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92-94 Kolokotroni str.
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Tel: +30.6986564295
E-mail: irebiomeds@gmail.com

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Editorial

The Need and Value of Medical Curricula in Medical Education

Dimitrios Filippou[1,2]

[1] *Research and Education Institute in Biomedical Sciences (REIBS), Pireaus-Athens, Greece*

[2] *Dept. of Anatomy, School of Medicine, National and Kapodestrian University of Athens, Athens, Greece*

Medical education plays a crucial role in healthcare systems globally, as it molds the knowledge, skills, and capabilities of future healthcare professionals. To guarantee a thorough and encompassing education for medical students, the creation and application of structured medical curricula are vital. These curricula serve as a roadmap, guiding students through their educational path and ensuring they acquire the necessary expertise and empathy to excel as healthcare providers. The significance and benefits of medical curricula in medical education are deep and varied.

The establishment of standardized content and learning objectives in medical curricula is of utmost importance for maintaining consistency in medical education. These curricula guarantee that students, regardless of the institution they attend, acquire a similar foundation of knowledge and training. This uniformity in education enables medical professionals to easily transition and practice in different regions or countries, without facing significant gaps in their knowledge. Achieving standardization and consistency in medical curricula involves considerations in terms of content, structure, assessment, and accreditation.

When it comes to the content, the key characteristics of medical curricula can be summarized as follows. Firstly, they should clearly outline the core competencies that all graduates need to possess. These competencies typically encompass medical knowledge, patient care, communication skills, professionalism, and the ability to engage in lifelong learning. Secondly, there should be consistency in terms of the clinical exposure provided to students, ensuring that they gain practical experience in a range of medical settings. Standardization is crucial to ensure that all students receive a comparable level of exposure to different patient populations and medical conditions. Lastly, the curriculum should incorporate principles of evidence-based medicine, teaching students how to critically evaluate scientific literature and apply the latest research findings to their clinical practice.

Various parameters should determine the structural consistency of these programs. To guarantee that students from different institutions receive an equivalent education, it is crucial to standardize the duration and structure of the medical curriculum. This standardization includes a balanced allocation of preclinical and clinical years. Additionally, promoting a uniform method of integrating fundamental scientific principles with clinical aspects facilitates a smooth transition from theory to practice. By incorporating elements of public health, ethics, and social determinants of health, interdisciplinary collaboration and learning are encouraged, leading to the development of well-rounded healthcare professionals.

Continuous assessment, Accreditation, and Quality Assurance are vital elements of these programs, and they must adhere to predetermined standards. Objective Structured Clinical Examinations (OSCEs) that are standardized and objective can be utilized to evaluate clinical skills uniformly across various institutions. The implementation of standardized national or international examinations guarantees that students are evaluated in a consistent manner, enabling equitable comparisons of their knowledge and skills. Consistent assessments throughout the curriculum offer continuous feedback and facilitate the identification of areas that need improvement. The standardization of assessment methods fosters fairness and reliability.

Recognized accrediting bodies play a crucial role in the accreditation of medical schools. They lay down standards for curriculum quality, faculty qualifications, and facilities. To ensure the curriculum remains current and in line with

evolving medical knowledge and practices, regular internal and external reviews are conducted. Feedback from students, faculty, and healthcare professionals is invaluable for continuous quality improvement. The qualifications and competencies of faculty members should be standardized to guarantee that students learn from experienced educators. To keep up with advancements in medical education and healthcare, institutions should support ongoing professional development for faculty.

Ultimately, it is important to recognize the significance of technology in medical education. By standardizing its use, students are able to access modern tools, resources, and learning platforms, which encourage a tech-savvy approach to healthcare. The incorporation of virtual and augmented reality technologies can greatly enhance the educational experience by providing realistic simulations and expanding practical training opportunities. Furthermore, maintaining standardization and consistency in medical curricula is crucial for producing competent and well-rounded healthcare professionals. This can be achieved through defining clear content standards, ensuring structural consistency, implementing standardized assessments, promoting accreditation and quality assurance, supporting faculty development, and integrating technology. By adopting this approach, medical education can uphold high standards and adapt to the ever-evolving healthcare landscape, ultimately benefiting students, healthcare institutions, and, most importantly, the patients they will serve.

The field of medicine is constantly changing and advancing, with new discoveries and progress occurring frequently. To keep up with these developments, medical curricula are designed to include the latest evidence-based practices, cutting-edge research, and emerging technologies. This ensures that students are well-informed and up-to-date in healthcare. This adaptability is crucial in delivering high-quality patient care. In addition to scientific knowledge, medical curricula also incorporate training in empathy, communication, ethics, and cultural competence. These aspects are vital for healthcare professionals to provide patient-centered care that focuses on the individual as a whole, rather than just their illness.

Medical curricula offer a structured approach to clinical training, enabling students to gradually develop their skills and abilities. They start by observing clinical settings and then progress to actively participating in patient care, under the supervision of experienced professionals.

Curricula play a crucial role in ensuring that students achieve predetermined learning outcomes and competencies through continuous assessment. Regular evaluations help pinpoint areas for improvement and provide customized feedback to enhance individual learning. This guarantees that students are well-prepared to meet the healthcare demands of their communities. Moreover, curricula can be tailored to address specific healthcare needs in a particular region or community. For instance, they can focus on training healthcare professionals in areas where there is a scarcity or specific health concerns. In addition, modern medical curricula emphasize the importance of interdisciplinary collaboration. By encouraging students to collaborate with other healthcare professionals like nurses, pharmacists, and social workers, curricula promote the delivery of comprehensive and coordinated patient care. This collaborative approach is vital in tackling intricate healthcare challenges.

Medical curricula emphasize the significance of lifelong learning, promoting the idea of constantly improving and developing professionally. This mindset is crucial in a field that is constantly evolving in terms of knowledge and practices. Lifelong learning is an essential and integral part of medical education, reflecting the ever-changing nature of healthcare and the continuous advancements in medical knowledge, technologies, and practices. The importance and need for lifelong learning within medical curricula are evident in various significant aspects.

Rapid Advancements in Medical Knowledge. The field of medicine is constantly progressing through new research discoveries, findings, and inventions. Lifelong learning is crucial for healthcare professionals to stay updated with the latest practices based on evidence and integrate

them into their patient care. The medical technology is rapidly evolving, ranging from diagnostic tools to treatment methods. Continuous learning enables healthcare practitioners to adapt to and utilize new technologies for better patient outcomes.

Changing Demographics and Epidemiology. Moreover, lifelong learning plays a vital role in comprehending and responding to changes in population health dynamics. This includes understanding shifting disease patterns, emerging epidemics, and the impact of social determinants of health. As the global population continues to age, healthcare professionals require ongoing education to tackle the unique healthcare challenges associated with older individuals, such as effectively managing chronic diseases and providing palliative care.

