.9% saline) was included to discern treatment-specific effects. After 6 hours, peritoneal fluid, spleen and blood cells were collected. Phenotyping of myeloid cell populations was performed via flow cytometry. Chemokine levels in the peritoneum were assessed via multiplex immunoassays.

Results

Comparison of TGM-treated versus vehicle mice exhibited successful induction of acute peritonitis. Notably, in GAL2/3-R KO mice the induction of chemokines, especially RANTES (regulated on activation, normal T cell expressed and secreted), IP-10 (Interferon gamma-induced protein 10), and MIG (Monokine induced by Gamma-Interferon), upon TGM treatment was less prominent compared to WT mice. Simultaneously, increased levels of peritoneal macrophages were detected by flow cytometry. Immunophenotyping of blood and spleen revealed reduced neutrophil levels in both compartments upon induction of peritonitis in GAL2/3-R KO compared to WT mice, accompanied by elevated levels of dendritic cells in the blood.

Conclusions

GAL2/3-R KO mice lacked the characteristic induction of neutrophils by the innate immune system but showed induction of cells involved in early initiation of the adaptive immune responses. The observed alterations in chemokine levels and immune cell populations specifically in GAL2/3-R KO mice suggest a regulatory role for GAL2/3-R in modulating the immune response in peritonitis. Consequently, antagonism of GAL2/3-R could potentially dampen the sometimes overshooting immune response observed in peritonitis, thus representing a promising avenue for therapeutic interventions.

Acknowledgements

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Therapeutic Drug Monitoring in critically ill patients with urosepsis

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Objective

Sepsis remains one of the leading causes of death worldwide which is defined as a dysregulated response to microbial infection. There is a strong recommendation for early and effective antimicrobial treatment. However, as antimicrobial treatment may “kill the germ but also the patient”, a therapeutic drug monitoring (TDM) may be used to optimize and individualize antimicrobial therapy.

Methods

A single-center retrospective analysis of patients with urosepsis and therapeutic drug monitoring was performed. The influence of different factors such as SOFA-Score, origin of urosepsis, pathogen in urine and blood samples, and the use of renal replacement on the target concentration of optimal and minimal trough levels was investigated. Using logistical regression, the impact of various parameters on the minimum and optimal plasma-level of antibiotics in TDM was analyzed.

Results

Between 2017 and 2019, 222 patients were treated for urosepsis at our institution, of which 84 patients needed intensive care treatment. In 20 cases, a therapeutic drug monitoring was performed. Plasma level of antimicrobial therapy in patients with urosepsis caused by *E. coli* and *Proteus mirabilis*, the most common pathogen in blood and urine culture was significantly more frequent in the target concentrations of the optimal trough level of antimicrobial treatment. In addition, there was a significant correlation between the SOFA-Score and target concentrations: the higher the score, the higher the probability that the concentrations were within the target range.

Conclusions

TDM supports early and effective antimicrobial treatment in urosepsis. Patients with a low SOFA score and pathogens others than *E. coli* or *Proteus mirabilis* may profit from TDM with more plasma levels being within target range. A more pronounced organ dysfunction (high SOFA-Score) correlates positively with the achievement of the desired trough level. TDM should be considered in every patient with urosepsis.

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First results from a multimodal day-care psychosomatic post-COVID treatment approach

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Objective

The WHO defines post-COVID syndrom as a range of different symptoms that persist or develop at least three months after a COVID infection, persist for a minimum of two months and cannot be explained otherwise (1). Patients with post-COVID syndrome are in urgent need of an adequate treatment option (2). However, published studies with an interdisciplinary, multimodal approach for the therapy of post-COVID syndrome are still limited (3). We established a half-day multimodal treatment programme at the Department of Psychosomatic Medicine and Psychotherapy in a large acute care hospital for post-COVID patients. Women and men with post-COVID have been treated there and scientifically monitored to evaluate the effects of the psychosomatic treatment.

Methods

This observational study between January 2022 and March 2023 conducted as documentation the Patient Health Questionnaire (PHQ-D consisting of PHQ-15 (somatization), PHQ-9 (depressive symptoms), PHQ-Stress and GAD (anxious symptoms)), the ICD-10 Symptom Rating (ISR) and specialized psychological measurement like the Fatigue Scale (FS) and the Health Status Questionnaire (SF-12 consisting of the Physical Composite Score (PCS) and the Mental Composite Score (MCS)) at admission and discharge. Therapy lasted 4 weeks and consisted of a multimodal psychosomatic treatment as well as neuropsychological training and individualised physical training.

Results

A total of 65 patients, 48 women and 17 men, consented to post-COVID treatment after an appeal via the public media. At admission, PHQ and FS showed a high level of somatoform complaints (PHQ-15: M = 16.00, SD = 5.57) and fatigue symptoms (FS: M = 27.06, SD = 4.42) whereas depressive (PHQ-9: M = 13.98, SD = 5.27) and anxious symptoms (GAD: M = 9.55, SD = 5.62) were moderately pronounced. SF-12 revealed values below the 75th percentile (PCS: M = 29.16, SD = 6.65; MCS: M = 31.16, SD = 12.81). Ten patients ("dropout group") discontinued treatment after an average of one week. Symptom burden in these patients was significantly higher in all measured scales compared to the continuing treatment group (effect sizes ranging from d = 0.51 to d = 0.60). Compared to patients from our standard clinical settings, including patients with somatic comorbidity, post-COVID patients had a comparably high or even higher psychological symptom burden (e.g. PHQ-15: p < .001, d = 0.79; PHQ-9: p < .05, d = 0.39). Compared to admission, symptomatology at discharge was significantly improved (e.g. PHQ-15: p < .01, d = 0.26; PHQ-9: p < .001, d = 0.43; GAD: p < .001, d = 0.38; FS: p < .01, d = 0.32; SF-12, MCS: p < .001, d = 0.39).

Conclusions

Despite the short treatment time compared to standard psychosomatic therapy, all patients were able to significantly benefit from the treatment. Further data will show whether increasing the duration of treatment can further strengthen the positive effects of multimodal psychosomatic therapy.

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The ubiquitin-proteasome system component Zbtb preferentially interacts with pathogenic variants of SLC26A4 (pendrin)

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Objective

The SLC26A4 gene codes for the electroneutral Cl⁻/I⁻/HCO₃⁻ exchanger pendrin (PDS). The amino acid (AA) substitutions p.L236P and p.R409H are found in two of the most common pathogenic PDS protein variants leading to Pendred syndrome and non-syndromic autosomal recessive deafness B4 (DFNB4) within the Caucasian population (1). A yeast two-hybrid screening identified the zinc finger and BTB domain-containing protein (Zbtb), which is part of the ubiquitin-proteasome system (UPS) (2), as a potential PDS-interacting partner. Based on this, we want to elucidate the degradation pathway of PDS.

Methods

Mice cochlea sections were immunostained with anti-PDS and anti-Zbtb antibodies and imaged by confocal microscopy. HEK cells were co-transfected with wild type (WT), L236P, or R409H PDS with or without Zbtb, or transfected with WT PDS or C-terminal truncated PDS variants. Cells were incubated with or without a proteasome inhibitor. Western blots or co-immunoprecipitation (Co-IP) experiments were done.

Results

PDS and Zbtb co-localize within the stria vascularis of the mouse cochlea. There is a direct molecular interaction between Zbtb, WT PDS and PDS L236P & R409H. WT PDS and PDS L236P & R409H are ubiquitinated. Zbtb preferentially interacts and ubiquitinates PDS L236P & R409H compared to the WT. The truncated PDS variants 738X, 674X, and 584X show significantly decreased expression levels compared to the WT, while PDS 530X levels were not decreased.

Conclusions

The co-localization of PDS and Zbtb in the inner ear, their direct molecular interaction, as well as the increased ubiquitination levels of PDS variants in the presence of Zbtb indicate that the UPS might be responsible for the degradation of WT PDS and the pathogenic PDS variants. The lack of degradation of the PDS 530X indicates that the interaction site between PDS and the UPS is located between the AA positions 530 and 584. Targeting this sequence might represent a new pharmacological strategy for Pendred syndrome/DFNB4.

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Comparison of image quality in CT neck imaging between different protocols with linearly reduced radiation doses and contrast agent amounts

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Objective

One of the primary aim in CT imaging is to reduce radiation dose while maintaining diagnostic image quality, according to the ALARA principle (as low as reasonably achievable). Another aim, especially in elderly patients and in patients with impaired renal function is to reduce the amount of administered contrast agent/media (CA/CM). Therefore, continuous improvement is necessary especially in case of neck imaging, where organs sensitive to radiation are located such as the thyroid gland and salivatory gland.

Methods

Patients randomly distributed to six groups consisting of at least 34 clients each group undergone a CT scan of the neck without preselection. Body weight adapted doses at 120 kV to a final lowest dose of 70 kV in steps of ten with corresponding diminished dose of contrast agent have been applicated. Dependent on the concentration (mg/ml) of the CA the amount was calculated in corresponding steps of 10 %. ROI-evaluation of different target organs was performed with measured correcting values of Hounsfield units at five different levels of surrounding air. Furthermore, a semiquantitive evaluation of the quality of obtained scans with correlated to a Likert scale was obtained. The corresponding parameters of each kV-level are correlated, and the MANOVA-analysis was the statistical method we used.

Results

The hypothesis is that there is no difference in diagnostic value in varying amounts of CA at different kV-levels. Diagnostical value of the scans are evaluated with a semiquantitive Likert scale. The results show a decrease in the image quality with diminishing kV-level. In levels of 100, 90 and 80 kV there is almost no difference. The level with 70 kV differs slightly with a lower score of averaging around 2,5. Further results show differing variance in organs as the thyroid and the sternocleid muscle by almost no variance of HU in the other organs/structures. Last part indicates no lack of diagnostic information. Furthermore we reduce the cost of CA at almost halving it.

Conclusions

Preliminary results show only slightly varying variance in kV-levels of 100, 90 and 80 with reduced image quality at 70 kV. In correlation with reduced consumption of CA at reasonably rates the aim to reduce amount the volume of it at reduced radiation doses are achieved. The diagnostic value by fostering radiosensitive organs according to the results of the Likerts scale show reduced imaging quality at low levels at 70 kV.

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Within and between effects of mothers' and fathers' attachment, mentalizing and caregiving



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Objective

Parental sensitivity towards their children's needs is one of the most important factors influencing a child's social, emotional and cognitive development. Recent studies indicate that secure attachment representations (1) as well as the ability to reflect on one's own and others' mental states has a positive effect on sensitive caregiving in mothers (2) and fathers (3). However, it remains unclear how these traits and skills of one parent influence the other parents' skills and interaction patterns. Thus, the goal of the present study was to investigate the interplay between maternal and paternal attachment representations and reflective functioning (RF) on parental sensitivity, using a family system perspective.

Methods

We observed N = 40 first-time families in a longitudinal, multi-method study. We used the Adult Attachment Interview to assess parental attachment and general RF during pregnancy, and the Parent Development Interview to measure mothers and fathers parental RF. When children were 6 months (Mage = 6.5 month), we observed interactions between each parent and their child and used the Emotional Availability Scales to assess parental sensitivity.

Results

A structural equation model showed good fit ($X^2 = 15.34$, $p = .571$, $CFI = 1$; $RMSEA < 0.001$). The model reveals individual associations between attachment representations and general RF in mothers ($\beta = 0.68$, $p < .001$) and fathers ($\beta = 0.71$, $p < .001$), mothers and fathers general RF ($\beta = 0.46$, $p < .001$), as well as a mediating effect of fathers parental RF on the association between mothers' parental RF and paternal sensitivity ($\beta = 0.14$; $b [95\% CI] = 0.12 [0.02; 0.26]$). Fathers' parental RF does not appear to influence maternal sensitivity directly or indirectly (all $p > .05$).

Conclusions

These results suggest that parents might influence each other in their reflective functioning and caregiving behavior, supporting family system theory. The findings align with recent evidence showing interdependencies between mothers and fathers (4). This study extends beyond previous research by focusing on attachment representations and reflective abilities as an important basis for sensitive interactions. This research contributes to a more holistic understanding of the modern family by investigating the effects of both mothers and fathers on each other and their children in a longitudinal study employing multiple non-self-report methods.

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Deckung komplexer pararektaler Beckendefekte: Rolle der freien myokutanen Musculus vastus lateralis Lappenplastik

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Objective

Hintergrund: Aufgrund eines fortgeschrittenen Rektumkarzinoms kann eine Eviszeration mit Rektumamputation notwendig werden. Dabei können vor allem bei entsprechenden Voroperationen und neoadjuvanter Radiatio, ausgedehnte sowie tiefgreifende Weichteildefekte entstehen, die eine freie mikrovaskuläre Gewebetransplantation nötig werden lassen. In dieser Fallserie zeigen wir die erfolgreiche Kombination der muskulokutanen M. vastus lateralis-Lappenplastik (MVL) mit direktem Anschluss an die A. glutealis superior (1).

Methods

Material und Methoden: Wir untersuchten über einen Zeitraum von 47 Monaten, 11 retrospektiv Fälle von Patienten, bei denen dorsale Beckendefekte nach Eviszeration und Rektumamputation bestanden, die mit lokalen oder regionalen Mitteln nicht zu verschließen waren. Bei all diesen Patienten erfolgte bei ausgedehnten Defekten mit tiefen pararektal Wundhöhlen eine Defektdeckung durch eine freie myokutaner MVL-Lappenplastik mit direkte Gefäßanschluss an die superioren Glutealgefäße.

Results

Ergebnisse: Die Defektgröße betrug im Mittel 290,0 cm² (SD: 131,2; Range: 200 – 600 cm²). Die Defekttiefe betrug im Mittel 10,5 cm. Die Defekte machten somit MVL-Lappenplastiken mit einer mittleren Größe von 336,3 cm² notwendig. Es waren aufgrund von Nachblutungen drei operative Revisionen nötig. Es traten weder arterielle noch venöse Thrombosen sowie kein Lappenverlust auf. Einzig wurde eine Lappenspitzennekrose beobachtet, die sekundär per Direktnaht korrigiert werden konnte. Die Auswertung des Case-Mix ergab einen Wert von im Mittelwert 24,251 (SD: 21,699; Range: 7,036 – 65,748) Punkten, was die Komplexität der Fälle unterstreicht.

Conclusions

Schlussfolgerungen: Unsere Ergebnisse zeigen, dass eine freie mikrovaskuläre MVL-Lappenplastik eine praktikable Therapieoption für pararektale Defekte darstellt, die nicht durch lokoregionale Methoden verschlossen werden können. Die A. glutea superior ist dafür ein sicheres und suffizientes Anschlussgefäß. In Kombination lassen sich auch ausgedehnte Defekte erfolgreich verschließen.

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Influencing factors on SARS-CoV-2-specific IgG antibody development following vaccination

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Objective

Achieving immunization of the entire population by utilizing vaccine formulations targeting the same molecular structure was one of the goals during the severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2) pandemic. This presupposes that a uniform vaccine will generate a comparable antibody response in all individuals, resulting in similar antibody levels. Influencing factors that affect our immune system are likely to have a substantial impact on the response towards an immunization. (1) Therefore, the presented study focused on the immune response following SARS-CoV-2 vaccination by considering various influencing factors, including the type of vaccine and its combinations, time, sex assigned at birth, body mass index (BMI), age, chronic diseases, and long-term treatment.

Methods

A single venous blood sample (serum, 3 ml) was taken from subjects (aged 18 years and older, n = 1,106) from the county of Salzburg (Austria) between January and August 2022. All participants were vaccinated and had not knowingly acquired coronavirus disease 2019 (COVID-19). A questionnaire was distributed to the participants to assess their health state, the kind and date of vaccination(-s), anthropometric data, pre-existing illnesses, and chronic disorders. SARS-CoV-2 spike-protein-specific IgG was then detected utilizing the VITROS® Anti-SARS-CoV-2 IgG detection technique in an automated chemiluminescence immunoassay. The results are displayed in terms of binding antibody units (BAU) per ml. Statistical analysis was performed using the IBM SPSS Statistics (version 27) and GraphPad Prism (version 9.2.0) software.

Results

Within this population study, the 3 times vaccinated subjects had a higher median antibody titer (835.5 BAU/ml) compared to the 2 times vaccinated participants (361.5 BAU/ml). Immunization with various vaccines results in significant variations in the titer for the 3 times vaccinated group (Spikevax 1,855 BAU/ml, Comirnaty 831.5 BAU/ml, Vaxzevria 304.5 BAU/ml). The highest antibody median value was obtained with 2 doses Comirnaty with 1 Spikevax dosage (2,115 BAU/ml) followed by 3 doses Spikevax and 1 dose Comirnaty with 2 doses Spikevax (1,780 BAU/ml). A strong negative connection was discovered between the amount of IgG antibodies and the weeks after the previous vaccination in the 3 times vaccinated group ($r = -0.65$; $p\text{-value} \leq 0.0001$). Concerning the ongoing medication as an influencing factor, participants taking medication had a significantly lower median antibody titer (716 BAU/ml) than those who did not take any medication (921 BAU/ml). Sex assigned at birth ($p\text{-value} 0.126$), BMI ($r: -0.008$; $p\text{-value} 0.815$), age ($r: -0.052$; $p\text{-value} 0.11$), and chronic illnesses ($p\text{-value} 0.106$) had no significant impact on the antibody titer.

Conclusions

The results of this study showed, that the number, the type of vaccine and its combinations as well as the time to the last immunizing event and the intake of ongoing medication have an impact on the amount of SARS-CoV-2 specific IgG antibodies. This data is essential for future vaccine development, particularly in the context of personalized treatment.

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Collection efficiency of mononuclear cells in offline extracorporeal photopheresis: can processing time be shortened?

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Objective

Extracorporeal photopheresis (ECP) is a well-established but lengthy and burdensome cell-based therapy for various diseases such as cutaneous T-cell lymphoma, graft-versus-host disease and organ rejection after transplantation. The number of mononuclear cells (MNCs) that needs to be collected to obtain a clinical response to ECP is still under debate. The purpose of this retrospective study was to determine the number of lymphocytes, monocytes and neutrophils in mononuclear cell products (MCP) by flow cytometry and the collection efficiency in the offline ECP setting.

Methods

We collected data from 10 different patients undergoing 162 ECP procedures using the Spectra Optia device for MNC collection. White blood cell (WBC) count of MCP was determined using a hematology analyzer. MNCs were analyzed for CD45 and CD14 expression by flow cytometry to exactly determine the collected lymphocyte and monocyte fractions.

Results

Collected MCP showed high cell yields with 55.3 x 10⁶/kg MNCs and 41.1 x 10⁶/kg lymphocytes. MCP were characterized by high MNC (81.3 %) and low neutrophils (18.7 %) percentage. Mean collection efficiency for WBCs and for MNCs was 23.9 % and 62.0 %, respectively. The MNC fraction showed a moderate to high correlation between peripheral blood cell count of patients and MCP count.

Conclusions

This study is one of a few reports showing the monocyte-to-lymphocyte relation in MCP for ECP determined by flow cytometry. In comparison to historical data from inline ECP, the offline ECP processing one total blood volume results in considerably higher cell yields. For this reason, and to reduce the burden on patients, we propose that the offline ECP processing time can be substantially reduced.

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Characterization of patients with classical myeloproliferative neoplasms: A retrospective, single-center analysis.

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Objective

Classic Philadelphia-chromosome negative myeloproliferative neoplasms (MPN) are a group of clonal malignant hematologic disorders. They include polycythemia vera (PV), essential thrombocythemia (ET) and myelofibrosis (MF). Patients with MPN have an increased risk for thromboembolic events. PV or ET can evolve to MF over time, and transformation into blast phase, i. e. acute leukemia, is possible. We aim to analyze the course of disease in all patients treated at our center over the last 20 years. Here, we provide a first characterization of the cohort, with the goal of further data collection within the Austrian Myeloid Registry of the Austrian Group Medical Tumor Therapy (AMR-AGMT).

Methods

Data were collected retrospectively. We conducted a search in the clinical database of the Department of Internal Medicine III and collected data of all MPN patients diagnosed and/or treated at our center since 2003. Statistical analysis is descriptive. For this analysis, patients with unclassifiable MPN were excluded.

