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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

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საქართველოს სამედიცინო სიახლენი

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თანამშრომლობითა და მისი პატრონაჟით

Guest Editor – Professor Elene Giorgadze

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მოწვეული რედაქტორი – პროფესორი ელენე გიორგაძე

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией и Международной академией наук, образования, искусств и естествознания (IASEIA) США с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения.

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GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

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Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or computer-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

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In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

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10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

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1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

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4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

НАУКА

IVANE JAVAKHISHVILI TBILISI STATE UNIVERSITY IS 100 YEARS OLD

Ivane Javakhishvili Tbilisi State University is the firs-ever national university in Georgia and in the Caucasus. It was founded in January 26, 1918.

In 1989 the Tbilisi State University (TSU) was named after its founder, Ivane Javakhishvili. TSU offers a wide variety of degree programs at undergraduate, graduate and doctoral levels and short courses offered in English language, attracting students from all over the world. The internationalization of TSU is fast-paced and aims at creating multicultural environment that will enhance teaching and research opportunities. TSU promotes the equal access opportunity to education and believes in engaging and valuing all students and staff.

With 100-year history of successful achievements, TSU is ranked today at the top 2% of the world universities (359) by the U.S News & World Report-Best Global Universities Ranking (2017); Times Higher Education World University Ranking (2016) – 801+;

TSU is the leading research university in Georgia with over 200 research projects and about 500 publications in journals with high impact factors.

TSU is in a leading position by the number of implemented projects, winning the grants announced by the Shota Rustaveli National Science Foundation in 2017: out of 86 funded projects, 45% were from TSU.

Tbilisi State University holds the leading position in Education research scholarship competitions among the PhD Students: out of 40 funded projects, 14 (35%) were from TSU.

Up to 22 000 students are carrying on with their studies in 67 BA, 95 MA, 51 PhD and 3 One-step Medical and Dentistry and vocational programs at TSU.

Along with bachelor's, master's and doctoral degree programs, the Tbilisi State University also implements higher vocational education, as well as short and long-term certification programs. Based on close cooperation with foreign universities, Georgian students have opportunities to participate in exchange and joint international educational programs and gain double academic degrees.

Tbilisi State University is an active member of leading international education networks and is proud of its alumni - prominent professors, scientists and professionals, who have successfully integrated into the European community and gained the recognition worldwide.

The University has over 300 000 alumni.

Studies and research activities are carried out at seven faculties and sixteen research institutes.

The Faculty of Medicine is one of the most active faculties of TSU.

The Faculty has more than 40 affiliated clinics and hospitals for clinical practices.

TSU Faculty of Medicine, together with Georgian Medical Association, publishes an online Journal "Translational and Clinical Medicine – Georgian Medical Journal".

There is an actively functioning Students' Scientific Board at the Faculty. Our students are members of EMSA (European Medical Students' Association). Students' Scientific Board, together with EMSA-TSU has been organizing two regional and one University Conferences annually, summer and winter seminars for students and young scientists.

The Faculty has 1700 Students, including over 500 foreign students, 90 academic staff; Educational programs: BA 1, One-Cycle Educational Program – 3 - including English language program, MA-2, PhD -3;

One-Cycle Educational Programs, "Medicine" (Georgian, English) - Goals of the Program: The program aims at providing students with the knowledge consistent with the modern international medical standards and developing appropriate skills.

The educational program provides students with knowledge and skills in the following areas: Scientific Basis of Medicine; Clinical knowledge and skills; Population Health and Health Systems; Professional Values, Ethics and Behaviour; Com-

munication skills; Critical thinking and scientific research; Information management.

One-Cycle Educational Program „Dentistry" - Goals of the Program: to provide the students with the education and help develop professional skills in accordance with the international medical standards; training of the highly qualified dentists, whose professional activities will contribute to raising the levels of dental services, oral disease prevention and health improvement. Development graduates' observation, ability of logical analysis of the observed signs and symptoms, in order to assess the whole pathogenetic process, to plan and approve comprehensive dental treatment plan and patient management tactics. Also, graduates should acquire a basic manual skill, which will provide conducting of prophylactic and treatment measures by specialists trained at the program of general dentistry.

PhD Program - Clinical and Translational Medicine - Goals of the Program: to provide PhD students with a deep modern knowledge about etiology, pathogenesis, diagnostics, prognosis and treatment of the pathologic conditions;

To develop in doctoral students ability of critical analysis of literature data and of the results of their own research, aptitude for making logical conclusions - using the principles of evidence-based medicine;

To develop qualified researchers capable of conducting independent and collaborative scientific work and future faculty members for successful academic careers.

PhD program - Public Health and Epidemiology - Goals of the Program: the primary goal of the program is to help a doctoral student to get outstanding and innovative knowledge in the field of public health, health care management and epidemiology. Respectively, with the subject of scientific interest and research a doctorant will get the latest information, deepen knowledge and improve professional skills in the following areas: biostatistics; study of the phenomenon of health in population; environmental health; national health policy, evidence-based public health; priorities of public health and health care management; assessment of population's and community's health needs; health services administration; primary health care management; information technology in healthcare; bioethics, health care legislation and patient's rights in the sphere of healthcare; epidemiology of communicable and non-communicable diseases, immunological epidemiology;

PhD Program -Translational Biomedicine (Direction – "Hepatology") - Goals of the Program: to provide PhD students with a deep modern knowledge in liver morphology and surgery related to liver morphogenesis, regeneration and cholestasis.

To contribute to responding to the challenges of the fundamental and regenerative hepatology, improve existing treatment methods and develop new clinical approaches;

To fill the gap between fundamental biological and clinical researches and promote the introduction and development of the translational research in the bio-medical field at TSU.

To improve the quality of research and education, develop skills in doctoral student in critical analysis concerning literature data and the results of their own research, abilities to make logical conclusions - using the principles of evidence-based medicine;

To support the internationalization of the scientific research and improvement of the knowledge and skills of PhD students and academic staff through the promotion of inter-institutional cooperation and optimal exploitation of existing scientific potential.

To train qualified researchers able to conduct independent and collaborative scientific work and future faculty members worthy of successful academic careers.

MA programs - Public Health (Georgian, English) - Goals of the Program: deep and thorough study of fundamental issues of health care organization and management, development of analytical thinking and deepening of practical skills, namely: the basic demographic and social trends of Georgia, national health care policy, health care strategic development plan, the health care priorities, other countries' health care systems, organization of health care system in Georgia, structure of the system, the primary health

care system management, hospital management, organization of health care among specific population groups, evaluation of needs of population in the sphere of health care, providing of medical services to the medical market, procurement of medical services, health care legislation, et. Program aims: Mastering of basic theoretical, methodological and research principles of Public Health; Learning of professional and contextual issues related to the practice of Public Health

Bachelor Programs „Occupational Therapy" - Goals of the Program: to prepare competent (with related professional knowledge, skills and attitudes) occupational therapists able to work in any field of occupational therapy practice using evidence based and ethical approach.

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POSTGRADUATE MEDICAL TRAINING COURSES ON DIABETES - SHORT HISTORY

The European Association for the Study of Diabetes (EASD) was founded in 1965 in Montecatini, Italy and is governed by an Executive Committee which in turn reports to the members who meet once a year during the EASD Annual Meeting. The EASD Annual Meeting is held each year in a major European city and is attended by some 16 000 people. In addition to this major international meeting, the largest medical meeting on diabetes and its complications in the world, the European Association for the Study of Diabetes has a long history of organizing innovative clinical postgraduate courses on diabetes both in Europe as well as outside of Europe.

The first postgraduate courses were organized during the times of Cold War under the guidance of Jean-Philippe Assal. They proved to be very successful and, more importantly, of great value for the doctors who attended. For many years EASD continued to organize 3-4 courses per year and also went on to develop smaller, more hands-on learning events such as the Robert Turner Course and the Scientist Training Course. However, during the chairmanship of Prof. Leszek Czupryniak (who has been a driving-force behind the success of the courses for many years, having first served as secretary of the postgraduate committee for some time before becoming chairman), the EASD postgraduate committee expanded its activities dramatically, organizing up to 20 courses per year in Europe and far beyond the European borders in the Middle East, Asia, Africa and South America. It is interesting to note that by the end of 2017, EASD will have trained over 25 000 health care professionals in over 150 Postgraduate Medical Training Courses. Through EASD postgraduate courses EASD helps health care providers worldwide to keep abreast of the rapid advancements in diabetes research and care that in turn provide millions of diabetic patients with updated care and treatment.

In addition to these "live" events, EASD has developed the EASD Virtual Meeting, offering thousands of presentations online and live-streams of the EASD Annual Meeting as well as postgraduate courses.

One of the main reasons behind the success of the EASD courses is their focus on unbiased, evidence and research based medicine which offers modern, practical and comprehensive knowledge on diabetes. Another important aspect of the courses is the maximum interaction between faculty members and participants during group discussions (workshops). Because of their popularity as well as being the most useful and practical elements of the courses for the attendees,

workshops have become the dominant focus of these learning events.

Contrary to the long history of postgraduate courses held by EASD, we have to admit that Georgia has a short history of organizing EASD postgraduate courses.

The first EASD course was held in Tbilisi in October 1994 and was chaired by Prof. Andrew J.M. Boulton. This course was based on the IDF/WHO twinning program and was attended by about 100 delegates. Most of these delegates came from Georgia itself but a number also attended from Armenia and Azerbaijan. Taking into account social and economic problems of the country at that time, the organization of this very important course was extremely difficult.

The second EASD postgraduate course in Georgia was held Tbilisi in May 2015 with more than 250 attendees. Apart from the delegates from Georgia, a significant number of participants attended from other countries, including Kazakhstan, Kyrgyzstan, Tajikistan, Uzbekistan, Turkmenistan, Turkey, Moldova, Azerbaijan, Russia, Armenia, Ukraine and Belarus.

In 2015, the three-day programme of the course included 4 sessions and 9 workshops with 11 foreign and 15 local faculty members. The general sponsors of the course were EASD and National Institute of Endocrinology, however, many local pharmaceutical companies also sponsored the course, including Gold Sponsors: Servier, Berlin-Chemie Menarini and Worwag-Pharma; Silver Sponsors: Sanofi, IME-DC, Novo-Nordisc, Takeda and Welfar and Sponsors: Novartis, Asfarma, Dr. Sertus, World Medicine and Rotapharma.

Three yearthe great success of the second EASD course in Georgia, the EASD Executive Committee unanimously decided to once again hold an EASD Postgraduate course, in Tbilisi, Georgia, in May 2018. This course will host 220 delegates from Georgia and foreign countries. Ten international speakers will participate in workshops and lectures during the three-day programme together with local speakers who will also be actively involved in the scientific programme. As the interest in workshops was much more high than in lectures, the upcoming event will consist almost entirely of workshops with only two lectures to open and to close the event. The general sponsors of the course will be EASD, National Institute of Endocrinology and Ivane Javakhishvili Tbilisi State University, which celebrates its 100-th anniversary this year.

MILD CASE OF INSULIN RESISTANCE IN A PATIENT WITH TYPE 2 DIABETES MELLITUS (CASE REPORT)

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Type 2 Diabetes mellitus (DM) is a chronic metabolic disorder characterized by hyperglycemia, insulin resistance and relative insulin deficiency. Long-term complications of diabetes include cardio-vascular disease, diabetic retinopathy, nephropathy and neuropathy, which can result in blindness, kidney failure, and poor blood flow to the limbs leading to amputations. Due to these life-threatening complications, diabetis patients are associated with a 10 years shorter life expectancy compared to non-diabetic population. There are rare cases when even higher dosages of insulin are insufficient to control glycemic values. Insulin resistance can be mild, moderate or severe.

Case report: A 46 year-old female patient was diagnosed with DM type 2 ten years ago. At the same time a diagnosis of concomitant acanthosis nigricans and along obesity was established. The patient had a family history of type 2 diabetes (her mother and brother). For the first seven years from the diagnosis the patient was treated with oral anti-diabetic medications. For the first four years on metformin 1000 mg BID monotherapy the values of HbA1c were below 7.5%, and no chronic diabetic complications have been revealed. Subsequently, the HbA1c values started to increase, and sulfonylurea was added to the therapy regimen. The patient started to pay even more attention to her eating habits, however high blood pressure (145/95 to 155/100 mmHg) and non-proliferative retinopathy were diagnosed. We included ACE-inhibitor enalapril (10 mg QD) in her therapy, and the retinopathy was closely monitored. Because of her diabetes and comorbidities, we evaluated the patient for Polycystic Ovary Syndrome (PCOS). The hormone values (estrogen, FSH, LH) were within normal ranges. She had regular menstrual cycle and the ultrasound of the ovaries detected no cysts. A physical examination was also performed and there was no expressed hirsutism. During the next two years, the HbA1c values stayed within the range of 7-8%, and the blood pressure was normalized. At the seventh year after the diagnosis of diabetes, her glycemic values rapidly increased (FPG: 10.5 - 11.5 mmol/L, PPG: 14 - 17 mmol/L). The patient refused to start the advised insulin therapy and continued with the previously prescribed regimen. By the next follow-up visit, her metabolic control had worsened: HbA1c was 11.5%, she had dyslipidemia, the creatinine values were above 130 mmol/L (normal values 45-109), her blood pressure was 150/95 mmHg and the retinopathy had progressed. After all the possible outcomes of her disease were explained to her in detail, she agreed to the insulin therapy. We started with conventional insulin therapy, with two doses of premix insulin (Insuman comb 25) 0.5 IU per kg, with 60% of the units to be taken in the morning and 40% at night. Her BMI at that time was 31 kg/m^2, and her body weight was 84 kg. To control the blood pressure, we added thiazide diuretic (Hydrochlorothiazide) 25 mg per day, and increased the dosage of the ACE-inhibitor (10 mg BID). For dyslipidemia we prescribed 20 mg rosuvastatin at night. Despite her weight loss, the glycemic values did not improve after starting insulin therapy. She insisted that she was following dietary recommendations. In order to determine the main reason for her high glycemic values, she was hospitalized at the University Clinic of Endocrinology in Skopje (four months after the start of the insulin therapy). During the hospitalization, we checked HbA1c (10.5%), as well as blood glucose in the morning, after meals, getting high glycemic values (FPG: 18 -21 mmol/L; PPG: 22 - 26 mmol/L). The insulin units were increased and fast acting human insulin was added before lunch, thus achieving a small correction of glycemic values. Due to the absence of any significant improvements, we eliminated human premix insulin (insuman comb 25 and fast

acting-insulin insuman rapid), and started premix insulin analogues novomix 30 (insulin aspart-rys) twice a day, as well as a fast acting insulin analogue novorapid (insulin aspart) before lunch. We gradually increased the dosage of insulin up to 1.8 IU per kg of body weight, and we got slight improvements. Furthermore, we added metformin 1,000 mg QD. The patient was discharged in ten days with recommendations of diet and physical activity. The patient reported a significant weight loss within the period of next 6-8 months (almost 25 kg), however her glycemia remained unsatisfactory. Additional complaints included difficulty sleeping, diarrhea, intolerance to heat, increased heart rate at rest, and perspiration. The patient was readmitted for a thyroid work up and was diagnosed with hyperthyroidism. The prescribed anti-thyroid drug therapy included thiamazole 20 mg 2x1, B-blockers - propranolol 40 mg 2x1/2. The insulin therapy was intensified with three doses of rapid-acting insulin novorapid (insulin aspart), and one dose of long-acting insulin levemir (detemir). We increased the units of insulin to the scale of 2.3 IU/kg, but the set goals for blood glucose values were not achieved. Symptoms and signs of hyperthyroidism have improved. HbA1c was 10.5%, the creatinine values were slightly increased compared to the previous hospitalization, and the retinopathy had progressed, particularly in the right eye. Because of the progress of the retinopathy, laser photocoagulation was performed on the patient's right eye. Even with relatively high daily insulin dosage, the glycemic values were not satisfactory, so we changed the insulin regimen again and started with 3 daily injections of human rapid acting insulin (insuman rapid) and 2 doses of human intermediate acting insulin (Humulin N-Insulin isophane). With this insulin regimen, the patient was receiving a total of 130 insulin units per day, with a low carbohydrate diet. With this insulin therapy, as well as metformin (2000 mg per day), we achieved satisfactory glycemic values, and in 4 months the HbA1c reached 8%. One year after the start of therapy for hyperthyroidism, because of remission of the disease, we stopped the therapy, although the need for high insulin dosage remained.

This is the case report of a mild insulin resistance in a female patient. No antibodies were tested. However, the patient was obese at the beginning of the insulin therapy, had acanthosis nigricans and did not respond to the initial regimen of insulin therapy. After a few changes in the insulin therapy and dosage in the hospital environment, a satisfactory glycemic control was achieved. At the moment, the patient is stable with 130 insulin units per day, despite her weight of only 60 kilograms.

Type 2 Diabetes Mellitus (T2DM) is a condition that results from an imbalance between insulin sensitivity and secretion, leading to the development of hyperglycemia following diminished insulin secretion by pancreatic beta cell on the background of insulin resistance [5]. The role of insulin resistance in type 2 diabetes could be an important part of the course of the patients diabetes in our case report, especially considering the fact that she presented with concomitant acanthosis nigricans and obesity at the beginning [3]. In addition, a family history of T2DM is another risk factor for insulin resistance in the case of our patient [1]. Studies have shown that patients with family history of T2DM are at a higher risk of insulin resistance than those without [2,4]. Severe insulin resistance, where exceptionally large amounts of insulin are required, is usually related to syndromes that can be divided into distinct phenotypes. Type A insulin resistance is due to the insulin receptor absence or dysfunction, while Type B is due to the autoimmune-mediated disruption of the insulin receptor. Severe insulin resistance as a whole is rare entity, although the study of the syndromes and manifested genetic conditions has led to valuable insight into the different physiological mechanisms. Despite this, we still do not know the full picture, and treatment options remain nonspecific and limited. There has been some reported success with all sub-types by using agents such as biguanides, thiazolidinediones, phenytoin bezafibrates and vanadium salts. Essentially, all of them work on different downstream pathways to improve insulin sensitivity.

Conclusion: In this particular case, which can be considered as a mild insulin resistance, no immunosuppressive therapy was utilized, since we managed to achieve glycemic control with

moderately high doses of insulin. Oftentimes patients with mild insulin resistance get overlooked by the health practitioners and lost in the system. The discussions should be focused on the issues of when it is important for specialists to recognize insulin resistance and what to consider as a primary treatment in obese patients with insulin resistance symptoms and signs.

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SUMMARY

MILD CASE OF INSULIN RESISTANCE IN A PATIENT WITH TYPE 2 DIABETES MELLITUS (CASE REPORT)

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Diabetes mellitus type 2 is a chronic metabolic disorder characterized by hyperglycemia, insulin resistance, and relative insulin deficiency. There are rare cases when even higher doses of insulin are insufficient to control the values of glycemia. The insulin resistance can be mild, moderate or severe.

Authors present a clinical case report of a mild insulin resistance in a 46 year-old female patient with clinical symptoms of insulin resistance (including obesity), treated for seven years with oral antidiabetic drugs. Because of poor glycemic control and diabetes complications, insulin treatment was suggested. Glycemic control was not acheived with different types of insulin at the initial stage of the insulin therapy. The patient was hospitalized and after regimen adjustment with various insulin combinations, glycemic control was achieved with 2 insulin units per kilogram (130 IU per day in total), while the patient weighed 60 kilograms.

In the presented case, which can be considered a mild insulin resistance, the satisfactory glycemic control was established with use of moderately high doses of insulin. Oftentimes people with mild insulin resistance get overlooked by the doctors and lost in the system. The discussions should be focused on the issues of when it is important for specialists to recognize insulin resistance and what to consider as a primary treatment in obese patients with insulin resistance symptoms and signs.

Keywords: insulin resistance, Diabetes mellitus type 2.

РЕЗЮМЕ

ЛЕГКАЯ СТЕПЕНЬ ИНСУЛИНОРЕЗИСТЕНТНОСТИ У ПИЦИЕНТА С САХАРНЫМ ДИАБЕТОМ ТИПА 2 (СЛУЧАЙ ИЗ ПРАКТИКИ)

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Сахарный диабет типа 2 - хроническое метаболическое заболевание характеризуется

инсулинорезистентностью и ее относительной недостаточностью или преимущественным дефектом секреции инсулина с инсулинорезистентностью или без нее, в результате чего развивается гипергликемия. Встречаются случаи, когда высокие дозы вводимого инсулина не приводят к нормализации гликемии. По всей вероятности, это связано со степенью инсулинорезистентности, которая может быть легкой, средней и тяжелой.

В статье описан клинический случай женщины, больной сахарным диабетом типа 2, которая на протяжении 7 лет лечилась различными классами антигипергликемических пероральных препаратов, однако стойкой компенсации гликемии достигнуть не удалось, пациентку пришлось перевести на инсулинотерапию. Апробированы разные схемы инсулинотерапии. Субкомпенсация гипергликемии достигнута лишь на высоких дозах инсулина.

Представленный клинический случай демонстрирует проблемы лечения сахарного диабета типа 2 с выраженной инсулинорезистентностью. После госпитализации, в результате неоднократных попыток удалось достичь целевых показателей гликемии и урегулирования резистентности в отношении инсулина высокими его дозами (2 IU/kg, в сумме 130 IU в день), несмотря на нормальный вес пациентки (60 кг).