Adapting to Healthcare Policies and Regulations. Continuous learning is essential for healthcare professionals to effectively adapt to and apply changes in healthcare policies, regulations, and reimbursement models. It ensures adherence to standards and the provision of high-quality patient care. Ongoing education enables healthcare practitioners to stay up-to-date with evolving ethical and legal considerations, thus promoting patient-centric care while adhering to established guidelines.

Interdisciplinary Collaboration. Lifelong learning also facilitates productive collaboration with professionals from various healthcare disciplines. Recognizing and valuing the roles played by other team members contributes to comprehensive patient care and better outcomes. Continuous education enables healthcare professionals to incorporate insights from fields such as psychology, sociology, and communication studies, thereby improving their ability to communicate with and understand patients holistically.

Patient-Centered Care and Well-being. Lifelong learning encompasses the acquisition of cultural competence, which equips healthcare professionals with the ability to deliver patient-focused care to individuals from various backgrounds. Through continuous education, communication skills are refined, enabling healthcare practitioners to effectively relay intricate medical information, engage in collaborative decision-making, and establish trusted patient relationships. Lifelong learning also encompasses resilience training and methods for stress management, preventing burnout, and promoting the mental well-being of healthcare professionals. Additionally, continuous education includes skills development for effectively balancing professional and personal life, fostering a sustainable and satisfying healthcare career.

Innovations in Teaching and Learning. Educators in the field of medicine are encouraged to engage in lifelong learning, which involves adopting innovative teaching methods, utilizing educational technologies, and implementing interactive learning approaches. This is done in order to enhance the effectiveness of medical education. Additionally, ongoing self-assessment and reflective practices are important components of lifelong learning as they enable healthcare professionals to identify areas for improvement, accept feedback, and continuously refine their skills.

Lifelong learning is not a mere choice, but a necessity in the medical field. It empowers healthcare professionals to provide the highest level of care, adapt to the constantly evolving healthcare landscape, and contribute to the well-being of patients and communities. By promoting a culture of continuous learning within medical programs, institutions ensure that graduates are not only well-prepared for current challenges, but also equipped with the skills and mindset necessary to excel in the future of healthcare.

To summarize, medical curricula are vital for medical education, functioning as a guide to ensure students receive thorough and current training. They are crucial in preparing healthcare professionals to deliver excellent care, adapt to changing healthcare demands, and uphold ethical and professional standards. The importance of structured and inclusive medical curricula is clear, as they shape the future healthcare workforce and ultimately enhance patient outcomes and community well-being.

Review Article

Menstrual Dysfunction and COVID19 Vaccine

Sinou Natalia,[1,2] Sinou Nikoleta,[1,2] Filippou Dimitrios[1,2]

[1] *Research and Education Institute in Biomedical Sciences (REIBS), Pireaus-Athens, Greece*

[2] *Dept. of Anatomy, School of Medicine, National and Kapodestrian University of Athens, Athens, Greece*

Correspondence Address: Natalia SINOU, Email: sinou.natalia@gmail.com

Abstract

Introduction: There has been an increasing concern that the vaccination against the novel COVID19 disease is likely to provoke various side effects for the general population including menstrual cycle dysfunctions for women in the reproductive age. There are some risk factors that enhance the possibility for post-vaccine implications on the menstrual health. Such risk factors are smoking, past COVID19 infection and the lack of usage of oral estrogen-containing contraceptives.

Aim. The aim of this report is to clarify the relationship between the vaccines against the SARS-CoV-2 and the menstrual cycle dysfunction in the women of reproductive age.

Materials and Methods: an extend research was made via the PubMed database using the following keywords: "menstrual", "dysfunction", "COVID19", "vaccine". No further filters and eliminations were used.

Conclusion: There are several mechanisms through which vaccines are able to alter the menstruation cycles. The irregularities are not permanent and after a short period of time, menstrual cycles return to normal. Women of reproductive age are still encouraged to be vaccinated.

KeyWords: menstrual, dysfunction, COVID19, vaccine

Introduction

Protective vaccines against SARS-CoV-2, that provokes the novel coronavirus disease (COVID19), have been recently developed in the early 2020. Various general adverse effects have been described, but only recent reports mention menstrual dysfunctions in women of reproductive age.

Multiple technologies were used for the development of the vaccines, such as the mRNA technology, the usage of vector and finally the usage of protein subunit. The vaccines of every type diminishes the possibility of infection in case of exposure, moderates the symptoms and the severity of the illness in case of infection and finally it reduces the likelihood of someone infected to transverse the virus to others (1). The great infectiousness of COVID-19 leads to the need of massive vaccinations for the general population. Of particular interest, among them, women of reproductive age, breastfeeding women and women currently pregnant or intending to be pregnant were encouraged to be vaccinated. Similar to every vaccine, there are some adverse effects. In the general population the main side effects of the COVID19 vaccine include fatigue, dizziness, nausea, muscle pain, fever and chills. Local inflammation at the sight of the injection was also common.

For women of reproductive age menstrual cycle irregularities provoked by the vaccine, might be a possible adverse effect.

As the COVID-19 pandemic insists, women of reproductive age, among the rest of population, continue being vaccinated to get the protection from the infection with SARS-CoV-2 virus. As such, it is of great significance to be clarified whether the vaccine schemes are safe enough as it comes to the sexual and menstrual health of women of reproductive age. The aim of this report is to examine whether the vaccine against COVID-19 is likely to give rise to menstrual dysfunction in young women of reproductive years.

Materials and Methods

An extend research of the relatively published bibliography was conducted via the PubMed database. The keywords used for the search were:

"Menstrual Dysfunction" AND "COVID-19 vaccine". Data were extracted using a common data elicitation form, using the aforementioned keywords. The study was performed with respect to the PRISMA-ScR guidelines.

Specifically, as it concerns the PRISMA, the records that were identified through PubMed search were initially 5 and the additional ones that came up through the review of references were 4. So the records that were screened were 9. The articles excluded because of non-relevant title, abstract and full-text were 3. Finally, 6 references fulfilled the above-mentioned criteria and were used in the present review. *(Figure 1)*

Results and Discussion

The menstrual cycle regulation is a physiological process of grave significance in the well-being of women of reproductive age, which is inextricably linked to the general health and fertility. A typical cycle consists of 26-35 days including approximately 5-7 days of menses. There are various factors that may provoke menstrual disorders including biological features (such as body weight, age, genetics), lifestyle factors (such as stress, emotional stress, alcohol, smocking, drugs, exercise), personal history (adrenarche, menarche, parity) and finally environmental factors (such as chemicals and toxins that affect the endocrine system).

The regulation of menstrual cycle depends on the hypothalamic-pituitary-gonadal axis (HPG axis) and the circulating hormones exceeded by this axis. The HPG axis arranges the endometrium thickening and shedding. The hypothalamus via the CRH and the pituitary gland via the ACTH hormone are also responsible for the release of cortisol from the adrenal glands. It is a hormone excreted in response to stress, immunization and inflammation. When exposed to a stressful stimuli, CRH stimulates an inflammatory pattern in the female reproductive system influencing the evaluation and the degeneration of the corpus luteum. In other words, CRH and cortisol upon exposure to stressful stimuli, lead to cycle abnormalities, because of low female sex hormone levels (1).