Results

Overall, 882 patients were included into the database, of which 124 were excluded for unclassifiable MPN, thereby leaving 758 patients. The largest subgroups were PV (n=348) and ET (n=338), followed by MF (n=150). 34 patients with PV (9,7%) and 32 patients with ET (8,6%) transformed into MF, respectively. Therefore, 84 patients were classified as primary MF (56%). Overall, 12 patients (1,70%) transformed into blast crisis. A JAK2V617F mutation was detected in most patients with PV (97,1%). It was also the most common mutation in ET (66,1%) and MF (65,3%). Mutations in CALR and MPL were found in 21,8% and 6% of patients with ET, and in 22,7% and 4,4% with MF. Of the entire cohort, only 4,5% patients had no classic driver mutation. For patients with a diagnosis of PV or ET (without transformation), at least one thrombotic event was documented in 36,5% and 31,5% of patients, respectively, whereas 21% and 33% of patients with primary and secondary MF had a thrombotic event. A cytoreductive therapy with hydroxyurea was performed in 76% of patients with PV and in 61% with ET, whereas anagrelide was used in 10,9% of ET. Overall, interferon alpha was chosen for 109 patients, mainly PV (n=50) and ET (n=57), whereas ruxolitinib was given to 132 patients. Of the patients with PV, 15% received interferon alpha and 16% ruxolitinib. 49 patients with primary MF and 43 patients with secondary MF received ruxolitinib, meaning that 61,3% of patients with MF received the JAK2 inhibitor.

Conclusions

In our cohort, PV and ET are the most prevalent, with fewer patients with MF. The distribution of driver mutations is comparable to other studies. Potentially disease-modifying treatment with interferon alpha and ruxolitinib was chosen in a significant proportion of patients. The cohort seems suitable for more in depth analysis within the AMR-AGMT.

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A personalised and customisable serious gaming system for children with movement disorders

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Objective

Special body-controlled computer games known as "serious games" are very well suited to motivating children with neurological movement disorders to engage in therapeutic exercises. Between 2016 and 2018, I conducted a study with 20 patients to gain initial experience in the use of serious games and obtain patient feedback. The result of the study at that time was that although the exercises were very motivating, they were not challenging enough and did not focus enough on the patients' goals: 50% of the children did not work directly on their rehabilitation goals at that time¹. Our aim was to develop a system based on this feedback that allows the body-controlled games to be tailored precisely to the therapists' requirements and the patients' goals.

Methods

Initially, the therapy system was developed iteratively in close consultation with patients and therapists. To adapt the system to the patients, we developed a "Body Selector" that allows therapists to easily enter goals by clicking on body parts and selecting the desired functional results. In addition, we have developed small gamified assessments so that the system can adapt to the patient's conditions, for example to the individual range of motion, and thus remain challenging. For long-term motivation, we developed a virtual world in which the patient can move independently as an "avatar" to the next therapeutic exercise, collect coins and solve tasks. The system was then certified as a medical device and standardized, anonymous feedback from patients and therapists was obtained from digital questionnaires in 6 different partner clinics after over 1000 therapy sessions. Standardized questions were rated on a scale from 0 to 100.

Results

Patient feedback showed that over 70% patients very much enjoyed the therapeutic games and they were neither too easy nor too difficult for over 65% to train. The Serious Gaming System was mostly used by the therapists for mixed therapy goals (63%), otherwise for coordination (17%), range of motion (8%) and balance (6%). More than 85% of therapists rated the therapy as effective or very effective for the therapy goal of the respective session.

Conclusions

The Serious Gaming System was mostly used by the therapists for mixed therapy goals (63%), otherwise for coordination (17%), range of motion (8%) and balance (6%). More than 85% of therapists rated the therapy as effective or very effective for the therapy goal of the respective session. The data suggest that the Serious Gaming System now provides the right level of challenge and effort and is largely effective for the therapy goals set by the therapist.

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Relationship between Education and Steatotic liver disease

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Objective

A lower level of education has been shown to be associated with a higher risk of developing various health conditions like myocardial infarct or stroke (1). This is due to unhealthy and sedentary lifestyle and limited access to healthcare (2). But, in case of non-alcoholic fatty liver disease (NAFLD) this association remains unclear. Therefore, the aim of this study was to prove if there is an independent relationship between NAFLD and educational level, defined by the International Standard Classification of Education (ISCED).

Methods

This cross-sectional study included 8,315 participants from the Paracelsus 10,000 study. Subjects were randomly selected from local population. The primary finding of the study was to address the etiological question of NAFLD in relation to education through relative risk analysis. The primary endpoint was NAFLD defined by the Fatty liver Index (FLI). A score ≥ 60 was considered elevated (1). Education level was defined by: (i) those with a low education level (less than a high-school education), (ii) those with an intermediate education level (from high school to less than university or college degree) and (iii) those with a high education level (university or college degree) (3). Statistical analyses, included descriptive statistics, logistic regression models and risk analysis. Outcomes were adjusted for the covariables of age and sex in model 1 and for income, employment, and marital status in model 2. Included were those with an assessment for FLI, ISCED score and supplied data regarding age, sex, income, employment, and marital status. Those with known viral hepatitis or excessive alcohol consumption ($>40g$ in females and $>60g$ in males) were excluded.

Conclusions

The studies findings indicate that a lower education level increases the risk of NAFLD independent of confounding factors. Therefore, these findings highlight the potential impact of educational attainment on NAFLD risk and emphasize the need for targeted interventions in vulnerable populations.

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Caring for a relative with dementia and the lived experiences of boundaries in caregiving – a qualitative study in a rural area of Salzburg

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Objective

Family caregivers of persons with dementia provide an important contribution to the care of community-dwelling older people, especially in rural areas. Besides positive aspects, caring for a relative with dementia is often a demanding process (1). If caregiver burden leads to feelings of caregiver overload, the boundaries of dementia caregiving are reached and the institutionalization phase of the relative with dementia sets in. Objective of the study: How do families caring for relatives with dementia perceive the boundaries in family caregiving and what are their lived experiences when making decision to institutionalize the relative with dementia?

Methods

A qualitative approach was used to explore the life-world of family caregivers within a case study design and a phenomenological framework. For data collection 21 problem-centred interviews with family caregivers in Salzburg county were conducted. The interviews were analysed according to the hermeneutical sociology of knowledge approach.

Results

The results illustrate specific life-world aspects of family caregiving that exemplify the boundaries in the course of caregiving. Core characteristics described are "a build-up of events in the lived experience", "dramatic events", or "cascading recruitment of formal services", whereby typical boundaries experienced by family caregivers are described.

Conclusions

The results indicate that the experience of boundaries is not an isolated episode, but a core aspect in the course of caring for a relative with dementia. The crossing of boundaries and dangerous courses of caring for a relative with dementia could be prevented with a counselling concept that takes a lifeworld approach.

Acknowledgements

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Interatrial block improves prediction of new-onset atrial fibrillation after cardiac surgery

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Objective

This study seeks to examine the relationship between interatrial conduction block and postoperative atrial fibrillation, a condition that can lead to acute cardiopulmonary instability and is linked to heart failure, stroke, and increased mortality after cardiac surgery (1, 2).

Methods

Perioperative 12-channel electrocardiograms from 3405 patients undergoing myocardial revascularization, valve surgery, ascending aorta surgery, or combinations thereof, were considered. Clinical and electrographic parameters were compared between patients with and without atrial fibrillation, and significant variables were analysed using univariate and stepwise multivariate logistic regression. Statistical significance was defined as $p < 0.05$.

Results

Among 2108 analysed patients, 764 (36.2%) developed atrial fibrillation. Preoperative interatrial block was a strong independent predictor (3.18[2.55,3.96], $p < 0.001$) and improved atrial fibrillation prediction, enhancing the area under the ROC curve from 71.8% to 75.6%. Delong's test confirmed the model with interatrial block had superior discrimination performance ($p = 0.013$). Other independent predictors of atrial fibrillation included advanced age (1.05[1.03,1.07], $p < 0.001$), female gender (1.86[1.45,2.38], $p < 0.001$), history of cardiogenic shock (1.44[0.99,2.09], $p = 0.057$), reduced left ventricular ejection fraction $< 40\%$ (1.57[1.06,2.33], $p = 0.024$), β -blockers (1.17[0.95,1.46], $p = 0.145$), CHA2DS2-VASc and EuroScore II (0.87[0.79,0.97], $p = 0.01$ and 1.04[0.99,1.11], $p = 0.138$), preexisting left bundle branch block (1.59[0.92,2.74], $p = 0.097$), cardiopulmonary bypass time (1.00[1.00,1.00], $p = 0.049$), bicaval cannulation (1.45[0.88,2.41], $p = 0.035$), cardiac surgery-associated acute kidney injury (3.19[2.45,4.15], $p < 0.001$), and postoperative atrioventricular block (1.20[0.96,1.51], $p = 0.105$), particularly Mobitz I (6.73[1.98,31.51], $p = 0.005$).

Conclusions

Incorporating ECG-derived parameters, especially interatrial block, can enhance the predictive accuracy for postoperative atrial fibrillation. Additional research is needed to clarify the relationship between conduction abnormalities and postoperative atrial fibrillation, which will aid in the targeted delivery of prophylactic therapies and interventions for patients at high risk.

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Novel genetic variants lead to sensorineural hearing loss and Enlarged Vestibular Aqueduct (EVA)

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Objective

Biallelic pathogenic variants in the SLC26A4 gene, coding for the anion exchanger pendrin, are responsible for Pendred syndrome and nonsyndromic recessive hearing loss DFNB4. Both these clinical entities are associated with an enlarged vestibular aqueduct (EVA), which is the most common malformation of the inner ear (1). We have recruited the first Austrian cohort of 33 patients with hearing loss and EVA to define the prevalence and type of pathogenic sequence alterations in SLC26A4 and discover novel EVA-associated genes.

Methods

The coding region and intron-exon boundaries of known EVA genes were amplified by end-point PCR and Sanger sequenced. The possible presence of the Caucasian EVA (CEVA) haplotype was determined with the rhAmp® SNP Assays (IDT). Copy number variation (CNV) in the SLC26A4 and STRC genes was assessed using the TaqMan™ Copy Number Assays and QuantStudio 3D Digital PCR. For patients who remain undiagnosed, whole exome sequencing (WES) was performed. The pathogenicity of novel SLC26A4 and TJP2 variants was evaluated by functional and molecular assays of the corresponding proteins.

Results

Biallelic pathogenic variants in SLC26A4 were detected in 5/33 patients (15%). Based on the positive perchlorate discharge test, one of these 5 patients (1/33, 3%) had Pendred syndrome. Monoallelic variants in SLC26A4 were detected in 5/33 patients (15%). Of these, two were benign based on functional and molecular tests. The CEVA haplotype was found in 6/33 (18%) of patients, 3 of whom carried monoallelic pathogenic SLC26A4 variants, 2 carried biallelic pathogenic SLC26A4 variants, and one carried a monoallelic non-pathogenic SLC26A4 variant. Furthermore, biallelic pathogenic variants in FOXI1 (1/33, 3%), monoallelic X-linked pathogenic variants in POU3F4 (2/33, 6%), and biallelic pathogenic variants in GJB2 (2/33, 6%) have been found. No CNV of SLC26A4 and STRC genes was found. WES of patients with bilateral EVA and negative for known causative genes (15/33, 45%) detected mutations in 6 EVA-unrelated genes (SCD5, REST, EDNRB, TJP2, TMC1, and CDH23) in 5/33 patients (15%). Cell-based assays showed that the novel gene variant in TJP2 leads to an aberrantly localized protein product, supporting its pathogenicity.

Conclusions

Sequence alterations in SLC26A4 and/or the CEVA haplotype, FOXI1, POU3F4, and GJB2 genes are responsible for hearing loss and EVA in 42% (14/33) of patients of this cohort. WES led to the identification of 6 genes previously not associated with EVA and allowed for the diagnosis of an additional 15% (5/33) of patients. The genetic causes remain unidentified in 42% (14/33) of patients. Functional and molecular studies are needed to assign or exclude the pathogenicity of novel variants and establish a causal link with disease.

Acknowledgements

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Oxidative stress-related cellular aging causes dysfunction of the Kv3.1/KCNC1 channel reverted by melatonin

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Objective

Kv3.1/KCNC1 is a voltage-gated channel that is abundantly expressed in fast-spiking principal neurons and GABAergic inhibitory interneurons throughout the ascending auditory pathway and in various brain regions. Inactivating mutations in the KCNC1 gene lead to various forms of epilepsy, and Kv3.1 expression within the auditory pathway declines with age, which might contribute to age-related hearing loss (1). As oxidative stress plays a fundamental role in the pathogenesis of both epilepsy and age-related hearing loss, we hypothesized that an oxidative insult might affect the function of this channel.

Methods

To obtain a cellular model of oxidative stress-related aging, HEK 293 Phoenix cells were exposed to 100 mM D-galactose (D-Gal) for 3-72 hours and melatonin (100 μ M for 48 hours) was used as an antioxidant. As a control, 100 mM D-Mannitol (D-Man) was used to obtain equal osmolarity of the cell culture medium. Total intracellular ROS levels were evaluated with 2',7'-dichlorofluorescein diacetate. Potassium currents were measured by patch-clamp in whole-cell configuration. Total RNA was extracted from cultured cells and Kv/KCN transcripts were quantified by RT-qPCR. Western blot analysis was performed to test the abundance of Kv3.1a protein at the plasma membrane, calreticulin, GAPDH, tubulin, phosphorylated Src, and phosphorylated Cav-1.

Results

In this model of oxidative stress-related aging, intracellular ROS were dysregulated and the current of Kv3.1 was significantly reduced. The Kv3.1 reduction of function was not determined by a reduction in its transcript levels. Instead, exposure of cells to D-Gal resulted in a reduction of Kv3.1 protein abundance in the plasma membrane-enriched fraction. Melatonin reverted all these effects. The increased Src and Cav-1 phosphorylation levels, as well as metabolic reprogramming and endoplasmic reticulum stress denoted by elevated GAPDH and reduced calreticulin expression respectively, might have all contributed to a decreased Kv3.1 trafficking to the plasma membrane.

Conclusions

These data identify Kv3.1 as a novel target of oxidative stress and suggest that Kv3.1 dysfunction caused by oxidative stress might contribute to age-related hearing loss and increased prevalence of epilepsy during aging. The pharmacological use of the antioxidant melatonin might be protective in these settings.

Acknowledgements

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Fructose appears to be able to influence the immune system

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Objective

The respiratory burst of phagocytes is an important part of the innate immune defense. Oxygen radicals are formed to eliminate pathogens. At the Institute¹ we investigate the influence of different hexoses in different concentrations on the respiratory burst of human phagocytes.

Methods

The desired cell fraction was isolated directly at the institute from fresh whole blood from volunteer, clarified donors. This was carried out in hexose-free solutions. After the isolation, the cells were transferred to solutions with the appropriate concentrations of hexoses. We trigger the respiratory burst using PMA. We determine the activity of this respiratory burst by detecting H_2O_2 using the Amplex Red method (1). Two to three different hexoses were examined simultaneously in one essay. Glucose was set as control to establish a reference and comparability with other measurements.

Results

The different hexoses have very individual characteristic changes on the H_2O_2 production during the respiratory burst. As an example, eosinophils with fructose and glucose are presented here. Eosinophils have a reduced maximum H_2O_2 production with fructose. In the first 25 min of the measurements there were no differences in rate of production at different D - fructose concentrations. Later (>25 min) results clearly deviating at different concentrations with fructose. Our previous evaluation by determining V_{max} is insufficient here as the differences at the end could not be represented, therefore the first derivative was determined additionally at the time $t=90$ min.

Conclusions

It appears that eosinophils metabolize fructose with a slight delay. However, this does not occur in the first 25 min, when the highest production rate of H_2O_2 is found. It can be observed that an initial plateau begins at all fructose concentrations between 20 and 25 min before the increase continues at the high fructose concentrations. The storage capacity for glycogen of the cells can be calculated from the values measured in the measurements without hexose.

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Influence of the isolation method on the measurement of the respiratory burst

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Objective

At the Institute¹ we are investigating various factors influencing the respiratory burst of human phagocytes. We currently have two methods at our disposal for isolating the desired cell fraction. A ready-to-use isolation kit (MACSxpress® (1) to extract the target cell fraction from the unprocessed whole blood with antibodies in a magnetic field and a method with density gradient centrifugation and subsequent separation of the cell fractions using antibodies in a magnetized column.

Methods

We trigger the respiratory burst in the desired cell fraction using PMA. We determine the activity of the respiratory burst by detecting H₂O₂ using the Amplex Red method (2) in a fluorescence assay. The two methods were compared by repeating the identical experiments in which only the method of isolation was varied.

Results

For neutrophils, there were no differences between the two methods, outside the variance. There was a clear difference between the two methods for eosinophils. Even by changing the manufacturer's instructions, only a slight increase in H₂O₂ production was achieved, but no comparable results were obtained.

Conclusions

Both methods appear to provide equivalent results for the isolation of neutrophils. However, it should be noted that in density gradient isolation, the neutrophils are loaded with antibodies. With the MACSxpress® method, the neutrophils should be isolated untouched according to the manufacturer. Despite adaptation of the MACSxpress® instructions, there are still clear differences in the eosinophils. Whether this difference is due to other buffers / antibodies in the MACSxpress® kit or to the eosinophils themselves has not yet been determined, as the manufacturer does not wish to disclose the components of the isolation kit. The measurements by Patch-clamp support the measurement results we obtain with the density gradient isolation.

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Telemedicine for the management of behavioral disorders in nursing home residents with dementia

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Objective

The management of behavioral disorders in Nursing Homes (NHs) residents with dementia (BPSD – Behavioral and Psychological Symptoms of Dementia) is particularly difficult and often leads to unnecessary hospitalizations and incorrect or excessive use of physical and pharmacological restraint (1). Telemedicine can become the means to deliver quality care in individuals with BPSD in NHs, as other studies have shown (2, 3). However, an evaluation of specific health outcomes is needed. The aim of the study is to verify the effectiveness of teleconsultations for the management of BPSD in residents with dementia and to assess NH staff's satisfaction with the new method.

Methods

This prospective cohort study involves monthly teleconsultations between the Geriatrician of the Memory Clinic of Bolzano and the General Practitioners (GPs) and Head Nurses (HNs) in charge of two NH in the Province of Bolzano: one where the Geriatrician visited in person monthly before the pandemic (Egna/Montagna) and one where consultations had never been conducted before (Renon). Two trainings were prepared for the staff involved, one in the technical area for the use of the POHEMA telemedicine platform, and one in the clinical area for the recognition of BPSD and delirium. At each teleconsultation, the characteristics of residents affected by dementia and BPSD were noted, and three outcome indicators were registered: the number of referrals to emergency rooms (ERs) or memory clinics for problems related to behavioral disorders, the number of physical restraints, and the number of therapeutic adjustments, according to STOPP/START criteria. The data were compared with data for the year 2019 from the NH software. Every 6 months NH staff completed an ad-hoc composed satisfaction questionnaire. For statistical comparisons, the Fisher exact test was used.

Conclusions

One year of frequent and constant telemedicine contacts between the Bolzano Memory Clinic and the two NHs have helped to avoid sending any patients to ERs or Memory Clinics for reasons related to behavioral disorders. The data is comparable to that obtained when the Geriatrician traveled to the facility in person. In contrast, the use of physical restraints was not shown to be related to telemedicine (higher number of restrained subjects in 2023 than in 2019). The findings could be explained by an increase in physical restraint during the Covid-19 pandemic, as supported by literature. The number of therapeutic adjustments demonstrates that the presence of the Geriatrician (in person or remotely) contributes to better management of residents with dementia. The results of the operator satisfaction questionnaire encourages the use of teleconsultations in other NHs and memory clinics in the area.

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Impact of sugars on reactive oxygen species production during the respiratory burst of phagocytes

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Objective

Reactive oxygen species (ROS) are produced by NADPH oxidase during the respiratory burst of phagocytes (1). This is crucial for defending against bacteria as well as for signal pathways. However, high production of ROS causes oxidative stress and tissue damage. ROS generation is substrate dependent and sugars are preferably used. However, little is known about the impact of common monosaccharides on ROS production.

Methods

We compared the impact of glucose, fructose, galactose and 2-deoxyglucose on H₂O₂ production using the fluorometric amplex red method in three different phagocytic cells: a genetically modified leukemia cell line PLB-985 X-CGD SgpsIBW (BW), neutrophils and monocytes, freshly isolated from human peripheral venous blood. Furthermore, we investigated the gene expression of glucose transporters using real-time PCR.