რეზიუმე

მსუბუქი ხარისხის ინსულინრეზისტენტობა შაქრიანი დიაბეტის მქონე პაციენტთან (კლინიკური შემთხვევა)

ა. მუჩა

ენდოკრინოლოგიის, დიაბეტის და მეტაბოლური დარღვევების საუნივერსიტეტო კლინიკა, სკოპიე, მაკედონია

შაქრიანი დიაბეტი ტიპი 2 არის ქრონიკული მეტაბოლური დაავადება,რომელიც ხასიათდება ჰიპერგლიკემიით,ინსულინის მიმართ რეზისტენტობით და მისი შეფარდებითი უკმარისობით. არსებობს შემთხვევები,როდესაც ინსულინის საკმაოდ მაღალი დოზებიც არ არის საკმარისი გლიკემიის კომპენსაციის მისაღწევად. ინსულინის მიმართ რეზისტენტობა შესაძლოა იყოს მსუბუქი, საშუალო ინტენსივობის და მძიმე.

სტატიაში განხილულია იშვიათი შემთხვევა: ინსულინის მიმართ რეზისტენტობის კლინიკური სიმპტომებით ქალი 7 წლის მანძილზე მკურნალობდა პერორალური ანტიჰიპერგლიკემიური საშუალებებით. დიაბეტის დეკომპენსაციისა და გართულების გამო მას დაენიშნა ინსულინოთერაპია. ინსულინოთერაპიის დაწყების და სხვადასხვა ტიპის ინსულინის მონაცვლეობის მიუხედავად გლიკემიის მაჩვენებლების კომპენსირება ვერ მოხდა. ჰოსპიტალიზაციისა და ინსულინის სხვადასხვა კომბინაციების არჩევის მრავალგზის მცდელობის შემდეგ მდგომარეობა გაუმჯობესდა მაღალ დოზებზე გადაყვანის საშუალებით (2 IU/კგ-ზე, ჯამში 130 IU დღეში) პაციენტის მცირე წონის მიუხედავად (60 კგ).

არსებული კლინიკური შემთხვევა ასახავს ინსულინის მიმართ გამოხატულ რეზისტენტობას. მრავალი მცდელობისა და ჰოსპიტალიზაციის შემდეგ, საბოლოოდ მოხერხდა სამიზნე გლიკემიის მაჩვენებლების მიღწევა. ინსულინის მიმართ რეზისტენტობის დარეგულირება განხორციელდა ინსულინის შედარებით მაღალი დოზით.

DIABETIC NEPHROPATHY IN PREGNANT WOMEN WITH TYPE 1 DIABETES (MULTIPLE CASES REVIEW AND DISCUSSION)

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Pregnancy in women with pre-existing diabetes is associated with a doubled, or even up to four-fold increased risk of preeclampsia, preterm delivery, and perinatal mortality compared to the risk observed in a background population [1].

Diabetic nephropathy (DN) is a progressive disease that affects about one third of diabetic patients and is among the most frequent causes of the end stage renal disease (ESRD) worldwide [2]. The first clinical sign of DN is microalbuminuria (urinary albumin excretion (UAE) rate between 30 and 300 mg per 24 hours). If microalbuminuria is not properly treated, it advances into overt nephropathy, characterized with proteinuria, hypertension, gradual decline in the glomerular filtration rate, and renal failure.

In the random population, DN is present in up to 7% of women with type 1 diabetes mellitus (T1DM), and it represents the most common chronic kidney disease occurring in graviditas [2,3], complicating between 2.5% and 5% of T1DM pregnancies [4, 5]. Although maternal and perinatal morbidity and mortality rates in the pregnancies complicated with DN have declined over time, pregnancy related health complications are still more common in women with DN compared to those observed among diabetic women with normal UAE rates.

On the other hand, preeclampsia is generally a leading cause of both maternal and fetal morbidity and mortality [6,7]. This syndrome affects between 2% and 7% of pregnancies among non-diabetic women in developed countries [8,9]. When it comes to the pregnant women with a developed glucose metabolism abnormalities, it is important to point out that both pre-gestational and gestational diabetes further increase the risk of preeclampsia development. Preeclampsia is also the most frequent complication of pregnancy in women with DN, and it seems to be related to the degree of proteinuria detected in the early pregnancy [10].

Preeclampsia is diagnosed among women presenting with new onset hypertension and proteinuria during the second half of pregnancy, but can also be diagnosed in the absence of proteinuria in hypertensive women with pulmonary edema, progressive renal insufficiency, impaired liver function, thrombocytopenia, or new onset of cerebral or visual disturbances [11]. Preeclampsia represents a risk factor for the future cardiovascular disease and stroke [12,13]. Delivery is the only known cure for preeclampsia, while the effective prevention strategies are still lacking.

Women with the developed DN are exposed to an increased risk of renal failure (both during and after the pregnancy), as well as of increased cardiovascular morbidity and mortality rates. A level of proteinuria typically rises during the pregnancy but usually decreases to the near-pre-pregnancy range after giving a birth [14, 15]. Although a temporary decline in the renal function during gestation is a common finding, it seems that pregnancy does not have an influence on ESRD progression. However, this grossly depends upon a degree of pre-pregnancy renal impairment. Generally, pregnancy outcome is favorable in women with the mild elevation in serum creatinine level (less than 124 μmol/l), a low level of proteinuria (less than 1 gram per 24 hours), and a normal blood pressure. Conversely, the serum creatinine level greater than 176 μmol/l and severe hypertension, proteinuria in the nephrotic range, and/or pre-existing cardiovascular disease are associated with a higher risk of an adverse maternal and fetal outcomes [16].

At the same time, DN may adversely affect the outcome of pregnancy through various mechanisms. These include a development of

severe hypertension accompanied by the maternal renal function deterioration, the preterm delivery caused by high maternal blood pressure and preeclampsia, and the fetal growth restriction and distress caused by the placental dysfunction [2]. Additionally, the severe congenital malformations have been described with a higher prevalence in newborns born to women with DN compared to those born to the diabetic women with normal renal function [17], but this may also be, at least partly, attributed to the poorer metabolic control in the early pregnancy.

As it has been mentioned, the preeclampsia is characterized by hypertension and proteinuria, and women with microalbuminuria or overt nephropathy diagnosed before the pregnancy are at an increased risk of developing preeclampsia, and may already present with an elevated blood pressure in the early pregnancy. Preeclampsia develops in up to two thirds of women with DN, especially in the presence of reduced kidney function, hypertension at the pregnancy start, or a nephrotic range proteinuria [2]. Likewise, in the case of overt nephropathy presence, women with T1DM and microalbuminuria are also exposed to an increased risk of developing preeclampsia in comparison to T1DM women with normal UAE rates. Nevertheless, women with T1DM and DN are usually characterized by the higher rates of UAE, blood pressure, and glycated hemoglobin (HbA_{1c}) levels in an early pregnancy compared to T1DM women who did not develop preeclampsia [18]. The signs of vascular dysfunction accompanied by both increased oxidative stress and reduced antioxidative activity are usually present in T1DM women with preeclampsia [2, 19, 20]. Additionally, preeclampsia in women with T1DM is also associated with an elevated level of anti-angiogenic factors in the third trimester of graviditas [21]. The pathogenesis of preeclampsia development in T1DM women with overt nephropathy or microalbuminuria includes the presence of endothelial dysfunction, an impaired maximal vasodilation, and the increased levels of prorenin and cardiac overload markers [22-24]. It is worth mentioning that all these abnormalities are capable of being modulated by an appropriate antihypertensive treatment.

Although maternal and perinatal morbidity and mortality associated with DN complicated pregnancies are steadily declining over time, a growing number of T1DM women with developed DN willing to accomplish their parental potential require further strategies aimed at the reducing burden associated with these high-risk pregnancies.

The aim of this paper is to show the impact of DN on maternal and fetal outcomes in women with T1DM, through presentation of the cases from a real-world clinical practice.

Case 1. Worsening of diabetic nephropathy and proteinuria during the pregnancy: A thirty-two year old T1DM woman at the 6th gestational week of twin pregnancy was referred to our clinic by the regional hospital. She had an eighteen year history of diabetes and had been treated with the basal/bolus insulin regimen with a long-term poor glycemic control. Three years prior to the pregnancy she was diagnosed with DN, with a proteinuria level of 625 mg per 24 hours and a serum creatinine of 119 μmol/l. She had been treated with an angiotensin-converting enzyme (ACE) inhibitor which was replaced with methyldopa after the graviditas was confirmed. Patient also had an established non-proliferative diabetic retinopathy. During the course of pregnancy the proteinuria was gradually increasing (200, 941, 1111, 1644, 2461 and 6485 mg per 24 hours at the 6th, 17th, 22nd, 25th, 32nd, and 35th gestational weeks, respectively), while at the same time the serum creatinine level was also gradually elevating (78, 91, 93, 99, 127 and 138 μmol/l at the same respective weeks), with the parallel improvement in the glycemic control (HbA_{1c} of 7.0, 6.4 and 5.8 % at the 6th, 22nd and 32nd gestational weeks, respectively), and the optimally controlled blood pressure. Based on the obstetric indications the Caesarean section was performed at the 35th week of gestation with the birth of male (body mass of 2590 g, body length of 45 cm and Apgar score of 8/9) and female (body mass of 2150 g, body length of 45 cm and Apgar score of 6/7) twins. Both newborns suffered from a second grade respiratory distress syndrome and neonatal jaundice. Six months after delivery, patient had a proteinuria level of 2740 mg per 24 hours, serum

creatinine of 89 μmol/l and HbA_{1c} of 6.6%. Seven years after delivery patient was presenting with a proteinuria level of 150 mg per 24 hours, serum creatinine of 80 μmol/l and HbA_{1c} of 7.5%.

Case 2. Diabetic nephropathy and preeclampsia: A twenty-six year old T1DM woman in the first trimester of pregnancy was referred to our clinic by the regional hospital. She had a twenty-three year history of diabetes and was treated with the insulin pump for the past two years. The diagnosis of DN was established at the age of thirteen, and the last measurement of a proteinuria level prior to the pregnancy was 647 mg per 24 hours. She also had a history of proliferative diabetic retinopathy treated with the laser treatment, and the clinical signs of diabetic polineuropathy. She was also taking levothyroxine due to a primary hypothyroidism. Prior to the pregnancy she was treated with ACE inhibitor which was subsequently replaced with methyldopa. During the course of pregnancy the proteinuria was gradually increasing (2100, 2200 and 5000 mg per 24 hours in the first, second and third trimester, respectively), with an increase in the serum creatinine levels observed only during the last trimester (85 μmol/l), followed by a suboptimal glycemic control (HbA_{1c} of 7.0, 6.7 and 6.8 % in the first, second and third trimester, respectively), and the satisfactory controlled blood pressure. However, due to the superimposed preeclampsia development, the Caesarean section was indicated, and a newborn (body mass of 3290 g, body length of 49 cm and Apgar score of 7/8) was delivered at the 34th gestational week. Six months after delivery, the patient had a proteinuria level of 5200 mg per 24 hours, serum creatinine of 89 μmol/l and HbA_{1c} of 7.1%. Two years after delivery patient was presenting with a proteinuria level of 2420 mg per 24 hours, serum creatinine of 83 μmol/l and HbA_{1c} of 7.3%.

Case 3. Worsening of diabetic nephropathy and renal failure during the pregnancy: A twenty-one year old T1DM woman at the 24th gestational week was referred to our clinic by the regional hospital. The diagnosis of diabetes was made at the age of three, and she was treated with the basal/bolus insulin regimen. She was presenting with the adavanced stages of the chronic microvascular complications of diabetes (DN with preterminal renal insufficiency and the proliferative diabetic retinopathy resulted in blindness). The previous pregnancy was artificially terminated at the 16th gestational week due to the safety concerns caused by the maternal kidney failure. At the presentation, the serum creatinine level was 398 μmol/l, while the proteinuria was 2470 mg per 24 hours. At the 30th gestational week, the serum creatinine level increased to 440 μmol/l and a proteinuria level raised to 5000 mg per 24 hours. Due to the fetal growth retardation, the Caesarian section was performed with the delivery of a live newborn. The postpartum kidney function (the serum creatinine level of 456 μmol/l) was requiring the initiation of a hemodialysis treatment. Three years after the delivery patient died.

Conclusion. Although maternal and perinatal morbidity and mortality in the pregnancies complicated with DN are becoming less common, the cases similar to those presented in this paper are a warning that this condition still can seriously jeopardize both pregnant woman and her offspring.

The adequate pre-pregnancy counseling and a tailored approach to the treatment of women with DN during the pregnancy are crucial for an avoidance of the adverse maternal and fetal outcomes. Intensive glycemic control, optimal antihypertensive treatment, and perhaps a low-dose aspirin therapy, are of great significance before the conception among the women with overt nephropathy or microalbuminuria [2]. As far as the renal outcomes are concerned, a risk of pregnancy-induced decline in the maternal kidney function leading to ESRD during graviditas or shortly afterward, can be the most precisely predicted by the pre-pregnancy serum creatinine level greater than 176 μmol/l [16]. Additionally, the screening for diabetic retinopathy and a laser treatment, if indicated, are also important, since the progression to severe diabetic retinopathy is prevalent during the pregnancy, especially in those women with the higher blood pressure and DN in the early pregnancy [25]. The optimal treatment of women with DN during the pregnancy includes a strict glycemic control (HbA_{1c} less than 6.0%), intensive antihypertensive treatment with pregnancy-friendly drugs with the target value of blood pressure at least below 135/85 mmHg, the maintenance of UAE rate under 300 mg per 24

hours, and most likely a timely low-dose aspirin initiation [2]. The close obstetric monitoring is highly important in these high-risk pregnancies.

The future large-scale randomized clinical trials should address some of the issues regarding the proper pharmacological treatment of T1DM women with overt nephropathy and microalbuminuria in both pre-conception period and during the pregnancy.

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SUMMARY

DIABETIC NEPHROPATHY IN PREGNANT WOMEN WITH TYPE 1 DIABETES (MULTIPLE CASES REVIEW AND DISCUSSION)

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Pregnancy in women with pre-existing diabetes is associated with a doubled, or even up to four-fold increased risk of preeclampsia, preterm delivery, and perinatal mortality compared to the risk observed in a background population. Diabetic nephropathy (DN) is a progressive disease that affects about one third of diabetic patients and is among the most frequent causes of the end stage renal disease (ESRD) worldwide. In the random population, it is present in up to 7% of women with type 1 diabetes mellitus (T1DM), and it represents the most common chronic kidney disease occurring in graviditas, complicating between 2.5% and 5% of T1DM pregnancies. Although maternal and perinatal morbidity and mortality rates in the pregnancies complicated with DN have declined over time, pregnancy related health complications are still more common in women with DN compared to those observed among diabetic women without DN. The adequate pre-pregnancy counseling and a tailored approach to the treatment of women with DN during the pregnancy are crucial for an avoidance of the adverse maternal and fetal outcomes. This paper is highlighting the impact of DN on maternal and fetal outcomes in women with T1DM, through presentation of the cases from a real-world clinical practice.

Keywords: diabetic nephropathy; preeclampsia; pregnancy; type 1 diabetes mellitus.

РЕЗЮМЕ

ДИАБЕТИЧЕСКАЯ НЕФРОПАТИЯ У БЕРЕМЕННОЙ С САХАРНЫМ ДИАБЕТОМ ТИПА 1 (КЛИНИЧЕСКИЙ СЛУЧАЙ И ОБСУЖДЕНИЕ)

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При сахарном диабете у беременных в сравнении с общей популяцией увеличивается риск развития преэклампсии, преждевременных родов и перинатальной смертности. Диа-

бетическая нефропатия (ДН) характеризуется прогрессивным течением заболевания, встречается у 1/3 больных диабетом и является самой частой причиной последней стадии заболевания почек, обнаруживается в 7% случаев у женщин с сахарным диабетом типа 1, осложняет течение беременности в 2,5-5% случаев. Несмотря на уменьшение числа случаев заболеваемости и смертности среди беременных и плода, проблемы, связянные с беременностью, более выраженны у женщин с ДН. Вовремя принятые профилактические мероприятия, проведенные до беременности, и адекватное лечение женщин в период беременности являются ключевым моментом для исключения неблагоприятного исхода для матери и плода.

В данной публикации подчеркивается отрицательное влияние ДН на здоровье матери и плода при сахарном диабете типа 1 и анализируются клинические подходы в таких случаях.

რეზიუმე

დიაბეტური ნეფროპათია შაქრიანი დიაბეტი ტიპი 1-ით დაავადებულ ორსულებში (კლინიკური შემთხვევა)

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ვოჟვოდინას კლინიკური ცენტრი, უნივერსიტეტი ნოვი სადი, მედიცინის ფაკულტეტი, [1]ენდოკრინოლოგიის, დიაბეტის და მეტაბოლური დარღვევების კლინიკა; [2]გინეკოლოგიის და მეანობის კლინიკა, სერბია

ქალებში შაქრიანი დიაბეტით ორსულობის დროს ორიდან-ოთხჯერ იზრდება პრეეკლამფსიის, ნაადრევი მშობიარობის და პერინატალური სიკვდილობის რისკი ზოგად პოპულაციასთან შედარებით. დიაბეტური ნეფროპათია (დნ) არის პროგრესულად მიმდინარე დაავადება, რომელიც გვხვდება დიაბეტის მქონე პირების ერთ მესამედში და წარმოადგენს თირკმლის დაავადების საბოლოო სტადიის ყველაზე ხშირ მიზეზს. ის გვხვდება შაქრიანი დიაბეტი ტიპი 1-ით ქალების 7%-ში, წარმოადგენს თირკმლის ხშირ ქრონიკულ დაავადებას ორსულობის დროს და 2.5-5%-ში ართულებს მის მიმდინარეობას. მიუხედავად იმისა, რომ სადღეისოდ დედისა და ნაყოფის სიკვდილობა-ავადობის შემთხვევების რიცხვი ორსულებში დნ-თი შემცირებულია, ორსულობასთან დაკავშირებული ჯანმრთელობის პრობლემები უფრო მეტად არის გამოხატული ქალებში დნ-ით შედარებით იმ ქალებთან, ვისაც არ აღენიშნება დნ. დაორსულებამდე ჩატარებული ადექვატური ღონისძიებები და ორსულობის პერიოდში ქალების სწორი მკურნალობა საკვანძოა დედისა და ნაყოფის არასასურველი გამოსავლის თავიდან ასაცილებლად. აღნიშნულ სტატიაში ხაზგასმულია დნ-ის უარყოფითი გავლენა დედისა და ნაყოფის ჯანმრთელობაზე შაქრიანი დიაბეტი ტიპი 1-ით ქალებში და გაანალიზებულია კლინიკური მიდგომები ასეთ შემთხვევებში.

LOCAL USE OF GRANULOCYTE-MACROPHAGES COLONY STIMULATING FACTOR IN TREATMENT OF CHRONIC DIABETIC NEUROPATHIC ULCER (CASE REVIEW)

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Individuals with Diabetes Mellitus (DM) appear to have a higher risk of developing foot ulcers. In patients with diabetic peripheral neuropathy, the pain sensation is reduced therefore ulcers develop in the areas under prolonged pressure against the skin and underlying tissue, which makes the foot predisposed to ulcer development, even without any trauma [1].

Furthermore, diabetic macro- and micro-vasculopathy, due to ischemia also increase the risk of developing an ulcer. 15% of individuals with DM will develop a foot ulcer during their lifetime [2]. These chronic ulcers are the main cause of non-traumatic amputations in hospitalized patients with DM [3]. Most of these ulcers either have delayed healing time or do not heal at all. The chronic non-healing ulcers are responsible for the 70-80% of the amputations to individuals with DM [4]. The definitive cicatrization of the ulcer requires the synchronization of the following mechanisms: homeostasis, inflammatory response, proliferation, epithelialization and tissue remodeling. Disruptions in these mechanisms may lead to a chronic non-healing ulcer [5,6].

Treatments that contribute to the faster healing of the ulcer could avoid the amputation of the patients' limbs.

The aim of our work is to study the Granulocyte Macrophage-Colony Stimulating Factor (GM-CSF) effect on healing process of the chronic non-healing neuropathic foot ulcer, when it is applied topically.

Case Report: Sixty-five-year-old female with 15 year history of DM type 2 and a diabetic neuropathy (peripheral and autonomous neural system neuropathy), retinopathy, chronic renal failure (creatinine=2,5 mg/dl), coronary artery disease and cardiac failure, was admitted to our Diabetes Center with a deep non-healing 18 month old ulcer (2nd stage based on Wagner staging) located in the middle of the right foot.

The measurement with biothesiometer was >50V, the orthostatic and Valsalva Maneuver tests were abnormal, Mean Circular Resultant (MCR)=0, Standard Deviation (SD) of R-R=8, Expiration/Inspiration (E/I) index=1,02 and 30:15 index was pathological.

The ulcer was on the plantar surface of the right foot at the projection of the tarsal bones; it was deep and infected despite the frequent surgical treatments. Its diameter was 5 cm, with possible fistula to the 5th metatarsal bone, suspicious for possible adjacent osteomyelitis (Fig. 1A).