There are various factors, besides the vaccine, that correlate with COVID-19 and may cause menstrual dysfunction. As such, these confounding variables complicate the causal relationship between the vaccine and the menstrual dysfunction. To begin with, the radical change in the lifestyle because of the lockdown and the stress of the pandemic and the infection with SARS-CoV-2 themselves may have an impact on the HPG axis (2). Menses were reported longer and with larger volume than usual. Furthermore, a corticosteroid drug called dexamethasone was prescribed to treat hospitalized patients with a severe infection. The mechanism of the drug acts through the endometrial cortisol, influencing the maturation of the endometrial blood vessels. Thus, dexamethasone by definition affects the menstrual cycle function. However, these changes in the menstrual cycle are considered to be temporary and as the stimuli passes by, the normal function of the menstrual cycle returns with no-longer impacts (3).

There are two possible mechanism pathways that may explain the changes in the menstrual cycle because of the COVID-19 vaccine. Firstly, it is highly possible that the innate immune cells which are triggered by the vaccination, interfere with the reproductive hormones and may prolong the follicular phase, leading to an abnormal cycle. The second biological mechanism interferes with the breakdown and the regeneration of the endometrium by the macrophage and the natural killer cells.

It has been also noticed that women of reproductive age who consume estrogen-containing contraceptives per os have a reduced risk of post-vaccination adverse effects regarding their menses (4). This phenomenon can be explained by the fact that in these women the concentration of circulating progesterone and estrogen is higher, because of the drugs. These hormones are immunomodulators and they also have an anti-inflammatory action against severe COVID19 infection (5).

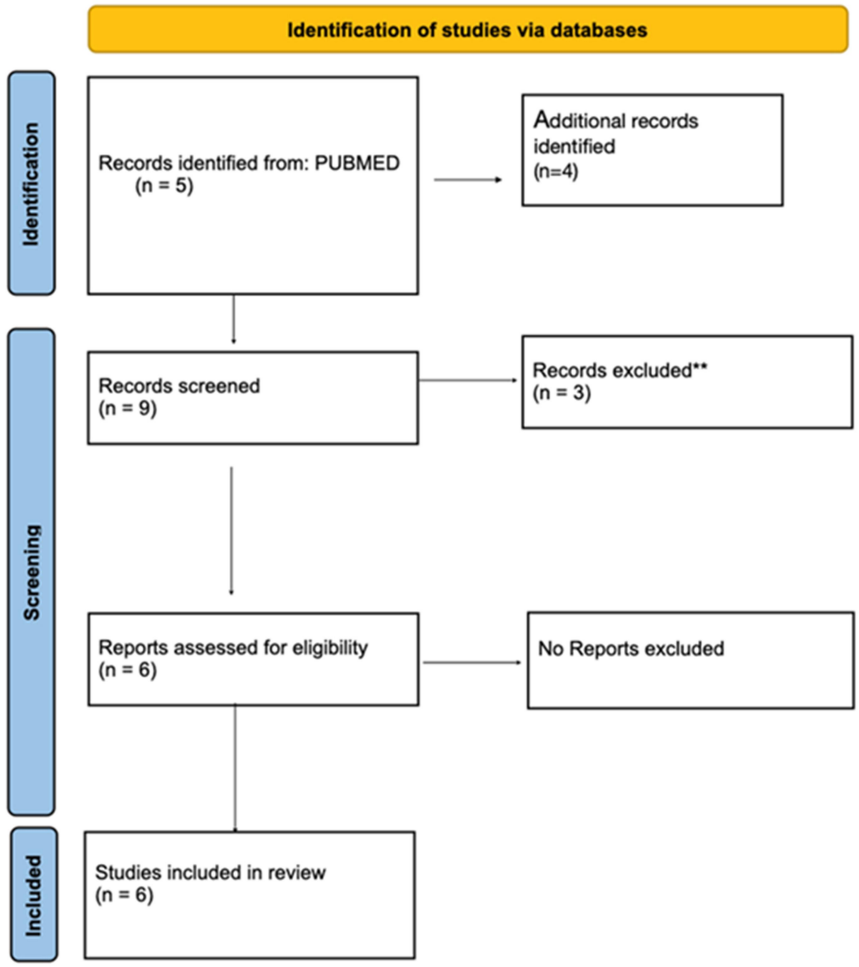

Figure 1. *Flow chart*

There was also evidence that women not using hormonal contraceptives had a delay of averaged 2.3 days on the post-vaccination menstrual period, compared to the pre-vaccination cycle. However the timing of the vaccination regarding to the menstrual cycle did not have any effects on the flow and the volume of the subsequent period. Finally, the type of the vaccine had not affected neither the timing nor the flow of the forthcoming menstrual period (6).

It has been reported that any irregularities in the menstrual cycle after the vaccination for the COVID-19 are related to past COVID-19 infection, smocking, contraceptive type and other menstrual changes over the past year. On the contrary, age, ethnicity, body mass index, physical activity, period length and flow, irregular cycle, vaccination type, vaccination timing, parity, medication use, supplements / vitamins consumption, endometriosis, polycystic ovarian syndrome, uterine polyps/fibroids, thyroid disease and eating disorders are not associated with the changes in the menstrual cycle in the post-vaccination period (4). The concern that the vaccination is likely to provoke menstrual cycle irregularity forms a source of vaccination hesitations and may also burst anti-vaccination campaigns.

In order to overcome the blurry scenery around

the impact of the vaccines against COVID19, future studies should observe and record the relationship between the vaccines and the menstrual cycle. To be accomplished that, it is important that the mechanism/type of the vaccine and the number of doses and boosters are considered. Moreover future studies should clarify the time needed for the menstrual cycle with irregularities to get back to normal. Additionally, it would be useful if future studies compared the menstrual dysfunction because of the vaccine to the one because of the infection with the SARS-CoV-2 virus. As so, there will be a spherical opinion around the impact on the menstrual and sexual health of the women of reproductive age (3).

Conclusions

To conclude with, this was a systematic review that tried to highlight the concerns about the involvement of the vaccination for protection against the COVID19 disease to the women's menstrual cycle. There were discussed mechanisms with which the vaccines may provoke menstrual cycle dysfunctions in women of reproductive age. However there are no evidence that there are neither long term or permanent dysfunctions in the cycle. Irregularities may occur by numerous factors related to COVID19 including changes in the lifestyle, drugs treating an infection from the virus, vaccines and the virus itself. They may disturb reproductive women for a short period and then the run away and the menses get back to normal. Also, it is possible that a personalized diagnostic strategy might be needed in order that the menstrual homeostasis is reestablished. This strategy includes the evaluation of the thyroid gland function, the personalized hormonal status and social aspects (1). Thus, young women of reproductive age and women who are or intend to be pregnant are encouraged to be vaccinated. Further research needs to be fulfilled so as to make the things clear around the vaccination and its impact on the menstrual health.