Results

H₂O₂ production by leukemia cell line BW, neutrophils and monocytes after incubation with different concentrations of several sugar substrates: glucose, fructose, galactose and 2-deoxyglucose was investigated. Glucose is a substrate for NADPH oxidase and triggers ROS generation. The minimal concentration of external glucose effecting H₂O₂ production in BW cells and neutrophils is 100µM and the maximal – 3mM. For monocytes the minimal concentration of glucose is below 10µM and maximal above 30mM. The difference in the concentrations of glucose effecting H₂O₂ production inbetween cells suggest difference in glucose transporting. Fructose and galactose are not a substrate for H₂O₂ production. 2-deoxyglucose competes with glucose and inhibits glucose-6-phosphate dehydrogenase in neutrophils, therefore H₂O₂ production decreases. For BW cells and monocytes 2-deoxyglucose without presence of external glucose has no effect. Values are means ± SD. n = 3 Differentiated and not differentiated BW cells were harvested on the stated day with subsequent RNA isolation and gene expression of GLUT1 was determined using real-time PCR, GAPDH was used as housekeeping gene. n = 2, mean ± SD. No change in GLUT1 mRNA expression was seen on day 1 and 6 during DMSO-induced differentiation compared to undifferentiated cells (d0). Values are mean ± SD, n = 2.

Conclusions

Our results show that sugars play a substantial role in ROS generation in phagocytes and thus might affect oxidative stress. ROS production seems to be highly dependent on glucose but not on other monosaccharides. Glucose is transported via GLUT1 transporter into BW cells. Gene expression of GLUT1 does not change during differentiation process of BW cells into phagocyte-like cells.

Acknowledgements

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Embroidered silk fibroin scaffolds for ACL tissue engineering

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Objective

Anterior cruciate ligament (ACL) rupture requires reconstruction due to poor healing capacity of the ACL. The resulting joint instability increases the risk for the onset of osteoarthritis (OA). Silk has been used since centuries for medical applications due to high cytocompatibility and biomechanical strength. Bombyx (B.) mori (silk worm) derived silk consists of two components, fibroin and sericin. The latter is usually removed to reduce immunogenicity and improve biocompatibility as well as processability. Embroidering allows adaption of biomechanical properties by selecting biomimetic embroidery patterns. This project aims to identify an embroidered silk fibroin-based scaffold variant facilitating ACL tissue engineering and ligamentogenesis.

Methods

For removal of sericin, two different cleaning procedures were applied to the silk threads: a standard ("raw silk") and a novel ("purified silk") technique patented (DE102021118652A1) by the start-up company providing the threads. Silk fibroin threads of both cleaning degrees were either used to embroider pure silk scaffolds or were combined with PLA-co-caprolactone (P(LA-CL)) fibers (7:0). A previously established and approved zig zag embroidery pattern (1.8 stitch length, 15° stitch angle, 0.2 duplication shift) was conducted with a lower and upper thread and three embroidered plies were stacked together by means of a silk locking thread. Scaffolds had the dimension of the rabbit ACL (10 x 4 x 2-3 mm) and were disinfected with 70% ethanol. Hence, four groups (1: "raw silk", 2: "raw silk/P(LA-CL)", 3: "purified silk", 4: "purified silk/P(LA-CL)") were seeded with lapine cruciate ligament fibroblasts (LCL-Fb, 1.5-2 mio cells per scaffold, dynamical cultivation). Cytotoxicity assays were conducted with extracts (48 hours extraction in growth medium) of each scaffold variant using MTS assay and LCL and L929 fibroblasts (Fbs). Cell adherence and vitality was monitored with fluorescein diacetate/propidiumiodide and immunostaining of cytoskeletal and extracellular matrix proteins after 7 and 14 days.

Results

The fibroin single fiber diameters of un/treated silk was nearly similar. LCL-Fb adherence on scaffolds differed, being low on the scaffolds made of conventionally treated silk, higher on raw silk/P(LA-CL). Highest cell adherence was found on the purified silk scaffolds and purified silk/P(LA-CL). Interestingly, the P(LA-CL) integration into the scaffold increased also the cytocompatibility of raw silk fibers. Cell survival on the scaffolds was high for the whole observation period (14 days). The focal adhesion component paxillin was abundantly expressed in cells on purified silk scaffolds underlining intimate cell material interaction and also typical ECM could be detected.

Conclusions

Purified silk fibroin threads are highly cytocompatible and represent a versatile material, suitable to prepare embroidered LCL-Fb carriers without the necessity of further functionalization.

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Transcriptomic analysis unveils the regulatory network of Sturge-Weber syndrome-associated Gαq protein during neural differentiation

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Objective

Sturge-Weber syndrome (SWS) is a rare neurovascular disorder attributed to a spontaneous mutation in the GNAQ gene, responsible for encoding the guanine nucleotide-binding protein G(q) subunit alpha (Gαq). This syndrome presents distinct clinical features, including a facial port-wine birthmark (PWB), glaucoma, and various neurological symptoms such as intellectual disability and seizures. Despite the prevalence of neurological manifestations, there is a significant knowledge gap regarding the molecular intricacies underlying SWS within neural cells. This study aims to uncover the molecular mechanisms regulated by Gαq in neural cells.

Methods

Pluripotent stem cells (PSC) were subjected to neuronal differentiation using a dual SMAD inhibition protocol established in our lab. Gαq knockouts were generated using the CRISPR-mediated non-homologous end-joining method. Knockout samples were screened via western blot analysis, and validation was carried out using Sanger sequencing. Transcriptional differences between control and Gαq knockout neural stem cells (NSC) were assessed through RNA sequencing. Gene ontology analysis was performed using the online tool PANTHER, while pathway enrichment analysis was carried out using Integrated Molecular Pathway Level Analysis (IMPALA).

Results

Confirmation of neuronal differentiation using wild-type PSC was shown by elevated levels of neural markers NESTIN and MAP2. The expression patterns of the Gαq gene showed an increase during the proliferative stage of neural stem cells, indicating its potential role in neural proliferation. RNA sequencing analysis comparing knockout and control cells revealed increased differential expression of genes in Gαq knockout neural stem cells compared to Gαq knockout embryonic stem cells, aligning with previous qPCR results. Fifteen genes, predominantly non-coding RNA, were identified as commonly differentially expressed between embryonic stem cells and neural stem cell knockouts, with more than a 1.5-fold difference. Further analysis focusing on neural stem cells showed differential regulation of 94 genes in Gαq knockout NSC. Pathway analysis using the IMPALA tool highlighted neural differentiation as the top pathway represented by 8 of the 94 genes, with a very high p-value. Notably, Gαq knockout in NSC modulated ASCL1, a master regulator of neurogenesis.

Conclusions

Sturge-Weber syndrome associated Gαq protein modulates genes related to neural differentiation, potentially contributing to the neurological symptoms observed in this condition.

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EZH1 - a new therapeutic target for biliary tract cancer?

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Objective

Biliary tract cancer (BTC) is a tumor with limited therapeutic options and dismal outcome. Hence, the identification and investigation of new therapeutic approaches is of utmost importance. The polycomb repressive complex 2 (PRC2) is a multi-protein complex that regulates gene expression via trimethylation of lysine 27 at histone 3 (H3K27me3). The canonical PRC2 consists of the histone methyltransferase EZH2 and the core subunits EED and SUZ12. Aberrant PRC2 activity is associated with epigenetic silencing of tumor suppressor genes and tumor progression. Recently, a non-canonical PRC2 has been described, harboring EZH1 instead of EZH2 as the histone methyltransferase. Interestingly, inhibition of EZH2 did not result in sufficient re-expression of PRC2-target genes, which might be explainable by compensatory function of EZH1. Consequently, combined EZH1/EZH2 inhibition has been identified as an attractive therapeutic strategy, which resulted in the development of dual EZH1/EZH2 inhibitors. Currently, there are no data available regarding EZH1 and BTC. Hence, in this study, we aim for an initial investigation of the effect of dual EZH1/EZH2 inhibition in BTC. Additionally, we want to clarify, whether EZH1 is expressed in BTC patient samples and whether EZH1 expression can be associated with clinical BTC progression and aggressiveness.

Methods

The in vitro experiments were performed using a comprehensive BTC cell line model (n = 9 BTC cell lines and n = 1 non-tumor cell line). mRNA levels of EZH1 were measured using rtPCR. Protein levels of EZH1/EZH2 and H3K27me1/2/3 were analyzed using Western Blot. Cytotoxic effects of Valemestostat were evaluated via a resazurin assay.

Results

We found that EZH1 and EZH2 are heterogeneously expressed in BTC cells. Similarly, H3K27me1/2/3 were expressed in a cell line-dependent manner. Interestingly, we found no correlation between expression levels. Next, we tested whether the dual EZH1/2 inhibitor Valemestostat shows cytotoxicity in BTC cells. Therefore, we treated the cells with different concentrations of Valemestostat for 72 hours. However, no specific cytotoxic effect was found. Therefore, we established a new protocol that allowed long-term incubation of BTC cells with Valemestostat for up to 14 days. Using this new protocol, we observed a significant decline in cell viability in selected cell lines following treatment for 10 to 14 days.

Conclusions

We here demonstrate that EZH1 is expressed in BTC cells. However, we found no correlation between EZH1 expression and protein levels of EZH2 and H3K27me1/2/3. Furthermore, we found that long-term incubation with Valemestostat results in cell line-dependent decline of cell viability. In a next step, we aim to test whether treatment of BTC cells with Valemestostat results in reduced H3K27me1/2/3 levels and re-expression of EZH1/EZH2 target genes - in comparison to the effect of sole EZH2 inhibition. We will complement these data by double EZH1/EZH2 knockdown experiments. Lastly, we will analyze EZH1 expression in BTC patient samples and investigate, whether EZH1 expression can be associated with clinical outcome.

PREVALENCE OF METABOLIC DYSFUNCTION-ASSOCIATED FATTY LIVER DISEASE (MAFLD) AND EFFECTS OF GLUCOSE-LOWERING MEDICATIONS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Objective

The aim of this study is to investigate the effects of antidiabetics on liver steatosis and fibrosis in a big cohort of patients with type 2 diabetes (T2D) and non alcoholic fatty liver disease (NAFLD) and to evaluate the correlations between liver stiffness and other clinical and biochemical parameters in T2D patients

Methods

101 consecutively patients affected by T2D and concomitant liver steatosis were enrolled from november 2022 to november 2023. All patients underwent biohumoral samplings and anthropometric values, upper abdominal ultrasound (for steatosis) and fibroscan at T0. NFS score, APRI score, FIB-4 and NAFLD score for liver fibrosis were calculated. All the enrolled patients started treatment with antidiabetic therapy with one or more of the new oral antidiabetics (PPAR-gammaAr; SGLUT-2 In; GLP1-ra) at T0. All the above data were then collected at 6 months and 12 months after the start of the T2DM treatment

Results

37.9% of the patients presented metabolic syndrome hepatic steatosis at T0. A significant reduction in GGT and ALT was documented at T6. In addition, a significant reduction in triglyceride levels, glycated Hb and blood glucose was documented at the end of the follow up (T12). With regard to fibrosis, APRI score and NFS score showed a significant reduction at T6 and T12, whereas no significant changes in liver stiffness (LS) were observed. No drugs correlated with changes in APRI score or NFS score, or with LS, probably due to the small sample size studied

Conclusions

Diabetes, metabolic syndrome and NAFLD/NASH are often related (1). Treatment of diabetes improves blood sugar but also liver metabolism (2). The improvement of liver metabolism and the decrease in liver inflammation leads to rearrangement of free fatty acids with their decrease and improvement of the general metabolism as well as the systemic inflammatory state (1, 2). A longer follow-up is needed to define the effects of T2D treatment on liver fibrosis

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Risk of Interprosthetic Femur Fracture Is Associated with Implant Spacing - A Biomechanical Study

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Objective

Ipsilateral revision surgeries of total hip or knee arthroplasties due to periprosthetic fractures or implant loosening are becoming more frequent in aging populations. Implants in revision arthroplasty usually require long anchoring stems. Depending on the residual distance between two adjacent knee and hip implants, we assume that the risk of interprosthetic fractures increases with a reduction in the interprosthetic distance. The aim of the current study was to investigate the maximum strain within the femoral shaft between two ipsilateral implants tips.

Methods

A simplified physical model consisting of synthetic bone tubes and metallic implant cylinders was constructed and the surface strains were measured using digital image correlation. The strain distribution on the femoral shaft was analyzed in 3-point- and 4-point-bending scenarios. The physical model was transferred to a finite element model to parametrically investigate the effects of the interprosthetic distance and the cortical thickness on maximum strain. Strain patterns for all parametric combinations were compared to the reference strain pattern of the bone without implants.

Results

The presence of an implant reduced principal strain values but resulted in distinct strain peaks at the locations of the implant tips. A reduced interprosthetic distance and thinner cortices resulted in strain peaks of up to 180 % compared to the reference. At low cortical thicknesses, the strain peaks increased exponentially with a decrease in the interprosthetic distance. An increasing cortical thickness reduced the peak strains at the implant tips.

Conclusions

A minimum interprosthetic distance of 10 mm seems to be crucial to avoid the accumulation of strain peaks caused by ipsilateral implant tips. Interprosthetic fracture management is more important in patients with reduced bone quality.

Acknowledgements

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Trauma-focused art therapy in patients with miscarriage or stillbirth: Psychometric treatment effects of the randomized controlled MALT! study

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Objective

Women who experienced a miscarriage or stillbirth are at elevated risk of suffering from symptoms of post-traumatic stress, anxiety or depression.[1] While watchful waiting is often recommended, art therapy offers the opportunity to process and integrate the experience. The aim of the MALT! study was to examine whether trauma symptoms decrease to a greater extent after an art therapy intervention compared to a watchful waiting condition.

Methods

In a randomized controlled trial, women were assigned to either an eight-week outpatient one-on-one trauma-focused art therapy (AT)[2] or a watchful waiting (WW) group within six months after miscarriage/stillbirth. Participants were examined at the beginning (T1) and after three months (T2). At T1, a control group (CG) of women without miscarriage/stillbirth was recruited. Primary outcome measure was change in post-traumatic symptoms, using the Impact of Event Scale - Revised (IES-R). Secondary outcome measures included depression, using the Patient Health Questionnaire 9 (PHQ-9). Statistical analyses were carried out cross-sectionally using ANCOVAs and longitudinally using mixed models with repeated measures (intent-to-treat).

Results

For the study, 41 women after miscarriage/stillbirth were randomized, 20 in the AT group (age M = 33.5; SD = 5.7), and 21 the WW group (age M = 34.7; SD = 4.6). The CG consisted of 28 women (age M = 27.3; SD = 1.4). At T1, women after miscarriage/stillbirth showed significantly higher scores than the CG in the PDS, IES-R and PHQ (all $p < .001$) with high effect sizes (all Cohen's $d > 1.00$). From T1 to T2, we found significant changes in IES-R (main effects for TIME), but no significant interactions between the AT and the WW group. Post-hoc analyses showed greater reductions in the symptoms of intrusion for the AT group ($d = -1.0$) than for the WW group ($d = -0.5$). In exploratory analyses, we found that for women with depression at T1, intrusions were only reduced by AT ($d = -0.9$) and not by WW ($d = +0.1$).

Conclusions

Women after miscarriage or stillbirth were more psychologically and biologically stressed than women without an event. MALT! art therapy lead to a significant reduction in intrusions, especially in participants with depression. Results indicate that art therapy plays an important role in the processing of traumatic events such as stillbirth and miscarriage and is feasible as a method for the prevention of PTSD symptoms.

Acknowledgements

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The voltage-gated proton channel discovers its family and function

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Objective

In each species investigated, there is only a single gene representing voltage-gated proton channels. This dogma is reversed by our discovery of a whole new ion channel family.

Methods

We used modern bioinformatics, patch-clamp, and MD simulations to show the structure and function of proton channels.

Results

At least 4 new voltage-gated proton channels have been discovered.

Conclusions

HVs have numerous connections to human health (Immune system, cancer, reproduction, energy homeostasis ...). The full range of implications of HVs tissues/cells are up to date unknown. Not every cell or species express HVs. Commonly used standard model systems as: *Drosophila melanogaster*, *Saccharomyces cerevisiae*, *Caenorhabditis elegans*, *Dictyostelium discoideum*, show no indication of HVs. HVs evolved before 1.8 billion years during the appearance of Eukaryotes. Metabolically active cells and/or gametes use HVs to regulate membrane potential and/or pH homeostasis. After the Perm-Trias mass extinction (2000 ppm CO₂ atmosphere // 95 % of marine species died) Molluscs recovered well, potentially due to better adaptation. Proton channels might function as a scaffold for additional protein tasks.

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PATHOGENIC PENDRIN (SLC26A4) VARIANTS ARE FUNCTIONALLY RESCUED BY CARFILZOMIB

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Objective

Approximately 466 million people globally, or 5% of the world's population, experience disabling hearing loss, which significantly impacts adults and notably about 34 million children (1). Our research focuses on Pendrin, a vital protein for ion management in the inner ear, thyroid, and kidneys. Genetic variants of Pendrin, frequently associated with Pendred syndrome and DFNB4, manifest in hearing and vestibular dysfunctions. These variants are often characterized by reduced functionality and diminished expression levels, hinting at potential degradation processes. This observation has prompted us to hypothesize that such degradation might occur through the ubiquitin-proteasome system (UPS), a hypothesis we aim to investigate further in our study, with the additional aim of understanding how to recover this decrease in functionality and expression.

Methods

To investigate pendrin ubiquitination, HEK 293 Phoenix cells were transfected for 48 hours with plasmid vectors encoding FLAG-tagged wild-type pendrin and the pathogenic variants PDS L236P and PDS R409H. Post-transfection, co-immunoprecipitation was performed using an anti-FLAG antibody, followed by Western blot analysis with anti-ubiquitin and anti-FLAG antibodies. We assessed the functionality of pendrin variants by measuring the iodide influx in transfected HEK 293 Phoenix cells. Additionally, we evaluated pendrin expression levels in transfected HeLa cells using EYFP emission intensity, which we normalized against DAPI emission intensity.

Results

The results highlight ubiquitination and a significant reduction in the expression levels of pathogenic variants of pendrin compared to the wild-type form, confirming their degradation mediated by the ubiquitin-proteasome system (UPS). Furthermore, it has been demonstrated that the use of carfilzomib, a proteasome inhibitor, effectively restored both functionality and compromised expression.

Conclusions

Our study demonstrates the involvement of the ubiquitin-proteasome system (UPS) in the degradation of pathogenic pendrin variants associated with sensorineural deafness. Additionally, we highlight the potential therapeutic benefit of utilizing carfilzomib, a proteasome inhibitor, in restoring pendrin expression and transport function. These findings offer novel insights into the treatment of hearing loss linked to pathogenic pendrin variants and propose the UPS as a promising target for future therapeutic interventions.

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WGS-based characterization of putative hypervirulent *Klebsiella pneumoniae* identified in a tertiary care hospital in Germany 🍷

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Objective

Hypervirulent *Klebsiella pneumoniae* strains (hvKp), in contrast to classical *K. pneumoniae* strains, can cause invasive community-acquired infections in healthy patients of all ages. In this study, *K. pneumoniae* isolates from routine microbiological diagnostics were tested via string-test for hypermucoviscous phenotype and PCR for virulence genes to screen for hvKp, which were further analyzed by whole-genome sequencing (WGS). The prevalence of “hidden” hypervirulent hvKp, including non-invasive strains and their population structure should be analyzed in a tertiary-care hospital in Southern Germany(1).

Methods

For the study period 1.5 years, all *K. pneumoniae* isolates were string-tested. A multiplex PCR for hvKp genes was applied to all string-test positive isolates. PCR-positive isolates were subjected to WGS to determine genotyping and phylogeny.

Results

A total of 10.9% (331/3044) isolates with hmKp phenotype were detected by string-test. The patients' age ranged from 0 to 95 years, with a mean of 69 years. In total, 13.3% (44/331) isolates were tested positive by PCR for genes associated with hvKp. cgMLST revealed that 41.5% of sequenced isolates belonged to international hvKp clonal lineages ST23/K1 with high virulence scores and close phylogenetic relationships. In contrast, 22.6% of isolates belonged to the ST86/K2 with lower virulence scores. Isolates of liver abscesses (7.5%) belonged to ST23, ST25 and ST268, but without phylogenetic relatedness to other isolates.