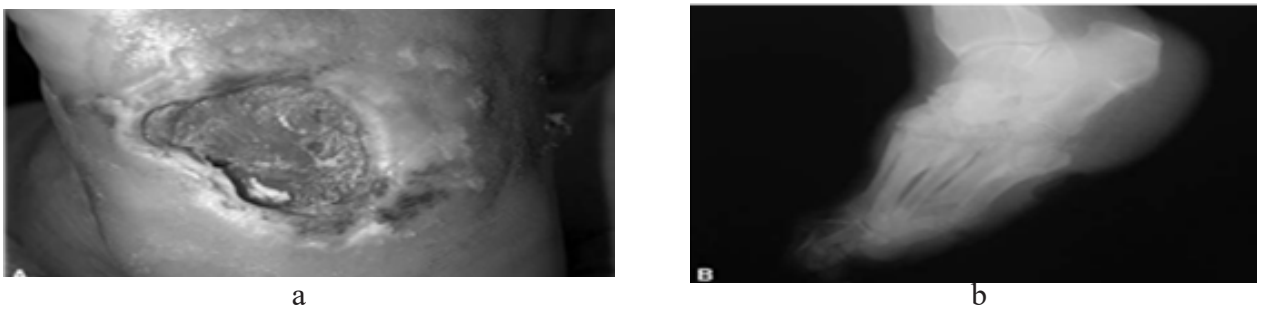
The patient's treatment for DM consisted of intermediate acting-biphasic human insulin (Mixtard 30- 100IU/ml) 50IU/twice per day; her HbA1c was 8,5%.

The patient was diagnosed with Charcot arthropathy in both tarsi by a radiologist 5 years ago. The right 4th toe was amputated 1.5 year ago because of osteomyelitis. Both posterior tibial and the dorsalis pedis arteries had a well palpable pulse.

The first blood test showed: White Blood Cells 9.400/mm^3 (50% polymorphonuclear), Erythrocyte Sedimentation Rate 61mm the 1st hour and CRP 20,3 mg/l. The X-ray of the right foot (Figure 1B) showed deterioration compatible with Charcot arthropathy at the tarsal bones and intensive dilution of bone density at the ampulla of the 5th metatarsal bone with possible detachable fracture, without explicit findings of active osteomyelitis.

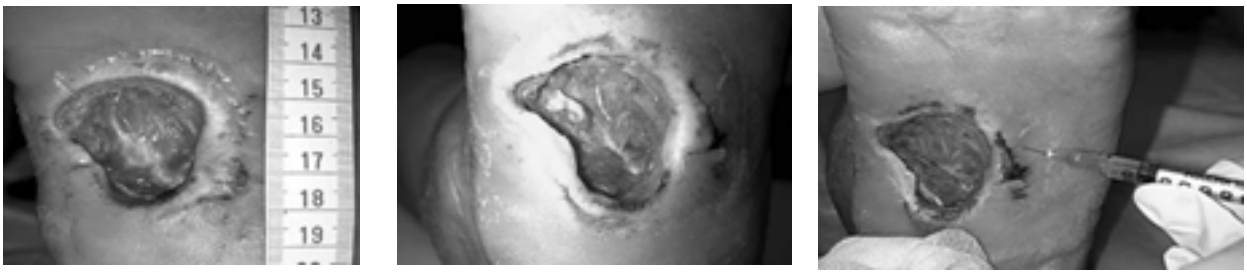
To rule out osteomyelitis diagnosis, the patient subsequently underwent the scintigraphy.

Initially, the patient recieved the autologous, labeled with ^{99m}Tc-HMPAO white blood cells scintigraphy, using the following technique: blood



a b

Fig. 1. a) ulcer of plantar foot surface in diabetic patient, diameter 5 cm, before the treatment with growth factor, b) X-ray of right foot: Charcot arthropathy at the right tarsus, without findings of active osteomyelitis



a b c

Fig. 2. a) Start of treatment with growth factor, b) After one week of treatment, c)After one month of treatment (diameter 3,5 cm)

sampling 50 ml, separation and labeling of white blood cells with ^{99m}Tc-HMPAO and then re-administration to the patient 90 minutes later. The labeling efficiency was 70% and the injected activity was 7mCi. Before the scintigraphy, the ulcer dressing was replaced with the fresh gauze, to avoid false findings, because of the ratio-labeled white blood cell concentration on the gauze discharge. Static images of the feet were taken in various positions 4 hours after the re-administration of labeled white cells. Emphasis was placed on the correct feet position, in order to match fully the findings of the scintigraphy. The labeled white cell scintigraphy revealed an increased concentration of labeled white cells at the right plantar surface.

The comparative assessment of scintigraphy ruled out osteomyelitis in the right foot. Thus, the patient started the ulcer treatment, which included the placement of patches with the growth factor every 15 days and the local administration with the same factor in the ulcer edges, for 2 months (Fig. 2).

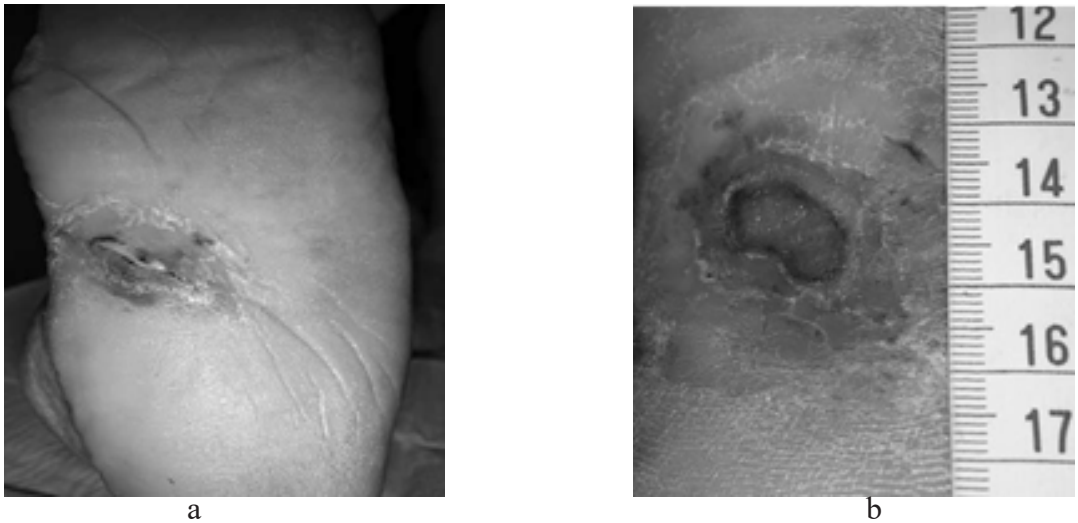
The dosage of the growth factor GM-CSF was 400 mcg per session. The white blood cells levels were not affected by the treatment.

Gradual healing of the ulcer, with significant reduction in its diameter (ulcer diameter 1,5 cm), was seen after 7 months and almost full closure was noticed after 1 year of treatment with GM-CSF (Fig. 3).

The iterative scintigraphy with labeled white cells was negative for infection and it confirmed the good outcome of the treatment.

At the time of the patient's first visit to our Diabetes Center, the amputation seemed inevitable, because the patient had Charcot arthropathy and 18-month old ulcer of the foot. Moreover, the ulcer was infected; the osteomyelitis diagnosis was ruled out by the scintigraphy and the X-rays.

Labeled leukocytes do not generally accumulate at sites of injured bone in the absence of infection. Labeled leucocyte scan (either with 99mTechnetium or with 111 Indium) is the radionuclide procedure of choice for diagnosing diabetic foot osteomyelitis. Furthermore, labeled leukocyte scan is the imaging modality of choice for assessing response to medical treatment. Unlike radiographs, bone scans and MR images which remain positive for months even in patients who respond to treatment of osteomyelitis,



a b

Fig. 3. a) 7 months after the start of treatment (diameter 1,5 cm)

labeled leukocyte scan images revert to normal early after successful treatment and is a reliable imaging method for providing evidence of cure of osteomyelitis [7,8].

Bone biopsy for culture and histological examination of the specimens is the gold standard for the diagnosis of osteomyelitis, identifying the causative organism and guiding antibiotic treatment. However, bone biopsy is an invasive procedure and it is not routinely performed in the fragile diabetic foot, especially in patients with Charcot foot. Drawbacks of bone biopsy with needle or trocar include sampling errors (in cases of patchy bone infection) and risk of contamination of the specimen by overlying soft tissue infection. Furthermore, the expertise for performing a bone biopsy may not always be available and some concern also exists about the safety of the procedure in patients with peripheral vascular disease [9].

The healing of an exogenous injury of soft tissue starts immediately after the damage with activation of the homeostasis mechanisms and the granulocytes concentration. Further normal total healing of the ulcer demand complicated processes, synergy and synchronization of the connective tissue (formation), of the local multiple cells concentration and multiplication and of multiple growth factors' production and activation. These mechanisms are disturbed in individuals with DM and may affect the normal ulcer closure. Firstly, the collagen synthesis in DM is reduced. This collagen distribution concerns its production and deconstruction, too [10].

These collagen distributions in DM involve the fattening of the basic vascular membrane, the reduced joint mobility and the non-healing ulcers. Furthermore, the reduced macrophages functionality is observed within the inflammatory reaction in DM [11].

The skin keratinocytes production is also reduced in DM [12]. This is a very important step in the total ulcer healing, as the keratinocytes multiply on the ulcer edges and the new cells migrate to the ulcer center. As soon as the re-epithelialization is complete, the basic keratinocytes form particles that tie up steadfast the newborn skin cells. Therefore, during the delay of healing, the epidermis growth and the ulcer closure is inhibited [13,14].

As a result of all the above mentioned, the ulcer remains at the inflammatory stage of healing. The fluid analysis of these chronic non-healing ulcers revealed the increased quantity of metalloproteinase that is needed for the ulcer healing [15].

The growth factors affect the normal healing through inhibitory or stimulating actions at the local inflammatory environment of the ulcer. The growth factors of the platelets, the fibroblasts and the Vascular Endothelium (VEGF) were detected in the fluid of these ulcers. These factors cause chemotaxis, migration, stimulation and multiplication of the cells and of the extracellular matrix. The above processes are significant for the ulcer

healing. Therefore, the disturbed secretion or the absence of these agents results the non-healing ulcer [16].

The recombinant human factor that stimulates the growth of granulocytes-macrophages (rhu GM-CSf) has been studied as a hematopoietic growth factor. Because of its pleiotropic action on multiple cells and tissues, it was studied in healing of the difficult ulcers. Receptors for GM-CSF are expressed on various cells of granular and monocytes line, on Langerhans, dendritic and endothelial cells and on muscle-fibroblasts. T-lymphocytes, macrophages, endothelial cells, fibroblasts and keratinocytes produce GM-CSF. The growth factor GM-CSF is produced by the keratinocytes immediately after the ulcer formation and contributes to the multiplication of the epidermis cells. This results the multiplication of the keratinocytes on the ulcer edges, the increased formation of granular tissue and increase of neovascularization [17]. Consequently, the growth factor GM-CSF contributes to the healing of the full skin thickness in the ulcerated area. Furthermore, it probably contributes to increased neovascularization, through the de-novo production of VEGF by the inflammatory cells [18].

The non-healing ulcer is a microbial source and, by extension, a potential cause of infection, as an additional aggravating factor for the patients' health [9].

Also, the co-existence of diabetic neuropathy could contribute to non-healing ulcers, through the decreased secretion of vascular-kinetic factors and decreased neovascularization of the ulcer area [19].

Relieving the areas of feet subjected to the increased pressures, contributes to the ulcer healing. The ulcer is formed on areas under increased pressure at the plantar surface of the foot. In this case, because of the cardiac failure, patient was immobilized. Despite the immobilization the ulcer did not heal for 18 months. The patient was also immobilized during the treatment with the growth factor.

The absence of osteomyelitis in this patient could be an additional beneficial factor for the good outcome of the treatment. In patients with ulcers and coexisting osteomyelitis the treatment with growth factors did not turn out to be successful [20].

Conclusions. The local treatment, although for a short period, with growth factor GM-CSF of the non-healing foot ulcer of the patient with DM contributed to the spectacular healing of the ulcer.

Presupposition of the treatment with the growth factor was the exclusion of osteomyelitis. The correct use of the growth factor in ulcer healing can prevent the risks of future amputations.

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SUMMARY

LOCAL USE OF GRANULOCYTE-MACROPHAGES COLONY STIMULATING FACTOR IN TREATMENT OF CHRONIC DIABETIC NEUROPATHIC ULCER (CASE REVIEW)

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One of the main causes of amputations in patients with Diabetes Mellitus patients is a chronic diabetic foot ulcer. The authors present a clinical case and discussion of a successful use of Granulocyte-Macrophages Colony Stimulating Factor (GM-CSF) treatment for the promotion of healing of a chronic diabetic foot ulcer.

A 65 year-old woman was admitted to the Diabetes Center with complaints of a deep non-healing chronic foot ulcer for the last 18 months. At the examination a 5 cm ulcer on the plantar surface of the right foot was revealed. The patient had a 15-year history of Diabetes Mellitus type 2, complicated by neuropathy (peripheral and autonomic), retinopathy, nephropathy and Charcot joints in both legs and the right 4th toe had been amputation. She also had a history of heart failure. Healing of the ulcer could not be achieved with prior administered treatment. The decision was made to use GM-CSF treatment option in the area of the ulcer. Patient received local intradermal injections of GM-CSF (400 mcg twice a week) into the ulcerated foot for the duration of two months. The ulcer healed completely after one year of treatment with GM-CSF. Osteomyelitis was ruled out by scintigraphy. The patient did not develop any clinical side-effects or peripheral blood cell count abnormalities to the treatment.

GM-CSF is a safe and effective treatment for chronic non-healing diabetic foot ulcers.

Keywords: treatment with GM-CSF.

РЕЗЮМЕ

ЭФФЕКТИВНОСТЬ СТИМУЛИРУЮЩЕГО ФАКТОРА КОЛОНИИ ГРАНУЛОЦИТ-МАКРОФАГОВ В ЛЕЧЕНИИ ХРОНИЧЕСКИХ ЯЗВ ДИАБЕТИЧЕСКОЙ СТОПЫ

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Целью исследования явилось оценить эффективность стимулирующего фактора колонии гранулоцит-макрофагов в лечении хронических язв диабетической стопы.

В статье описан случай лечения незаживляющей глубокой язвы стопы. 65-летняя больная сахарным диабетом типа 2 обратилась в Диабетический центр по поводу незаживляющей глубокой язвы на стопе. Длительность сахарного диабета типа 2 составила 15 лет. Отмечались следующие осложнения: диабетическая нейропатия, ретинопатия, нефропатия, артропатия Шарко. У пациентки ампутирован IV палец правой стопы. За 18 месяцев до поступления в стационар у пациентки на плантарной поверхности правой стопы образовалась язва диаметром 5 см. При помощи сцинтиграфии исключено наличие остеомиелита. Несмотря на традиционное медицинское вмешательство, язва не заживала. Было решено применить лечение стимулирующим фактором колонии гранулоцит-макрофагов (сф-кгм). В течение 2 месяцев пациентке в области язвы, подкожно вводили инъекции сф-кгм (400 мг, дважды в неделю). В результате лечения язва полностью зажила. В процессе лечения побочных явлений не наблюдалось.

На основании проведенного исследования авторами делается вывод, что сф-кгм является безопасным и эффективным лечебным средством при незаживляющих язвах диабетической стопы.

რეზიუმე

გრანულოციტ-მაკროფაგების კოლონიის მასტიმულირებელი ფაქტორის ეფექტურობა დიაბეტური ტერფის ქრონიკული წყლულის მკურნალობაში

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ა. ხაციტოლიოს, ტ. დიდანჯელოს

შინაგან სნეულებათა პროპედევტიკის I კლინიკა, საუნივერსიტეტო ჰოსპიტალი ANEPA, არისტოტელეს უნივერსიტეტი, სალონიკი, საბერძნეთი

დაწყლულებული დიაბეტური ტერფი წარმოადგენს ამპუტაციის ძირითად მიზეზს. კვლევის მიზანს წარმოადგენდა გრანულოციტ-მაკროფაგების კოლონიის მასტიმულირებელი ფაქტორის ეფექტურობის შეფასება დიაბეტური ტერფის ქრონიკული წყლულის შეხორცებაში. სტატიაში წარმოდგენილია ტერფის ღრმა, არაშეხორცებადი წყლულის მკურნალობის შემთხვევა. 65 წლის ქალმა მიმართა დაიბეტის ცენტრს ტერფის ღრმა, არაშეხორცებადი წყლულის გამო. მარჯვენა ტერფის პლანტარულ ზედაპირზე აღინიშნებოდა 5 სმ დიამეტრის წყლული, რომელიც განვითარდა 18 თვის წინ და სამედიცინო ჩარევის მიუხედავად არ შეხორცდა. შესაბამისად,არჩეული იყო წყლულის გრანულოციტ-მაკროფაგების კოლონიის მასტიმულირებელი ფაქტორით (გმ-კმფ) მკურნალობის ტაქტიკა. 2 თვის მანძილზე წყლულის არეში ადგილობრივად კეთდებოდა გმ-კმფ-ს კანქვეშა ინიექციები (400 მგ ორჯერ კვირაში). მკურნალობიდან ერთი წლის თავზე წყლული მთლიანად შეხორცდა. სცინტიგრაფიით გამოირიცხა ოსტეომიელიტის არსებობა. პაციენტს შაქრიანი დაიბეტის დიაგნოზი დაესვა დაახლოებით 15 წლის წინ და აღენიშნებოდა დიაბეტის ისეთი გართულებები, როგორიცაა: ნეიროპათია (პერიფერიული და ავტონომიური), ორივე ქვედა კიდურის შარკოს ართროპათია, რეტინოპათია, ნეფროპათია. ანამნეზში აღ-

ენიშნებოდა მარჯვენა ფეხის მე-4 თითის ამპუტაცია და გულის უკმარისობა. გმ-კმფ მკურნალობის პროცესში პაციენტს არ განვითარებია რაიმე სახის გვერდითი მოვლენა.

გამომდინარე კვლევის შედეგებიდან, ავტორები დაასკვნიან,რომ გმ-კმფ არის უსაფრთხო და ეფექტური სამკურნალო საშუალება არაშეხორცებადი დიაბეტური ტერფის წყლულის დროს.

A YOUNG ADULT WITH GENERALIZED LIPODYSTROPHY AND DIABETES MELLITUS (CASE REPORT)

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Lipodystrophies are a group of rare disorders of diverse etiology which are characterized by variable loss of body fat. The loss of body fat may affect nearly the entire body (generalized), only certain body regions (partial) or small areas under the skin (localized). Depending on the severity and extent of body fat loss, patients may be predisposed to metabolic complications associated with insulin resistance.

While lipodystrophy is characterized by the loss of fatty tissue in certain areas of the body, tissues such as liver and muscle exhibit significant abnormal accumulation of fat, which impairs metabolic activity. People with this disorder also exhibit insulin resistance, thus having a high risk of developing diabetes. They may also present with lipid abnormalities.

The loss of body fat can result from underlying genetic defects (genetic lipodystrophies including autosomal recessive or dominant subtypes) or from autoimmune mechanisms (acquired lipodystrophies including generalized or partial subtypes), or drugs (e.g. highly active antiretroviral therapy (HAART)-induced partial lipodystrophy in human immunodeficiency virus (HIV)-infected patients or localized lipodystrophies from insulin and other injected drugs) [1-3].

The severity of the metabolic abnormalities is usually proportional to the extent of the fat loss, and patients with congenital and acquired generalized lipodystrophies develop complications at early ages. Localized lipodystrophy is not associated with metabolic derangements and it is mostly an aesthetic problem.

Management of lipodystrophies focuses on preventing and treating metabolic complications. Diet and exercise are an integral part of management.

Treatment of lipodystrophy also includes the administration of insulin, oral hypoglycemic agents, and lipid-lowering drugs. Even with the treatment, people with lipodystrophy continue to have severely high levels of triglycerides, leading to recurrent attacks of acute inflammation of the pancreas; severe problems effecting blood glucose levels, posing risks of developing diabetic complications; and fat accumulation in the liver, which can result in cirrhosis and liver failure.

Many patients with lipodystrophy have low leptin levels due to the lack of fat cells that produce the hormone and research has demonstrated beneficial effects of leptin treatment on insulin sensitivity and fat metabolism in a number of tissues.

In February 2014, the FDA announced that leptin (Myalept™) was approved for treatment of generalized lipodystrophy (genetic or acquired) in addition to dietary restrictions. Patients may still need conventional medicines (e.g., lipid-lowering drugs or insulin), but required dosages of those medicines are markedly lower with leptin therapy. In some cases patients are able to discontinue insulin therapy [4-6].

Case report: Patient A. A., an 18-year-old female, was hospitalized at the Endocrinology Service in January 2016 for inaugural Diabetes Mellitus.

She was diagnosed with severe hypertriglyceridemia at the age of 8 and has been hospitalized at least three times by the Pediatric Service related to this condition.

Lipodystrophy developed at the age of 11 years, initially effecting the arms and the upper part of the body, gradually spreading all over the body, sparing only the face and the neck.

Based on her medical records: during her last admission at the age of 14 for the follow-up and completing exams for her continuous high levels of tryglycerides and cholesterol, she had evidence of hyperglycemia (fasting plasma glucose 136 mg/dl), but her physician did not give any specific recommendations for a follow-up.

She was noted to have elevated transaminase levels (2x upper normal value) at that time. She was treated with a statin (Fluvastatin 40 mg/day) – but without any improvement in the lipid profile.

The latest hospitalisation was the first for the patient after a transition from pedriatic to adult endocrinologist (almost 4 years without any close follow-up).

The patient was admitted for inaugural Diabetes Mellitus and hypertriglyceridaemia. At the time of the current admission, the patient was noted to have numerous xanthomata on the hands, elbows and knees, and complained of pain at the lower and upper joints. In addition, she was noted to have almost generalized lipodystrophy, sparing only the face and neck.