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Review Article

Retatrutide: A triple incretin receptor agonist showing promise in obesity treatment

Giotas Ilias,[1] Filippou Dimitrios[1,2]

[1] *Dept. of Anatomy, School of Medicine, National and Kapodestrian University of Athens, Athens, Greece*
[2] *Research and Education Institute in Biomedical Sciences (REIBS), Pireaus-Athens, Greece*

Correspondence Address: Ilias GIOTAS, Email: iliasgiotas2001@gmail.com

Abstract

The increasing prevalence of obesity poses a significant challenge for healthcare providers worldwide. However, the recent advancements in the development of drugs for obesity treatment offer hope for effectively addressing this global health concern. The success of semaglutide and tirzepatide, GLP-1 receptor agonists, in targeting the neuroendocrine mechanisms responsible for obesity represents a significant milestone. The introduction of retatrutide, a novel drug for obesity treatment, is also a promising development for the field.

The ongoing phase 2a clinical trials provide an opportunity to evaluate the safety and efficacy of this new therapeutic option. Aim of this systematic review is to present comprehensive information on the anti-obesity action of this GIP-1 receptor agonist at hand. Detailed research was conducted via the PubMed database using the keywords: "retatrutide" and "obesity or weight loss". No further filters were applied.

Clinical trials have shown substantial weight loss with the use of Retatrutide, in patients with obesity. Further research is necessary to ascertain the safety of this GLP-1 receptor agonist in question and to conduct comparative analyses with other similar agonists. These clinical trials will provide valuable insights into the efficacy and performance of the drug, which will be useful in determining its potential for use in medical treatment for obesity.

KeyWords: retatrutide, obesity, weight loss, GLP-1, GLP-1 Receptor Agonists

Introduction

Retatrutide (LY3437943) is a peptide agonist that binds to GIP, GLP-1, and GCG receptors and is currently being investigated in phase 2 clinical trials. GLP-1 receptor agonists have been found to effectively stimulate insulin production and inhibit the release of glucagon, which plays a crucial role in regulating blood glucose levels. Moreover, these agonists exert a central effect on appetite and food intake, suggesting their potential as a treatment option for obesity.(1) Remarkably, retatrutide has demonstrated promising outcomes in terms of weight reduction during clinical trials.(2)

Materials and methods

Extensive research was conducted using the PubMed database's published bibliography, using precise keywords such as "retatrutide" and "obesity or weight loss". To ensure accuracy, data was extracted using a standard data elicitation form and following PRISMA-ScR guidelines. After an initial search, 13 records were identified, but no additional ones were found through reference review as they were similar to the initial ones. From the PubMed database, 13 full-text articles were assessed for eligibility, and 4 were excluded due to non-relevant abstracts. Upon thorough evaluation, all 9 references have been deemed eligible and relevant for this study, meeting the required criteria for suitability.

Results

Based on the research results, it has been observed that retatrutide has a significant effect on reducing weight and shows great potential in treating obesity in the future. After 48 weeks of treatment with the GLP-1 receptor agonist, the average weight loss percentage in the group receiving a 12-mg dose of retatrutide was approximately 24%. The forthcoming clinical trials will provide important information about the safety and effectiveness of our product in a larger and more diverse population. It is crucial to gather the required data to confidently assess the

comprehensive range of its positive effects.

Discussion

Retatrutide (LY3437943) is an agonist of the glucose-dependent insulinotropic polypeptide, glucagon-like peptide 1, and glucagon receptors. Its mechanism of action involves the stimulation of these receptors, which initiates a series of physiological responses aimed at regulating appetite and metabolism. This, in turn, leads to weight loss and offers promising potential for effectively treating obesity.(1) Results from the phase 1b clinical trial indicate that retatrutide is considered safe, and its pharmacokinetics support a convenient once-weekly dosing regimen, with a maximum dose of 12 mg.(3) It is noteworthy that the study found the impact of increasing dosages of retatrutide, a GLP-1 receptor agonist, on weight loss among individuals with obesity to be dose-dependent. However, it is important to consider that the study's active comparator was dulaglutide, another GLP-1 receptor agonist that is not approved for obesity treatment and was administered at a significantly lower dose of 1.5mg compared to the highest approved dose of 4.5mg. These findings indicate the need for further research to evaluate the efficacy of retatrutide in treating obesity, considering the limitations of the current study.(4) The phase 2 clinical trial included 338 adult participants, with 51.8% men and women comprising the cohort. To be eligible for the study, participants needed to have a body-mass index (BMI) of 30 or higher, or a BMI of 27 to less than 30 along with at least one weight-related condition. The study involved randomized assignment of participants in a 2:1:1:1:1:2:2 ratio to receive subcutaneous retatrutide (1 mg, 4 mg [initial dose, 2 mg], 4 mg [initial dose, 4 mg], 8 mg [initial dose, 2 mg], 8 mg [initial dose, 4 mg], or 12 mg [initial dose, 2 mg]) or placebo once weekly for 48 weeks. The main aim of the study was to determine the percentage change in body weight over a span of 24 weeks. Secondary objectives included assessing the percentage change in body weight after 48 weeks and measuring the reduction in weight of 5%, 10%, or 15%, or more from the initial weight.(5,6,7) After 48 weeks of treatment, the group of participants who received retatrutide showcased a considerable reduction in weight in contrast to the group treated with placebo. The degree of weight loss varied according to the dosage, with the participants in the 1 mg group showing an average percentage change of -8.7%. The combined 4-mg group exhibited an average percentage change of -17.1%, while the combined 8-mg group showed an average percentage change of -22.8%. Notably, the 12-mg group exhibited the greatest average percentage change of -24.2%. In contrast, the placebo group only displayed a modest average percentage change of -2.1%. Furthermore, at the end of the 48-week treatment period, it was observed that a notable 92% of participants who received a dosage of 4 mg of retatrutide experienced a weight reduction of 5% or more. A substantial 75% and 60% of cases also demonstrated a weight reduction of 10% or more and 15% or more, respectively. Similarly, for those administered with 8 mg, the percentages of participants achieving a weight reduction of 5% or more, 10% or more, and 15% or more were 100%, 91%, and 75%, respectively. The highest dosage of 12 mg demonstrated even more promising results, with 100%, 93%, and 83% of participants achieving the respective weight reduction thresholds. In stark contrast, the placebo group only exhibited meager percentages of 27%, 9%, and 2% in terms of weight reduction of 5% or more, 10% or more, and 15% or more, respectively. The data indicates that retatrutide is a promising treatment for weight loss, with higher dosages yielding more significant and consistent results.(5,6,7) During the treatment period, adverse events were observed in a significant proportion of participants in the placebo group and the retatrutide groups, with the highest incidence being recorded in the 8-mg and 12-mg groups. The participants in the retatrutide groups experienced gastrointestinal adverse events, such as nausea, diarrhea, vomiting, and constipation, more frequently than those in the placebo group. These events occurred primarily during the dose escalation period, were mainly mild to moderate in severity, were more frequent in higher-dose groups, and were partially mitigated

by the use of a lower starting dose (2 mg vs. 4 mg). Moreover, gastrointestinal adverse events were the most commonly reported adverse events leading to treatment discontinuation.(5,8) As a side effect, retatrutide has also been found to increase heart rate by up to 6.7 beats per minute.(9)

Conclusions

The use of retatrutide as an intervention for obesity has shown promising results. The group that received retatrutide had a significant weight reduction compared to the group that received the placebo. This suggests that retatrutide could be an effective approach to managing weight loss in obese individuals in the near future. The available evidence suggests that retatrutide may be more effective than other GLP-1 receptor agonists. However, it is important to note that such comparisons may not be meaningful, and further research is necessary to establish the safety of retatrutide in larger and more extended trials. It is important to weigh the benefits and risks of any medication before initiating treatment. Healthcare providers must be aware of potential complications. Further research is needed to fully understand the mechanisms behind these effects and to determine whether certain patient populations may be at higher risk for experiencing these side effects.