Conclusions

We identified hypervirulent *K. pneumoniae* within the study period with an overall prevalence of 1.4%. No transmissions were identified. Isolates were assigned to the international hvKp lineage ST23/K1 and lineage ST86, bearing the potential to spread further in the community. The known association of multidrug-resistance ST86, was not observed in this study. Presented cases of liver abscesses seem to represent individual occurrences, so far. In conclusion, the screening of hmKp phenotypes in routine diagnostics seems to be a suitable surveillance method. Further, the population size and structure of “hidden” putative hvKp were more complex than expected.

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Impact of Mesenchymal Stem Cells Derived Laminin-Binding Extracellular Vesicles on Schwann Cells and in Peripheral Nerve Regeneration Processes

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Objective

Injuries to peripheral nerves is a common health problem, often resulting in sensory and motor dysfunction in respective parts of the body. One of the most important facilitators of the regeneration process are Schwann cells (SCs), which basement membrane is chiefly comprised of laminin. Extracellular vesicles (EVs) are considered playing an important role in the intercellular communication and transfer of biological information. Especially, Mesenchymal stem cell-derived EVs (MSC-EVs) have been identified as a promising novel therapeutic option due to their potential function as target-directed drug delivery vehicles. However, the precise delivery of EVs upon administration is still a huge challenge due to the accumulation of EVs at off-target sites. To remedy this problem, this study focuses on the production of laminin-binding EVs derived from MSCs by modification of the large extracellular loop (LEL) of the overexpressed EV surface marker protein CD81, from the tetraspanin protein family, to increase their binding affinity to laminin.

Methods

Specific CD81-LEL sequences are cloned into lentiviral vectors encoding the expression cassette for full-length CD81 proteins fused with eGFP or Akaluciferase under the control of human cytomegalovirus promoter. Stable cell lines are obtained upon transformation of Wharton's Jelly MSCs (WJ-MSCs). EVs derived by WJ-MSCs are further isolated and characterized by NTA. Their uptake by SCs is evaluated by detecting the emitted fluorescence with FACS.

Results

Our results obtained from NTA demonstrate the successful cloning and production of laminin-binding EVs. The positive tracking of fluorescence with FACS verifies their binding affinity on rodent laminin and their increased uptake and pro-regenerative effect on SCs.

Conclusions

This study represents a substantial advance for further investigation on EVs regarding their influence on peripheral nerve regeneration processes.

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Concentrations of antiseizure medications during pregnancy and breastfeeding in women with epilepsy: evaluation of acute side effects and systematic follow-up of development of breastfed infant. A international multicenter study.

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Objective

Despite that recent position papers and guidelines recommend women with epilepsy (WWE) to breastfeed and highlight the benefits of breastfeeding, for both mother and child, only 42% of WWE breastfeed at three months. Several factors are involved, but the main one is the misconception that drugs taken by the mother are transferred to the baby through breastmilk and could cause acute or long-term adverse events. Although different studies have quantified antiseizure medications (ASMs) in breastmilk of WWE, there are limited data on the safety of specific ASMs during lactation, based on clinical experience, case reports and case series or observational studies. In addition, data on the possible effect of drugs on a child's neuro-cognitive development are also very scarce. Related to the premise, the objective of the current study is to characterize the second and third-generations ASMs concentrations in breastmilk and nursing-infant's plasma and assess adverse effect on the child's exposure to maternal drugs.

Methods

Women of childbearing age with a confirmed diagnosis of epilepsy (according to the ILAE 2014 practical definition), any type of seizure (focal or generalized), age > 18 years, on mono-or polytherapy with ASMs will be selected and enrolled. Breast milk samples, maternal and infant serum/plasma for quantification of the ASMs concentration will be collected until 4-8 weeks postpartum. Short and long-term adverse events on infant will be evaluated. Short-term breastfed infant outcomes are both clinical (impaired suckling, rash, sluggish, hypotonic, sedated, tremor, unmotivated sobbing) and laboratory tests (elevated platelet counts, alterations on electrolytes or hepatic profile enzymes). The long-term effect includes neurodevelopmental outcome of the infant at 12-24 months will be assessed using clinical scales.

Results

This is an international, multicenter, prospective study, which will be developed involving four epilepsy centers in Austria and Italy. The number of cases required to calculate the statistical power of the study is difficult to realize because it depends on the number of WWE wishing to become pregnant. However, considering that the reported rate of use of ASMs in pregnant women (3-4 cases per 1000) and the 2022 birth rate in the centers involved (total of 16.210 pregnancies), we consider enrolling approximately 80 women and children. The study received the approval of the South Tyrol Ethics Committee in November 2023 and was discussed in December 2023 in Salzburg Ethics Committee. It also received funding from the South Tyrol Health Authority.

Conclusions

The expected results of this study may be essential to guide epileptologists in the management of WWE taking ASMs during breastfeeding and to provide them with information on the safety of breastfeeding.

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Digital assessment of real-world walking activity in pulmonary hypertension: A prospective bicenter clinical trial

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Objective

Pulmonary hypertension (PH) has a prevalence of around 1% in the global population and comprises five main clinical subtypes that reflect a different pathophysiology. Shortness of breath and fatigue are the most important symptoms, and the significant loss of mobility makes it difficult to perform tasks of daily living (1,2). The clinical endpoints currently used in PH studies (e.g. six minute walk test) reflect impairments in daily mobility only to a limited extent. A digital recording of activity in the home environment over a longer period of time is therefore an attractive way to quantify the actual loss of mobility in more accurately. The aim of this study is to assess whether digital mobility outcomes (DMO) are suitable for monitoring the response to treatment, predicting the course of the disease or whether they can be helpful in the risk stratification of patients with PH.

Methods

This prospective observational study in pre-capillary PH is conducted at Klinikum Nuremberg and Robert Bosch Hospital in Stuttgart. At each time of medically indicated right heart catheterization, real life walking activity for seven consecutive days will be recorded with the Axivity AX6 sensor and characterized through eight newly validated DMOs: walking speed, step count, number of walking episodes, walking episode duration, cadence, number of body turns, stride duration, stride length (3). Primary endpoint will be the correlation of walking speed with hemodynamic data from RHC in a baseline and follow-up examination after 3 months. Along patient-reported outcomes, further clinical and laboratory data will be analysed in depth to characterize their relationship to real-world walking activity. Sample size calculation showed that 70 patients have to be included over a recruitment period of two years. Extensive analysis of the sensor's raw data will involve two different algorithms to interpret walking parameters.

Results

The study was successfully initiated at the two study centers in April 2024, with the first patient enrolled on April 19th.

Conclusions

This study will generate comprehensive real-world data on mobility of PH patients and the correlation and usefulness of DMO in research and clinical practice. In addition, a structured database for patients with PH in Stuttgart and Nuremberg will be implemented to facilitate further research, also comprising real-world effectiveness of PH-specific medications.

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Patient's Perspective and Expectations in Dupuytren's Disease Treatment

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Objective

Severity and duration of occurrence of the characteristic nodules and cords are important factors in the treatment of the neoplastic fibromatosis Dupuytren's disease (DD). Nevertheless, clinical practice shows and confirms that health-related aspects also significantly influence treatment and outcomes. It is necessary to include the patient's expectations and perspectives in the treatment process to achieve positive and realistic results. Although these aspects and their influence are always part of the treatment, they are rarely investigated in this progressive, non-curable disease, and there is no systematic overview on the available evidence. The aim of this study was to identify, classify and present the evidence base of patients' perspectives, expectations, and needs in DD treatment.

Methods

Using a systematic search strategy multiple electronic databases (PubMed, CINAHL) and hand specific journals were searched for relevant and available information. The studies were classified using the Oxford Level of Evidence (LoE) and their findings were linked to the International Classification of Functioning, Disability and Health (ICF) and classified into four categories ("expectations of treatment", "expectations of results", "need during treatment" and "knowledge for the future") relevant for the treatment.

Results

Of the 1.604 publications found, five publications could be included in this review. The sample size of the five included studies ranged from seven to 24 patients and the LoE from IIIb to IV, respectively. The 34 findings were linked to the ICF-components "body function", "body structure", "activities" and "participation" as well as the ICF-domains "neuromusculoskeletal and movement-related functions", "structures related to movement", "sensory function and pain", "learning and applying knowledge", "communication", "self-care" and "interpersonal interactions and relationships". The results of this review show that aspects such as involvement in decisions, communication of knowledge about the disease, treatment options including possible outcomes are essential for patients in DD treatment.

Conclusions

The results demonstrate the inadequate evidence base of health-related aspects in DD treatment. In addition to physiologically measurable parameter, health-related aspects are an issue and expected by patients with DD. Nevertheless, it is difficult to determine the individual contribution of these topics and to assess their value to subsequently use them adequately for the benefit of patients in DD treatment or developing and improving health services.

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BARRIEREN DES ZUGANGS ZU PALLIATIVE CARE IM KRANKENHAUS

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Objective

Palliative Care kann Leiden verringern, die Lebensqualität von Patient*innen und deren Angehörigen verbessern sowie die Kosten am Lebensende reduzieren. Diese Erkenntnisse förderten die Implementierung neuer Palliative Care-Angebote und erleichterten den Zugang. Im klinischen Alltag hängt dieser jedoch meist von der konkreten Zuweisungspraxis ab, welche wiederum von institutionellen Faktoren, individuellen Überzeugungen und soziokulturellen Variablen beeinflusst wird. Der Zugang zu Palliative Care ist damit nach wie vor kontingent und zahlreiche stationär behandelten Patient*innen erhalten keine Palliativversorgung. Eine systematische Aufbereitung potenzieller und existierender Barrieren könnte die Entwicklung von Strategien zu deren Überwindung befördern.

Methods

Systematisches Mixed-Methods-Review unter Verwendung eines integrierten konvergenten Ansatzes und thematischer Synthese. Die Datenbanken Cochrane Library, MEDLINE, CINAHL und PsycINFO wurden nach Studien des Zeitraums 10/2003 (letztes Review zu Zugangsbarrieren im Krankenhaus) bis 12/2020 durchsucht. Studien jeglichen Designs, die Evidenz zu Hindernissen des Zugangs zur im Krankenhaus verfügbaren Palliativversorgung bieten, wurden inkludiert.

Results

Nach initialem Screening von 3359 Datenbankeinträgen und Prüfung von 555 Volltexten wurden 79 Studien eingeschlossen. Die thematische Synthese ergab 149 zugangsbezogene Phänomene in sechs Hauptkategorien: (1) Soziodemografische Merkmale, (2) Gesundheitsbezogene Merkmale von Patient*innen, (3) Individuelle Überzeugungen und Haltungen, (4) Interindividuelle Kooperation und Unterstützung, (5) Verfügbarkeit und Zuteilung von Ressourcen sowie (6) Emotionale Herausforderungen. Während die Ergebnisse für die meisten soziodemografischen Faktoren nicht konklusiv waren, kristallisierten sich folgende Barrieren heraus: eine andere Erkrankung als Krebs oder geringe Symptomlast, ein generell kurativer therapeutischer Fokus zulasten palliativer Maßnahmen, die Nicht-Akzeptanz der bestehenden Prognose, negative Wahrnehmungen zu Palliative Care, missverständliche Kommunikation und widersprüchliche Versorgungspräferenzen, fehlende Ressourcen, schlechte Koordination, unzureichende Fachkenntnisse sowie emotionales Unbehagen des medizinischen Personals.

Conclusions

Die Ergebnisse des Reviews verdeutlichen, dass der Zugang zur Palliativversorgung in Krankenhäusern mit diversen mehrdimensionalen Barrieren verbunden ist. Der Vergleich mit früheren Reviews zeigt zudem, dass zahlreiche dieser Barrieren über Jahrzehnte hinweg persistieren. Es besteht somit nicht nur praktischer Bedarf an Abbau und Prävention von Barrieren, sondern auch an Forschungsprojekten, welche die Mechanismen der Aufrechterhaltung dieser Barrieren durchleuchten.

The assessment of biological maturation in academy soccer players: a comparison of two methods

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Objective

The calculation of biological age and maturity status is highly relevant in the care of adolescent soccer players, as this information can have an impact on performance and injury risk. While various methods exist for assessing this, they are often expensive and challenging to implement (i.e., X-ray and MRI). The aim of this study was to assess an ultrasound-based examination method for evaluating skeletal age (SA), predicted adult height (PAH) and the biological maturation status (BMS, % of PAH) in a group of selected youth soccer players.

Methods

A total of $n = 17$ youth male soccer players (\bar{x} 13.21 years; range 12.65-13.62 years) of an Austrian Soccer Academy (U14) completed two measurements to assess biological maturity status outcomes at the start of the season 2023/24. Each player underwent an MRI and ultrasound diagnostics with the SonicBone device (from BAUSportTM) of the left wrist. A Bland-Altman analysis was conducted to evaluate potential differences. Furthermore, the level of agreement between the methods was assessed.

Results

The Bland-Altman analysis showed that more than 95 % of the values in the graph are within the limits of agreement for the mean value in the estimation of SA, PAH and BMS. Correlations of SA ($r=0.84$; $p<0.001$), PAH ($r=0.87$; $p<0.001$) and BMS ($r=0.85$; $p<0.001$) were highly significant.

Conclusions

The results highlight the measures usefulness and suggest that the SonicBone can serve as an alternative predictor of biological maturation within elite youth soccer. The biological maturity status should be taken into consideration in talent selection to avoid discrimination between early and late developers.

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Minimally invasive ascending aortic surgery: operative and mid-term outcomes

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Objective

Minimally invasive approaches, such as partial-sternotomy (PS), could reduce the surgical trauma and were proven to be safe for valve-related procedures [1]. We aimed to investigate the in-hospital and mid-term outcomes of patients undergoing ascending aortic surgery (AAS) through a partial or a full-sternotomy approach through a propensity matching analysis.

Methods

We retrospectively included all patients (n=167), who underwent elective AAS for aneurysm in our institution between 2013 and 2020. Patients, who received a surgical treatment in cases of emergency situations for aortic dissection were excluded. Study population was divided in two groups according to the surgical access (n=40 in partial sternotomy or "PS", and n=127 in full sternotomy, or "FS"). Due to the significant differences between the groups, a propensity matching 1:3 was applied. Age, BMI, gender and EuroSCORE II were used as covariate variables and the propensity score was computed based on the combined aortic valve operation. The Mahalanobis distance including the propensity score was used as distance calculation method. The order for matching was done at random. No maximum number of iterations were set for the optimization algorithm. After propensity matching, only the preoperative EF was significantly different between the two groups. In-hospital complications, survival and reoperation at follow-up were investigated.

Results

No operation started with a partial upper sternotomy had to be converted into a median full sternotomy during the operation. The majority of patients were operated with a brachiocephalic cannulation (PS=70% vs FS=61%, p=0.3) and selective cerebral perfusion (PS=65% vs FS=58%, p=0.3) in both groups. A combined aortic valve surgery was performed in the 92% of patients in the PS-group and 76% of patients in FS-group (p=0.06). PS group showed higher X-clamp and cardiopulmonary bypass times (94.2 min vs. 83 min and 164.2 min vs. 126.8 min). Moreover, the mean postoperative ventilation time was significantly higher in the PS group (41.5 hours±98.8 versus 22.5 hours±58.5), however not affecting the length of stay in ICU (3.6 days±4.7 versus 2.9 days±3.3; p=0.1). The incidence of bleeding, stroke and in-hospital mortality were similar between PS and FS group (11% vs. 3%, 3% vs. 6%, 5% vs 3%, respectively). After a median follow-up of 2±1.98 years, the Kaplan-Meier analysis showed no significant differences between the PS and FS group (log-rank, p=0.17) in term of survival. Cardiac reoperations were observed in 2 cases (6%) of the PS-group and in 8 (7%) of the FS group. In the PS group the reason accounted for hemodynamic relevant pericardial effusion, that was successfully treated with a subxiphoidal drainage placement. In the FS-group patients were reoperated because of pericardial effusion (n=3), sternal complications (n=2), tricuspidal valve insufficiency (n=1), aortic valve replacement (n=1) or tube prosthesis endocarditis by *Streptococcus gallolyticus* (n=1).

Conclusions

The surgical ascending aorta replacement through a partial sternotomy is associated with longer operative times, but this does not affect the early as well as the long-term follow-up. Surgical ascending aorta replacement can be safely performed through a minimally invasive approach.

Acknowledgements

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ATR-FTIR as tool for quality control of extracellular vesicles

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Objective

Extracellular vesicles (EVs) represent an exciting new research field with great therapeutic and diagnostic potential. Especially in the field of drug delivery, they open a promising field as novel vehicles for active pharmaceutical ingredients beside their inherent biological activity. Like any product for pharmaceutical purpose, a proper quality control is vital. In this context, ATR-FTIR can be a valuable tool. Here we evaluate the potential of ATR-FTIR techniques to determine important quality control parameters like lipid and protein content and composition as well as purity. For this purpose, we applied multivariate analysis methods for the acquired IR spectra in conjunction with classical colorimetric and biochemical techniques. As test subject, we used milk-derived vesicles that were isolated by tangential flow filtration due to their easy accessibility and high yield.

Methods

In order to assess the quality of milk derived extracellular vesicles, ATR-FTIR spectra of the vesicles were acquired in conjunction with colorimetric BCA and SPV assays to determine the protein and lipid content. In addition, an SDS PAGE and a LC-MS/MS analysis of excised gel bands was performed to analyze the protein content of EV samples with different purity grades. ATR-FTIR spectra were analyzed using a PLSR model. The EV samples themselves were purified by tangential flow filtration and purity was determined by size exclusion chromatography.

Results

The protein content of EV samples with different purity grades is changing. Samples with low purity show an accumulation of BSA and keratin. Regarding the protein and lipid content, the protein/lipid ratio is decreasing with higher purity which demonstrates that the protein/lipid ratio can be used for determination of EV sample purity. A prediction of purity using simply IR spectra in conjunction with a PLSR model is a suitable alternative. The test set gave a coefficient of determination of 0.78.

Conclusions

The Protein/lipid ratio can be predictive for EV sample purity, but requires additional markers for higher accuracy. EV sample purity can also be predicted by IR spectroscopy in conjunction with a PLSR model. However, a more diverse training set and proper post processing of the spectra may improve performance of the model. In addition, the PLSR model revealed spectral markers of purity, some of known biomolecules, others still need to be assigned to a certain class of biomolecules

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Ozanimod – Safety and Efficacy in a real-world-MS-cohort

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Objective

The shift towards "early intense therapies" for multiple sclerosis (MS) raises concerns about immune competence during pandemics as caused for example by the severe acute respiratory syndrome coronavirus type two (SARS-CoV-2) in 2019. So safety issues, especially concerning a potentially compromised defence, are becoming more and more relevant. We aimed to assess the baseline demographics and disease characteristics, the safety profile as well as efficacy of ozanimod, one of the newer, more selective, sphingosine 1-phosphate (S1P)₁ and S1P₅ receptor modulators, under real world conditions, in comparison to the SUNBEAM and RADIANCE approval studies.

Methods

We included 19 MS patients (range 22-45 years; 84% female) treated with ozanimod from our MS outpatient clinic of which all finished the projected one year observation period. Safety parameters including laboratory monitoring especially considering liver enzymes, lymphocyte counts, blood pressure, infections and expanded disability status scale (EDSS) were monitored at baseline/before treatment initiation (T0) and at follow-up control visits every three months (T3M-T12M), magnetic resonance imaging (MRI) control scan was performed at T12M.

Conclusions

In this real-life study, our patient cohort was comparable to that recruited in the pivotal studies. Accordingly, our results in terms of side effects as well as disease-suppressing effects match the published findings.

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The Influence of Chronotype on Interictal Epileptiform Discharges and Sleep Quality in Individuals with Epilepsy: A Study of Sleep-EEG Findings

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Objective

The aim of this study is to investigate the influence of sleep characteristics in patients with suspected first seizure on data obtained from sleep-deprivation EEG (S-EEG) recordings.

Methods

44 patients (45.5% female, mean age 49 years) were prospectively enrolled. The following data were collected: seizure semiology, demographics, neuroimaging, S-EEG results (sleep parameters, number and characteristics of IEDs). Patients also completed questionnaires to assess chronotype, insomnia, excessive daytime sleepiness (ESD).