The laboratory findings were the following: glucose- 420 mg/dl (23.3 mmol/l), HbA1c – 11.2%, total cholesterol - 778 mg/dl (20.11 mmol/l), triglycerides – 2360 mg/dl (26.64 mmol/l), high density lipoprotein cholesterol (HDL-C) – 65 mg/dl, alaninaminotranspherase (ALT) - 97 (7 to 55 U/L), aspartataminotranspherase (AST) - 79 (8 to 48 U/L), alkaline phosphatase (ALP) - 125 (45 to 115 U/L), Lactate dehydrogenase (LDH) - 200 (122 to 222 mmol/L), C-peptide - 1.2 ng/ml (0.4-1.6 ng/ml).

Urine: Glucose 1%, ketones trace, negative albumin. Renal and thyroid labs within the normal range. ECG- sinus rhythm.

The patient had no family history of DM, dyslipidemia or cardiovascular diseases.

Basal-bolus insulin therapy was initiated: Regular human insulin, 3 times daily (with meals) at doses gradually rising up to 20-26 IU/meal and Glargine (Lantus) 46 IU at 22.00hrs

A strict diet was prescribed to the patient [three days without enteral food, and perfusions (3-5 l/day)], following the liquid foods for 5 days without sweet drinks, with 1400 kcal/day, 1.5 g/kg protein and only unsaturated fats in small quantity. Glycaemic profile was monitored with fingerstick glucose test regularly. Fluvastatin was increased to 80 mg/day (Lescol XL).

Liver function tests were repeated and showed no change.

Fenofibrate was added after one week in the dosage of 160 mg/day (to try to improve her triglycerides). Aspirin 100 mg/day was added to her treatment, due to high blood concentration, in the context of hypertriglyceridemia. All her family members were tested for any type of lipid abnormalities but results were negative.

Patient was discharged after 20 days with a slight amelioration of glucose control and lipid profile. A close follow-up plan with regular phone consultations and laboratory exams was implemented.

Different causative factors of severe lypodystrophy were analysed, including leptin. Leptin levels (measured in Ioaninna/ Greece) were very low 1.5 ug/L (ref range 4-10 ug/L in women).

At her next consultation on May 2016 the laboratory findings were: HbA1c 8.9%, Glycaemic profile 200-260 mg/dl (11.1-14.5 mmol/l), triglycerides – 1860 mg/dl (21.03 mmol/l), total cholesterol – 427 mg/dl (11.04 mmol/l), HDL-C – 60 mg/dl, ALT - 109 (7 to 55 U/L), AST - 87 (8 to 48 U/L), ALP - 87 (45 to 115 U/L), LDH – 178 (122 to 222 mmol/l).

Total Daily Dose of Insulin was increased to 202 IU (138 Regular Insulin + 64 IU Glargine). In order to decrease insulin resistance, metformin 850 mg twice daily was added to the therapy; the patient was taking > 5 IU/kg insulin and eating more than recommended. Fenofibrate was increased to 160 mg twice daily to improve triglycerides level.

On September 2016 the laboratory findings

Table. Summary of laboratory findings

	JANUARY 2016 Fluvastatin 40 – 80mg Fenofibribrate 160 mg	**MAY 2016 Metf 2 x 850mg Fenofibribrate 2x160 mg**	**SEPTEMBER 2016 Metformin 2 x1000mg Omega-3 3x250 Rosuvastatin 20 mg**
HbA1C	11.2	8.9	8.2
TOT CHOL	778	427	326
TRYGLICERIDE	2360	1860	1640
HDL- CHOL	65	60	56
LDL- CHOL	--	--	--
ALT	97	109	87
AST	79	87	70
ALP	125	87	77
LDH	200	178	167
WEIGHT	42	45	47
INSULIN TDD	116	220	260

were: HbA1c 8.2%, Glycaemic profile within 180-240 mg/dl (10-13.3 mmol/l), triglycerides – 1640 mg/dl (18.52 mmol/l), total cholesterol – 427 mg/dl (8.43 mmol/l), HDL-C – 56 mg/dl, ALT - 87 (7 to 55 U/L), AST - 70 (8 to 48 U/L), ALP - 77 (45 to 115 U/L), LDH – 167 (122 to 222 mmol/l).

Total Daily Dose (TDD) of Insulin was increased to 260 IU. Metformin was increased to 1000 mg twice daily, due to increase in TDD of insulin. Omega-3 fatty acids were added at a dose of 3x 250 mg, to reduce triglyceride levels. Fluvastatin was replaced with Rosuvastatin 20 mg/day, for further improvment of the lipid profile. The aim of Rosuvastatin prescription was to reach the goal and change the treatment plan to fenofibrate and omega-3.

On January 2017 the patient was recruited for leptin therapy in USA.

On May 2017 was our last follow-up with the patient. She was treated with Insulin Glargine once daily (TDD was 24 – 30 IU), Metformin 850 mg twice daily and Fenofibrate 160 mg once daily. Her glycemic and lipid profiles have improved.

Conclusions. In a patient with newly diagnosed diabetes mellitus, hypertriglyceridemia and loss of adipose tissue, lipodystrophy should be suspected, especially if glycemic and lipid profiles are not normalised after intensive therapy. In such cases leptin should be measured. If patient has hypoleptinemia, leptin therapy should be started.

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SUMMARY

A YOUNG ADULT WITH GENERALIZED LIPODYSTROPHY AND DIABETES MELLITUS (CASE REPORT)

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Lipodystrophies are a group of heterogeneous disorders characterized by varying degrees of body fat loss and predisposition to insulin resistance and its metabolic complications. Lipodystrophy associated metabolic abnormalities include insulin resistance, that often lead to diabetes mellitus and its complications, hypertriglyceridemia that may be severe enough to cause acute pancreatitis, and hepatic steatosis that may lead to cirrhosis.

We present the case of an 18-year-old female who was hospitalized as an inaugural Diabetes Mellitus. She was diagnosed with severe hypertriglyceridemia, when she was 8 years old and was hospitalized at least three times by the Pediatric Service related to this condition. Lipodystrophy developed at the age of 11. The reason for the latest hospitalisation was hyperglycemia, hypertriglyceridemia and elevated transaminase levels. Leptin levels were very low 1.5 ug/L (ref range 4-10 ug/L in women). She was given Insulin and antihyperlipidemic therapy. However there was little improvement in laboratory results even in 2 months. A year after her hospitalisation at our clinic she started leptin therapy and her laboratory values improved.

In a patient with a newly diagnosed diabetes mellitus, hypertriglyceridemia and loss of adipose tissue, lipodystrophy should be suspected.

Keywords: lipodystrophy, metabolic syndrome, diabetes mellitus, leptin.

РЕЗЮМЕ

СЛУЧАЙ САХАРНОГО ДИАБЕТА В СОЧЕТАНИИ С ГЕНЕРАЛИЗОВАННОЙ ЛИПОДИСТРОФИЕЙ У ПАЦИЕНТА МОЛОДОГО ВОЗРАСТА

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Липодистрофии относятся к гетерогенным нарушениям, которые характеризуются потерей массы тела за счет жировой клетчатки, инсулинорезистентностью и связанными с этим осложнениями: развитие сахарного диабета типа 2, гипертриглицеридемия, панкреатит, стеатозный цирроз печени.

18-летняя женщина госпитализирована в клинику по поводу впервые выявленного сахарного диабета типа 2. В анамнезе у пациентки диагноз гипертриглицеридемии установлен в 8 лет, в 11 лет у нее развилась липодистрофия. На момент госпитализации у больной выявлены: гипергликемия, гипертриглицеридемия и увеличенный уровень трансаминаз. Уровень лептина в крови понижен - 1,5 ug/L (референсные данные нормы у женщин 4-10 ug/L). Пациентке назначены инсулинотерапия и антигиперлипидемические препараты. Спустя 2 месяца после проведенной терпии отмечалось незначительное улучшение в анализах. Спустя 1 год после последней госпитализации решено начать лечение лептином, что привело к улучшению как состояния пациентки, так и лабораторных данных.

У молодых пациентов с сахарным диабетом, гипертриглицеридемией и потерей жировой клетчатки необходимо исключить наличие липодистрофических нарушений.

რეზიუმე

ახალგაზრდა პაციენტი შაქრიანი დიაბეტით და თანდართული გენერალიზებული ლიპოდისტროფიით (კლინიკური შემთხვევა)

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საუნივერსიტეტო ჰოსპიტალის ცენტრი «დედა ტერეზა», ენდოკრინოლოგიის და მეტაბოლურ დაავადებათა სამსახური, ტირანა, ალბანია

ლიპოდისტროფიები მიეკუთვნება ჰეტეროგენული დარღვევების ჯგუფს, ახასიათებს სხეულის ცხიმოვანი ქსოვილის სხვადასხვა ხარისხით კარგვა, ინსულინის მიმართ რეზისტენტობა და მასთან დაკავშირებული გართულებები: ჰიპერტრიგლიცერიდემია,პანკრეატიტი და ღვიძლის სტეატოზური ციროზი.

ქალი 18 წლის ასაკში ჰოსპიტალიზებული იყო კლინიკაში პირველად აღმოჩენილი დიაბეტის დიაგნოზით. პაციენტს მწვავე ჰიპერტრიგლიცერიდემიის დიაგნოზი დაესვა 8 წლის ასაკში, 11 წლის ასაკში განუვითარდა ლიპოდისტროფია. მისი ბოლო ჰოსპიტალიზაციის მიზეზი იყო ჰიპერგლიკემია, ჰიპერტრიგლიცერიდემია და მომატებული ტრანსამინაზების დონე. სისხლში ლეპტინის დონე იყო ძალიან დაბალი - 1.5 ug/L (რეფერენსული მაჩვენებელი ქალებში - 4-10 ug/L). ავადმყოფს დაენიშნა ინსულინი და ანტიჰიპერლიპიდური მკურნალობა. მკურნალობიდან 2 თვის შემდეგ ანალიზებში აღინიშნა მცირედი გაუმჯობესება. ბოლო ჰოსპიტალიზაციიდან 1 წლის შემდეგ პაციენტს დაენიშნა ლეპტინი, რის ფონზეც ლაბორატორიული ანალიზები მკვეთრად გაუმჯობესდა.

ახალგაზრდა პაციენტებში შაქრიანი დაიბეტით, ჰიპერტრიგლიცერიდემიითა და ცხიმოვანი ქსოვილის კარგვით აუცილებელია გამოირიცხოს ლიპოდისტროფიული დარღვევების არსებობა.

MISDIAGNOSED PATIENT WITH LATENT AUTOIMMUNE DIABETES IN ADULTS (CASE REPORT)

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Latent Autoimmune diabetes in Adults (LADA) is often misdiagnosed because it lacks both the awareness [1] and standardized diagnostic criteria [2–4]. LADA is characterized by an adult-onset and by circulating autoimmune antibodies. Therefore, patients may present clinically with characteristics of both type 1 and type 2 diabetes [3–6]. Usually it is defined as initially non-insulin requiring diabetes diagnosed in 25-50 years with antibodies against glutamic acid decarboxylase (GAD) [7]. Diagnosing LADA at a later stage may increase the risk of diabetes complications, thus making the timely diagnosis is vital for the patient's quality of life. The rate of type 2 diabetes in Republic of Macedonia is increasing rapidly. However, diagnosing patients with LADA is very rare and in most cases patients receive wrong treatment, not warranted by further investigations. According to the UK Prospective Diabetes study, 6% to 10% of the people with diabetes have LADA, which makes it more common than type 1 diabetes. In Republic of Macedonia the prevalence of diabetes is 12%, from which 1% are patients with type 1 diabetes

mellitus. This number raises the question how many patients with LADA are misdiagnosed or diagnosed at a later stage?

Case report. Thirty-year-old patient (D.A.) initially consulted his GP because of abdominal pain, nausea and vomiting. He did not report any sudden weight change. He has a mother with type 1 diabetes. His primary medical examination did not reveal any abnormalities. His blood pressure was 125/90mmHg, heart rate 79/min. and Body Mass Index (BMI) - 25kg/m^2. His blood glucose level was 12,7mmol/L and HbA1c level was 10.1%. His metabolic control was slightly impaired with triglycerides level of 3.1mmol/L and Cholesterol level of 6.3mmol/L. Other blood test results including serum creatinine, serum urea, aspartate aminotransferase and alkaline phosphatase, as well as the urine analyses were within the normal range. Because of severe hyperglycemia he was admitted to the local hospital and was given intra venous fluid infusions. Abdominal ultrasound was also without any specific abnormalities. After less than 24 hours he was discharged and advised to visit an endocrinologist. Within the next 48 hours D.A. visited the endocrinologist at the University Clinic of Endocrinology, Diabetes and Metabolic Diseases in Skopje. Patient's initial diagnosis was type 1 diabetes, but the possibility of LADA was not ruled out. He was further examined for GAD (glutamic acid decarboxylase) antibodies, Insulin antibodies (IAA), Islet cell antibodies (ICA) as well as IA-2 (islet antigen-2) to determine the type of diabetes. Because the lab results were expected to be after two weeks, the endocrinologist decided to initiate insulin therapy with small doses of aspart and detemir, as well as advised the patient to follow fixed carbohydrate and reduced fat diet. Despite the clear advice from the doctor the patient refused to receive insulin therapy and only followed the recommended meal plan. Without the therapy, with increased physical activities, his glycemic profiles were satisfactory: his fasting plasma glucose levels were always below 5.6mmol/L, and his postprandial glucose levels were below 10mmol/L. The tests for autoimmune diabetes were positive for GAD antibodies, and negative for all the rest of the tested antibodies and antigens. Despite the result, and the advices from the endocrinologist, the patient still refused the insulin therapy and insisted that he did not need it, because of the glycemic values he measured following the fixed carbohydrate diet. Three weeks after the positive test for GAD antibodies, he went to a private hospital and consulted another doctor who diagnosed him with type 2 diabetes (whether the doctor was aware or not of the positive GAD antibodies we are not informed). He was given dietary restrictions and soon after that, treatment with sulfonylurea was initiated. Following the next 7 months the patient's HbA1c values decreased, but were never below 8.8%. Within the first year of the diagnosis the glycemic measurements rapidly worsened, and the sulfonylurea treatment was intensified. Despite the advices from doctors the patient still refused insulin therapy.

The similarities between type 1 diabetes, type 2 diabetes, and LADA can make diagnosis difficult [1]. However, there are other characteristics for this population that may prompt diagnostic screenings and help to distinguish LADA from type 1 or type 2 diabetes [4,5]. The Immunology of Diabetes Society (IDS) has proposed three criteria to standardize the definition of LADA: 1) age usually ≥30 (25) years, 2) positive titer for at least one of the four autoantibodies, and 3) no treatment with insulin was needed within the first 6 months after diagnosis [4,5]. The patient in this case closely fits the proposed IDS criteria for LADA. He is 30 years of age, he was positive to GAD antibodies and he was not treated with insulin within the first 6 months after had been diagnosed. Furthermore, the rapid progression of the disease indicated that patient had LADA and was misdiagnosed with type 2 diabetes and received wrong treatment.

Conclusion. Making the right and timely diagnosis is crucial for patients with diabetes. This case is very specific because it shows the variable picture of physicians' decision-making process. Patients with LADA are often misdiagnosed due to the use of arbitrary screening criteria such as age [1] and the slow progression of the disease just like in patients with type 1 diabetes. Health care providers must learn to recognize the characteristics of LADA, in order to improve the treatment options and glycemic control [1] and

potentially decreasing the risk of long-term complications. In addition to insulin, other therapy options that preserve β-cell function, including dipeptidyl peptidase-4 inhibitors, glucagon-like peptide 1-receptor agonists, and thiazolidinediones, could be considered for patients with LADA [1]. Conversely, therapy options such as sulfonylureas that increase the rate of deterioration of C-peptide secretion, further depleting insulin levels, should be avoided [8-14]. By recognizing that a patient has LADA, we can ensure that the patient is also screened for other autoimmune diseases in a timely manner [1]. Furthermore, from this case, we can see the patient's mindset and negative attitude towards insulin therapy. This raises the question of the awareness and knowledge about diabetes and its complications in Macedonian population.

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SUMMARY

MISDIAGNOSED PATIENT WITH LATENT AUTOIMMUNE DIABETES IN ADULTS (CASE REPORT)

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Latent Autoimmune Diabetes in Adults (LADA) is often misdiagnosed because it lacks both awareness and standardized diagnostic criteria.

A 30-year-old patient with high blood glucose, HbA1c level 10.1% and positive GAD antibodies

was diagnosed with type 1 diabetes but LADA was not ruled out. Patient refused to receive insulin therapy. He chose to follow the dietary restrictions and therapy with sulfonylurea, initiated by another physician. Following 7 months the patient's HbA1c values decreased, but never achieved the goal. Furthermore, after the first year of diagnosis his glycemic values rapidly worsened.

The similarities between type 1 diabetes, type 2 diabetes, and LADA can make diagnosis difficult. The Immunology of Diabetes Society (IDS) has proposed three criteria to standardize the definition of LADA. 1) age usually ≥25 years 2) positive titer for at least one of the four antibodies, and 3) no treatment with insulin was needed in the first 6 months after diagnosis. The patient in this case closely fits the proposed IDS criteria for diagnosing LADA.

Making the right diagnosis at the right time is crucial for patients with diabetes. Patients with LADA are often misdiagnosed due to the use of arbitrary screening criteria such as age. Health care providers must learn to recognize the characteristics of LADA, in order to improve the treatment options, glycemic control and potentially decrease the risk of long-term complications.

Keywords: LADA, latent autoimmune diabetes in adults, type 1 diabetes, type 2 diabetes.

РЕЗЮМЕ

ЛАТЕНТНОТЕКУЩИЙ АУТОИММУННЫЙ ДИАБЕТ ВЗРОСЛЫХ (СЛУЧАЙ ИЗ ПРАКТИКИ)

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Латентнотекущий аутоиммунный диабет взрослых (LADA) часто остается нераспознанным ввиду нечетких диагностических критериев и неосведомленности врачей.

30-летний молодой мужчина обратился в клинику по поводу гипергликемии. На момент обследования HbA1c составил 10,1%, тест на GAD (глутаматдекарбоксилаза) антитела - положительный. На основании результатов обследования поставлен диагноз сахарного диабета типа 1. Диагноз LADA не был исключен. Пациент категорически отказался от назначенной инсулинотерапии и обратился к врачам другой клиники, где больному были назначены диетотерапия и препарат сульфонилмочевины. На протяжении 7 месяцев уровень гликемии снизился, хотя не дошел до целевого уровня. Спустя 1 год после поставленного диагноза уровень гипергликемии и состояние пациента резко ухудшились.

Сходство жалоб и лабораторных данных у пациентов с сахарным диабетом типа 1 и LADA осложняет постановку правильного диагноза. Диабетическая ассоциация иммунологов (IDS) предложила следующие критерии диагностики LADA: 1) возраст пациента ≥ 25 лет; 2) положительный тест на 1 вид из 4 антител - к островковым клеткам поджелудочной железы (ICA), тирозинфосфатазе (anti-IA-2), глутаматдекарбоксилазе (anti-GAD) и инсулину (IAA); 3)отсутствие необходимости в инсулинотерапии на протяжение первых 6 месяцев после диагностирования гипергликемии. Данные пациента соответствовали вышеприведенным 3 критериям.

Вовремя и правильно поставленный диагноз сахарного диабета позволяет определить адекватную тактику лечения пациента, что исключает риск развития осложнений сахарного диабета. При постановке диагноза сахарного диабета необходимо учитывать не только возраст пациента, но и вышеприведенные критерии.

რეზიუმე

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ზრდასრულებში ლატენტურად მიმდინარე აუტოიმუნური დიაბეტის (LADA)

დიაგნოზი ხშირად ვერ ისმევა ზუსტი დიაგნოსტიკური კრიტერიუმების არ არსებობის გამო.

30 წლის მამაკაცმა კლინიკას მიმართა გლიკემიის მაღალი მაჩვენებლების გამო, HbA1c-ს დონით 10,1% და GAD ანტისხეულებისადმი დადებითი ტესტით, რის საფუძველზეც დაისვა შაქრიანი დიაბეტი ტიპი 1-ის დიაგნოზი, თუმცა არ გამოირიცხა LADA-ს არსებობა. ექიმის რჩევის მიუხედავად პაციენტმა უარი განაცხადა ინსულინოთერაპიაზე. მან აირჩია სხვა ექიმთან მკურნალობა,რომელმაც დაუნიშნა მხოლოდ დიეტოთერაპია და სულფანილშარდოვანას პრეპარატები per os. 7 თვის მანძილზე პაცეინტის გლიკემიის მაჩვენებლები დაქვეითდა, თუმცა არ მიაღწია სამიზნე მაჩვენებლებს. დიაგნოზის დასმიდან 1 წლის შემდეგ გლიკემია მკვეთრად გაუარესდა.

შაქრიან დიაბეტ ტიპ 1-ს, ტიპ 2-სა და LADA-ს შორის მსგავსება საკმაოდ ართულებს დიგნოზის დასმას. დიაბეტური იმუნოლოგების ასოციაციის (IDS) მიერ შემოთავაზებულია LADA-ს სამი დიაგნოსტიკური კრიტერიუმი:

1. ასაკი ≥25 წელზე;
2. დადებითი ტესტი ოთხიდან სულ მცირე ერთ ანტისხეულზე;
3. 6 თვის მანძილზე ინსულინოთერაპიის დაწყების აუცილებლობის არარსებობა. გამოკვლეული პაციენტი აკმაყოფილებს სამივე დიაგნოსტიკურ კრიტერიუმს.