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Review Article

The covid-19 impact on the pituitary gland

Sinou Nikoleta,[1,2] Sinou Natalia,[1,2] Filippou Dimitrios[1,2]

[1] *Research and Education Institute in Biomedical Sciences (REIBS), Pireaus-Athens, Greece*

[2] *Dept. of Anatomy, School of Medicine, National and Kapodestrian University of Athens, Athens, Greece*

Correspondence Address: Nikoleta SINOU, Email: nikoletta.sinou@gmail.com

Abstract

The Coronavirus 2019 (Covid-19) disease pandemic continues to infect a great number of human population, causing severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Global healthcare system has been significantly burdened since the percentages of mortality and morbidity are highly rising. As time passes and more studies have been conducted, it is increasingly clear that Covid-19 does not only affect the respiratory system, but has also multiple effects on cardiovascular, endocrine and neurological systems.

Detailed research was performed via the PubMed database using the following keywords: covid-19, infection, impact, pituitary gland, vaccination. The research was made in the articles from 2019, when Covid-19 first emerged and subsequently.

Covid-19 virus has cellular access through the angiotensin-converting enzyme 2 (ACE2) receptor. This process requires the transmembrane serine protease 2 (TMPRSS2) protein. Both ACE2 and TMPRSS2 are widely expressed in many endocrine glands.

This review analyzes the endocrine manifestations of Covid-19 on the pituitary glands. On this review we underline the most common pituitary diseases that Covid-19 is responsible for, which are the pituitary apoplexy, hypophysitis, hypopituitarism and adrenal cortex insufficiency.

KeyWords: covid-19, infection, impact, pituitary gland, vaccination

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first emerged in late 2019-early 2020 and was identified as the cause of universal spread of a fatal pulmonary virus. The subsequent pandemic Covid-19 is recognized as one of the most serious challenges that the worldwide healthcare system faces with. The impact that Covid-19 has on patients does not only regards the pulmonary system, but also the cardiovascular and the pituitary system (1-3).

Covid-19 was initially identified as a lethal respiratory virus that causes SARS-CoV-2. However, as the Covid-19 continues to exist on global health care systems, extrapulmonary manifestations have been found. Covid-19 has been proven to directly affect the cardiovascular, neurological and endocrine system. The extrapulmonary infection of Covid-19 is due to the expression of angiotensin-converting enzyme 2 receptor (ACE 2), which allows the virus to enter the cells, resulting in the damage of multiple organs and tissues. This process requires the transmembrane serine protease 2 (TMPRSS2) protein, as both ACE2 and TMPRSS2 are widely expressed on many endocrine glands (4). In our study, we will analyze the effects that Covid-19 has on the endocrine system and specifically on the pituitary glands, reporting the "endocrine phenotype" of Covid-19 (1). Aim of this study is to shortly review the manifestations of Covid-19 on pituitary glands and its implications on pituitary diseases which can be at increased risk with respiratory complications.

Materials and methods

The PubMed database was searched extensively using specific keywords such as covid-19, infection, impact, pituitary gland, vaccination for relevant published sources. To ensure accuracy and adequacy, information was gathered through a common data extraction form designed for the aforementioned keywords. The research study

adhered to the guidelines of PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews), a comprehensive approach for conducting scoping reviews. By following PRISMA guidelines, a total of 19 records were initially identified through the PubMed search, and an additional 3 records were obtained through a thorough review of references.

After removing duplicates, the final number of screened records was 22. A total of 8 full-text articles were assessed for eligibility, resulting in the exclusion of 14 articles, titles, and abstracts that were not relevant. Hence, the specific article is based on the information retrieved from 8 reliable references (Table 1).