Results

An increased number of IEDs was found in patients with a morning chronotype compared to a serotonin chronotype (13.86 ± 11.21 vs. 2.62 ± 3.62 , $p=0.013$), with no differences in sleep parameters, including total sleep time (TST) (20 ± 17.95 min vs. 18.5 ± 15.51 min, $p=0.875$). Patients with ESD show a non-significant increase in TST (26.78 ± 21.87 vs. 18.23 ± 13.60 , $p=0.228$), with no difference in the number of IEDs (3.14 ± 6.38 vs. 7.97 ± 25.33 , $p=0.62$). Patients with insomnia had a higher number of IEDs (8 ± 18.1 vs. 6.5 ± 3.9 , $p=0.015$) with no difference in TST (20.1 ± 19.30 vs. 18.95 ± 16.44 , $p=0.78$).

Conclusions

This study demonstrates a correlation between patient chronotype and the number of IEDs in S-EEG, which is higher in patients with morning chronotype. Insomniac patients also show an increased number of abnormalities, unlike ESD patients. Finally, no correlation was found between sleep duration and the number of IEDs, suggesting that the usefulness of this examination may be independently related to sleep deprivation, as opposed to sleep attained during recording.

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Risk factors for prolonged length of stay after first single-level lumbar microdiscectomy

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Objective

The objective is to identify risk factors that potentially prolong the hospital stay in patients after undergoing first single-level open lumbar microdiscectomy.

Methods

A retrospective single-centre study was conducted. Demographic data, medical records, intraoperative course, and imaging studies were analysed. The outcome measure was defined by the number of days stayed after surgery. A prolonged length of stay (LOS) stay was defined as a minimum of one additional day beyond the median hospital stay in our patient collective. Bivariate analysis and multiple stepwise regression were used to identify independent factors related to the prolonged hospital stay.

Results

Two hundred consecutive patients who underwent first lumbar microdiscectomy between 2018 and 2022 at our clinic were included in this study. Statistical analysis of factors potentially prolonging postoperative hospital stay was done for a total of 24 factors, seven of them were significantly related to prolonged LOS in bivariate analysis. Sex ($p = 0.002$, median 5 vs. 4 days for females vs. males) and age ($r_s = 0.35$, $p \leq 0.001$, $N = 200$) were identified among the examined demographic factors. Regarding preoperative physical status, preoperative immobility reached statistical significance ($p \leq 0.001$, median 5 vs. 4 days). Diabetes mellitus ($p = 0.043$, median 5 vs. 4 days), anticoagulation and/or antiplatelet agents ($p = 0.045$, median 5 vs. 4 days), and postoperative narcotic consumption ($p \leq 0.001$, median 5 vs. 4 days) as comorbidities were associated with a prolonged hospital stay. Performance of nucleotomy ($p = 0.023$, median 5 vs. 4 days) was a significant intraoperative factor. After linear stepwise multivariable regression, only preoperative immobility ($p \leq 0.001$) was identified as independent risk factors for prolonged length of postoperative hospital stay.

Conclusions

Our study identified preoperative immobility as a significant predictor of prolonged hospital stay, highlighting its value in preoperative assessments and as a tool to pinpoint at-risk patients. Prospective clinical trials with detailed assessment of mobility, including grading, need to be done to verify our results.

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Burden of spinal cord injury, 1990 2019: a systematic analysis for the Global Burden of Disease Study 2019 🏠

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Objective

Spinal cord injuries contribute to a major burden of disabilities causing health loss due to premature mortality and residual disability. While spinal injuries are a public health issue, no comprehensive report on their global temporal, spatial and demographic patterns has not been published. We aimed to measure the global, regional, and national incidence, prevalence, and years lived with disability (of spinal injuries from 1990 to 2019 using data from the Global Burden of Diseases, Injuries, and Risk Factors Study.

Methods

Data on incidence, prevalence, and YLDs of spinal injuries were derived systematically from the GBD 2019 study. Using the framework of GBD 2019 we provide numbers and age standardized rate changes with 95% uncertainty intervals (for incidence, prevalence, and YLDs of spinal injuries at neck level and below neck level globally and for 21 GBD regions and 204 countries and territories, among all age groups and both sexes from 1990 to 2019. We tried to detect and report meaningful trends based on location, age and gender.

Results

Globally, there were 20.6 million (95% UI 18.9 to 23.6) individuals living with SCI in 2019. The incidence of SCI was 0.9 million cases (95% UI 0.7 to 1.1) with an estimated 6.2 million (95% UI 4.4 to 8.1) YLDs. SCI rates increased considerably from 1990 to 2019 for global prevalence (81.5 UI 74.2 to 87.1), incidence (52.7 UI 30.3 to 69.8) and YLDs (65.4 UI 56.3 to 76.0) (Figures 1-2). However, global age standardized rates per 100,000 population showed slighter changes for prevalence (5.8 UI 2.6 to 9.5), incidence (6.1 UI 1.7 to 1.5) and YLDs (1.5 UI 0.5 to 3.2). The incidence, prevalence, and YLDs of SCI have consistently been higher in men globally, with a slight and steady increase observed for both sexes from 1990 to 2019 (Figure 3). In 2019 the number of SCI increases by age until 15-19 years where it remains reasonably constant until 85 years of age. Prevalence and YLDs showed similar patterns with one peak at around 45 to 54 years (Figure 4).

Conclusions

While age standardized rates of incidence, prevalence, and YLDs for SCI changed slightly, absolute counts increased substantially from 1990. There is also a wide geographical heterogeneity in demographic, spatial and temporal patterns of SCI both at national and regional level, which should be considered by policy makers to reduce the burden of SCI locally.

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VALIDATION OF THE ARTHROPLASTY REGISTER OF SOUTH TYROL BETWEEN 2010-2020 – DATA ANALYSIS OF THE SABES HOSPITALS

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Objective

To validate an Arthroplasty Register (AR) means to proof its robustness in producing complete and correct data. Existing literature showed missing revision rates from 12% to 20% and data entry error of 2%. The AR of South Tyrol, nested in the Italian one, began in year 2010. Its completeness was 98% for hips and 100% for the knees. Every year reports are published, but correctness of those data has to be checked. Aim of this work is to discuss the validation project

Methods

Retrospective analysis of register data of hip and knee arthroplasty between 2010 and 2020 has been performed (around 20,000 procedures, in seven public hospitals). 5% of primary and 10% of revision procedures were checked. Missing records checked as well. Particular attention has been made by registered aseptic loosening procedures.

Results

We found a general data entry error rate of 2 to 4%. Higher rates were related to revision procedures. Data entry errors were divided in tipping- and syntax ones, with a clear reduction during time, due to learning curve. False coding for aseptical revisions was about 7% of all loosening revisions. (2% of all revision cases). This was due to lacking correction of the data already entered in register, after receiving positive antibiogram. Missing cases are 3% for primary procedure and 14% for revision ones.

Conclusions

The resulted error rate after 10-year arthroplasty register in South Tyrol is aligned with previous validated national register around the world. Further correction steps needed to be undertaken to reduce overall error in all categories. Therefore, SABES implemented a novel internal AR-database with open-access to every competent authority. Preventive medicine must rely on complete and corrected register data.

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How primary care physicians deal with the climate crisis: preliminary results of a scoping review

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Objective

In 2009 a LANCET commissions called the climate crisis "the biggest threat for health in the 21st century". Physicians in primary care are increasingly confronted with its direct and indirect health impacts e.g. on infectious diseases, allergies, mental health and heat-related diseases. At the same time healthcare contributes significantly to greenhouse gas emissions - in Austria: 7% of national carbon emissions.¹ A transformation of patient care is needed in order to reduce its footprint (climate mitigation) and to provide a proactive response to the unavoidable climate-health consequences (climate adaptation).

Methods

A scoping review is performed according to the Joanna Briggs Institute (JBI) approach² to map available evidence on climate change mitigation and adaptation in primary care. Reference search was conducted via PubMed, Medline and Web of Science and a hand search applied.

References were reviewed by an interdisciplinary research team. Only references reporting interventions from EU countries the UK, Norway and Switzerland, published between January 2012 and May 2023 were included. With regard to the sources, an open format was chosen. Reporting is done according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR)³ scheme.

Results

As this is an ongoing research project only preliminary results can be presented. 2.769 references were screened. Only six references included for final analysis were relevant to primary care physicians. All of those articles covered aspects of climate mitigation (travel&transport (5), pharmaceuticals (2), circular healthcare & waste management (2), electricity (2), greater health system effectiveness (2) food/nutrition (1) and buildings & Infrastructure (1)) but not climate adaptation.

Conclusion

Preliminary results show that there is very little evidence on actual implementation of climate mitigation and adaptation in primary care practices esp. with regard to validation of effectiveness of measures. However, the provision of sound evidence-based guidance is essential in order to increase the climate resilience of patient care and thus the population. Therefore, in depth research is urgently needed.

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SEX DIFFERENCES IN PAIN COURSES IN PATIENTS WITH HIP OR KNEE OSTEOARTHRITIS AFTER MULTIMODAL SPA THERAPY IN THE AUSTRIAN VALLEY OF GASTEIN

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Objective

Sex-differences in perceived pain have been discussed widely throughout the literature pointing, among others, towards the role of intervention type in the association of sex and perceived pain. Therefore, pain outcomes after interventions should be evaluated separately for men and women enabling determination of adequate treatment intervals and sex-specific modulation of interventions. The current study aimed to shed light on sex-differences in the course of pain in patients with hip or kneeosteoarthritis (OA) after multimodal spa-therapy in the Austrian valley of Gastein.

Methods

Longitudinal analyses of prospectively collected registry data from the ongoing “Radon indication registry” collecting data directly before (baseline), directly after and 3; 6 and 9 months after multimodal spa-therapy were conducted. Multilevel mixed-effects linear regression models were computed to explore the association of timepoint of measurement with a) pain in motion and b) pain in rest (both measured on an 11-point numeric rating scales; 0=no pain, 10=worst pain imaginable) separately for men and women while adjusting for age and body mass index (BMI) and accounting for individual differences through inclusion of patient identification number as random effect parameter.

Results

The sample consisted of 34 women and 52 men with a mean age of 59 (SD 6.4) & 58 (SD 7.9) years and a mean BMI of 26.0 (SD 4.3) & 28.3 (SD 3.4), respectively. Both sexes showed significant improvements in pain in rest and motion until up to 9 months after treatment when compared to baseline. However, improvements were larger and in case of pain in rest sustained longer in women than in men.

Conclusions

These results point towards the relevance of individualized treatment intervals while accounting for sex and might give rise to treatment plan modulation to support sustained treatment results specifically for men with OA who receive multimodal spa-therapy in the Austrian Gastein valley. They also support previous findings that emphasize the necessity of sex specific intervention evaluation and development.

Comparison of naturally produced EVs and artificial CDVs

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Objective

In the development of a Parkinson's Disease (PD) vaccine, a biomarker to identify patients at risk is crucial. Currently, extracellular vesicles (EVs) stand out as promising candidates. This demands the production of model vesicles as reference material in large quantities. Isolation methods such as TFF are time-intensive, requiring weeks to collect sufficient cell supernatant due to a limited number of 100-1000 EVs released by cells daily. In comparison, an extrusion could significantly speed up the process. Here, cells are pressed through an extruder membrane, which produces a high number of extracellular particles, as depicted in figure 1. Therefore, this experiment sets out to analyse the characteristics of such CDVs to determine if they have comparable properties to secreted EVs. Due to its relevance for PD research, this experiment focused on one fluorescent neuroblastoma cell line (SH-SY5Y GFP) which expresses GFP-labelled α -syn, a key protein for PD development and progression. Two control lines HEK CD63 mNEON and HEK-WT were included for comparison.

Methods

CDVs were extruded from three cell lines (SH-SY5Y GFP, HEK CD63 mNEON, HEK-WT) comparing two extruder models (Extr. a / Extr. b). Resulting particles were imaged through cryo-transmission electron microscopy (cryo-TEM), counted by tunable resistive pulse sensing (TRPS) and further evaluated by fluorescence nanoparticle tracking analysis (f-NTA). Dot blots confirmed the EV identity by tetraspanin expression and presence of α -syn. TFF-EVs served as comparison material.

Results

Characterisation of extruded CDVs: Three different cell lines were used (SH-SY5Y, HEK CD63 mNEON, HEK-WT) to produce CDVs comparing two extruders (Extr. a / Extr. b). Graphs are formed from the mean of the results of three extrusions. For all experiments no difference between the two extruder models could be detected. It could be confirmed by Cryo-TEM that the produced particles were EVs and CDVs with a double membrane. Particle count: Size distribution and concentration of CDVs and EVs, both measured by TRPS. CDVs from all three cell lines show a similar size distribution with a mean size of about 120 nm (mode size 90 nm). This is slightly bigger than reported values of naturally produced EVs from HEK cells (mean size 90 nm) (Görgens et al., 2022). The CDVs were concentrated at 1011 particles/mL which is slightly higher than TFF-EVs (at 1010). EV identity: Dot blots of tetraspanin and α -syn at 1 second exposure time confirmed the expression of all three tested tetraspanins (CD9, CD63, CD81) in all cell lines and the expression of α -syn in SH-SY5Y. Fluorescence Analysis: Fluorescence positivity of CDVs measured by f-NTA. The fluorescence analysis via f-NTA showed that CDVs were less fluorescent than EVs. While approximately 80% of the HEK CD63 mNEON EVs were fluorescent, only 10% of the CDVs expressed mNEON. SH-SY5Y-EVs and -CDV fluorescence was <1%. (g) Double-positive HEK CD63 mNEON EVs and CDVs for CD63 and mNEON measured by f-NTA. In the HEK CD63 mNEON samples, mNEON was expressed by 60% of the CD63+ EVs and 20% of the CD63+ CDVs.

Conclusions

Extruded CDVs have a high concentration and show similarities with EVs in terms of size. They also express tetraspanins and in case of the SH-SY5Y cells α -syn. However, there seem to be major losses of fluorescence during cell extrusion, as CDVs were 10-fold less fluorescent than EVs. To better understand the mechanisms behind cell extrusion, we could conduct additional experiments to test extrusion parameters such as membrane pore size, stabilizers, cell numbers, temperature etc. Additional filtration and concentration steps could be added to further improve the quality of the samples.

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Physicians' Perspectives, Well-being, and Fulfilment in Telemedicine

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Objective

Telemedicine, a safe way of medical care appreciated by patients, has proven to have different benefits for our healthcare systems. Studies on patient experiences and outcomes in telemedicine are thriving. However, few studies have explored the possible associations between telemedicine and physician work-life balance or mental health.

Methods

We conducted a cross-sectional survey for physicians who practiced in Switzerland. Physicians who participated answered validated questions about work-life balance, professional satisfaction, emotional exhaustion, and depression. There were three groups: a control group with physicians who did not practice telemedicine (n=30), an experimental group with physicians who practice telemedicine (n=32), and a third group with physicians who left telemedicine (n=31). The 42-question survey was open between June and August of 2023. Participation was optional, anonymous, and voluntary.

Results

In total, 93 participants completed the questionnaire. In terms of work-life balance, the best results were observed in the telemedicine group (4.63 vs 4.35 in the control group). A high level of exhaustion was observed in 26.7% of the control group, compared to 12.5 % of the telemedicine group. Low professional fulfilment was present in 62.5% of participants in the telemedicine group vs. 46.7 % in the control group. Among the telemedicine physicians, 21.9% were suspected of having depression.

Conclusions

Practicing telemedicine as a profession may have a positive impact on physicians' work-life balance and burnout. We found no significant statistical differences among groups regarding professional fulfillment and depression. Further research is necessary to explore long-term effects of telemedicine on physicians' mental health.

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Characterisation of variants in the SLC26A4 gene identified in a Slovak cohort with non-syndromic enlarged vestibular aqueduct and Pendred syndrome

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Objective

Pathogenic variants in the SLC26A4 gene, encoding for Cl⁻/HCO₃⁻ and I⁻ anion transporter pendrin, are one of the most common causative factors of hereditary hearing loss worldwide and can be associated with non-syndromic hearing loss with enlarged vestibular aqueduct (NSEVA) or Pendred syndrome (PDS), manifested by thyroid dysfunction and goiter (1). The aim of this study was to characterize the functional and molecular features of five pendrin variants identified in Slovak patients with sensorineural hearing loss (NSEVA or PDS) and assess a correlation with the patient's clinical symptoms.

Methods

Pendrin variants were introduced into SLC26A4-encoding mammalian expression vectors by site-directed mutagenesis and expressed in HEK293 Phoenix cells and HeLa cells. The ion transport efficiency of pendrin variants was determined by fluorometric analysis by using the iodide-sensitive EYFP variant H148Q;I152L to monitor iodide influx. Quantitative confocal imaging was performed to determine the total expression level of pendrin variants. The subcellular localisation of pendrin variants was determined by analysing the co-localisation with plasma membrane (PM) or endoplasmic reticulum (ER) markers.

Results

Functional tests showed that five out of six studied pendrin variants (p.G139R, p.M147I, p.Y530S, p.D754IfsX5, and p.F161I) exhibit significantly reduced function compared to wild-type pendrin, while the function of the variant p.R47Q was preserved. By quantitative confocal microscopy, we confirmed a massively reduced expression of pendrin variants p.G139R, p.M147I, p.Y530S, and p.F161I compared to wild-type. The p.R47Q variant showed a wild-type-like expression. Moreover, variants p.G139R and p.Y530S showed retention in the ER in comparison to the wild-type protein and severely diminished co-localization with the PM. Variants p.M147I and p.F161I showed moderate, but significant retention in ER compared to wild-type pendrin and significantly reduced PM targeting. Variant p.R47Q was identical to the wild-type.

Conclusions

Our results demonstrated reduced function and impaired subcellular localization of variants p.G139R, p.M147I, p.Y530S, p.D754IfsX5, and p.F161I. The experiments confirmed the potentially pathogenic character of these five variants and their association with symptoms of NSEVA/PDS in affected patients. On the other hand, the variant of unknown significance p.R47Q was reclassified as benign and its role in the pathogenesis of mild hearing loss has not been confirmed.

Acknowledgements

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Prognostic and predictive factors (clinical data, histological and molecular data, laboratory values) under palliative first-line therapy for squamous cell carcinoma of the lung with chemotherapy plus immunotherapy

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Objective

Patients with squamous cell carcinoma of the lung have low 5-year survival rates (2). This study examines various prognostic and predictive factors (clinical data and blood values) in patients with chemotherapy plus immune checkpoint inhibitors in palliative first-line therapy.

Methods

Data collected from 61 patients (2018 to 2023) were analyzed retrospectively. All Patients suffered on a squamous cell lung cancer and received a combination of at least one cycle of the ICI pembrolizumab and chemotherapy (carboplatin and (nab-)paclitaxel) as part of palliative therapy. Significant parameters were identified using log-rank test and chi-square test: Cox regression was applied.

Results

The 61 patients examined had a median age of 65 years and 72.1% were male. The median overall survival was 19.9 months and the median progression-free interval was 9.9 months. In the multivariate analysis, age ≥ 65 years ($p=0.001$) and a body mass index value ≤ 25 ($p=0.01$) were significant independent prognostic parameters for longer median overall survival. Age ≥ 65 years ($p=0.007$) and PD-L1 status > 0 ($p=0.039$) are significant for progression-free survival. An increased CRP value before the second cycle ("dynamic change") showed predictive relevance for a poorer prognosis in the univariate analysis. A PD-L1 status > 0 ($p = 0.016$) and normal G-GT value before the start of immunochemotherapy ($p = 0.008$) are positive predictors of treatment response.

Conclusions

Clinical and laboratory parameters can give an outlook on the response and course of therapy of patients with squamous cell carcinoma of the lung with immunochemotherapy.

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Metabolic Footprint of Ketosis-inducing Diets in Mice

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Objective

Emerging evidence associates diet-induced ketosis with several beneficial effects on health and disease, inter alia reduced inflammation, improved lipid profiles, weight loss, and improved diabetes management (1). However, little is known about the effect of different ketosis-inducing dietary approaches on the metabolome. Therefore, we aimed to characterize the metabolic profile of multiple matrices, namely plasma, liver, spleen, white adipose tissue, duodenum, and feces of mice fed with different ketosis-inducing diets, including caloric restriction (CR), intermittent fasting (IF), fasting-mimicking diet (FMD), ketogenic diet (KD), and regular mouse chow.