დროულად სწორი დიაგნოზის დასმა ძალიან მნიშვნელოვანია შაქრიანი დიაბეტის მქონე პაციენტისთვის.

კვლევის შედეგებზე დაყრდნობით, ავტორებს გამოტანილი აქვთ დასკვნა, რომ LADA-ს დიაგნოზის დასმის დროს ყურადღება უნდა ექცეოდეს არა მხოლოდ ასაკს, არამედ გათვალისწინებული იყოს ზემომოყვანილი ყველა კრიტერიუმები.

CLINICAL CASE OF TYPE 2 DIABETES REMISSION

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The specialists have increased attention towards the remission of diabetes mellitus (DM) [1-7]. The possibility of remission is high with metabolic surgery [6,7]. Studies show, that the extremely low-calorie diet is also effective [3,4].

We would like to present the case of type 2 diabetes remission achieved by changing the lifestyle, including the use of a low-calorie (but not extreme) diet and a significant increase in physical activity.

Case Report. A.V., a 48-year-old man with decompensated DM was admitted to VM Center of Endocrinology, Diabetology and Metabolism (Baku, Azerbaijan Republic) on 13.06.2008. Patient was diagnosed with type 2 diabetes approximately 2 years ago. He did not follow any diet recommendations; moreover, consumed meal rich in carbohydrates, sweets and fat. Patient was physically inactive. His alcohol intake has been frequent and unlimited (hard alcoholic drinks) and was heavy smoker for a long period of time (≈ 60 cigarettes per day).

The patient's body weight was 121 kg, his height was 185 cm and body mass index (BMI) was 35.4 kg/m^2. Blood pressure was 125/75 mmHg and heart rate 92 bpm. Physical cardiopulmonary examination was normal with no sings of cardiac failure. Pheripheral pulse was normal. There were

no abdominal bruits and no hepatomegaly. The thyroid gland was not enlarged, and there were no signs of thyroid dysfunction. Results of neurological and ophthalmological examinations were normal. Electrocardiogram (ECG) - sinus tachycardia. Laboratory examination: Glycemic hemoglobin (HbA1c) - 9.4%; fasting glucose - 118 mg/dl; fasting insulin 37.4 mU/ml; $HOMA_{IR}$ - 11; $HOMA_{\%\beta}$ - 249; aspartate aminotransferase (AST) - 46 IU/l; alanine aminotransferase (ALT) - 74 IU/l; De Ritis ratio (AST/ALT ratio) - 0.62; creatinine -0.91 mg/dl; Urea 40 mg/dl; glomerular filtration rate (GFR EPI) - 99.3 mL/min/1.73m^2, total cholesterol – 210 mg/dl, high-density lipoprotein cholesterol (HDL)-42 mg/dl, low-density lipoprotein cholesterol (LDL) – 128 mg/dl, triglycerides – 200 mg/dl.

According to the results of patient's examination and lab work-up, his full diagnosis was the following: type 2 diabetes mellitus (with insulin resistance), obesity class II, alcoholic liver disease and dyslipidemia type II b (by classification of Fredericson).

The patient was recommended to change his lifestyle, including exclusion of sweets and alcoholic drinks and increase in physical activity. According to his type and characteristics of diabetes he was prescribed metformin 1000 mg twice per day (morning and night); gliclazide MR 30 mg per day.

The patient was not following the recommended diet plan and by 28.06.2013 his HbA1c range was 6.5%–7.9%.

According to the certain events, alcohol was completely excluded from the diet and the quantity of sweets was markedly decreased. The total daily calorie intake was 1500 - 1800 kcal. Physical activity was increased significantly and the patient began to lose weight. By 03.11.2017 he lost 28 kg in total and his body weight and BMI became 93 kg and 27.2 kg / m^2, respectively. Glyclazide MR was stopped, the dose of metformin was reduced soon afterwards, and approximately in one month was also terminated.

All data of HbA1c, ALT and AST values from 13.06.2008 to 03.11.2017 are presented in Fig. 1.

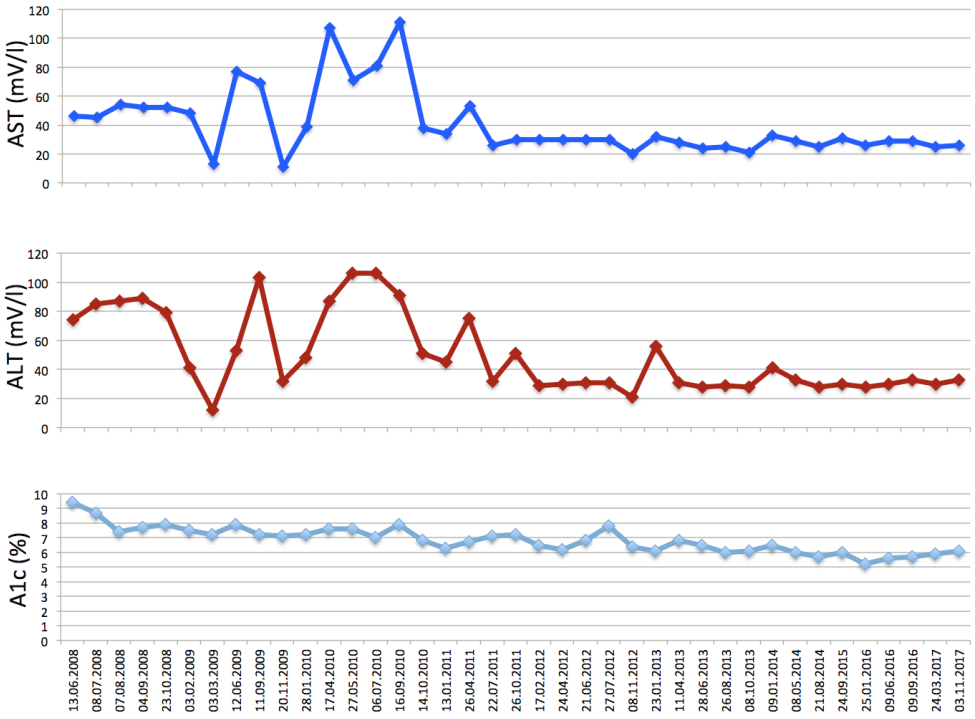

Fig. 1. Patient A.V.: HbA1c, ALT and AST values from 13.06.2008 to 03.11.2017

As it is seen from Fig. 1, HbA1c level was constantly below 6.5% after August 28, 2013. ALT and AST have returned to normal ranges.

Changes of $HOMA_{IR}$ and $HOMA_{\%\beta}$, taking place at the same term, are shown in Fig. 2.

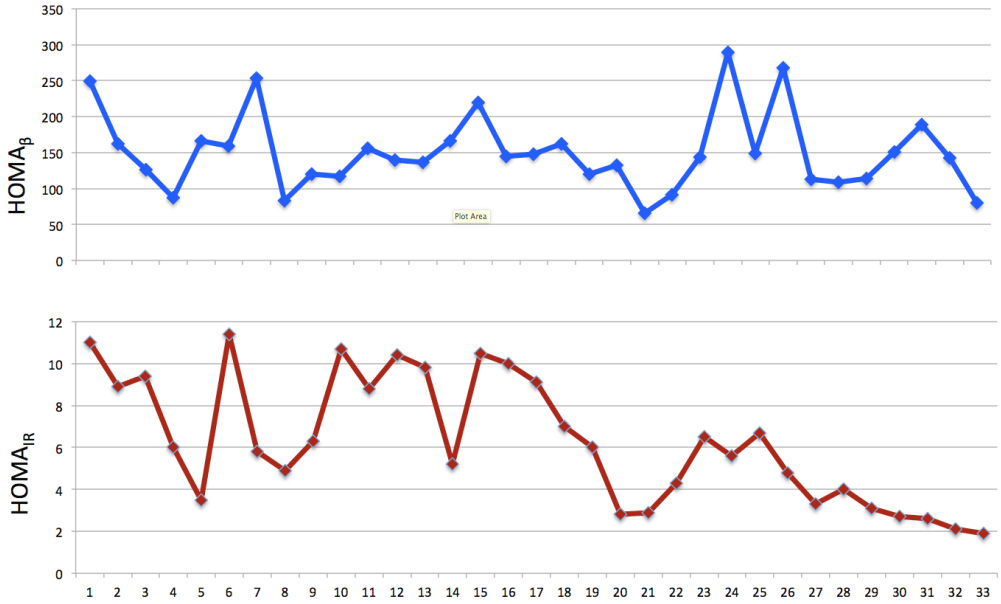

Fig. 2. Patient A.V.: HOMA$_{IR}$ and HOMA$_{\%\beta}$ values from 13.06.2008 to 03.11.2017

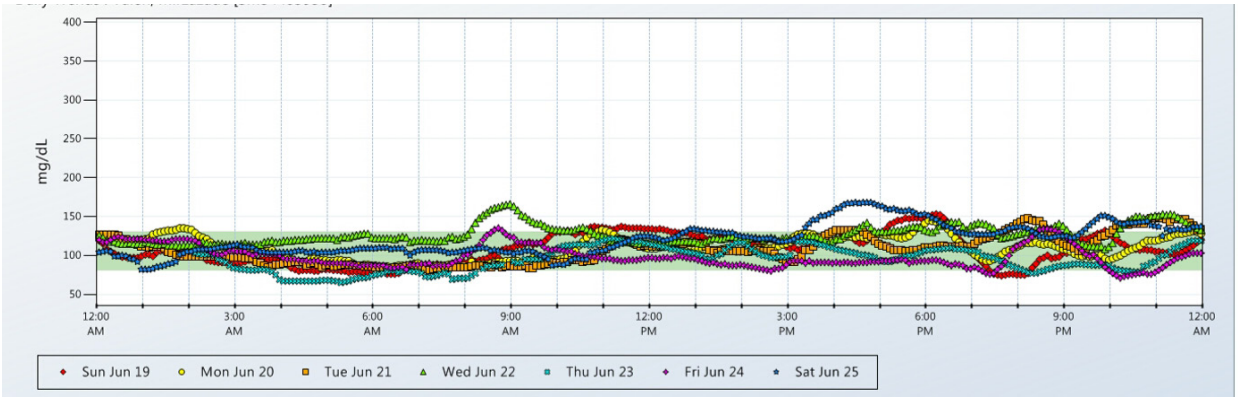

Fig. 3. Patient A.V.: CGM results received by Dexcom 4G (Dexcom, USA)

As it is seen from Fig. 2, the values of HOMA$_{IR}$ and HOMA$_{\%\beta}$ decreased from 11.0 to 1.9, and from 249 to 80, respectively, in a period from 13.06.2008 to 03.11.2017. These results demonstrate normalization of sensitivity to insulin and normalization of insulin secretion (termination of insulin hyper secretion).

CGM results received by Dexcom 4G (Dexcom, USA) are shown in Fig. 3.

As it is seen from Figure 3, 24-hour glucose variations were at the optimal range [8].

Thus, lifestyle changes accompanied by a decrease in body weight, an increase in insulin sensitivity and normalization of insulin secretion, led to a prolonged normalization of carbohydrate metabolism. Taking into account the absence of currently hypoglycemic pharmacotherapy, the condition can be considered as a remission of diabetes. In our opinion, it is interesting that the remission of diabetes in this case was achieved not as a result of the metabolic surgery or an extreme diet.

In our opinion, this result demonstrates that not only biofuel intake decrease, but also increase of biofuel consumption (in optimal situation all together) may be a really effective way of achieving diabetes remission in obese patients.

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SUMMARY

CLINICAL CASE OF TYPE 2 DIABETES REMISSION

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Authors present a clinical case of a 48-year-old male patient diagnosed with type 2 diabetes mellitus (with insulin resistance), obesity class II, alcoholic liver disease and dyslipidemia, who was able to achieve a T2DM remission after lifestyle modification by using low-calorie (1500-1800 kcal), rather than extreme diet, and a significant increase in physical activity.

This result demonstrates that not only biofuel intake decrease, but also increase of biofuel consumption (in optimal situation all together) may be a really effective way of achieving diabetes remission in obese patients.

Keywords: type 2 diabetes mellitus, lifestyle modification, remission.

РЕЗЮМЕ

КЛИНИЧЕСКИЙ СЛУЧАЙ РЕМИССИИ ДИАБЕТА ВТОРОГО ТИПА

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Частота ремиссий после метаболических операций достаточно высокая. Представлен клинический случай ремиссии сахарного диабета типа 2 на фоне низкокалорийной (1500-1800 ккал) диеты и значительного увеличения физической активности. Установлено, что изменение образа жизни, сопровождающееся снижением массы тела и повышением чувствительности к инсулину, приводит к длительной нормализации углеводного обмена. В представленном клиническом случае не применена гипогликемическая фармакотерапия, что дает основание оценить состояние пацинета как ремиссию сахарного диабета. Интересно, что ремиссия диабета в этом случае была достигнута без применения метаболической хирургии и экстремальной диеты.

რეზიუმე

შაქრიანი დიაბეტი ტიპი 2-ის რემისიის კლინიკური შემთხვევა

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აზერბაიჯანის ენდოკრინილოგების,დიაბეტოლოგების და თერაპიული განათლების ასოციაცია, ბაქო, აზერბაიჯანი

მეტაბოლური ქირურგიის შემდეგ რემისიის სიხშირის მაჩვენებელი საკმაოდ მაღალია. სტატიაში აღწერილია შაქრიანი დიაბეტი ტიპი 2-ით ავადმყოფის კლინიკური რემისიის შემთხვევა და-

ბალკალორიული (1500-1800 კკალ) დიეტის და ფიზიკური აქტივობის მნიშვნელოვანი მომატების ფონზე. დადგენილია რომ, ცხოვრების წესის შეცვლა, რომელსაც თან ახლავს სხეულის მასის დაქვეითება და ინსულინის მიმართ მგრძნობელობის მატება, იწვევს ნახშირწყლების ცვლის ხანგრძლივ ნორმალიზაციას.

წარმოდგენილი შემთხვევა საინტერესოა იმ თვალსაზრისით,რომ დიაბეტის რემისია მიღწეული იყო მხოლოდ დაბალკალორიული დიეტით და ფიზიკური აქტივობის მნიშვნელოვანი მატებით, მეტაბოლური ქირურგიის,ექსტრემული დიეტისა და ანტიდიაბეტური პრეპარატების გამოყენების გარეშე.

CLINICAL CASE REPORT ON ACUTE PANCREATITIS WITH CONCOMITANT T2DM AND HYPERTRIGLYCERIDEMIA

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A worldwide incidence of diabetes is 425 million, and about 352 million have impaired glucose tolerance. Over 4 million deaths were attributed to the diabetes in 2017 [1] Vascular complications are the most frequent cause of diabetes mortality and morbidity. Prospective studies have shown continuous associations of glucose levels with the risks of major vascular events [2]. However, previous randomized trials, evaluating the effects of glycemic control in patients with diabetes, have provided inconsistent evidence of its effects on macrovasvular outcomes. Nevertheless, the current guidelines recommend a target glycemic hemoglobin (HbA1c) level of<7.0% for most patients with diabetes [3].

However, potential benefits of glycemic control must be balanced against such factors as limited life expectancy, existence of comorbid conditions or increased risk of adverse events (e.g. severe hypoglycemia). Baseline HbA1c and presence of microvascular complications may reduce the expected individual benefits. Therefore, patients' risk profiles and personal preferences should be considered while setting individual targets for treatment [4].

Elevated triglyceride levels (TGs), or hypertriglyceridemia, are often caused or exacerbated by uncontrolled diabetes, obesity and unhealthy lifestyle. The last two are globally considered the leading risk factors for most non-communicable diseases. In epidemiologic and interventional studies hypertriglyceridemia is stated to be a risk factor for coronary artery disease [5].

Type 2 diabetes (T2DM) and hypetrirglyceridemia often coexist. The hypertriglyceridemia of diabetes is classified as mild-to-moderate (TGs between 150–499mg/dL) and severe (TGs ≥500mg/dL).

Predominantly, hypertriglyceridemia is caused by impairment or deficiency of lipoprotein lipase (LPL). LPL is a vascular enzyme that degrades chylomicrons into remnant particles and liberates the triglyceride (TG) free fatty acids for energy use from fat storage. In some cases, severe familial dysbetalipoproteinemia (type III hyperlipidemia) or overproduction of very low-density lipoprotein cholesterol (VLDL-CH) (familial hypertrygliceridemia) may result in severe hypertriglyceridemia. If the level of total cholesterol (TCH) exceeds 300 mg/dL and TGs concentration is between 500 and 1000 mg/dL, the patient may have a genetic cause of dyslipidemia (type III or familial combined hyperlipidemia). Serum TGs are primarily carried in apoB-containing lipoproteins and have been demonstrated to be predictive of coronary heart disease risk. High levels of fasting TGs (>200mg/dL) often represent an increase

in plasma concentration of VLDL-CH particles, the cholesterol content of which is correlated with the number of atherogenic particles. According to National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) guidelines, statins are recommended as an initial therapy for reducing low-density lipoprotein cholesterol (LDL-CH) and a non-high density lipoprotein cholesterol (non-HDL-CH) in patients with hypertriglyceridemia (200-400mg/dL). However, statin monotherapy is often insufficient to achieve non-HDL-CH targets. For patients with persistent hypertriglyceridemia (>200mg/dL), who receive statin therapy, adding TG-lowering agents is recommended to reduce non-HDL-CH levels [6].

The management of severe hypertriglyceridemia (chylomicronemia syndrome) includes aggressive reduction of TGs with intravenous insulin, fibrates, omega-3 fatty acids, and/or niacin therapy to avoid the risk of pancreatitis [7].

Fibrates are drugs that efficiently decrease triglycerides, increase HDL, and improve the prognosis both in patients with and without diabetes. However, the effects of fibrates on glycemic control, blood pressure, fasting serum insulin, and leptin concentrations are not clear.

Therapeutic measures include restriction of dietary fat and simple carbohydrates to reduce chylomicrons and VLDL-CH. Drug therapy with niacin and fibrates is initiated, if dietary therapy fails. Fibrate use is recommended, if primary abnormality is an increased TGs and low HDL-CH levels. Combination of fibrate/niacin, and fibrate/omega-3 fatty acids can also be used for hypertriglyceridemia management.

Familial hypertriglyceridemia is also a common autosomal dominant disorder, occurring in 1 to 2% of the general population. Affected family members have isolated elevated triglycerides. A unifying molecular mechanism is lacking. The phenotype is stable, with affected family members consistently showing isolated hypertriglyceridemia on repeated analyses. The disorder is characterized by primary overproduction of TG. Lipoprotein particles tend to be large, consisting of increased amounts of TG relative to apo-B. For a given level of cholesterol, these patients have lower numbers of lipoprotein particles and a decreased apo-B concentration. The relationship between this disorder and cardiovascular risk is uncertain. Those affected do not appear to be predisposed to premature vascular disease, though they are at risk for the chylomicronemia syndrome, when an additional risk factor for hypertriglyceridemia, such as poorly controlled diabetes, is present [8].

Familial hypertriglyceridemia often leads to diabetes, pancreatitis, myocardial infarction (MI), and less commonly skin xanthoma.

Our aim was to study the changes in glycemic and triglyceride levels in a patient with newly onset T2DM and hypertriglyceridemia, who was treated with fenofibrate and insulin.

Case report. Our patient MM, is a 46 years old female, Caucasian, hospitalized for the first time with acute abdominal pain. Before hospitalization the patient was feeling well and was not on any medication. The patient stated that she had never taken alcohol, or smoked, though her lifestyle was passive. She had never been hospitalized except for two deliveries.

He abdominal pain developed in the evening after a heavy meal. The pain was located in the middle of the abdomen and irradiated to her back. The pain had persisted for 2h when she was taken to the hospital.

Preliminary diagnosis of appendicitis was stated, but performed computed tomography (CT) of the abdomen revealed an enlarged pancreas, while the appendix and gallbladder were within the normal ranges. The test performed showed elevated amylaze concentration, which was consistent with the diagnosis of acute pancreatitis (Table 1).

Pancreatitis often develops secondary to gallbladder stones, alcoholism, or specific genetic defects. Our patient did not suffer from the first two conditions, but stated that her father had lipid abnormalities and died of MI. Whether or not he had T2DM was unknown. Based on the information provided, inherited hypertriglyceridemia was suspected.

Moreover, the patient stated that she had lost 4-5 kg during the past 6 months and had developed narcolepsy, general weakness, excessive thirst and polyuria, especially at night. At the admission her BMI was 32.2kg/m², T/A-

Table 1. Lipid profile data at admission

Measurements	Results	Normal references
TCH	6.5mmol/L (250mg/dL)	n< 200.mg/dL
LDL-CH	3.0mmol/L (116mg/dL)	n< 100mg/dL
HDL-CH	1.0mmo/L (39mg/dL)	n>40mg/dL
TG	5.2mmol/L (4,602mg/dL)	n<2mmol/L

Table 2. Insulin Therapy Algorithm

Blood glucose values	Insulin titration
BG <4mmol/l (72 mg/dL)	No insulin subcutaneous
BG 4-8 mmol/l (72 -144mg/dL)	2 unit of subcutaneous insulin
BG 8-12mmol/l (144-216 mg/dL)	4 unit of subcutaneous insulin
BG 12-16mmol/l (144-288mg/dL)	6 unit of subcutaneous insulin
BG >16mmol/l (288 mg/dL)	8 unit of subcutaneous insulin

Table 3. Laboratory Data 3 month after

Measurements	Values	Normal ranges
TCH	190mg/dL	n< 200.mg/dL
LDL	100mg/dL	n< 100mg/dL
HDL	39mg/dL	n>40mg/dL
TG	50mg/dL	n<30-149 mg/dL
HbA1c	7%	Target 6.0-6.5%
C-Peptide	500pmol/L	n -400pmol/L
Amylaze	110U/L	n- 40-140U/L

130/80mmHg, blood glucose (BG) level 12 mmol/L (216mg/dl), HbA1c-8.7%, C-peptide 1100pmol/L (n -400pmol/L), amylaze210U/L (n- 40-140U/L); Glutamic Acid Decarboxylase (GAD)-antibodies were negative. Her plasma TG concentration was measured together with plasma TCH, LDL-CH and HDL-CH and are shown in Table 1. Elevated C-peptide level indicates the presence of insulin resistance.