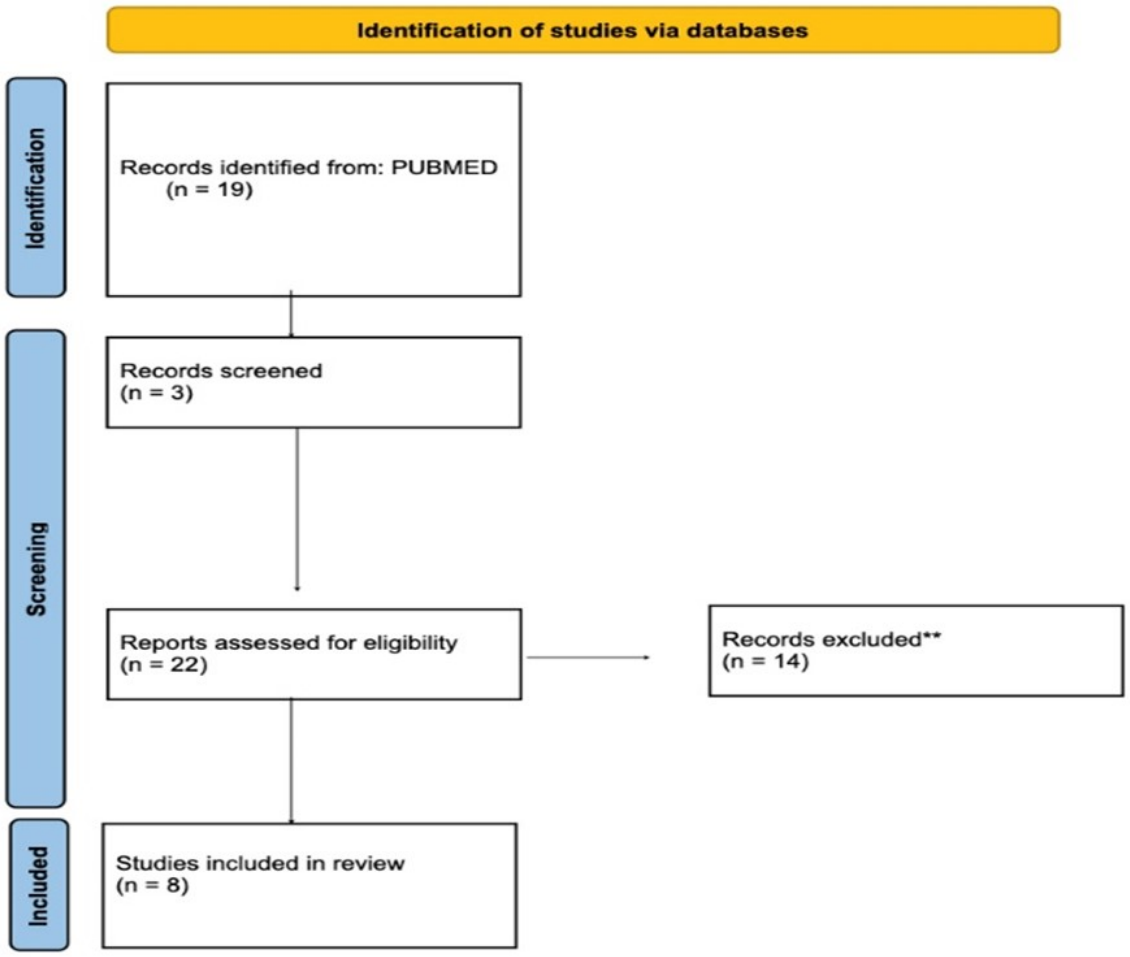

Figure 1. *Flow chart*

Discussion

Pathophysiology. As we mentioned above, SARS-CoV-2 infects host cells by binding the ACE2 receptor. The mRNA of this protein is expressed in many tissues and therefore the virus has the possibility to widely spread to many organs causing infection outside the respiratory system (5). Specifically, ACE2 is expressed in hypothalamus, pituitary, pancreas, thyroid and gonads, which are possible targets for the virus. Therefore, these organs are vulnerable to Covid-19 infections. The virus enters the brain either via the general circulation, passing through the blood brain barrier (BBB) or via the nasopharyngeal epithelial through

the olfactory bulb (6). Pituitary gland has rich vascularity and therefore can be damaged during Covid-19 infection. Moreover, pituitary can be damaged by conditions that alter the platelets' function and coagulation. Patients after the inflammatory state of SARS-CoV-2, have increased hypercoagulability with thrombocytopenia and high levels of fibrinogen and D-dimers. Thus, these patients are in high risk of pituitary damage and dysfunction of the endocrine system (4).

Pituitary Apoplexy. Covid-19 can cause thrombopenia, coagulopathy and dysfunction of platelets, and therefore it may have direct vascular damage to pituitary gland with ischemic and hemorrhagic signs of necrosis, due to ACE2 expression on cerebral vascular epithelium. Therefore, multiple studies have proven that Covid-19 could cause pituitary apoplexy. In particular, pituitary apoplexy is an acute clinical and surgical syndrome of sudden hemorrhage of pituitary gland, in which there is usually a pituitary microadenoma. Sudden onset of acute headache, visual disturbances and palsy of the ocular nerve are the main symptoms that patients report and they are due to a necrotic mass that compress the surround pituitary structures. As many studies report pituitary apoplexy is a rare event that presents to 2-12% of patients with microadenomas, but Covid-19 infection has highly increase the percentage of patients with pituitary apoplexy (1,5,7).

Hypophysitis. Hypophysitis is common adverse-effect of the anticancer immunotherapy with immune checkpoint inhibitors (ICPs) such as the monoclonal antibodies anti-CTLA4, anti-PD-1 and anti-PD-L1. These monoclonal antibodies express immune system against tumor cells causing severe endocrine diseases.

There are not yet enough studies that relate hypophysitis with Covid-19 infection. However, it is considered that patients with Covid-19 that receive a specific treatment, present reduced or at least a non-increased incidence of hypophysitis. That can be explained since Covid-19 treatment is based on the administration of glucocorticoid, which are also used for the resolution of hypophysitis.

Hypopituitarism and adrenal insufficiency. ACE2 receptor has been identified to be present in the adrenal cortex and specifically, in the zona fasciculata and reticularis (glucocorticoid and androgen production), but not in the zona glomerulosa (mineralocorticoid production). In addition, TMPRSS2 is present in all 3 zones of adrenal cortex (4).

Adrenal function remains stable during Covid-19 infection in most cases. However, a great number of studies have reported that Covid-19 infection affects the hypothalamic-pituitary-adrenal (HPA) axis. In particular, there are some case reports following Covid-19 that have been reviewed with adrenal insufficiency secondary to acute adrenal infarction and adrenal hemorrhage (7).

Specifically, it is indicated that Covid-19 patients have highly increased levels of cortisol and adrenocorticotropic hormone (ACTH) and in patients with severe COVID-19 in comparison with those with mild-to-moderate disease forms, these hormones are significantly higher. However, cortisol levels are significantly lower in fatal cases of Covid-19 (4).

In summary, adrenal function has been retained in most patients with Covid-19. The high levels of cortisol are due to the treatment of Covid-19 infection with glucocorticoid, whereas the significantly low levels may be due to the damage of adrenal function, suppressing the hypothalamic-pituitary-adrenal axis (1,4,6,8).

Covid-19 vaccination and pituitary diseases. Published data and previous studies have reported some particular cases of adverse effects or some contradictions in relation to pituitary diseases as regards the vaccines, causing endocrine dysfunction. Specifically, hypophysitis has been reported not only after Covid-19 infection, but also after vaccination. ACTH deficiency of pituitary atrophy has also been described one day after mRNA Covid-19 vaccination. These vaccines have also been accused for apoplexy of pituitary glands. Vaccine efficacy can be reduced in patients who are immune suppressed or receive glucocorticoid treatment. In a survey of Pituitary Society Members most clinical doctors reported that they maintain the replacement dose of glucocorticoid

during vaccination and they increase it only in cases of adverse effects, as fever (1,6).

Conclusion

Covid-19 pandemic has disrupted every aspect of our life and consist a high challenge for doctors, healthcare system and patients. In this review, we underline the involvement of coronavirus in the endocrine system and in particular, in the pituitary glands, as coronavirus enters endocrine cells via ACE2 and TMPRSS2 expressed on these tissues. Moreover, our review analyzes the pituitary apoplexy, hypophysitis, hypopituitarism and adrenal cortex insufficiency, as the most common pituitary diseases that Covid-19 is responsible for. Finally, risk factors and some adverse-effects have been reported on Covid-19 vaccination, which points out that more research and development need to be conducted for minimizing Covid-19 impact on human life and any adverse-effect of Covid-19 vaccination.

Abbreviations

ACE2: angiotensin-converting enzyme 2 receptor

TMPRSS2: transmembrane serine protease 2 protein

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2

HPA: hypothalamic-pituitary-adrenal

ACTH: adrenocorticotropic hormone

ICPs: immune checkpoint inhibitors

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

Availability of Data and Materials

The data were collected via PubMed database. The information of this systematic review is available and accessible in the database mentioned using the keywords that have been mentioned above.