Methods

Male C57BL/6 mice were subjected to the following dietary regimes: CR (14 days 80% kcal of regular ad libitum chow intake), IF (28 days 100% food restriction every other day followed by 24h ad libitum refeeding), FMD (28 days, 3 cycles of 4 days fasting with 50% kcal of regular ad libitum chow intake on day 1, 10% kcal on days 2-4 with 7 days of refeeding), KD (28 days ad libitum ketogenic ratio 4:1), and regular chow (28 days ad libitum) (2). Samples were collected at a mouse age of 16 weeks for all dietary intervention groups. A comprehensive metabolomics analysis using the MxP® Quant 500 Kit (biocrates life sciences AG) enabled the quantification of 26 compound classes, such as amino acids, amino acid-related metabolites, bile acids, free fatty acids, cholesterol esters, acylcarnitines, sphingolipids, glycerophosphocholines, and glycerolipids.

Results

In the dietary groups, lipid and polar metabolite classes varied substantially in plasma and tissues. For instance, CR, IF, FMD, and KD reduced glycerolipid levels (di- and triacylglycerides) in plasma by 38%, 56%, 90%, and 49%, respectively, compared to regular chow. Moreover, two metabolites, namely proline betaine and trigonelline, were consistently reduced in plasma and in all organs, while 3-methylhistidine was consistently increased in all matrices except feces by the ketosis-inducing diets.

Conclusions

Our analysis provides a comparable multi-tissue metabolic footprint for each of the diets as a basis for understanding the various effects attributed to ketosis-inducing diets on a metabolic level. Further analysis will reveal the association of specific metabolic changes with diet-induced ketosis and its health benefits (e.g. association with inflammatory markers).

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Theranostic EV biomarkers from non-invasive liquid biopsies

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Objective

Extracellular vesicles (EVs) possess key roles in cell-to-cell communication in health and disease (1). Their presence in most tissues and body fluids makes them an excellent target for biomarker discovery. Here we are developing a theranostic Parkinson's disease (PD) biomarker to select candidate patients for vaccination and monitor their response. We selected, PD driving oligomeric α -synuclein (α -syn) as primary diagnostic target. Not knowing the location of α -syn inside EVs or as surface cargo, we apply methods preserving natural EV corona enabling extended downstream biomarker analysis.

Methods

EVs were enriched from healthy donor urine (uEV) via tangential flow filtration (TFF). Influence of storage at -80°C on EV quantity and size was analysed by tunable resistive pulse sensing (TRPS), and quality by tetraspanin+ biomarker expression in dot plots and super-resolution microscopy

Results

Small uEVs with a mode size 89.75 ± 0.59 nm (mean \pm SEM) were isolated by TFF. EV CD9/63/81 tetraspanin expression did not show significant differences before/after cryo-storage despite 63-86% loss of particle number from $3.0 \pm 0.5 \times 10^{10}$ to $1.6 \pm 1.0 \times 10^{10}$ particles/mL (mean \pm SEM) after thawing. Spiking a-syn-EVs as a representative biomarker into uEVs enabled comparing both sources for setting up a sensitive detection assay. Titration of a-syn-EVs will determine optimum pre-analytic conditions for subsequent biomarker detection based on ISEV uEV task force recommendations.

Conclusions

Developing new theranostic biomarker analysis methods from easy accessible non-invasive sources is important for patient acceptance and study performance. We develop a standardized protocol regarding sample retrieval, pre-processing, storage and EV isolation for biomarker studies

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Nanoindentation on Tendon Tissue

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Objective

Biomechanical testing of tendons is commonly performed by uniaxial tensile stretching along collagen fibre orientation. So far, only little is known about tendon biomechanical response to compression on a nanoscale, which may provide information on tissue quality not achievable by tensile testing.

Methods

Cryosections of unfixed healthy rat patella tendons derived from male SD rats and from tendons 2, 4 and 6 weeks after creating a 2 mm punch defect were examined with a Chiaro Nanoindenter (Optics11 B.V.). Measurements were performed at several time points after immersion, either in Phosphate Buffered Saline (PBS) or 8% polyethylene glycole (PEG) in PBS. For indentation, a cantilever with a stiffness of 0.5 N/m and a sphere tip with a radius of 52 µm was used. Stiffness was calculated using the Hertzian model.

Results

In healthy tendons, E(eff) declined from 23.4±3.6 kPa after 5 minutes to 11.3±2.9 kPa after 60 minutes, stiffness of the tendon defect area only declined from 4.9 ± 1.4 kPa after 5 Minutes to 3.6± 1.1 kPa after 60 minutes (Figure 1). Immersion in 8% PEG after 5 minutes hydration in PBS lead to an average stiffness of 135± 34.1 kPa after 10 minutes.

Conclusions

The observed decline in elasticity modulus due to PBS immersion needs to be considered for longer lasting measurements like surface mapping studies. Moreover, the use of PEG to avoid tissue swelling as it has been shown for tensile testing (1) of tendons is not suitable for tendon nanoindentation. As nanoindentation measurements can only be performed in aqueous solutions, the "in vivo degree of hydration" remains an unknown variable, favouring semiquantitative, within- experiment analyses.

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The clinical relevance of low-grade infected nonunion

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Objective

Treatment algorithms for fracture nonunion depend on the presence or absence of a bacterial infection. However, the clinical presentation of nonunion varies and an underlying infection is not always obvious. While patients with manifest infection present with clinical signs of infection, patients with low-grade infected nonunion present similarly to patients with aseptic nonunion. Only microbiology and histopathology of intraoperative obtained samples can reveal a low-grade infection. The aim of this study was to evaluate the clinical relevance of low-grade infection in the development and management of nonunion.

Methods

A prospective, multicenter clinical study enrolled patients with femoral or tibial shaft nonunion and regular healed fractures. Preoperatively, serum markers including C-reactive protein (CRP), leukocytes, and procalcitonin were determined, clinical infection signs were recorded, and a suspected 'septic' or 'aseptic' diagnosis was made. During nonunion revision or routine implant removal, tissue samples were collected for microbiology and histopathology, and osteosynthesis material for sonication. Nonunion patients were followed for 12 months. Definitive diagnosis of 'septic' or 'aseptic' nonunion was made according to diagnostic criteria for fracture-related infection (1), considering the follow-up period.

Results

110 patients with nonunion and 34 patients with regularly healed fractures were included. 27 nonunions were suspected to have an underlying infection, which was confirmed in 22 cases. 83 nonunions were assumed to be aseptic, but an underlying low-grade infection was diagnosed in 23 cases. Three cases with an unclear diagnosis were excluded from statistical analyses. Sensitivity and specificity for the suspected diagnosis were 49% (34-64% CI) and 95% (86-99% CI), respectively. The low-grade infection rate in presumed aseptic nonunion was 28%. CRP was the only serum blood marker with mean values above the reference range that was significantly higher in all nonunion groups compared with the regular healer group. Manifest and low-grade infected nonunions were commonly caused by coagulase-negative staphylococci (59% and 74%) and *Cutibacterium acnes* (23% and 52%). The latter was detected significantly more often in low-grade infections compared to manifest infections ($p=0.042$). Patients with low-grade infections were treated with systemic antibiotics significantly less frequently (55% vs. 96%, $p=0.002$) and for a significantly shorter duration than patients with manifest infections (6 ± 3 vs. 11 ± 5 weeks, $p=0.005$). Eight nonunions in the low-grade infection group consolidated during follow-up period without systemic antibiotics. The overall healing rate of low-grade infected nonunion (83%) was statistically comparable to that of manifest infected nonunion (62%) and aseptic nonunion (90%).

Conclusions

Our findings demonstrate a significant role for low-grade infection in the development of nonunion. The only difference between aseptic and low-grade infected nonunion was the intraoperative detection of bacteria and the associated need for systemic antibiotics. Combined with an effective surgical revision, a high healing rate could be achieved for low-grade infected nonunion.

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Bioanalytic methods in psychosomatic medicine

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Objective

Psychological and emotional stress triggers a cascade of physiological responses, including the activation of the hypothalamic-pituitary-adrenal (HPA) axis and the sympathetic-adrenal-medullary (SAM) axis. These processes can lead, among other things, to the increased production of reactive oxygen species (ROS). Chronic states of increased ROS levels are referred to as „oxidative stress“ and are characterized by lipid, protein and DNA damage. Oxidative stress contributes to a myriad of pathologies, such as cancer, autoimmunity, cardiovascular diseases and neurological disorders.¹⁾²⁾

Methods

Quantification of ROS levels: Electron Paramagnetic Resonance (EPR) EPR is a spectroscopic method based on the interaction between unpaired electrons and an external magnetic field. For the detection of ROS special membrane-permeable spinprobes are employed which produce less reactive and more stable species that can be readily detected by EPR.²⁾ Quantification of DNA damage: Single-cell electrophoresis („Comet Assay“) In the comet assay, cells are embedded in agarose on a microscope slide, lysed to remove cellular proteins, and subjected to alkaline denaturation with subsequent electrophoresis. During electrophoresis, DNA fragments migrate away from the nucleus towards the anode according to their size, forming a comet-like tail. The quantification of DNA damage is achieved through analysis of the tail moment, which is the product of the tail length and the fraction of DNA within the tail. Quantification of mitochondrial oxygen consumption rates: Oxygraph O2K „Oroboros“ The Oroboros oxygraph operates on the principle of high-precision polarography, where the oxygen concentration is detected amperometrically by a Clark-type electrode. The application of „SUIT“ (substate, uncoupler, inhibitor, titration) protocols allow the real-time monitoring of oxygen flux in various experimental conditions, thereby enabling the analysis of mitochondrial respiration and function of cells and organs.

Results

Preliminary data from the MALT study, which analysed the effectiveness of art therapy after a miscarriage or stillbirth, showed significantly increased levels of ROS in the blood and slightly but not significantly increased tail moment, indicative of DNA damage, in the study group compared to the control group. The participants were analysed under resting conditions (T-10), experimental stress (T0) and after regeneration (T+20). A Social Evaluated Cold Pressor Test (SECPT) was employed to induce a reliable stress response.

Conclusions

Finding biological marker for psychological stress may represent promising tools for future research and treatment.

Acknowledgements

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Detecting high risk neighborhoods and socioeconomic determinants for common oral diseases in Germany with geostatistics and machine learning models

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Objective

Ideally, health services and interventions to improve dental health should be tailored to local target populations. But this is not the standard. Little is known about risk clusters in dental health care and their evaluation based on small-scale, spatial data. To investigate this, i) analyses of the spatial distribution of oral diseases (periodontitis, severe caries, irreversible pulpitis, tooth loss), ii) identification of risk clusters, and iii) the description of these different risk clusters based on socioeconomic determinants are necessary.

Methods

A retrospective cohort study was performed to calculate the age- and sex-standardized incidence rate of oral diseases in a study population of privately insured and self-pay patients in Germany who received dental treatment between 2016 and 2021. This was based on anonymized claims data from the BFS health finance|arvato|Bertelsmann (BFS). The disease history of individuals was recorded and aggregated at the ZIP code 5 level (n = 8871). Statistically significant, spatially compact clusters and relative risks (RR) of incidence rates were identified. By linking disease and socioeconomic databases on the ZIP-5 level, local risk models for each disease were estimated based on spatial-neighborhood variables using different machine learning models.

Results

We found that dental diseases were spatially clustered among privately insured and self-payer patients in Germany. The relative risks (RR) for a new dental disease in primary risk clusters were 1.3-2.7, depending on the disease. Incidence rates within clusters were significantly elevated compared to incidence rates outside clusters. The methodology presented here enables the identification of disease clusters of greatest demand, which would allow implementing more targeted approaches and improve access to quality care where they can have the most impact.

Conclusions

Our results show that private claims data can be used to highlight locations and variables relevant to oral healthcare. A network-based, data-driven approach, that includes the use of non-traditional data sets, holds great potential in supporting resource-based management in the health system. The findings of our study can inform policymakers and researchers in focusing on oral disease incidence and socioeconomic predictors to mitigate disease risk and improve oral health.

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The Impact of Educational Status on the Occurrence of Colonic Diverticula

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Objective

The level of education often serves as an indirect indicator of socioeconomic status.(1) Preliminary investigations have suggested that individuals from lower socioeconomic backgrounds may be more susceptible to diverticulosis.(2) Based on data obtained from the United States, diverticular disease has emerged as a growing health problem with significant financial consequences.(3) Considering these circumstances, our research aimed to investigate the association between educational attainment and the occurrence of colonic diverticula.

Methods

We conducted a study involving 5,532 asymptomatic patients in Austria who were undergoing screening colonoscopy. The purpose of our investigation was to examine the connection between educational attainment and diverticulosis. To assess the educational level obtained through the questionnaire, we classified patients into three categories (low, medium, and high) using the updated Generalized International Standard Classification of Education (ISCED). To ascertain the relationship between educational status and the detection of diverticulosis, we employed multilevel logistic regression models, controlling for variables such as age, sex, metabolic syndrome, dietary habits, and physical activity. The local ethics committee for the province Salzburg approved the study protocol (approval no. 415-E/1262).

Conclusions

Individuals with lower educational status were more likely to have colon diverticula. People with a moderate level of education exhibited a lower incidence of diverticulosis, even after adjusting for relevant factors, with no apparent correlation to the distribution across different segments of the colon. This trend was also observed among individuals with higher levels of education. Implementing targeted strategies that consider socioeconomic conditions could potentially reduce the treatment costs associated with this condition.

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Optimised intraoperative radiotherapy treatment workflow using machine learning methods

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Objective

Intraoperative radiotherapy (IORT) complements teletherapy in a broad spectrum of applications in the treatment of cancer by delivering radiation directly to the tumor during surgery. This has a number of advantages i.e. sparing of organs at risk and a precise localization and targeting of the tumor bed, allowing for the application of high doses in one fraction. On the other hand, advances in treatment planning in teletherapy, especially using voxel-based 3D models, have far surpassed IORT dose calculation concepts. Leaving aside the lack of appropriate imaging devices until recently, one of the main reasons for this discrepancy is the tight time schedule in an operative setting. This project aims to address the challenges related to the laborious and time-consuming nature of treatment planning, the need for precise applicator positioning and the necessity of optimal placement of radioprotection shielding.

Methods

This project introduces new algorithms, capitalizing on the synergy of artificial intelligence (AI), advanced image processing and computational methods. The first major objective is to develop and validate an artificial neural network to automatically contour organs at risk and the applicator on Cone Beam Computed Tomography (CBCT) scans, that were acquired with the mobile Imaging Ring-m during IORT procedures. In recent years, U-Net models were the most popular architectures in the domain of medical image segmentation. However, transformer network architectures became the new trend for deep learning models due to their capability to learn long-range dependencies and therefore handling global context. Although, it is essential to emphasize that transformers may not perform as effectively in capturing the finer spatial details in images, which is an area where U-Net excels. Consequently, the idea is to use a combination of the UNet and Transformer architecture to enhance the segmentation accuracy on CBCT images. The algorithm is trained and validated using a dataset consisting of 69 CBCT scans. This dataset is obtained from breast cancer patients undergoing IORT in the university clinic of radiotherapy in Salzburg. Building on the AI-based contouring model, an algorithm to accurately position the radiotranslucent applicator within the treatment planning software RADIANCE (by GMV) can be implemented. In addition to this, the orientation of radioprotection shields with respect to the applicator can be automatically verified. Ensuring that the shields are positioned perpendicular to the applicator, minimizes the exposure of organs at risk to radiation. The accuracy and effectiveness of the algorithm is evaluated through rigorous testing and comparison with established manual placement techniques.

Results

Implementation of state-of-the-art deep learning algorithms for automatic segmentation will help save time to allow for the adoption of 3D model based treatment planning in an operative setting. In a first step, automated precise applicator positioning will result in improved treatment planning accuracy, minimizing the risk of radiation-related complications and enhancing patient safety.

Conclusions

Closing the gap in treatment planning between teletherapy and IORT has the potential to optimise the quality of IORT treatments and ultimately improve patient outcomes.

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PKC activators orchestrate neuronal immune modulation: Unveiling microglial dynamics in NF-KB activation and phagocytosis

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Objective

Chronic neuroinflammation, associated with central nervous system (CNS) pathologies, involves persistent microglial activation. Misfolded proteins in Alzheimer's disease and mechanical CNS lesions initiate prolonged immune responses, contributing to neuronal damage. Recent literature suggests the induction of controlled immune modulation to foster neuro-restoration. We propose the use of protein kinase C (PKC) activators to modulate CNS innate immune cells (i.e., microglia) for regenerative therapeutic approaches.

Methods

Therefore, we examined the molecular and functional effect of PKC activators (Prostratin and Bryostatin) in immortalized BV-2 cells and primary murine microglia.

Results

Western Blot (WB) and immunocytochemistry (ICC) analyses revealed significant increases in NF-KB phosphorylation (pNF-KB), one of the pathways downstream to PKC, in Prostratin-treated BV-2 cells. ICC analysis confirmed Prostratin-induced nuclear translocation of pNF-KB in BV-2 and primary murine microglia. Morphological alterations were investigated by quantifying microglial cell area and phagocytic activity was measured to explore microglial functionality. PKC activation increased microglial cell area associated with enhanced phagocytic activity. Finally, gene-expression and flow cytometry analysis were used to investigate the polarization of BV-2 microglia cells upon PKC activation. The absence of pro-inflammatory marker expression, together with the reduction of CD40 expression in lipopolysaccharide-exposed BV-2 cells, suggests potential neuroregenerative phenotypes for PKC-activated microglia cells.

Conclusions

Prostratin and Bryostatin's impact on microglial signaling reveals intricate complexities, with NF- KB activation hinting at pro-inflammatory responses. However, unexpected CD40 downregulation and absence of cytokine overexpression suggest diverse, unresolved pathways. The use of PKC activators holds therapeutic promise, offering transformative potential for neuroregenerative medicine by targeting microglial responses.

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Preliminary Data of a 3d Single-Limb-Squat Assessment of Laterality in Exercise-proficient Physiotherapists

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Objective

Single-Limb-Squat (SLS) is a common functional test and exercise in conditions such as ACL rupture, and degenerative knee or hip pathologies [1,2]. Lower limb valgus has been assessed two-dimensionally in numerous studies [3]. Although SLS is a multidimensional and neuromuscularly highly demanding task [4], only a few studies assessed its kinematics and kinetics three-dimensionally [2]. Previous pertinent studies differed in terms of sample size [5], non-consideration of the role of gender, or the role of health status and exercise proficiency on the SLS execution quality. So we investigated as a benchmark of performance quality if the dominant side differs from the non-dominant one regarding hip and knee frontal moments (fM) as well as frontal Range of Motion (fRoM) in performing SLS by a healthy exercise-proficient sample.

Methods

Eighteen (9 female / 9 male) healthy physiotherapists aged 19 to 62 (mean 34, sd 9.6) years performed five SLS with the right and left leg each. Data were captured using an optoelectronic movement analysis system with the modified Cleveland Clinical Markerset and a three-axis force plate. Processed trials were time-normalized for the down-phase and up-phase. Hip and knee fM, as well as fRoM were tested for difference between the dominant and non-dominant leg using one-dimensional parametric statistical mapping (1dSPM) with paired t-tests with alpha set at 0.05.

Results

The 1dSPM analyses did result in no statistically significant differences between the dominant and non-dominant leg in any of the parameters for the lower limb. The null hypothesis was thus not rejected by the sample, although the trajectories show a clear deviation in the knee fM.

Conclusions

To our knowledge this is the first study providing three-dimensional reference data of SLS performed by a healthy exercise proficient sample. Laterality seems to be relevant for knee fM, when defining feedback thresholds. Parameters characterizing the quality of exercise execution related to the control of dynamic leg alignment show smaller values compared to prior studies. Gender differences are subject to the analysis of the complete dataset. As a limitation, squatting velocity and depth was monitored only verbally, which however did not affect the homogeneity of relevant biomechanical outcomes. Based on well-executed exercises, the physiological range of kinematic and kinetic parameters' cut-offs shall be established, by opposing the data of the exercise proficient sample to that of less experienced exercisers.

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The degree of cyclic stretching influences lapine Achilles tenocytes and hMSCs in 2D culture and under 3D conditions on a Dura mater cell carrier

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Objective

Mobility can be severely impaired after tendon injuries. The self-healing and regenerative capacities of tendons are generally low. In the future, however, tissue- engineered constructs could be used to reconstruct injured tendons in order to prevent serious consequences. In the proposed basic research project, the effect of cyclic stretching on the formation of tendon tissue from both tenocytes and human mesenchymal stem cells (hMSCs) after 2D and 3D stimulation will be investigated in detail.