Plasma TGs are often increased in patients with newly diagnosed T2DM, but not to the degree, seen in our patient [9]. Therefore, an inherited hypertriglyceridemia was suspected.

The most common cause of familial hypertriglyceridemia is a defect in the LPL enzyme catalyzing the cleavage of TGs. Ideally, the LPL gene has to be analyzed to demonstrate a mutation in the N291S allele.

Though in this case we unfortunately were not able to analyze the LPL gene to confirm its mutation and diagnosis of familial hypertriglyceridemia.

Patient data and the results of the performed tests confirmed the diagnosis of T2DM and hypertriglyceridemia; based on family history, inherited hypertriglyceridemia was suspected.

Upon the admission, an acute pancreatitis treatment protocol was initiated, with the administration of saline solution, supplemented with potassium (closely monitored levels), and analgesics; a gastric tube was placed. Treatment with subcutaneous injections of rapid acting insulin analogue Glulisine (every 3 hours) was started (Table 2). Our aim was to lower a BG level to approximately 6-9 mmol/L (108-162 mg/dL). BG was measured every 3 h at bedside.

Hypertriglyceridemia leads to severe insulin resistance in liver and skeletal muscles; it may be due to accumulation of intracellular lipids, which inhibit insulin signaling. Thus, in order to reduce TG levels, it is very important to initiate low-fat

and low-carbohydrate (CH) diet and treatment with fenofibrates, which directly inhibits TG production. Besides, insulin therapy should also be initiated, in order to reduce hyperglycemia and to block TG formation by LPL activation. The role of insulin in inhibition of TG levels is very important, as finofibrates action does not start immediately.

After 2 days in the hospital setting, patient had recovered, the gastric tube was removed, and she started to eat. Her BG dropped to 8 mmol/L and her amylaze level decreased to 120U/L (n- 40-140U/L).

The patient was on a basal-bolus insulin regimen with short acting insulin analogue Glulisine and ultra-long acting insulin analogue Glargin. The prandial insulin Glulisine doses were 8-10-12IU (9am-2pm-7pm, respectively); and bedtime insulin Glargin dose was 25IU. The doses were adjusted based on the BG levels measured before each main meal and at bedtime. Daily CH counting (CH units/CHU) and CHU per each meal were calculated.

Short course of diabetes education was carried out, including following topics: what is T2DM, how to manage diabetes, principles of insulin therapy, dose adjustment, self-blood glucose monitoring (SBGM), CHU counting, healthy lifestyle, etc…

After recovery from the acute pancreatitis episode, (in 2 week) the patient was discharged on fenofibrate and intensive insulin therapy with a basal-bolus regimen with Glulisine (6-8-10 IU) and Glargin(20 IU/bedtime).

Because of the risk of arteriosclerosis, aspirin at a low dose (75 mg/day) was initiated.

The patient has been under ambulatory supervision. Three month after discharge patient's condition was satisfactory (see laboratory test results in Table 3), though target values of HbA1c and TG were not yet achieved.

The patient regularly performed SBGM that showed glycemic variability during past 3 months.

She feels well on recommended treatment and diet, though further reduction in HbA1c and TG levels is recommended, as due to elevated TG levels together with diabetes the risk of MI is high for this patient.

The patient has been advised to continue SBGM. She is under close follow-up monitoring at the Center.

Conclusion: Prevalence of T2DM is high and continues to increase globally. T2DM and hypertriglyceridemia often coexist. Hypertriglyceridemia seems to cause diabetes by inducing insulin resistance. Plasma TGs are often increased in newly diagnosed diabetes patients, but not to the degree exhibited by the patient. This indicates to the risk of presence of inherited hypertriglyceridemia. Intensive treatment of both conditions with diet, physical activity, fenofibrates and insulin is important, as it aims to reduce TG values and normalize glucose profile [10].

Fenofibrate is indicated to block TG synthesis. Besides, insulin treatment is also needed, in order to reduce hyperglycemia and to block TG formation by LPL activation. In the acute phase, insulin treatment is especially beneficial because of the lag in time before fenofibrates taking effect.

Elevated TG values associated with diabetes dramatically increase the risk of developing MI. Therefore, a good control of both conditions and close monitoring are mandatory for our patient.

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SUMMARY

CLINICAL CASE REPORT ON ACUTE PANCREATITIS WITH CONCOMITANT T2DM AND HYPERTRIGLYCERIDEMIA

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Authors present a clinical case review of a 46-years-old, otherwise healthy female patient, presented with acute abdominal pain. Examination and full work-up established a diagnosis of acute pancreatitis, T2DM and hypertriglyceridemia; based on family history, inherited hypertriglyceridemia was suspected. Elevated TG values associated with diabetes dramatically increase the risk of developing MI.

Subsequent to the pancreatitis treatment protocol completion, the patient has fully recovered from acute pancreatitis. Prescribed anti-diabetes and Fenofibrate treatment has achieved satisfactory glycemic and TG values. The patient is under close ambulatory control and monitoring at the National Center for Diabetes Research.

T2DM and hypertriglyceridemia often coexist. Intensive treatment of both conditions with diet, physical activity, fenofibrates and insulin is important, as it aims to reduce TG values and normalize glucose profile.

Keywords: T2DM, diabetes, familial hypertriglyceridemia, pancreatitis, fenofibrates.

РЕЗЮМЕ

КЛИНИЧЕСКИЙ СЛУЧАЙ ОСТРОГО ПАНКРЕАТИТА С СОПУТСТВУЮЩИМИ САХАРНЫМ ДИАБЕТОМ И ГИПЕРТРИГЛИЦЕРИДЕМИЕЙ

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Представлен клинический случай 46-летней пациентки, поступившей в клинику с жалобой на острую боль в области живота. На основании результатов проведённых обследований установлен диагноз острого панкреатита, сахарного диабета типа 2 и гипертриглицеридемии; основываясь на анамнезе, подозревалась наследственная гипертриглицеридемия.

По завершении протокола лечения острого панкреатита пациентка полностью оправилась от данного состояния. Проводимое лечение сахарного диабета и антилипидная терапия позволили достичь удовлетворительных показателей глюкозы крови и значений триглицеридов. Пациентка находится под регулярным амбулаторным наблюдением при Национальном центре исследований диабета.

Сахарный диабет типа 2 часто сопровождается гипертриглицеридемией. Важное значение имеет интенсивное лечение обоих состояний посредством диеты, физической активности, фенофибратов и инсулина, поскольку оно нацелено на снижение показателей триглицеридов и нормализацию профиля глюкозы крови.

რეზიუმე

სისხლში გლუკოზის კონტროლი ჰიპერტრიგლიცერიდემიის ფონზე (კლინიკური შემთხვევა)

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ავტორების მიერ წარმოდგენილია 66 წლის პაციენტის კლინიკური შემთხვევა,

რომელიც კლინიკაში შემოვიდა მუცლის არეში მწვავე ტკივილის ჩივილებით. ჩატარებული კვლევის შედეგად დაისვა მწვავე პანკრეატიტის, შაქრიანი დიაბეტი ტიპი 2-ის და ჰიპერტრიგლიცერიდემიის დიაგნოზი. ანამნეზზე დაყრდნობით ეჭვი მიტანილი იყო მემკვიდრეობით ჰიპერტრიგლიცერიდემიაზე. მწვავე პანკრეატიტის მკურნალობის პროტოკოლის შესრულების შემდეგ პაციენტი გამოვიდა მდგომარეობიდან. შაქრიანი დიაბეტის მკურნალობამ და ანტილიპიდურმა თერაპიამ შესაძლებელი გახადა სისხლის გლუკოზის და ტრიგლიცერიდების მნიშვნელობის დამაკმაყოფილებელი მაჩვენებლების მიღწევა. პაციენტი იმყოფება რეგულარული ამბულატორული დაკვირვების ქვეშ დიაბეტის კვლევის ეროვნულ ცენტრში. შაქრიანი დიაბეტი ტიპი 2-ს ხშირად თან ახლავს ჰიპერტრიგლიცერიდემია. უდიდესი მნიშვნელობა აქვს ორივე მდგომარეობის ინტენსიურ მკურნალობას დიეტის, ფიზიკური აქტივობის, ფენოფიბრატების და ინსულინის გამოყენებით, ვინაიდან ასეთი მკურნალობა მიმართულია ტრიგლიცერიდების დაქვეითებაზე და სისხლის გლუკოზის პროფილის ნორმალიზაციაზე.

BENEFITS OF EARLY SCREENING AND PROPER TREATMENT IN PATIENT WITH SIGNIFICANT RISK FACTORS FOR GESTATIONAL DIABETES MELLITUS (CASE REPORT)

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Gestational diabetes mellitus (GDM) is associated with an increased risk of maternal and perinatal short and long-term complications [1–4]. The condition is diagnosed by a positive oral glucose tolerance test (OGTT), which is either carried out in all pregnant women [7] or in a selected group of women identified by their demographic characteristics and obstetric history, as being at high risk for GDM.

GDM occurs in 2-9% of all pregnancies [8]. Evidence suggests that the use of insulin for the treatment of hyperglycemia in GDM reduces the risk of serious perinatal morbidity [9]. Pregnancy is an exciting time in a woman's life. However, once patient is diagnosed with GDM, she will be managed more intensively. GDM is managed using diet and exercise but one in six women with GDM requires insulin.

Case report. A 35-year-old woman at the 14th gestational week of her tenth pregnancy was seen for routine prenatal care. The patient's past obstetric history included the spontaneous abortion at 12th gestational week four consecutive times in a period of three years. After that, hysteroscopic transcervical resection of uterine septum was performed. Next three pregnancies have been terminated by spontaneous abortion at the 18th-20th gestational weeks. At the eighth pregnancy she had a spontaneous abortion on the 12th gestational week and the last pregnancy with spontaneous abortion at the 20th gestational week.

Her family history revealed that her mother has type 2 diabetes mellitus. In addition, the patient had a hypertension which was treated with ACE-inhibitor (Enalapril - 5mg twice daily) and hyperlipidemia which was treated with statins

Table. Glyaemic profile after hospitalization

	FPG 08:30	09:30	13:00	14:00	18:00	19:00	22:00	23:00
2nd day of hospitalization	7.3 mmol/l	8.7 mmol/l	4.2 mmol/l	8.0 mmol/l	5.5 mmol/l	7.3 mmol/l	6.1 mmol/l	6.0 mmol/l
4th day of hospitalization	6.3 mmol/l	10.5 mmol/l	4.3 mmol/l	8.8 mmol/l	4.7 mmol/l	8.7 mmol/l	4.8 mmol/l	7.2 mmol/l
8th day of hospitalization			4.0 mmol/l	7.1 mmol/l	4.5 mmol/l	5.0 mmol/l	4.6 mmol/l	5.1 mmol/l

(Rosuvastatin - 20 mg once daily) and fibrates (Fenofibrate - 145 mg once daily).

In the past years, for a certain period, she was treated with oral antidiabetic drugs (Metformin XR a 500 mg), but has stopped the therapy. Despite her hygiene-dietetic regimen and antihypertensive treatment, she still had several spontaneous abortions.

The patient was tested for several genetic mutations at the Center for Immune, Molecular and Genetic Investigations (CIMGI), where some genetic disorders were found (Thrombophilia (Heterozygote on F II, MTHFR C677T, A1298C, Fibrinogen. PAI- 1 5G/4G)).

The values of OGTT before hospitalization were 6.8 mmol/l (0'), 12.3 mmol/l (60') and 7.7 mmol/l (120'), respectively, and her HbA1c was 7.3%.

In the hospital setting, an insulin therapy in the form of long-acting insulin analogue (Levemir) and rapid-acting insulin analogue (NovoRapid) was initiated.

We started with three doses of NovoRapid (3+3+3 IU) and Levemir 10 IU at night. Control of the blood pressure was continued with Methyldopa (250 mg three times per day).

During the hospitalization, we checked thyroid status (TSH=0.427, fT4=11.7, ATPO=196) that was within the normal reference range. Other measurements, including electrolytes, urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total proteins, albumins, globulins and complete blood count (CBC) as well as urine sediment and 24h protein were within normal range.

The glycemic profiles during hospitalization were improving

The insulin doses were titrated during hospitalization and the final dosage before discharging the patient was NovoRapid 4+5+4 IU and Levemir 12 IU at night. At that time sufficient glycemic control was achieved. Follow-ups were planned at intervals of 1–2 weeks depending on the glucose levels.

GDM is defined as any degree of glucose intolerance with the onset or at the first detection during pregnancy [6]. The definition applies whether insulin or only diet modification is used for treatment, and whether or not the condition persists after pregnancy.

Early screening and proper treatment could play an important part in the course of the patient's GDM in the presented case, especially considering the fact that she had nine consecutive spontaneous abortions. In addition to this, a family history of T2DM is another risk factor for GDM in the case of our patient. Studies have shown that patients with family history of T2DM are at higher risk of GDM than those without. In this unusual case, which is considered as a GDM with high risk, no insulin therapy had been started during previous pregnancies, so we managed to achieve the goal with insulin. This could be one of the factors that could help a normal pregnancy and delivery. Frequently patients with high risk of developing GDM are not taken seriously by some specialists. The discussion should be focusing on early screening and proper treatment for GDM.

Conclusion. This is the case report of a GDM in a high-risk patient. However, the patient had 9 spontaneous abortions and probably had not been treated appropriately during this whole period. Early detection of hyperglycemia as well as early insulin treatment could be one of main factors for successful pregnancy and delivery. The risk of miscarriage is higher in women with

poor glycemic control compared to those with good glycemic control (9% vs 29 %), [5]. At her 21st gestational week patient's glucose levels were compensated on insulin therapy and she is currently feeling well.

It is well recognized that established GDM is an important risk factor for several serious adverse pregnancy outcomes and the risk is greater if glycemic control is poor. Consequently, screening high-risk women for undiagnosed diabetes in the first trimester (before 20 weeks gestation) as well as treatment with insulin is advisable.

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SUMMARY

BENEFITS OF EARLY SCREENING AND PROPER TREATMENT IN PATIENT WITH SIGNIFICANT RISK FACTORS FOR GESTATIONAL DIABETES MELLITUS (CASE REPORT)

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Gestational diabetes mellitus (GDM) occurs in 2–9% of all pregnancies. Evidence suggests that the use of insulin in treating hyperglycemia in GDM patients reduces the risk of perinatal morbidity. Pregnancy is an exciting time in a woman's life. However, once patient is diagnosed with GDM, she will be managed more intensively. GDM is managed using diet and exercise but one in six women with GDM requires insulin.

A 35-year-old woman at the 14th gestational week of her tenth pregnancy was seen for routine prenatal care. She had the history of nine consecutive spontaneous abortions. Patient was hospitalized and based on the revealed glucose values insulin therapy was initiated with long-acting insulin analogue - Levemir and rapid-acting insulin analogue - NovoRapid. Patient's diabetes

was compensated on insulin therapy. Follow-ups were planned at intervals of 1–2 weeks depending on the glucose levels.

This is the case report of a GDM in a high-risk patient. She's at the 21st gestational weeks and has passed "delicate weeks". At her 21st week of gestation patient's glucose levels are compensated on insulin therapy and she is feeling well.

In this unusual case report, no insulin therapy had been started during previous pregnancies, so we managed to achieve a good glycemic control with insulin treatment. This could be one of the factors that could help a normal pregnancy and delivery. The discussion should be focusing on early screening and proper treatment for GDM.

Keywords: Gestational diabetes mellitus, pregnancy.

РЕЗЮМЕ

РАННИЙ СКРИНИНГ И ЛЕЧЕНИЕ ПАЦИЕНТОВ С РИСК-ФАКТОРАМИ РАЗВИТИЯ ГЕСТАЦИОННОГО ДИАБЕТА (СЛУЧАЙ ИЗ ПРАКТИКИ)

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Гестационный диабет беременных встречается в 2-9% случаев. Доказано, что инсулинотерапия понижает риск перинатальной смертности. В случае гестационного диабета необходим строгий контроль беременной на протяжении всей беременности. Во время гестационного диабета беременная должна соблюдать диету и увеличить физическую нагрузку. Известно, что из 6 беременных с гестационным диабетом одна нуждается в инсулинотерапии.

35-летняя женщина с гестационным диабетом обратилась в клинику на 14 неделе беременности. Данная беременность была 10, предыдущие 9 заканчивались спонтанным выкидышем. Ввиду гипергликемии назначена инсулинотерапия аналогом человеческого инсулина ультракороткого действия – новорапидом и аналогом человеческого инсулина ультрапродлённого действия – левемиром. На фоне инсулинотерапии достигнута компенсация гликемии. Последующие визиты пациентки к эндокринологу спланированы с интервалом 1-2 недели в зависимости от показателей гликемии.

Представленный клинический случай подчеркивает значимость своевременной диагностики гестационного диабета и его адекватного ведения. Назначение инсулинотерапии обеспечило нормальное течение беременности и физиологические роды. Предполагается, что предыдущие 9 спонтанных выкидышей связаны с гипергликемией. Автор статьи считает целесообразным проведение обширной дискуссии по вопросу лечения и скрининга гестационного диабета.

რეზიუმე

გესტაციური დიაბეტის რისკის ფაქტორების მქონე პაციენტების ადრეული სკრინინგი და მკურნალობა (კლინიკური შემთხვევა)

ვ. ლიმანი

ენდოკრინოლოგიის, დიაბეტის და მეტაბოლური დარღვევების საუნივერსიტეტო კლინიკა,სკოპიე; PHI ცენტრალური ჰოსპიტალი "8th of September," სკოპიე,მაკედონია

გესტაციური დიაბეტი ყალიბდება ორსულობის 2-9%-ში. ინსულინოთერაპია გესტაციური დიაბეტის დროს ამცირებს პერინატალური სიკვდილობის რისკს. გესტაციური დიაბეტის დიაგნოზის შემთხვევაში აუცილებელია დიაბეტის ინტენსიური მართვა. გესტაციური დიაბეტის მართვა ძირითადად ხდება დიეტოთერაპიითა და ფიზიკური დატვირთვის გაზრდით, თუმცა სტატისტიკურად ექვსიდან ერთ ქალს ესაჭიროება ინსულინოთერაპია.

35 წლის ქალბატონმა მიმართა კლინიკას კონსულტაციისთვის მე-14 გესტაციურ კვირაზე. აღნიშნული ორსუ-

ლობა მისთვის იყო მეათე,ცხრა მიყოლებული სპონტანური აბორტის შემდეგ. მოხდა პაციენტის ჰოსპიტალიზაცია და გლიკემიის მაჩვენებლებიდან გამომდინარე დაწყებული იყო ინსულინოთერაპია ულტრაგახანგრძლივებული მოქმედების ინსულინის ანალოგ - ლევემირითა და ულტრახანმოკლე მოქმედების ინსულინის ანალოგ - ნოვორაპიდით. პაციენტის დიაბეტი წარმატებით დაკომპენსირდა ინსულინოთერაპიაზე. შემდგომი დაკვირვების ვიზიტები, გლიკემიის დონის გათვალისწინებით, დაიგეგმა 1–2 კვირის ინტერვალით. აღნიშნული შემთხვევა მეტად საინტერესოა, ვინაიდან წარსული ორსულობების დროს არც ერთ შემთხვევაში არ მომხდარა პაციენტის ინსულინით მკურნალობა. დაიგეგმა გლიკემიის მაჩვენებლების მოწესრიგება ინსულინოთერაპიით, რაც გახდა ორსულობის ნორმალური მიმდინარებისა და მშობიარობის საწინდარი. ავტორებს მიზანშეწონილად მიაჩნია გესტაციური დიაბეტის ადრეულ სკრინინგსა და შესაბამის მკურნალობასთან დაკავშირებით ჩატარდეს ფართო დისკუსია.

WEIGHT LOSS IN A YOUNG PATIENT WITH TYPE 2 DIABETES: CHALLENGES OF DIABETES MANAGEMENT USING ONLINE PROGRAM OF GOOD NUTRITION (CASE REPORT)

Krylov V.

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Obesity is a serious disease that provokes a large number of concomitant diseases and conditions, such as cardiovascular diseases, hypercholesterolemia, impotence, obstructive sleep apnea, certain types of cancer, osteoarthritis and depression. In the Russian Federation 59.8% of the adult population (>20 years old) are overweight and 26.5% are obese [1]. In many cases patients do not have an opportunity to consult the doctor-endocrinologist or a nutrition specialist; besides, during the visit it is not always possible to discuss all the aspects, and sometimes, some information is forgotten by patients themselves. Because of that, we created a "step-by-step online nutrition system" that helps a patient to maintain motivation after an appointment in order to change the attitude of people towards proper nutrition [2].