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Short Review – Historical Article

Christian Albert Theodor Billroth (1829-1894): a giant of surgery

Miltiadis Perdikakis,[1] Dimosthenis Papadimitrakis,[1] Dimitrios Filippou[2,3]

[1] *School of Medicine, National and Kapodestrian University of Athens, Athens, Greece*
[2] *Research and Education Institute in Biomedical Sciences (REIBS), Pireaus-Athens, Greece*
[3] *Dept. of Anatomy, School of Medicine, National and Kapodestrian University of Athens, Athens, Greece*

Corresponding Address: Miltiadis Perdikakis, National and Kapodistrian University of Athens School of Medicine, Athens, Greece, miltiper@gmail.com

Abstract

Christian Albert Theodor Billroth (1829-1894) is a prominent figure in the history of surgery and medicine in general. His operational innovations serve as pivotal advancements, as they introduced certain approaches that changed the medical landscape. This paper provides a concise overview of his life, academic career, surgical innovations, teaching skills, and prestigious awards. His remarkable musical talent is also discussed. Our goal is to justify his prominent status among the most influential physicians in history and to provide a distinct example of dedication to medicine.

Key Words: Billroth, surgery, history of medicine

The history of medicine is adorned with numerous physicians, both known and unknown, who dedicated their lives to science. It is the duty of historians to accord them a place in history worthy of their names and actions. One of the most prominent physicians, a pioneering surgeon who laid the foundations for modern surgical practices, is Christian Albert Theodor Billroth (1829-1894) (Figure 1). Thanks to his medical achievements, Billroth's name remains in the pantheon of surgeons who elevated medicine to a higher level of efficiency and professionalism. It serves as a reminder of the obligation that younger generations of physicians owe to those who paved the way for modern medicine.

His life

Christian Albert Theodor Billroth was born on the 26th of October 1829, in “Bergen auf Rügen” in the “Königreich Preußen” (Kingdom of Prussia), which was part of the German state of Prussia and lasted from 1701 to 1918. Information about his childhood is scarce and can be found in a short autobiographical essay. Billroth's father was pastor Karl Theodor Billroth, and his mother was Christine Billroth (Nagel). Theodor was the oldest of five brothers. Their grandparents' ethnic background was Swedish and French. His pastor father passed away from tuberculosis when he was only five years old, so he moved with his mother and brothers to Greifswald, where they had friends and relatives [1].

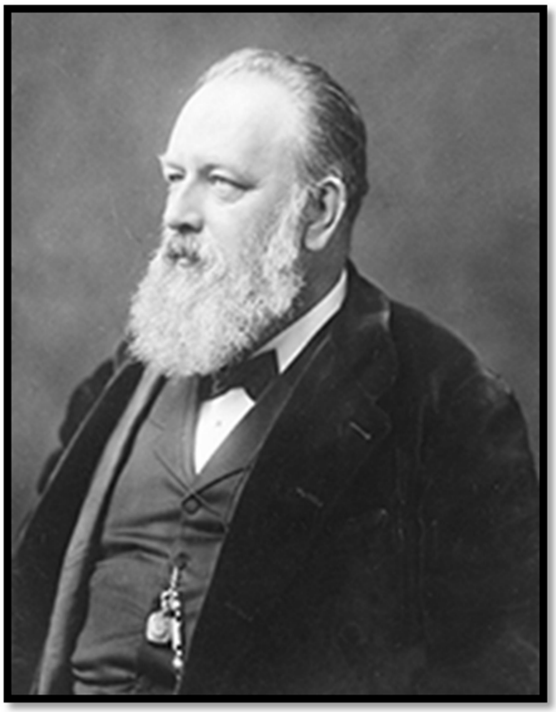

Figure 1: Christian Albert Theodor Billroth (1829-1894) (From: https://www.billrothhaus.at)

Theodor Billroth completed his schooling in Greifswald. He began his medical studies in 1848

and studied at the universities of Greifswald, Göttingen, and Berlin. He earned his doctorate from Berlin's University in 1852 by presenting his thesis, "De natura et causa pulmonum affectionis que nervo utroque vago dissecto exoritur" (The nature and cause of pneumonia caused by cervical vagotomy). After spending one year visiting the medical schools of Paris and Vienna, he returned to Berlin, where he acquired the position of assistant to Bernard Von Langenbeck (1810-1887), a prominent figure in surgery, at Berlin's University Surgical Clinic [2,3]. He started publishing and lecturing on surgery as well as giving practical surgical demonstrations (Figure 2).

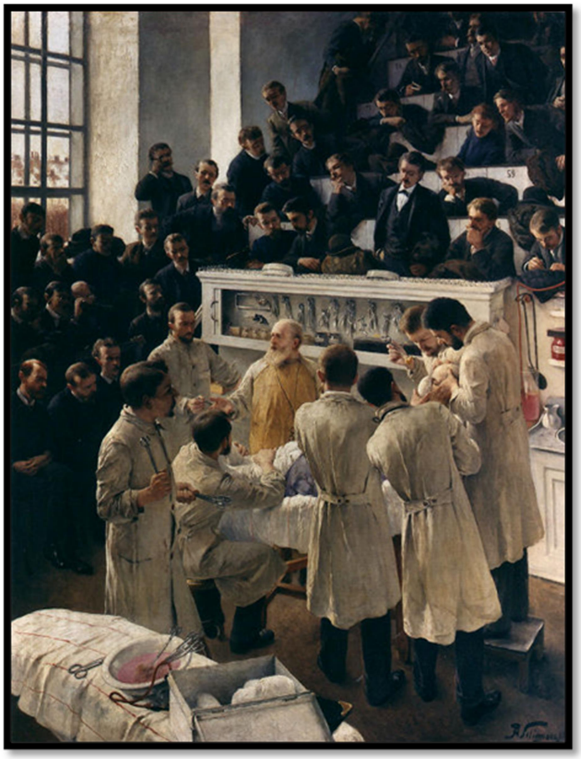

Figure 2. Theodor Billroth operating
(From:: https://en.wikipedia.org)

In Berlin, he met Christel Michaelis, whom he married in 1858. They had three daughters and one son. As his body of work expanded, he was appointed as a Professor of Surgery and the director of the surgical hospital in Zurich in 1860. In 1867, he was named a Professor at the University of Vienna and was appointed director of the 2nd Surgical Clinic at the city's hospital. It was in Vienna where he reached the pinnacle of his medical career and continued to work until his passing in 1894 [4].

Apart from his surgical achievements in later life, Theodor Billroth had a special aptitude for music. He would have pursued this field, had it not been for his mother's persuasion due to financial constraints, which led him to study medicine. He was proficient in multiple musical instruments, directed an orchestra, wrote music critiques, and formed friendships with musical composers [5]. He himself composed music in his younger years. Notably he left behind the first two chapters of a theoretical book on music titled "Wer ist Musikalisch?" (Who is musical?), which had already gone through four editions until 1912 [6]. It is not an exaggeration to say that his musical skills were an early indication of his future success in the field of surgery. One can only speculate what his accomplishments in music would be, had he followed the path that fate opened him early on.