Methods

For the 2D culture approach (1), silicone chambers (4 cm²) were seeded with Lapine Achilles Tenocytes (LAT) on the one hand and human hMSCs (6000 cells/cm²) on the other. After 24 hours of adherence, the stimulated chambers were exposed to either moderate or strenuous exercise, while the control chambers were not exposed to stimulation. For the 3D culture approach, decellularized dura mater was recellularized with either LAS or hMSCs analogous to the 2D experiments and then subjected to moderate or strenuous exercise. At the end of each training session, viability was qualitatively assessed with a viability assay and DNA and sulfated glycosaminoglycan (sGAG) content was quantitatively measured. In addition, RNA was isolated to enable future gene expression analyzes of the most important tendon-associated matrix components and thus better characterize tendon development.

Results

The viability test showed that the cells were viable due to the careful preparation of the dura and that there were only a few dead cells in the tissue. The viability was over 50%. Histological staining showed that the architecture of the tissue had been preserved, and thus a suitable matrix for revitalization was present. The viability test showed that both LAT and hMSCs predominantly survived not only the moderate but also the strenuous training in 2D and 3D culture. A first trend in the alignment of the cells after stimulation is also recognizable. Quantitative analyzes confirm that moderate stretching has a greater influence on the sGAG synthesis of hMSCs than on LAT.

Conclusions

The porcine dura halves were carefully removed as a whole, so that a sufficiently large "scaffold matrix" was available for subsequent experiments. Initial differences in cell viability have already been observed, not only between LAT and hMSCs, but also between training programs. The effects of 3D stimulation on cell behavior are greater than those of 2D stimulation.

Acknowledgements

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Lessel-Kubisch syndrome as a model to decipher the Achilles heel of p53

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Objective

Inducing cellular senescence of cancer cells is considered a potentially effective strategy against cancer. Cellular tumor antigen p53 or just p53 is a regulatory protein and a transcription factor. It plays a key role in balancing cellular destiny between many different molecular pathways involved in cell division, senescence, DNA damage response and repair, and programmed cell death (apoptosis) when DNA damage is irreparable. p53 is activated by stress, however in normal conditions, p53 levels are kept low through a continuous degradation. This is achieved by protein interaction with MDM2, which translocates p53 from the nucleus to the cytosol and ubiquitinates p53, therefore marking it for proteasomal degradation. p53 is coded by TP53 gene, and variants in TP53 are associated with various cancer types, highlighting its significance in maintaining cellular integrity and preventing malignant transformation. Somatic TP53 loss-of-function variants are the most common alterations in cancer and a major cause of chemo-resistance. In addition to its role in cancer prevention, p53 contributes significantly to the ageing process by influencing several features of ageing. To gain a deeper insight in the p53-regulated balance between cancer and ageing, we aim to identify p53 down-stream effectors through transcriptome analysis. We hypothesize that this could bring us to identify novel p53 downstream targets, that could be used in personalized cancer therapy, where p53 is dysregulated.

Methods

Primary dermal fibroblasts, lymphoblastoid (LCL) cell lines, human osteosarcoma (U2OS) and non-small cell lung cancer (H1299) cell lines are used in the functional analyses including cellular localization studies, cytokinesis block micro-nucleus assay, chromosome analysis and stability assays. Transcriptome analyses are used to identify p53 dependent dysregulated genes that can be used in therapeutic approaches.

Results

Previously, we discovered a homozygous anti-terminal mutation c.1492T>C in MDM2 that leads to Lessel-Kubisch syndrome (LSKB), characterized by premature ageing phenotype without tumor predisposition. On cellular level this specific homozygous C-terminal MDM2 variant leads to an increased p53 protein levels, increased p53 stability, and localization of p53 in the nucleolus, ultimately leading to an increased genome stability and decreased cell proliferation rate as well as a premature senescence phenotype. Transcriptome analysis of primary LSKB fibroblasts revealed 481 upregulated gene and 450 downregulated genes under normal conditions. From this, 35 up-regulated and 75 down-regulated were associated with senescence. We hypothesize that from these genes we could further select potential new targets for cancer treatment. Likewise, the identified genes will be classified in the cellular context and a signaling pathway analysis will be carried out. Top three hits for up- and downregulated genes will be further analyzed functionally.

Conclusions

p53 as a tumor suppressor has been excessively studied as well how loss of p53 activity contributes to human cancers. In LSKB fibroblasts we observed increased p53 activation, along with cellular senescence as well as chromosomal stability. Therefore, we believe that LSKB are an excellent cellular model for the deeper characterization of the p53 function, which may lead to new therapeutic options in oncology.

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The effect of UVC irradiation on germ density on breast implants and epidermis

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Objective

Bacterial colonization of breast implants is a side effect of their implementation. This can lead to infection or capsular contracture, which is the most common long-term complication (1). Since these adverse events can lead to reoperation, prevention of bacterial colonization is essential. The germicidal effect of conventional 254 nm UVC light is already known (2), but presents a risk for human skin or eyes due to its mutagenic and cytotoxic effect. In contrast, previous studies showed, that far-UVC light (207-222 nm) efficiently inactivates germs (3) without representing a health risk to human skin cells because of its limited penetration ability (4). Therefore, we aim to prove that 222 nm UVC light irradiation of sterile implants and surrounding skin can lead to a significant reduction of germ density.

Methods

Five samples were obtained from each patient (n = 18) undergoing breast reduction surgery. Pre-incision samples (Sample I-III) were collected using sterile implant shells (Polytech Health & Aesthetics GmbH, Germany), applied to the patient's submammary fold during surgery following standard sterile procedures. Implant shells underwent 222 nm UVC irradiation (Disinfection cabinet, Sterilsystems GmbH, Austria) either before (Sample I) or after patient contact (Sample II), while one sample remained untreated (Sample III). After surgical skin removal, resected skin was irradiated with UVC light (Sample V) or left untreated (Sample IV) and pressed against an implant shell. Consequently, the sterile breast implant shells were then pressed onto agar contact slides (HYCON® Contact Slides, Merck Millipore, Germany) and incubated at 35°C for 24-48 hours. Microbiological analysis determined germ density and diversity of isolated microorganisms. All statistical analyses were conducted using NCSS (NCSS 2022, NCSS, LLC, Kaysville, UT).

Results

In the analysis of pre-incision samples, 17 out of 18 cases revealed either lower or absent germ presence in the UVC-treated Sample II compared to Samples I (p-value 0.06) and III (p-value 0.128). Subsequently, post-incision samples exhibited significantly reduced germ density in UVC-irradiated Sample V versus non-UVC-irradiated Sample IV (p-value = 0.037). Staphylococcus species were the most frequently identified bacterial species.

Conclusions

The study demonstrates the germicidal efficacy of 222 nm UVC light, indicating its potential role in reducing microbial contamination during surgery and consequently decreasing the risk of associated surgical side effects in implant-based breast surgery. However, further research is necessary to strengthen these preliminary findings.

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DIAFILD – a study aiming to expedite DIAGnosis of Fibrosing Interstitial Lung Disease

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Objective

Fibrosing interstitial lung diseases (FILD) are characterized by significant morbidity and mortality (1). Accurate and timely diagnosis of FILD is clinically challenging yet crucial to improve patient outcomes by early initiation of disease-specific anti-fibrotic therapy. This study was designed to evaluate the significance of combining readily available non-invasive diagnostic methods with the aim to identify FILD patients early.

Methods

DIAFILD is a prospective observational study targeted to evaluate the cumulative diagnostic value of surveys assessing FILD-specific symptoms – namely the University of California San Diego (UCSD) shortness of breath questionnaire and the Cough Assessment Test (COAT) – in combination with electronic lung auscultation (ELAUS) and thoracic ultrasound (THUS) in patients with (cases) and without (controls) FILD. Presence of fibrotic indicators on auscultation (disease-characteristic findings called Velcro crackles) and thoracic ultrasound (B-lines and pathological pleural lines) were assessed and correlated to presence of lung fibrosis on high-resolution CT scan (HRCT, gold standard of diagnosing FILD).

Results

Here, we present preliminary results featuring characteristics of 19 consecutive FILD patients (case group) who were enrolled in the study between February and October 2021. Females (n = 10) and males were equally represented, median age at the time of study enrollment was 77.0 years (range 60.0 to 85.0 years) and median time since diagnosis and the time of study enrollment was 3.3 years (range 0.3 to 43.5 years). At the time of the initial study visit, about half of the patients (52.6%) were receiving antifibrotic treatment. Mean pulmonary function tests at the time of the initial study visit were generally well-preserved with a FEV1%FVC of 0.86 (SD +/- 0.2), a predicted FVC of 86.4% (SD +/- 19.1), a predicted TLC of 97.8% (SD +/- 21.7) and a predicted DLCO of 67.6% (SD +/- 20.1). Both symptom-assessing surveys indicated a mildly symptomatic patient cohort (median scores of UCSD and COAT were 16 (range 0 to 45) and 3 (range 0 to 16), respectively). On ELAUS, Velcro crackles were found in most patients (n = 14; 73.7%). On THUS, most patients were found to have B-lines (n = 16; 84.2%) and pathological pleural lines (n = 17; 89.5%). Presence of pathological pleural lines on THUS and fibrotic changes on HRCT correlated strongly (Spearman's $\rho = 0.561$, $p = 0.013$), however, no correlation was found between presence of Velcro crackles and fibrotic findings on HRCT (Spearman's $\rho = 0.001$, $p = 0.999$).

Conclusions

FILD-characteristic diagnostic patterns were identified using non-invasive methods in the case group. Interim analysis showed a strong correlation between indicators of lung fibrosis on THUS and radiological presence of lung fibrosis on HRCT. Comparison to the corresponding findings of the control group has yet to take place.

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A new approach for management of aneurysmal subarachnoid hemorrhage based on Manual and Artificial Intelligence blood volume measurement in Non-Contrast Head CT scans 🍷

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Objective

Utilize Artificial Intelligence (AI) and Machine-Learning (ML) methods to compute the volume of Subarachnoid hemorrhage blood (SAHV) and generate a 3D brain map from non-contrast CT scans. Compared to a Manual Method (MM), this approach aims to assess the precise volume of SAH blood more quickly, establish a potentially new imaging biomarker for just-in-time treatment options, and accelerate patient recovery.

Methods

The novel scan method, SAH Volumetric AI (SAHVAI-3D), was applied to a cohort of 10 patients (92 NCCT scans, \approx 182 slices each) in direct comparison to a Manual Measurement Method (MM). A proprietary AI-ML algorithm generated SAH Volumetric AI (SAHVAI) values. In both methods (AI-ML, MM), a 3D SAH brain map was created for each patient. The SAHVs were analyzed and compared to neurological outcomes and visual areas of thickest blood concentration concerning vasospasm.

Results

SAHVAI quantified the volume of SAH blood in 42 seconds and demonstrated superior speed to the MM (>60 minutes). The SAHVAI showed an accuracy of 99.8%, Dice of 0.701, FPR=0.0005, and NPV=0.999. The absolute difference of SAHVs between both methods was 5.67ml. The SAHVAI-3D brain map and volume at admission appeared highly associated with neurological outcomes (inverse with Glasgow Coma Scale, linear with length of stay in hospital), especially in areas of thick blood concentration.

Conclusions

The introduction of SAHVAI-3D and the resultant “SAHVAI-3D Brain map” represent a new neurologic imaging biomarker. This innovation fills a significant gap in current SAH imaging techniques, enabling rapid evaluation and targeted interventions to enhance patient care.

Acknowledgements

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Wound healing and self organization of skin cells is guided by protein corona-bearing extracellular vesicles

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Objective

Transport of functional protein cargo via extracellular vesicles (EVs) is an important mechanism in cell communication. We aim to understand the distribution of active cargo proteins between EV's inside and outside and the implication for therapeutic applications in wound healing.

Methods

Here we used skin organoids and a human-on-mouse skin model to investigate the contribution of EVs to this process. EVs from placenta-derived stromal (PLX) cell-conditioned medium or from human platelet lysate were enriched by tangential flow filtration (TFF) optionally followed by ultracentrifugation or size exclusion chromatography (SEC) to obtain EV preparations with different degrees of protein corona preservation. Self organization capacity in presence or absence of different EV preparations was analyzed in a high throughput organoid assay. Contribution of EVs to wound healing was assessed in an in vivo model transplanting human skin cells on NSG mice^{1,2}.

Results

Skin organoid formation by keratinocytes together with endothelial cells and keratinocytes or spheroid formation of human skin fibroblasts was significantly superior in the presence of TFF-purified EVs bearing a functional protein corona. Soluble factors alone or corona-depleted EVs after SEC did not initiate 3D organization. In vivo, TFF-purified EVs were essential for proper stratified organization of human skin cells in wound areas and provided sufficient vascular support.

Conclusions

This findings allowed us to develop a self-organizing human skin model in mice and show the important role of corona proteins for EV function. The surface-to-bulk partition of EV cargo for small EVs < 180 nm is in favor of surface cargo loading supporting the new concept of a functional EV corona.

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Beyond Stress: The Role of Attachment and Mentalizing for the Well-being among Elementary Educators

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Objective

The capacity to mentalize (1), in addition to the educator-child relationship (2), appears to function as a protective factor against stress, thereby enhancing the well-being of elementary educators, given their high workload. Educators who have positive mental models of relationships experience more positive affect in their interactions with children, which promotes their own well-being (3). Moreover, an appropriate perception of mental states allows for a more constructive approach to stressful situations (4), even in the absence of positive mental models of relationships, because negative affect can be identified and regulated. The aim of this study was to assess whether the ability to mentalize exerts a stronger influence on stress and well-being in an elementary educational context than attachment behavior.

Methods

To address the research question, we collected questionnaire data from N = 216 prospective elementary educators to examine their mentalizing capacity (MZQ), attachment behavior (ASQ), stress levels (TICS-SSCS), and well-being (SOC).

Results

Data revealed the anticipated correlations between attachment behavior and mentalization ability with well-being and stress levels. Additionally, mediation analyses showed that mentalization capacity partially explained the influence of attachment behavior on stress and well-being.

Conclusions

These findings indicate that attachment behavior plays a subordinate role in the context of stress and well-being, as its influence is partially explained by the ability to mentalize. Mentalizing can be trained and learned in adulthood (5), suggesting that mentalization training could support well-being and improve the abilities of elementary educators under stressful conditions.

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Short-term CD8⁺ T cells ablation reduces microgliosis in the hippocampus of old APP/PS1 animals

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Objective

Alzheimer's disease (AD) progression has been recently associated to the accumulation of CD8⁺ T cells into disease-affected brain parenchyma, where they tightly associate with microglial and neuronal structures (1, 2). However, the functional role of CD8⁺ T cells in the AD brain is still elusive. Therefore, we investigated the impact of short-term CD8⁺ T cell ablation on neuroinflammation in transgenic AD mice (APP/PS1).

Methods

CD8⁺ T cells ablation was performed via intraperitoneal injections of anti-CD8 antibody for three days in two-year-old APP/PS1 and wild-type male mice. Control groups received the respective isotype antibody (four animals per group). Heart-collected blood samples underwent flow cytometry analysis. After transcardiac perfusion, the brain tissue was processed for immunohistochemistry analysis.

Results

As expected, anti-CD8 injections resulted in a substantial decrease of CD8⁺ T cells from the blood circulation as well as brain parenchyma. We observed a slight reduction in amyloid plaque pathology upon anti-CD8 treatment and a statistically significant reduction in the percentage area of Iba1⁺ cells in the hippocampus of APP/PS1 mice treated with anti-CD8 antibody compared to isotype-treated mice.

Conclusions

Short-term CD8⁺ T cell ablation revealed a consistent reduction of microglial cell staining area in the hippocampus of treated animals. These results suggest that short-term CD8 ablation could influence microglia-driven neuroinflammation.

Acknowledgements

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3D Scanning and Printing Technology for Breast Reconstruction: Increased Aesthetic Outcomes and Quality of Life

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Objective

Sculpting a flap of autologous tissue into an aesthetically pleasing breast represents an integral challenge in modern breast reconstruction.(1) Several methods of assessment have been investigated to deviate from individual artistic skills towards objective breast shaping. Among them, 3D technology might provide the most promising support but needs validation in applicability and accuracy. Hence, the aim of this study was to evaluate the potential influence of 3D technology on autologous breast reconstruction with regards on postoperative breast appearance and quality of life.

Methods

Within this study, outcomes of 24 female patients who underwent autologous breast reconstruction assisted with 3D technology were analysed and compared with previous similar patients without the use of 3D technology. Based on individual 3D scans and simulation, patient-specific templates were used for reconstruction. Quality of life assessment and aesthetic evaluation was performed and compared with the control group. Appropriate statistical analysis was carried out.

Results

A total of 24 female patients met inclusion criteria and underwent autologous breast reconstruction using 3D technology. Quality of life scores showed increased values, postoperatively as well as compared with the control group. Overall aesthetic evaluation revealed notable improved outcomes on breast appearance. A critical appraisal of external plastic surgeons showed statistically significant better outcomes on breast shape. All patients would recommend and repeat breast reconstruction using 3D technology.

Conclusions

Using 3D dimensional patient specific templates represents a practical method facilitating personalized flap planning and shaping. The results of this study demonstrate that 3D technology enhances outcomes in breast reconstruction concerning aesthetics as well as postoperative quality of life.

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Impact of 2-hydroxypropyl- β -cyclodextrin inclusion complex formation on dopamine receptor-ligand interaction – a case study

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Objective

The octanol-water distribution coefficient (logP), used as a measure of lipophilicity, plays a major role in the drug design and discovery processes. While average logP values remain unchanged in approved oral drugs since 1983, current medicinal chemistry trends towards increasingly lipophilic compounds that require adapted analytical workflows and drug delivery systems. Solubility enhancers like cyclodextrins (CDs), especially 2-hydroxypropyl- β -CD (2-HP- β -CD), have been studied in vitro and in vivo investigating their ADMET (adsorption, distribution, metabolism, excretion and toxicity)-related properties. However, data is scarce regarding the applicability of CD inclusion complexes (ICs) in vitro compared to pure compounds.

Methods

In this study, dopamine receptor (DR) ligands were used as a case study, utilizing a combined in silico / in vitro workflow. Media-dependent solubility and IC stoichiometry were investigated using HPLC. NMR was used to observe IC formation-caused chemical shift deviations while in silico approaches utilizing basin hopping global minimization were used to propose putative IC binding modes. A cell-based in vitro homogeneously time-resolved fluorescence (HTRF) assay was used to quantify ligand binding affinity at the DR subtype 2.

Results

While all ligands showed increased solubility using 2-HP- β -CD, they differed regarding IC stoichiometry and receptor binding affinity. This case study shows that IC-formation was ligand-dependent and sometimes altering in vitro binding.

Conclusions

Therefore, IC complex formation can't be recommended as a general means of improving compound solubility for in vitro studies as they may alter ligand binding.

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BEATS – MIGRAINE: Biomarker Establishment of Activated Targets in Skin for Migraine

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Objective

Migraine is a common neurological disease affecting about one in five women under 50, making it the third most common worldwide (1). Until now, migraine diagnosis is based on clinical criteria as there is still no reliable test or any biomarker to validate the diagnosis (2). Temperature perception, olfactory sensitivity and osmophobia have been shown to play a considerable role in migraine (3, 4). Growing evidence shows that migraine pain may be caused by irritation of peripheral extracranial nerves, vessels or other soft tissues which led to innovative treatment options. Surgical extracranial trigger deactivation by decompression or removal of nerves and/or vessels in affected areas for severe migraineurs is a promising surgical treatment option (5-7). This procedure is accompanied by a simultaneous upper eyelid blepharoplasty. Immunohistochemistry (IHC) of these biopsies will reveal the spatial distribution of biomarkers and provide information on differences in expression levels. Extracellular vesicles (EVs) are key players in cell-to-cell communication in health and disease (8). Isolated EVs from blood samples will be the basis for proteome analysis to gain further insight into potential differences between healthy and migraine. Establishment of an EV-migraine signature allows validation of migraine diagnosis and will help to identify further treatment options for refractory patients. We hypothesize that spatial distribution, gene expression and EV signature in skin differs in patients diagnosed with migraine and migraine-free controls. Our goals are therefore to discover a migraine signature allowing for biomarker identification of activated receptors and other genes in patient skin and the establishment of skin as a testing system for migraine interventions and/or drug screening.