Case report. A 31-year-old male with a history of obesity, type 2 diabetes mellitus (T2DM) and hypercholesterolemia came to our clinic for medical weight-loss management. He also complained of decreased libido. According to his initial anthropometric measurements, his weight was 193 kg, height was 181 cm, and body mass index (BMI) was 58 kg/m^2. His HbA1C level was 7.1% and low-density lipoprotein cholesterol (LDL-C) - 5.1 mmol/L. The patient had begun gaining weight when he was 16 years old. Fifteen years ago, he was diagnosed with T2DM and hypercholesterolemia. His has a family history of diabetes, cardio-vascular disease and obesity. His primary care physician (PCP) prescribed a combination therapy with sulfonylurea and metformin (4 mg and 500 mg per day, respectively). For the management of dyslipidemia, the patient was taking simvastatin 10 mg per day.

For approximately 15 years the patient was inactive, followed by an unsuccessful attempt of playing tennis 2 years ago with a personal trainer. His diet has been high in fat and calories.

He works at an IT company as an IT technologist. His breakfast on the way to work consisted of bagels and burgers; brunch – of burgers or sausages. For lunch he has at least one pepperoni pizza. He often has chicken nuggets and burgers at the end of his working day. He regularly overeats and reaches excessive fullness. He and his friends eat out 2 to 3 times per week (pic. 1) Usually he has 2-3 alcoholic drinks per weak with excessive amount of soda and juices. Patient is a former smoker.

Pic. 1. Examples of typical meal examples consumed prior to enrolling into the program

We created a "step-by-step online nutrition system" that helps patient by watching video lessons to gradually form good habits about proper nutrition, without starvation, stress and debilitating physical exertion. Unfortunately, patients do not have even basic information about nutrition. To become an expert in any field, one must go through a long learning curve. The same is true about nutrition. For example, during the first week the patient learns to eat proper breakfast, next week refuses fried food, makes an effort to use an oven, quench without oil and drink water, tea and coffee, instead of sugary drinks, while still not changing his usual diet. Respectively, step-by-step, without stress and special efforts, patients form lifetime eating habits.

At the initial visit, the patient was advised to perform bariatric surgery but he refused. Afterwards, we advised him to start a low-calorie, low-fat, and low rapid-digested carbohydrate diet, in addition to walking just for 12 minutes per day.

In order to educate our patient about good nutrition, physical activity and the need of sun exposure we used an online system based on the video lessons, full of humor, pictures, and cartoons. Even one month of watching the short educational movies was sufficient for the patient to form the habits of healthy eating including restriction of fat and digestible carbohydrates and increase of the daily consumption of low-fat dairy products, slow carbohydrates, protein and fiber (pic. 2) [3]. His endocrinologist was regularly available for any questions and inquiries that the patient might have had.

Pic. 2. Typical healthy meal examples being consumed as a result of following the program recommendations

In order to avoid hypoglycemia due to reduced carbohydrate intake and weight loss, we replaced sulfonylurea with liraglutide 0.6 mg subcutaneously with up-titration to 1.2 mg per day after one week. The dose of metformin was increased to 1000 mg twice per day.

After 4 weeks from initiating recommended diet and physical activity the patient has lost 13 kg. His blood pressure was well controlled at 120/65 mm Hg. The dose of liraglutide was increased to 1.8 mg.

After Six weeks from treatment he lost additional 9 kg. His blood glucose, blood pressure and heart rate remained well controlled.

On the next follow-up visit 4 weeks later, the patient reported an additional loss of 8 kg and compliance with diet, exercise, and medications. His blood pressure remained well controlled, HbA1C decreased to 6.1%, and LDL was 3.2 mmol/l.

After several months the patient came to the clinic with the complaints of persistent hunger and urge of snacking. Liraglutide was further increased to 2.4 mg per day, which after 4 weeks resulted in

additional weight loss without feeling of hunger and snacking, with well controlled blood glucose [4]. After 8 months of treatment the patient has lost 58 kg in total, and reached 135 (pic. 3) kg from 193 (pic. 4); His metabolic characteristics have markedly improved, with HbA1C -5.6%, and LDL-C - 2.9 mmol/L; Moreover, patient had a motivation to continue weight loss program.

Pic. 3. Patient in 8 months after the program initiation

Pic. 4. Patient before enrolling into the program

Conclusion. Our case showed that in 8-month period the patient with BMI - 58 kg/m^2 and T2DM was able to lose 30% of his initial body weight with a low-carbohydrate diet, increased exercise and proper medications. Sulphonylurea - glymepiride was gradually reduced and replaced with increased doses of metformin and liraglutide.

Today, we live in a world of high technologies and lack of time. It is very important to know how to deliver proper information to an individual patient. Accordingly, we need to improve the quality of information delivery system, including using online technologies to improve the quality and duration of life of our patients.

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SUMMARY

WEIGHT LOSS IN A YOUNG PATIENT WITH TYPE 2 DIABETES: CHALLENGES OF DIABETES MANAGEMENT USING ONLINE PROGRAM OF GOOD NUTRITION (CASE REPORT)

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height - 181 cm, and body mass index (BMI) - 58 kg/m^2) patient had morbid obesity. In order to educate our patient about good nutrition, physical activity and the need of sun exposure we used an online system based on the video lessons, full of humor, pictures, and cartoons. Even one month of watching the short educational movies was sufficient for the patient to form the habits of healthy eating, including restriction of fat and digestible carbohydrates and increase in daily consumption of low-fat dairy products, slow carbohydrates, protein and fiber. Endocrinologist was regularly available for any questions and inquiries that the patient might have had. In addition to the dietary recommendations subcutaneous liraglutide 2.4 mg daily was initiated. After 8 months of treatment the patient has lost 58 kg and reached the body weight of 135 kg; moreover, he had motivation to continue losing weight.

Keywords:obesity, good nutrition, diabetes mellitus.

РЕЗЮМЕ

ПОТЕРЯ ВЕСА У МОЛОДОГО ПАЦИЕНТА С САХАРНЫМ ДИАБЕТОМ ТИПА 2: МЕНЕДЖМЕНТ ДИАБЕТА С ИСПОЛЬЗОВАНИЕМ ОНЛАЙН ПРОГРАММЫ ЗДОРОВОГО ПИТАНИЯ (СЛУЧАЙ ИЗ ПРАКТИКИ)

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Мужчина, возраст 31 год, с ожирением, сахарным диабетом типа 2 и гиперхолестеринемией обратился в клинику для снижения веса. При обследовании: вес 193 кг, рост 181 см, индекс массы тела – 58 кг/м^2. С целью обучения пациента правильному питанию, необходимости физической активности и инсоляции, использована онлайн система, основанная на видео уроках, анимационных и других иллюстрациях. Спустя один месяц после просмотра коротких обучающих видеороликов у пациента сформировалась привычка правильного питания, ограничение жирной пищи и легкоусвояемых углеводов, повышение потребления кисломолочных продуктов, трудноусвояемых углеводов, белка и клетчатки. В случае возникновения любых вопросов, пациент имел возможность консультироваться со своим врачом-эндокринологом. В дополнение к рекомендациям по питанию, пациенту назначен лираглутид 2,4 мг в день в виде подкожных инъекций. Спустя 8 месяцев после лечения, пациент похудел на 58 кг и достиг 135 кг, вместо изначальных 193 кг, сохраняя мотивацию к дальнейшему снижению веса.

რეზიუმე

შაქრიანი დაიბეტი ტიპი 2-ით ახალგაზრდა პაციენტის წონის კლება: დიაბეტის მართვა ჯანსაღი კვების სწავლების ონლაინ პროგრამის გამოყენებით (კლინიკური შემთხვევა)

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წონის კლების მიზნით 31 წლის მამაკაცმა შაქრიანი დიაბეტი ტიპი 2-ით, ჰიპერქოლესტერინემიით და სიმსუქნით მიმართა კლინიკას. პაციენტი იწონიდა 193 კგ-ს, 181 სმ სიმაღლის პირობებში, მისი სხეულის მასის ინდექსი შეადგენდა 58 კგ/მ^2. პაციენტისთვის ჯანსაღი კვების, ფიზიკური დატვირთვისა და ინსოლაციის სწავლების მიზნით გამოყენებული იყო ონლაინ სისტემა, დაფუძნებული იუმორით, ანიმაციითა და სურათებით გაჯერებულ ვიდეო გაკვეთილებზე. ვიდეო გაკვეთილების ჩატარებიდან ერთი თვის თავზე პაციენტს გამოუმუშავდა ჯანსაღი კვების ჩვევები: ცხიმიანი საკვების და ადვილადათვისებადი ნახშირწყლების შეზღუდვა და რძემჟავე პროდუქტების, რთულადათვისებადი ნახშირწყლების,ცილითა და უჯრედისით მდიდარი საკვების

მოხმარების გაზრდა. ნებისმიერი კითხვის შემთხვევაში ონლაინ სისტემის მეშვეობით პაციენტი უკავშირდებოდა უშვალოდ მის მკურნალ ექიმ-ენდოკრინოლოგს. კვებითი რეკომენდაციების გარდა პაციენტს დაენიშნა ლირაგლუტიდი 2.4 მგ/დღეში ინიექციის სახით, კანქვეშ. მკურნალობის აღნიშნული რეჟიმიდან 8 თვეში პაციენტმა დაიკლო 58 კგ და მისი წონა 193-დან შემცირდა 135 კგ-მდე. ამას გარდა, პაციენტი მოტივირებული იყო გაეგრძელებინა წონის კლების პროგრამა.

ASSOCIATION OF DIABETES COMPENSATION WITH SLEEPING HABITS AND WELL-BEING IN PATIENTS WITH DIABETES MELLITUS

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Diabetes Mellitus (DM) is one of the most common diseases encountered by the population worldwide, with high social and economic burdens. The prevalence of DM and obesity has increased dramatically over the last decade [6]; especially the age of diabetes onset has tendency to decrease [14]. Both diseases play a major well-established role in development of cardiovascular event [12; 13], which is known to be a leading cause of death worldwide. Thus, DM is a social, economic and multidisciplinary pathology, requiring special attention of public healthcare experts.

Sleep is a physiologic process of the body, when the metabolism is decreased to give a reparative time for glycogen storing and peptide synthesis [10]. In healthy individuals normal sleep is associated with reduction of glucose utilization in the brain and other metabolically active tissues [18]. Healthy sleep gives "a resting opportunity" to the body to recover the whole metabolic, energetic and other resources, expended during the day [2]. It has been reported that average sleep duration has decreased during the last several decades [18]. Some cross-sectional and longitudinal studies reveal a link between short sleep duration and the prevalence of type 2 DM, as well as the increased risk of obesity, and development of cardiovascular events, even in childhood [7,8]. Sleep deprivation in healthy individuals is shown to impair their glucose homeostasis [11]. Adequate sleep duration in adults is estimated to be 7-8 hours, and in children – 8-9 hours per night. During the last forty-fifty years sleep duration seems to have decreased approximately by 2 hours per night, as a result of our lifestyle, workload, social activities and access to technology, particularly to "blue-screen" [18]. The overwhelming majority of works shows the association of sleep duration with abnormalities in patients with obesity and type 2 diabetes [10], but there is a lack of data about type 1 DM. Several social, economic and public health consequences due to chronic sleep deprivation, as well as obstructive sleep apnea (OSA) are described in the literature [1]. Moreover, in some investigations Continuous Positive Airway Pressure (CPAP) treatment was performed in diabetic patients with OSA [5] showing a significant improvement of not only HOMA-index, but also of fasting and nocturnal glucose metabolism, versus placebo [9]. However, the effect of CPAP therapy on metabolic syndrome is still controversial [4]. Comorbidities in patients with diabetes and sleep deprivation include eating and attention deficit disorders and cognitive impairment, especially in patients with recurrent and severe hypoglycemia. Some data suggest, that depressive symptoms and clinical depres-

sion are seen much more frequently than they are diagnosed and treated [15]. Screening for sleep disorders and obstructive sleep apnea should be routinely performed in patients, who are at high risk, including patients with obesity, diabetes and hypertension [1]. On the other hand, Surani S.R. [16,17] rises a question in his review: "it is the prime time to push for OSA or sleep disorders screening for every patient walking in outpatient clinic or hospital?". Stop-Bang questionnaire, Berlin or NAMES questionnaire can be used as a screening tool according to author's opinion [3].

Therefore, the aim of this work is to evaluate the association between diabetes compensation and sleep quality and quantity in patients with type 1 and type 2 diabetes. And in addition, to establish any potential association with "screen" time, physical activity and well-being.

Material and methods. Forty-nine patients with diabetes were included in the study. Glycated-hemoglobin (HbA1c) levels were measured, patients filled out sleep habit and self-assessment questionnaire, indicating the sleep duration, any "screen" time period during the day (phone, TV, computer), average weekly physical activity and etc… Both type 1 and type 2 DM patients were examined. They were divided into two groups according to the type of diabetes: group 1 consisted of patients with type 1 DM (n=28), and group 2 consisted of patients with type 2 DM (n=21). They were matched by sex, age and diabetes duration. HbA1c < 7.5 was considered as a diabetes compensation. Statistical analyses were performed to determine the significance of findings. Non-parametric Pearson's chi-square test (Yates corrected if table 2x2) was used. Rates and ratios were calculated; where appropriate, z-test or t-test was applied. In all cases null hypothesis was rejected if $p < 0.05$.

Results and discussion. In total, 49 patients were enrolled in the study. The male/female ratio of investigated patients was 49%-51% (0.96), in the group 1 - 14/14 (1.0), and in the group 2 –10/11 (0.91). The average age was 32 years (range: 6 to 78): 15.46 and 54.3 in the group 1 and 2, respectively. According to the self-assessment questionnaire about patient's opinion on association of sleep duration with well-being, 40% of respondents indicated no connection. Based on this we can conclude, that they do not pay enough attention to the link between these two factors. Although, as shown in the Table 1, positive answer rate is significantly higher in the group 2 ($p < 0.05$). The mean sleep duration between two groups was also significantly ($p<0.05$) different, showing less night sleep time in the group 2 (Fig).

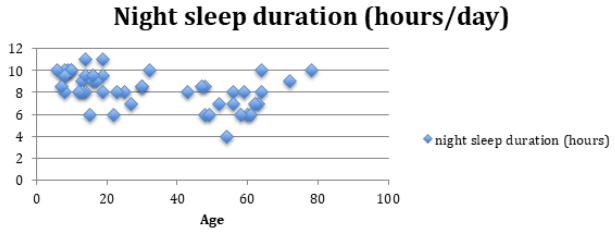

Fig. Night sleep duration by age in two groups of investigated patients with type 1 and type 2 DM

At the same time presence of nervousness showed no significant differences between two groups and was equally indicated in the questionnaire in both groups ($p>0.05$). This could be interpreted, that younger patients do not link their nervousness with the sleep duration and daily "screen time", but the link becomes evident with the age, although the difference of "screen" time between groups showed no significance ($p>0.05$). Daily spent "screen" time is found to have very weak correlation with age ($r=-0.194$), although the mean "screen" time was established as 5.35 hours/day. 38.8% of respondents indicated insomnia, but, as expected, only 2% of them indicated somniferous tablets intake. Most of respondents indicated sleep interruption (62%), out of which in 64.5% it was associated with nocturia ($p<0.001$). 49% of patients had nervousness, but, interestingly, 70.8% of them had both sleep interruption and nervousness ($p<0.05$). These data is indicative of a link between sleep duration, sleep quality (interruption) and nervousness, which was significantly high in the group 2 ($p<0.05$).

Another question is whether this reduction in sleep quantity and quality is associated with diabetes and its duration. We investigated the association of mean HbA1c and "screen" time period, average weekly physical activity, sleep duration, diabetes duration and age. No association was

Table. Comparison of several variables between two groups

	Group 1 (n=28)	Group 2 (n=21)	P value
Having insomnia (yes)	10,7%	76,2%	0.02
Mean night sleep duration (hours)	8.94	7.42	0.01
Mean weekly physical activity (hours)	12.4	12.1	0.95
Daily "screen" time (hours)	6.39	3.82	0.27
Sleep interruption (yes)	39.3%	95.2%	0.03
Link of well-being with sleep quality and quantity (yes)	33.3%	90.5%	0.04
Link of well-being with "screen" time (yes)	28.6%	47.6%	0.143
Nervousness (yes)	39.3%	61.9%	0.1
Diabetes mean duration (years)	5.2	8.67	0.27
Mean HbA1c (%)	8.5	8.98	0.22

found between diabetes compensation, duration and patients' age (p=0.208 and p=0.858, respectively). No connection between the mean HbA1c and mean "screen" time. Assessment of weekly physical activity time in groups 1 and 2 has revealed p=0.056 and p=0.686, respectively. It should be also mentioned, that weekly physical activity also showed no association with HbA1c levels. Probably this means, that our young patients with diabetes have similar physical activity as elders (p>0.05). But a significant association of diabetes compensation with sleep duration, as well as sleep interruption was found (p=0.02 and p=0.019). Based on these findings, we can assume, that sleep duration affects diabetes compensation and, vice versa, non-compensated diabetes may lead to nocturia, that result in sleep interruption and reduction in sleep duration, especially in group 2. Taking into account, that in contrast with HbA1c levels, sleep duration and insomnia were significantly different in two groups, it should be concluded, that compensation of DM in type 1 diabetic patients depends predominantly on the factors different from the sleep duration, sleep quality and "screen" time.

Conclusion. Association of diabetes compensation with sleep duration and quality is revealed, especially in patients with type 2 diabetes. More profound investigations should be conducted to evaluate the connection with sleep quality and quantity, as well as daily "screen" time in patients with type 1 diabetes.

In summery, physicians need to educate patients not only on the prevention of the risks of diabetes complications, but also on associations of diabetes with sleep disorders and cardiovascular disease prevention. Further investigations are needed to find out the approach of healthcare providers to preventative education. Each comorbidity of diabetes must be evaluated and the education of the patients should be concentrated on all of them as a whole and not separately as it is seen nowadays, because they are connected and exacerbate each other.

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SUMMARY

ASSOCIATION OF DIABETES COMPENSATION WITH SLEEPING HABITS AND WELL-BEING IN PATIENTS WITH DIABETES MELLITUS

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Recent data estimates that sleep deprivation and poor quality of night sleep have an impact on the incidence and prevalence of both obesity and type 2 diabetes, as well as cardiovascular events in all ages.

The aim of this work is to evaluate the association between diabetes compensation and sleep quality and quantity, comparing patients with type 1 and type 2 diabetes, as well as to establish any potential connection with "screen" time, physical activity and well-being. For this reason 49 patients with type 1 (n=28) and type 2 DM (n=21) were investigated. HbA1c levels were measured, and the patients filled out sleeping habits and self-assessment questionnaire. Association of sleep duration with the diabetes compensation was revealed ($p<0.05$), regardless of "screen" time and weekly physical activity ($p>0.05$). Significant difference in insomnia and sleep interruption was revealed between the two groups. The mean sleep duration between two groups was also significantly ($p<0.05$) different, showing less night sleep time in patients with type 2 diabetes. The mean "screen" time was established as 5.35 hours/day, but daily "screen" time was found having very weak correlation with age ($r=-0.194$). Presence of anxiety showed no significant difference between two groups and was equally indicated in the questionnaire in both groups ($p>0.05$). Thus, these sleep-relationships should be addressed rather together with the patients' well-being and quality of life than separately, and should be carefully assessed in primary care and endocrinology clinics.

Keywords: diabetes mellitus, sleep duration, sleep habit, diabetes compensation.

РЕЗЮМЕ

ЗАВИСИМОСТЬ КОМПЕНСАЦИИ ДИАБЕТА С САМОЧУВСТВИЕМ И ХАРАКТЕРОМ СНА У БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ ТИПА 1 И 2

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Согласно последним данным, бессонница и плохой сон влияют на заболеваемость и распространённость ожирения и сахарного диабета типа 2, а также кардиоваскулярные осложнения в любом возрасте.

Целью данного исследования явилось определение корреляционной связи между компенсацией диабета, количеством и качеством сна, проведение сравнительной оценки и выявление потенциальной связи компенсации диабета с периодом времени, проведенного у экранов (screen time), физической активностью и самочувствием у больных диабетом типа 1 и 2.

С этой целью исследовано 49 больных сахарным диабетом типа 1 (n=28) и 2 (n=21). Проведен опрос о самочувствии, характере и особенностях сна, определен гликированный гемоглобин (HbA1c). Выявлена статистически достоверная связь между компенсацией диабета и продолжительностью сна ($p<0,05$), в отличие от “screen time” и физической нагрузки ($p>0,05$). Определена достоверная разница между группами по параметрам бессонницы, средней продолжительности и прерывистости сна ($p<0,05$). Средняя продолжительность сна в I группе была достоверно выше, чем во II ($p<0,05$). Средняя продолжительность времени, проведенного у экрана, составила 5,35 час/день, однако она показала слабую корреляцию с возрастом ($r=-0,194$). Различий по показателям нервозности в группах не выявлено ($p>0,05$).

Согласно данным исследования, в эндокринологических клиниках и первичном звене здравоохранения вышеописанные параметры и сахарный диабет следует оценивать не отдельно, а в совокупности с самочувствием и качеством жизни пациентов.