Academic work and medical innovations

Billroth's imprint on surgery and medicine as a whole cannot be easily overlooked. His work included numerous lectures, practical demonstrations, and important scientific treatises. However, his most precious legacy to medicine was his groundbreaking surgical procedures, some of which were successful and paved the way for the immense development of surgery. Billroth's name is forever associated with some of surgery's most famous procedures. He is also rightfully regarded as the founding father of modern abdominal surgery. However, his contributions extended beyond abdominal surgery.

Billroth performed his first operation in 1852, which was a herniotomy. While at the Von Langenbeck clinic, he published numerous scientific articles on various topics, including the histology of the spleen, mucous polyps, tumors, and blood vessels. In 1858, during the war between Prussia and France, he shifted his focus to the management of gunshot wounds. Subsequently, he expanded his interest to the diseases that could develop from open wounds and how to prevent their outcomes. He hypothesized

that a microorganism was responsible for these diseases, a hypothesis that was later confirmed [7]. During his time in Zurich, he produced his most significant written work, the famous textbook "General Surgical Pathology and Therapeutics", which went through 16 editions and was translated into 10 languages. He also greatly contributed to the composition of the massive series of the "Handbuch der allgemeinen und speciellen Chirurgie mit Einschluss der topographischen Anatomie, Operations und Verbandlehre" (Handbook of general and special surgery with inclusion of topographic anatomy, operation and bandage instruction). Furthermore, one of his greatest achievements was his effect on the use of statistics. He insisted that this was the only way to scientifically compare surgical and conservative treatment methods. He therefore recorded for years the outcomes of his treatments. He strongly suggested that it was an imperative for Germany at the time that the physicians adopted this method [8].

In 1872 Billroth performed the first successful esophagectomy and in 1873 he conducted the first total laryngectomy. He pioneered many surgical procedures, including the first subtotal colectomy. His first successful partial gastrectomy on a patient with cancer of the jejunum introduced the renowned Billroth I gastrectomy, in which the partially resected stomach is connected to the duodenum. Subsequently, he successfully performed a technique in which a partial gastrectomy is followed by the connection of the stomach to the jejunum. This procedure has been established as the Billroth II procedure (Figure 3) [9]. Throughout his medical career, Billroth was known for publishing both his positive and negative surgical outcomes. He believed that the improvement of medical procedures was more important than an unblemished reputation. In one of his opening lectures he stated: "He who cannot quote his therapeutic experiences in numbers is a charlatan; be truthful for clarity's sake, do not hesitate to admit failures as they must show the mode and places of improvement" [10].

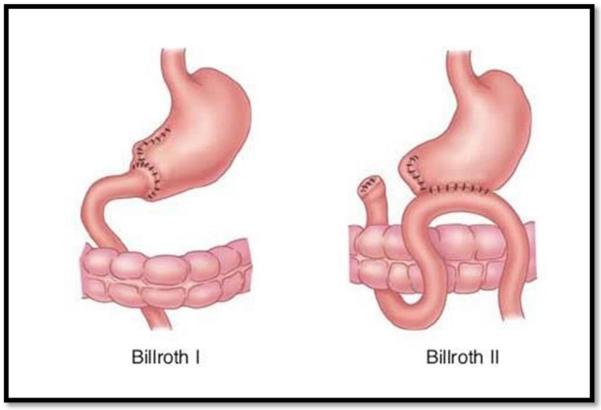

Figure 3: Billroth I and II procedures
(source: https://gr.pinterest.com/pin/296182112990308318/)

Another area of intense involvement for Billroth was thyroidectomy. Thyroidectomy was considered for centuries a deadly operation due to its complications, and many physicians refused to practice it. Billroth was the first, along with his pupil Theodor Kocher (1841-1917), to reopen this forbidden chapter of surgery. His early outcomes were not ideal, resulting in 16 deaths after 36 thyroidectomies. After a few years and under better antiseptic conditions he managed to reduce the mortality rate to 8.3% after 48 such operations [11]. However, the consequences of the removal of the parathyroids, including tetany, were dramatic and saddened the physicians. Billroth's pupils managed to mitigate this problem over time by preserving specific parts of the thyroid gland. This serves as a reminder that the science we admire today has often been accompanied by pain and suffering on its path of evolution.

Billroth's name also emerges in multiple medical terms, since he was the first to identify the respective entities. For example, the "cords of Billroth" describe the splenic cords of lymphoid cells, that constitute the tissue between the venous sinuses of spleen. They are found in the red pulp and play a major role in the organ's physiology and pathophysiology, since they expand in blood disorders that lead to splenomegaly [12]. Two diseases also carry the surgeon's name. Billroth's disease I is a pediatric disorder in which cerebrospinal fluid accumulate under the child's

scalp and Billroth's disease II is a malignant lymphoma. It is worth mentioning that the latter has not been considered a surgical disease since Billroth's time [13,14]. "Billroth's venae cavernosae" are small tributaries of the splenic vein in the pulp of the spleen and the Buerger's-Billroth's disease is a chronic inflammatory disease that affects the peripheral vessels, mostly the radial and ulnar arteries [15].

Billroth was known not only as a unique surgeon, but also as a methodical teacher. Despite his fame and authority, he displayed a well-documented passion for the training of young physicians. It was acknowledged by many of his students and colleagues. In fact, it is worth noting that he even wrote an entire book on the subject of medical training. It was named "Über das Lehren und Lernen der medicinischen Wissenschaften an den Universitäten der deutschen Nation" (Teaching and Learning the Medical Sciences in the Universities of the German Nation) [16]. He explained there, among others, the virtues of a good physician, such as being a scientist, being resilient, being an athlete (!) etc. To sum up, his position as a Professor did not prevent him from fulfilling with conscientiousness his teaching duties.

Awards

Theodore Billroth accumulated a variety of awards throughout his life, dedicated to his medical services. He was appointed as Imperial and Royal Aulic Councilor and Professor as well as President of the Imperial and Royal Medical Association of Vienna. He was furthermore appointed to the Austrian "Herrhaus" (House of Lords) [17]. This was a distinction rarely attributed to physicians. He was also elected member of the "Deutsche Akademie der Naturforscher Leopoldina" (German National Academy of Sciences Leopoldina).

Conclusions

Theodore Billroth died on February 6, 1894, from a medical complication related to the thesis he presented for his doctorate. Perhaps one of Billroth's most noteworthy accomplishments is the enduring memory he has left behind. He is not only remembered as a historic figure, but also as a vibrant legacy in medicine. Some of his techniques are still in use today. This is all the more remarkable, considering that in the century since his death, medicine has achieved significant advancements, fundamentally altering many of its historical practices.

Vienna, the city where Billroth achieved the pinnacle of his medical career, continues to honor him with the Theodor Billroth Prize. This prestigious award, presented by the medical association of Vienna, recognizes outstanding achievements in medical research and stands as one of the highest honors in the field in Vienna.

Conflicts of interest

All authors of this study have not any personal conflicts of interest or any financial conflicts of interest.

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