Methods

The department of Plastic, Aesthetic and Reconstructive Surgery at the Barmherzige Brüder in Salzburg offers the above-mentioned surgical treatment for migraineurs and is therefore eligible to collect skin samples for further examination. To achieve the stated goals we use qPCR, next generation sequencing (NGS), western blot, histology and immunocytochemistry, flow cytometry, establishment of tissue culture models as well as metabolomics. For isolation of patient EVs we follow our recently established protocol (9).

Results

Collection of skin biopsies and blood from migraine patients and migraine-free controls started with the beginning of May. Primary keratinocytes and fibroblasts have already been isolated from several biopsies and skin sections have been embedded in paraffin for subsequent IHC staining.

Conclusions

The establishment of a migraine signature will allow validation of migraine diagnosis and will probably help in the identification of further treatment options for refractory patients.

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(fett gedruckt = Erstautor*in)

Autor*in	Abstract Nr.		
A			
Abed, Selim	1	Borecká, Silvia	80
Aberman, Zami	97	Brachtl, Gabriele	97
Ablinger, Celina	2	Brandstötter, Christina	34
Acker, Jens Georg	3	Braun, Tobias	12, 13, 14
Aigner, Elmar	45, 57, 88	Breidung, David	10, 15 , 40
Aigner, Ludwig	90, 99	Breitwieser, Martin	16
Alberti, Paola	8	Brisch, Karl Heinz	33, 39
Altendorfer, Barbara	99	Brosch, Moritz	90
Ammon, Josephine	11	Brückl, Wolfgang	81
Angerer, Matthias	47, 69	Büchner, Susanne	17
Augat, Peter	5, 58, 85	Bükki, Johannes	67
Aurnhammer, Felix	62	Bürgler, Elisabeth	24
Avramovska, Irina	29	Büscher, Andreas	46
B			
Barth, André A.	15, 40	C	
Bauer, Andre	47	Caciagli, Lorenzo	20
Bauer, Florian	4	Cadamuro, Janne	41
Bauer, Johann	97	Cesur, Nevra Pelin	18
Baumeister, Dirk	5	Chaves, Gustavo	19 , 53
Beckert, Manuela	6	Couillard-Després, Sebastien	90
Beil-Hildebrand, Margitta	7 , 46	Crespo Pimentel, Bernardo	20
Benedetti, Ariane	90, 99	Cronemberger, André	97
Benedetti, Bruno	90	D	
Bergamo, Mattia	8	Datz, Christian	45, 88
Berger, Ursula	32	Datz, Leonora	88
Bernardinelli, Emanuele	9 , 37, 48, 61, 80	Dauriz, Marco	57
Bernegger, Sabine	90, 99	Deisl, Christine	55
Bernik, Rok	47	Devlitšarov, Daniel	21
Berns, Maresa D.	15	Delavari, Sarina	15
Bieler, Lara	71	Diener, Markus	29, 30
Billner, Moritz	10 , 15, 40	Dherin, Benoit	96
Binder, Heide-Marie	97	Dinzingler, Antonia	31, 39
Birkholz, Lorri	7	Dnyansagar, Rohit	82
Bitti, Roberta	11	Dono, Fedele	64
Blöchl, Constantin	97	Dorenkamp, Andrea	59
Bock, Marlene	32	Dossena, Silvia	9, 37, 48, 49, 61, 80
Bogensberger, Kathrin	77	Dubecz, Attila	29, 30
Bony, Mathilde	5	Duncan, John	20
Boor, Jan	95	Durstberger, Sebastian	91
		Duszka, Kalina	82

XII

E

Ebbert, Ronald	22
Ebner-Peking, Patricia	97
Eibl, Thomas	73
Edo, Alejandro Marti	15
Egle, Alexander	43
Ehebruster, Gurdrun	100
Ehrl, Denis	10, 15, 40
Engl, Michael	75
Eisendl, Agatha	17
Ellmauer, Klarissa	89
Eminger,	
Emmanuel, Katja	16
Emmanuel, Klaus	30
Enders, Bernadette	59
Erichsen, Sandra	85
Ernst, Anna Maria	55
Eschermann, Kirsten	23
Esenay, Isik Figen	24

F

Farmaki, Filitsa	30
Faustini, Bettina	84
Felder, Thomas K	82
Ferini-Strambi, Luigi	72
Ficker, Joachim	81
Fischer, Florian	25
Fischer, Thorsten	8
Fischlein, Theodor	13, 47, 69
Flamm, Maria	45, 88
Fleischmann, Nils	12, 28
Flore, Davide	72
Föhrenbach, Kim	43
Föttinger, Fabian	42
Foisner, Vera	26
Forster, Jennifer	99
Fuchs, Julia	77
Franco, Valentina	64
Freeman, William David	96
Freude, Thomas	16
Frey, Vanessa	44
Fricke, Angela	36
Fusch, Christoph	22

G

Gaisbauer, Stefanie	34
Gaisberger, Christoph	89
Gantenbein, Andreas	3

Gantschnigg, Antonia	34
Gašperíková, Daniela	80
Gehwolf, Renate	18
Geißler, Marie-Louise	95
Gensluckner, Sophie	45, 57
Gerber, Luis	59
Ghiani, Alessandro	65
Giroto, Giorgia	48
Giulini, Luca	29, 30
Glowalla, Claudio	58
Gögele, Clemens	12, 13, 14, 27, 28, 92
Gosch, Markus	32, 52
Grabmer, Christoph	42
Grechenig, Michael	30
Greif, Elke	31
Greil, Richard	43
Grieb, Gerrit	15
Gröger, Michael	59
Gu, Qiangqiang	96
Guenzler, Valentin	47
Gueths Gomes, Fausto	97
Gupta, Vikash	96

H

Haas, Christoph	26
Habboub, Basel	32
Hackl, Simon	85
Hackner, Klaus	95
Hantinger, Marion	33
Haller, Sophie	70
Hanneken, Jessica	87
Harrer, Andrea	71
Hartl, Arnulf	26
Haslauer, Theresa	34
Hass, Alexandra	59
Heger, Patrick	30
Hergan, Benedikt	95
Herrmann, Sven	58
Hertle, Christine	36
Heuser, Thomas	78, 97
Hitzl, Wolfgang	15, 29, 30, 35, 69
Hochmann, Sarah	78, 83, 97, 102
Höfler, Julia	20
Höhl, Rainer	35
Höll, Anna	101
Höllerer, Raffael	2
Hoffmann, Bernd	92
Hofmann, Hanna	36

Hofmann, Sabrina	22	Kofler, Barbara	34, 82, 102
Huber, Christian G.	97	Kohl, Thomas	62
Huber, Christoph	26	Kokozidou, Maria	12, 13, 14
Huber, Florian	37, 48, 61	Koller, Ulrich	97
Huber, Sara	34	Konrad, Jens	92
Huber-Cantonati, Petra	2, 56, 101	Koutny, Florian	45, 57
Hueber, Axel	65	Kubitz, Jens	35
Hüttenbrink, Clemens	35	Kuchukhidze, Giorgi	20
Hüttner, Felix	29, 30	Kundt, Firuzan Sari	7
Hummel, Christian	38	Kutschar, Patrick	7, 67
Hungerer, Sven	58	Krauß-Köstler, Eva	36
		Krutter, Simon	46
I		L	
Iglseder, Bernhard	45	Lamprecht, Bernd	95
Imlinger, Christina	95	Lang, David	95
Ismair, Selina	39	Lang, H.	33
		Langthaler, Patrick	45
J		Laner-Plamberger, Sandra	42
Jäger, Simon	65	Lapinskas, Simonas	15
Jakab, Martin	9, 37, 61	Lauth, Wanda	42
Johansson, Tim	87	Legname, Giuseppe	49
		Leiler, Spela	47
K		Leis, Stefan	102
Kaiser, Bernhard	95	Leisch, Michael	43
Kalisnik, Jurij Matija	47	Lell, Michael	11
Kalss, Gudrun	64	Lenhart, Armin	27, 28
Kamphausen, Anne	35	Lessel, Davor	93
Karcz, Konrad	10, 15, 40	Lettner, Thomas	84
Karl, Tanja	41	Ley, Pauline	78
Karner, Josef	89	Liebert, Adrian	73
Kartal, Orkan	42	Liesenberg, Tanja	28
Kemeter, Melissa	30	Lindlbauer, Nadja	42
Kerry, Ghassan	73	Lippert, Viktor	90
Kiem, Dominik	43	Liuni, Raffaella	37, 48, 49
Kiener, Teresa	2	Lobmann, Sebastian	50, 51
Kieninger, Bärbel	62	Lorenzl, Stefan	67
Kiesslich, Tobias	56	Lubian, Francesca	52
Kiwull, Lorenz	44	Lutz, Nina	65
Klenner, Friederike	65		
Klenk, Jochen	65	M	
Klinglmayer, Eva	70	Maeding, Nicole	78, 83, 97, 102
Knab, Katja	22	Mahorivska, Iryna	53
Kneiseler, Guntje	32	Majeed, Yasir	54
Koch, Oliver	30	Maieron, Andreas	45
Kocher, Thomas	97	Malnar, Mirjana	21, 55
Köbler, Paul	36	Malsagova, Asja T.	15
Köninger, Fabian	94	Manava, Panagiota	11
Köpp, Matthias	20		

XIV

Mani, Rakesh	55
Mantegna, Gianluca	49
March, Albert	52
Marino, Angela	49
Mariozzi, Sara	72
Markova, Gabriela	24, 39
Marr, Lisa	62
Marschhofer, Moritz	101
Matea, Cristian-Tudor	70
Mattke, Matthias	89
Mayr, Christian	56
Mayr, Daniela	56
Mega, Andrea	45, 57
Megas, Ioannis-Fivos	15
Meisner-Kober, Nicole	70
Melchardt, Thomas	43
Metzger, Ulrike	24
Minnich, Bernd	27
Mladek, Julia	13
Moazedi-Fuerst, Florentine	95
Mock, Jonas	5
Morabito, Rossana	49
Moser, Tobias	71
Mostacci, Barbara	64
Motloch, Lukas	14
Mrazek, Cornelia	42
Mrowetz, Heike	99
Mühling, Mischa	58
Mülleder, Patrick	67
Müller, Markus	36, 59
Müller, Silvana	27, 28
Musset, Boris	50, 51, 53, 60

N

Nasser, Houssein	37, 61
Neumann, Bernd	62
Neureiter, Daniela	56
Neurohr, Claus	65
Niemann, Stefan	62
Niklewski, Günter	79
Nguyen, Mai Quyen	63
Nguyen, Nhat	5
Nucera, Bruna	64 , 72

O

Obermayer, Astrid	27, 97
O'Brien, James	68
Ofir, Racheli	97

Oesterreich, Alina	24
Ombres, Laura	42
Oostingh, Gertie J.	41
Ortner, Felix	15
Osterbrink, Jürgen	67
Otto, Ferdinand	71

P

Paal, Piret	67
Paar, Vera	14
Pachmayr, Johanna	2
Pahernik, Sascha	35
Panebianco, Luca	64
Panzer, Simone	65
Patel, Vishal	96
Paulweber, Bernhard	45
Pelzman, Sonja	66
Picus, Roberto	75
Piravej, Nick	4
Pirich, Christian	2
Pitzer, Stefan	67
Pizzadili, Gina	28
Plachel, Maximilian	68
Pleyer, Lisa	43
Pollari, Francesco	69
Popoff, Alexander	70 , 101
Poupardin, Rodolphe	83, 97, 102
Prader, Sonia	8
Priewasser, Beate	24, 31, 39
Plattner, B.	33
Prusik-Lut, Olaf	59
Pruszek, Jan	21, 55
Püski, Tamas	15
Putz, Peter	91

R

Radermacher, Peter	36,59
Radlberger, Richard Friedrich	71
Radzikowski, Konrad	88
Rainer, Lucas	20
Raninger, Anna	83, 97
Rath, Anca	62
Reddy, Sanjana	96
Reich, Fabian	81
Reichert, Bert	15
Reinhardt, Alexander	12
Remigante, Alessia	49
Rendl, Gundula	2

Riazy-Hossfeld, Noosha	70	Schulze-Tanzil, Gundula	92
Rieder, Sophie-Marie	99	Schuster, Anja	41
Richter, Kneinja	3, 72	Schuster, Daniela	25, 70, 101
Rinaldi, Fabrizio	64, 72	Schwaiger, Karl	94, 100
Rinnert, Alexander	87	Schweizer, Matthias	53
Rinnerthaler, Gabriel	43	Sedghi Aminabad, Negar	78
Rinnerthaler, Mark	102	Seitelberger, Rainald	13
Ritter, Leonard	73	Semmler, Georg	88
Ritter, Markus	56, 77	Sharma, Rohan	96
Rochow, Niels	22	Sicorschi Gutu, Cristina	79
Roecken, Sofie	59	Singler, Katrin	32
Röder, Falk	89	Sirch, Joachim	69
Rösch, Sebastian	9, 37, 48, 61	Sklenár, Marek	80
Rohde, Eva	42	Sodmann, Johanna	81
Rohleder, Michael	59	Sörgel, Fritz	35
Rosenberg-Granzner, Adrian	22	Sommer, Carsten	79
Rückl, Alena	102	Somogyi, Krisztina	22
Rüdiger, Vivienne	12	Speer, Robert	32
Russe, Elisabeth	94, 102	Spinelli, Sara	49
Rupp, Bernhard	16	Spittler, Andreas	97
Ruznic, Elvis	89	Stana, Markus	89
S		Stangassinger, Lea M.	41
Safdarian, Mahdi	74	Stefan, Victoria E	82
Salman, Saif	96	Stefani, Antri	78, 83 , 102
Sandriesser, Sabrina	58	Stein, Barbara	36, 59
Santarelli, Marco	75	Stein, Stefan	53
Santoro, Robin	14	Steiner, Hans-Herbert	73
Sauerbeck, Annette	4	Steinhuber, Anna	83
Schauer-Berg, Johanna	76	Steinmann, Jörg	62
Schäfer-Eckart, Kerstin	27, 28	Stitzel, Andrea	76
Schider, Nicole	21	Stöggel, Thomas	68
Schmid, Barbara	73	Strubegger, Barbara	24
Schrader, Eva	53	Strunk, Dirk	78, 83, 97, 102
Schubert, Mario	101	Studnicka, Michael	95
Seiberl, Michael	71	T	
Sluet, Patrick	47	Tawk, Rabih	96
Schallmoser, Katharina	97	Temml, Veronika	25
Schmid, Barbara	11	Tempfer, Herbert	84
Schmidbauer, Josef	4	Teuschl-Woller, Andreas	92
Schmidt, Manfred	100	Tevini, Julia	82, 102
Schmitz-Grosz, Krisztina	79	Thomschewski, Aljoscha	74
Schneider-Brachert, Wulf	62	Thumfart, Lucas	29, 30
Schäfer-Eckart, Kerstin	92	Tomson, Torbjörn	64
Schröter, Moritz	77	Traweger, Andreas	18, 84, 92
Schropp, Jonas	39	Temml, Veronika	101
Schulze-Tanzil, Gundula	12, 13, 14, 27, 28	Trenkwalder, Katharina	85
Schumann, Lena	15	Trinka, Eugen	20, 45, 64, 72, 74

XVI

Tsolova, Dayana 15
Tutmann-Scheld, Michaela 15

U

Ugorová, Diana 80
Unger, Michael Stefan 99
Urbanczyk, Sophia 59, **86**

V

Vanacore, Nicola 52
Van der Zee-Neuen, Antje 77, 87
Varga, Lukáš 80
Vari, Balazs 97
Vittadello, Fabio 57
Vockner, Sara **89**
Völker, Sebastian **87**
Völkerer, Andreas **88**
Volk, Hans-Dieter 97
Vollmar, Christian 20
Von Imhoff, Phillip 15

W

Wagner, Andrea 18
Waller, Christiane 36, 59
Wandschneider, Britta 20
Wanninger, Anke 15
Weber, Daniela D. 82, 102
Weber, Lucia 69
Wechselberger, Gottfried 94
Weghuber, Daniel 45
Wehrmann, Julius 12
Wei, Yujia 96

Weinbender, Sofia Chanel **90**, 99
Weisemann, Ferdinand 85
Werner, Christian 12, 14, 28, 92
Wernly, Bernhard 45, 88
Wernly, Sarah 88
Wichlas, Florian 68
Widhalm, Klaus **91**
Wiedmann-Kline, Clea **92**
Wildburger, Sonja 77
Willim, Jana **93**
Wiltzsch, Sven 27, 28
Wimmer, Florian **94**
Winkler, Martin 5
Wipfler, Peter 71
Wipplinger, Anna 56
Wirtz, Mirja **95**, **96**
Wolf, Martin 78, 83, **97**, 102
Wosko, Paulina 67
Würflein, Dieter 81
Wusatiuk, Carmen **98**

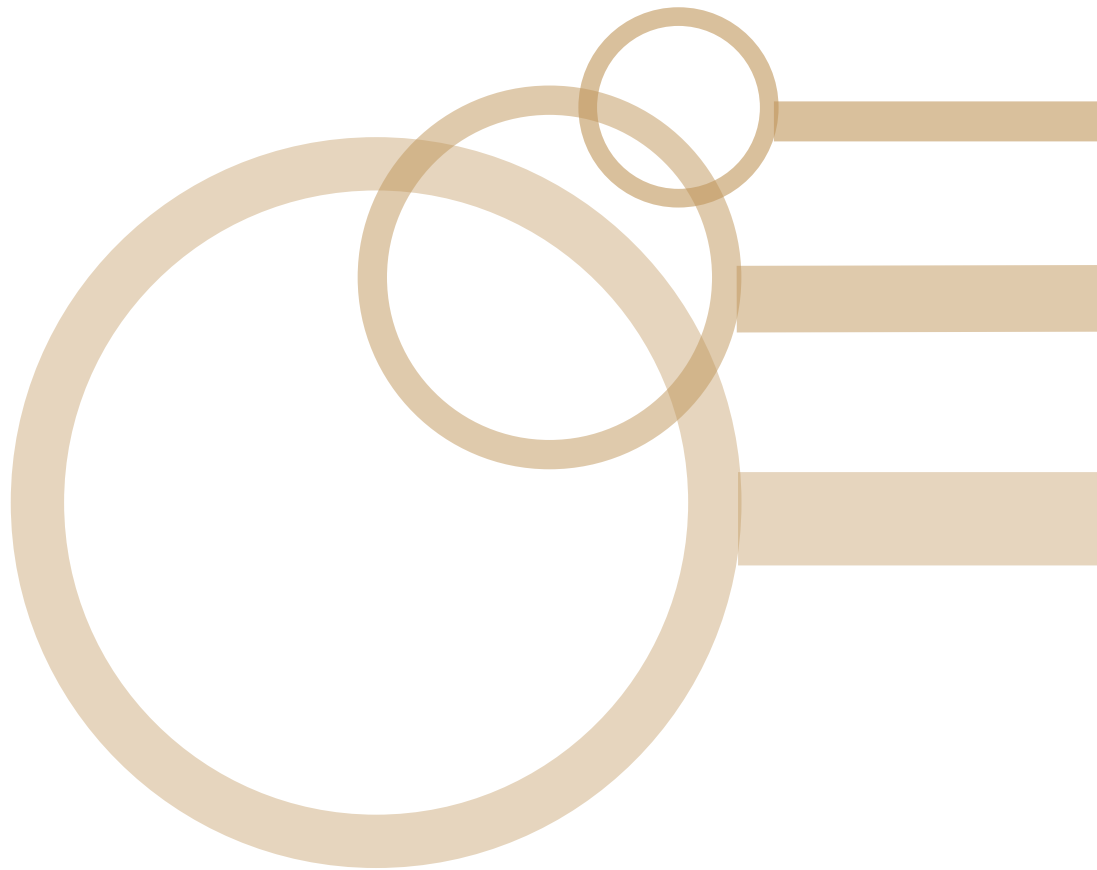
X

Xiao, Fenglai 20

Z

Zattoni, Marco 90, **99**
Zaussinger, Maximilian **100**
Zehentmayr, Franz 89
Zell, Lukas **101**
Zembacher, Stefan 95
Zimmermann, Georg 42, 64
Zink, Fabian 59
Zwicklhuber, Janine **102**

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