რეზიუმე

დიაბეტის კომპენსაციის კავშირი ძილის ჩვევებთან და კეთილდღეობასთან შაქრიანი დიაბეტი ტიპი 1 და 2-ით პაციენტებთან

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ერევნის სახელმწიფო სამედიცინო უნივერსიტეტი, [1]ენდოკრინოლოგიის დეპარტამენტი; [2]ფარმაცევტული მენეჯმენტის დეპარტამენტი, სომხეთი

უახლესმა კვლევება აჩვენა, რომ არასრულფასოვანი ძილი ყველა ასაკობრივ ჯგუფში დაკავშირებულია ისეთ დაავადებებთან, როგორიცაა სიმსუქნე, შაქრიანი დაიბატი ტიპი 2 და გულ-სისხლძარღვთა დაავადებები.

კვლევის მიზანს წარმოადგენს კომპენსირებულ დიაბეტსა და ძილის ხარისხობრივ და რაოდენობრივ მახასიათებლებს შორის კავშირის შესწავლა, ისევე როგორც ეკრანთან გატარებულ დროს, ფიზიკურ დატვირთვასა და კეთილდღეობას შორის შაქრიანი დიაბეტით ტიპი 1 და ტიპი 2-ით პირებში. კვლევაში ჩართული იყო 49 პაციენტი შაქრიანი დიაბეტის დიაგნოზით. დიაბეტის ტიპის მიხედვით პაციენტები განაწილდა ორ ჯგუფად (ტიპი 1 - n=28, ტიპი 2 - n=21). ყველა პაციენტს განესაზღვრა HbA1c. თითოეულმა მათგანმა შეავსო ძილის კითხვარი. კვლევის შედეგად გამოვლინდა ძილის ხანგრძლივობასა და დიაბეტის კომპენსაციას შორის კავშირი

(p<0.05), ეკრანთან გატარებული დროსა და კვირის მანძილზე ფიზიკურ დატვირთვის რაოდენობის მიუხედავად (p>0.05). ინსომნიასა და წყვეტილ ძილთან დაკავშირებით ორ ჯგუფს შორის გამოვლინდა მნიშვნელოვანი განსხვავება. ჯგუფები განსხვავდებოდნენ ძილის საშუალო ხანგრძლივობითაც (p<0.05); პაციენტებს შაქრიანი დიაბეტი ტიპი 2-ით უფრო ნაკლები დროის მანძილზე ეძინათ ღამის საათებში. ეკრანთან გატარებული საშუალო დრო შეადგენდა 5.35 სთ/დღეში. ამ პარამეტრს ძალიან სუსტი კავშირი ჰქონდა ასაკთან (r=-0.194), ნერვული აგზნებადობა ერთნაირი სიხშირით გვხვდებოდა ორივე ჯგუფში (p>0.05). ჩატარებული კვლევის შედეგებიდან გამომდინარე ძილის დარღვევების შეფასება უნდა მოხდეს არა განცალკევებულად, არამედ პაციენტის კეთილდღეობის და ცხოვრების ხარისხის შეფასებასთან ერთად, როგორც ოჯახის ექიმის, ისე ენდოკრინოლოგის მიერ.

FOURNIER'S GANGRENE, A RARE COMPLICATION OF DIABETES MELLITUS (CASE REPORT)

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First time Fournier's Gangrene (FG), was reported by dermatologist Bauriene in 1764. The name of this condition is associated with dermatovenereologist Jean Alfred Fournier, who was the first to characterize it as scrotal pathology in 1883 [1]. Interestingly, Avicenna had described the same disease in his book centuries ago [2]. Fournier has described the disease as a fulminant hepatitis of penis and scrotum, especially targeting healthy young males, starting suddenly and progressing quickly, with an uncertain cause. FG is characterized by the necrotizing fasciitis of perinea, genital and perianal areas, typical for synergistic polymicrobial infection. Only 600 cases have been reported worldwide between 1996 and 2006 [1]. Despite being a very rare disease, because of its insidious characteristics it has a high mortality and thus requires urgent surgery. Any delay on its diagnosis and treatment can be fatal, therefore a thorough investigation of the symptoms is important. Today, FG is mostly diagnosed in 50-60 year-old male patients. Men have a 10 times higher incidence of developing FG, the reason is an easier drainage of female perinea through vaginal path, reducing the chances of occurrence [3]. In women, the most frequent cause is anorectal infection [4]. Currently, in most FG cases the cause can be identified. Only 10% of FG cases remain uncertain [3,5]. Infections close to gateway zones like scars, burns, incisions; anorectal infections, genitourinary infections, abscess, anal fissures, colon perforations line up among the most frequent causes. It is also reported that in some cases FG can occur secondary to rectal carcinoma and diverticula [6]. It can also accompany some cases with compromised immune system (diabetes mellitus, chronic alcoholism) [5].

Case report. The presented case reports on 54-years old patient with T2 Diabetes mellitus who, due to hypoglycemic episodes on Insulin therapy, was treated with oral anti-hyperglycemic medications (Metformin). Because of end-stage renal disease, patient was on hemodialysis treatment. Moreover, he had various comorbid conditions: arterial hypertension, history of acute myocardial infarction, dilative cardiomyopathy, amaurosis and peripheral neuropathy. The patient

was diagnosed with early stage Fournier's gangrene during hospitalization at our department based on the symptoms, such as the small black spots, swelling and pain in the genital area (Fig.). Long acting Insulin was initiated at the admission. He stated that he had the history of alcohol use.

The patient's laboratory results were as follows: leukocytes: 6.1..18.9 /mm3, Hb: 95..77 gr/dl, platelets: 118..67 /mm^3, CRP: 36 mg/dl, urea: 23.9 mg/dl, creatinine: 4.9 mg/dl, ALT: 3 U/L, AST: 7 U/L, AP 41 U/L. His liver function tests were within normal ranges and his abdominal ultrasonography revealed enlarged kidney diameter as a consequence of long-term diabetes mellitus. Due to the increased leucocyte count and episodes of fever during hemodialysis, blood culture was taken, which was positive for Staphylococcus coagulase negative and broad-spectrum antibiotics were administered. Because of sepsis with positive hemoculture, the urologist was consulted regarding scrotum and penis black spots, and his decision was to perform a preoperative debridement as the first step of treatment. First, the necrotic skin tissue was removed completely. After two days we arranged a reconstruction surgery; the patient had cerebrovascular stroke, which worsened his health, resulting coma and death.

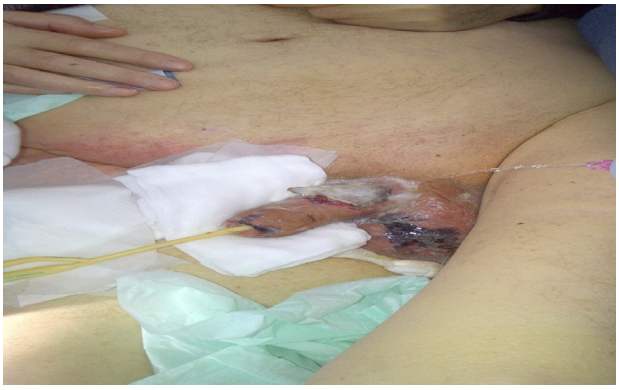

Fig. Fournier's gangrene

What is the link between diabetes and gangrene? Patients with diabetes have an increased risk of developing gangrene. High blood glucose levels can damage nerve fibers, which may cause a loss of sensation in the affected area. This can make it easier to develop an injury. High blood glucose can also affect blood vessels and limit the blood flow to the lower body and feet. This causes a chain reaction. If patient's feet aren't getting enough circulation, fewer infection-fighting cells are making their way to feet. If lacking these infection-fighting cells, any wounds can take longer to heal. Any potential wounds are also more likely to be infected. Other risk factors to consider include: peripheral arterial disease, atherosclerosis and Raynaud's phenomenon. Minor infections in people with weakened immune systems, due to diabetes, chemotherapy, HIV, malnutrition and kidney failure can also lead to gangrene.

Conclusion. Diabetes mellitus represents a worldwide pandemic disease, which induces number of serious complications, such as cardiovascular disease, chronic kidney diseases, resulting in the end-stage renal disease requiring hemodialysis, cerebrovascular disorders, various types of neuropathies and frequent infections. One of the rarest but very serious and urgent conditions, which appears as a complication in patients with Diabetes mellitus is Fournier's gangrene, which represents rapid and progressive fulminant infection of superficial tissue of the scrotum and penis. As a result of the improved approach of multimodality therapy, the mortality from FG in the hospital setting has decreased to 10%. In our experience, FG with diabetes mellitus always poses a greater challenge for reducing morbidity and mortality. It is recommended to adopt a multidisciplinary approach in treating a case of FG to achieve a low morbidity and mortality, especially in presence of the comorbidity like diabetes and multi organ failure.

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SUMMARY

FOURNIER'S GANGRENE, A RARE COMPLICATION OF DIABETES MELLITUS (CASE REPORT)

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The presented case reports on 54-years old patient with T2 Diabetes mellitus who, due to hypoglycemic episodes on Insulin therapy, was treated with oral anti-hyperglycemic medications. Patient was on hemodialysis due to the stage 5 chronic kidney failure and had various comorbid conditions: arterial hypertension, history of acute myocardial infarction, dilative cardiomyopathy, amaurosis and peripheral neuropathy. Besides his complicated medical history, patient developed an early stage of Fournier's gangrene. Diabetes mellitus represents a worldwide pandemic disease which induces a number of serious complications, such as cardiovascular disease, chronic kidney diseases, resulting in the end-stage renal disease requiring hemodialysis, cerebrovascular disorders, various types of neuropathies and frequent infections. One of the rarest but very serious and urgent conditions, which appears as a complication in patients with Diabetes mellitus, is Fournier's gangrene, which represents rapid and progressive fulminant infection of superficial tissue of the scrotum and penis.

Keywords: T2 Diabetes mellitus, CKD stage 5 on hemodialysis, Fournier's gangrene.

РЕЗЮМЕ

ГАНГРЕНА ФУРНЕ – РЕДКОЕ ОСЛОЖНЕНИЕ САХАРНОГО ДИАБЕТА (КЛИНИЧЕСКИЙ СЛУЧАЙ)

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Сахарный диабет - широко распространённое заболевание, вызывающее такие серьёзные

осложнения, как сердечно-сосудистые, хронические почечные заболевания вплоть до последней стадии почечной недостаточности и необходимости проведения гемодиализа, цереброваскулярные заболевания, разные типы нейропатии и частые инфекции.

Приводится клинический случай мужчины, больного сахарным диабетом типа 2 в возрасте 54 лет, который ввиду частых эпизодов гипогликемии на фоне инсулинотерапии, находился на пероральной антигипергликемической медикаментозной терапии. Больному ввиду хронической почечной недостаточности V стадии проводились процедуры гемодиализа. При обследовании выявлены множественные осложнения: артериальная гипертензия, перенесенный инфаркт миокарда, кардиомиопатия, амавроз и периферическая нейропатия. Кроме того, выявлено одно из самых редких, хотя очень серьезных и острых осложнений - гангрена Фурне, для которой характерно распространение на скротуме и частях пениса, неожиданное начало и быстрое прогрессирование.

Пациенту удалена некротическая ткань кожи. Спустя 2 дня проведена реконструктивная операция, состояние больного ухудшилось в результате цереброваскулярного инсульта, что вызвало кому и смерть.

რეზიუმე

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შ. მუჰარემი

ნეფროლოგიის ინსტიტუტი, შინაგან სნეულებათა დეპარტამენტი,
სტრუგა, მაკედონია

შაქრიანი დიაბეტი ფართოდ გავრცელებული დაავადებაა მსოფლიოში და იწვევს ისეთ სერიოზულ გართულებებს, როგორიცაა გულ-სისხლძარღვთა, თირკმლის ქრონიკული დაავადება, თირკმლის ბოლო სტადიის უკმარისობისა და ჰემოდიალიზის ჩატარების აუცილებლობით, ცერებრო-ვასკულური დაავადება, სხვადასხვა ტიპის ნეიროპათიები და ხშირი ინფექციები.

სტატიაში აღწერილია შაქრიანი დიაბეტი ტიპი 2-ით დაავადებული 54 წლის მამაკაცის კლინიკური შემთხვევა. პაციენტი ინსულინზე ჰიპოგლიკემიის ხშირი ეპიზოდების გამო მკურნალობდა პერორალური ანტიჰიპერგლიკემიური მედიკამენტებით. თირკმლის ქრონიკული უკმარისობის (V სტადია) გამო პაციენტი იმყოფებოდა ჰემოდიალიზზე. ამას გარდა, მას აღენიშნებოდა მრავალი სხვა გართულებები: არტერიული ჰიპერტენზია, გადატანილი მიოკარდიუმის ინფარქტი, კარდიომიოპათია, ამავროზი და პერიფერიული ნეიროპათია. მის რთულ სამედიცინო ანამნეზს დაემატა ფურნეს განგრენა.

ერთ-ერთი უიშვიათეს და სერიოზულ გართულებას წარმოადგენს ფურნეს განგრენა, რომელიც ლოკალიზდება სკროტუმსა და პენისის ნაწილებზე, იწყება მოულოდნელად და პროგრესირებს სწრაფად.

პაციენტს ამოკვეთეს კანის ნეკროზული ქსოვილი, 2 დღის შემდეგ ავადმყოფს ჩაუტარდა რეკონსრუქციული ოპერაცია, განვითარდა ცერებროვასკულარული ინსულტი, რამელმაც გამოიწვია მდგომარეობის გართულება და სიკვდილი.

WHICH FACTORS MAY AFFECT THE QUALITY OF LIFE IN PATIENTS WITH TYPE 1 DIABETES MELLITUS USING THE MEDTRONIC VEO CONTINUOUS SUBCUTANEOUS INSULIN INFUSION PUMP?

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Quality of life (QoL) in the course of a chronic disease is an important health outcome and its improvement represents the ultimate goal of all health interventions [1]. Type 1 Diabetes Mellitus (T1DM) is a complex disease with substantial impact on both lifestyle and health. It is a chronic disease, which follows those affected for the remainder of their lives and is associated with a drop in life- expectancy [2]. People with T1DM are required to make decisions in relation to their blood glucose levels that can pose difficulties for their everyday life. Hyperglycemia may lead to long-term diabetes related complications and the risk of developing hypoglycemia by insulin overdose. Hypoglycemia episodes contribute to substantial morbidity, and in extreme cases even mortality [3]. Moreover, patients with diabetes experience rates of depression that are higher than those found in the general population [4]. Besides the increased risk of acute or long-term complications, T1DM may have a negative impact on QoL because it is characterized by a high degree of self-management. Through the dietary requirements, self-medication, exercise and monitoring of blood glucose, T1DM often has a limiting effect on lifestyle [5]. Continuous Subcutaneous Insulin Infusion (CSII) is considered an effective therapeutic approach for T1DM. Over the last few years, technological advances in glucose monitoring, including real-time and retrospective Continuous Glucose Monitoring Systems (CGMS), have been proven very effective in optimizing glycemic control [6]. Although T1DM has been associated with a decrease in QoL in many studies [7-10], in literature there is limited information regarding the QoL in patients using CSII. The aim of the study was to investigate the QoL status and the impact of diabetes related factors on the QoL of patients with T1DM on CSII treatment, in a Greek urban population.

Material and methods. *Participants*

A cross-sectional study was conducted on 80 patients with T1DM using CSII. All subjects used the Medtronic Veo Continuous Subcutaneous Insulin Infusion Pump (MiniMed 530G, Medtronic Diabetes, Northridge, CA) combined with real-time CGM. It must be noted that the Medtronic Veo pump system offers an automatic insulin shut-off mechanism (Low Glucose Suspend - LGS), which can be activated in response to hypoglycaemia. The LGS system automatically suspends basal insulin delivery when the sensor glucose value reaches a preset threshold. The subjects had been attending specialized diabetes clinics for more than 1 year and were familiar with insulin pump therapy and the principles of self-adjustment of insulin regimen on the basis of blood glucose monitoring results. The follow-up of the study population was conducted at the public diabetes clinics (Alexandra) and a private (Hygeia) hospital. The study was carried out in accordance with the principles of the Declaration of Helsinki, as revised in 2013. All participants gave their written informed consent for study participation and the use of their data for research purposes. The participants' clinical characteristics are summarized in Table 1.

Assessment of study parameters

QoL was assessed using the patient self-administered EuroQol EQ-5D validated in Greek. It is a widely used two-part, generic measure of HRQOL developed by a multidisciplinary consortium of investigators from five European countries and includes five domains: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression [11]. Each domain was divided into three severity levels (from 1 to 3), corresponding to no problem, some problem, and

Table 1. Participants' demographic and clinical characteristics (data are expressed as mean ± SD)

Variable	Mean ± SD
n	80
Gender	43 female - 37male
Age	35.9 ±11.4 years
BMI	24.6 ± 3.5 kg/m^2
Duration of Diabetes	24.2 ± 10.3 years
Duration of Insulin Pump Use	7.1 ±3.9 years
HbA1c	7.7 ± 1.1 %
Total Daily Insulin Dose	46.4 ± 10 i.u
Basal / Bolus ratio	46.8 / 53.2 %
LGS activation	1.7 ± 1.6 times per day
Carbohydrate amounts entered into the pump / day	155 ± 75.2 grams

Table 2. Summary of the study results

Variable	Mean ± SD
Gold Score	2.8±1.5
Clarke Score	2.8±2.1
Hypoglycemia Fear Score	20.6 ±11.2
Number of Hypoglycemic episodes per week	4.3 ± 2.9
VAS score	68.7 ± 18.1
EQ index	0.79 ±0.24

extreme problem. The second part recorded the patient's self-rated health on a vertical visual analogue scale (EQ-VAS) from 0 to 100, where the endpoints are labelled 'The best health you can imagine' and 'The worst health you can imagine'. The VAS can be used as a quantitative measure of health outcome that reflect the patient's own judgement. Hypoglycemic episodes were evaluated with the assistance of the CareLink software data and by reviewing the patients' diaries. Hypoglycaemia expressed as number of episodes/ week. In addition, participants were asked to report the number of hypoglycemic episodes per week. A valid hypoglycemic episode was defined as blood glucose levels ≤70 mg/dl for ≥20 minutes or a blood glucose reading ≤70 mg/ dl. Hypoglycaemia Awareness was measured using the Clarke and the Gold Score questionnaires. The Clarke method [12] comprises of questions characterizing the patient's exposure to episodes of moderate and severe hypoglycemia. It also examines the glycaemic threshold for and symptomatic responses to hypoglycemia. A score of four and higher implies impaired awareness of hypoglycemia. The Gold method [13] poses the question "do you know when your hypos are commencing?" The respondent completes a 7-point Likert scale, with 1 representing "always aware" and 7 representing "never aware". A score of 4 or more implies impaired awareness of hypoglycemia. Fear of Hypoglycemia was measured using the worry subscale of the Hypoglycemia Fear Survey (HFS-W) [14]. It consists of fifteen items scored on a five point Likert scale from Never (0) to Always (4). Subscale scores are determined by adding item responses.

All statistical analyses were performed using SPSS statistical software 21.0 release (SPSS Inc., Chicago, IL, USA). Correlation and regression analyses were performed to examine the relationship between EQ index - EQ VAS scores and diabetes related factors. A p value of < 0.05 was considered statistically significant.

Results and their discussion. The results of the study are summarized in Table 2.

QoL was negatively correlated with Hypoglycemic episodes (r=-0.70, p<0.001), HbA1c (r=-0.048, p=0.036), the Hypoglycemia Fear Score (r=-0.50, p=0.017), as well as the Hypoglycemia Unawareness status (r=-0.44, p=0.03). Regression analysis revealed that both the higher number of hypoglycemic episodes (β=-0.822, p=0.02) and elevated HbA1c (β=-0.468, p=0.017) were significantly and independently associated with worse QoL.

Our study presents an evaluation of factors associated with the QoL in patinets with T1DM using CSII. The number of people using CSII therapy is increasing worldwide, and there is a great need to investigate the QoL status in this population. Although CSII use has been associated with numerous benefits, including improvements in glycemic control and low rates of hypoglycemic episodes, there is still big skepticism mainly because it requires attachment to a "foreign body" most of the time. In a Swedish general population QoL study the reported EQ-5D index ranged from 0.89 (20-29 years) to 0.74 (80-88 years). The mean score for people with diabetes was 0.74 (±0.024 SE) [15]. In a relevant study in patients with T1DM the mean EQ-5D score was 0.83 (range 0.79 to 0.87) [16]. The relatively big variations in EQ-5D score, between the different studies measuring the QoL, are mainly attributed to differences in the duration of diabetes between the study populations and the presence of diabetes complications. Regarding studies assessment of the QoL in patients on CSII, it must be noted that on several occasions, CSII is used in patients with diabetes complications, hypoglycemia unawareness or relatively unstable metabolic control. A recent study in UK conducted on 380 patients with T1DM (36% were on CSII), reported EQ-5D and VAS scores 0.8±0.02 (SE) and 73±1.2 respectively. In this study, patients with suboptimal glycemic control and recurrent hypoglycemia exhibited worse QoL scores [17]. In our study we found similar scores (EQ-5D 0.79±0.24 and VAS 68.7±18.1). Our study has revealed that increased levels of HbA1c and a greater frequency of hypoglycemia had a negative impact on the reported QoL of the patients. After regression analysis, only HbA1c and the number of hypoglycemic episodes per week remained independently related to QoL scores. The findings of our study are in agreement with previous research suggesting that QoL is significantly affected by hypoglycemia incidence and poor metabolic control [18-22]. Hypoglycemia episodes can have severe implications for everyday life including employment and productivity [23]. In addition, it has been shown that low glycemic levels can disrupt daily activities such as driving performance [24]. Regarding the impact of hyperglycemia on QoL, a relevant study from the Netherlands demonstrated that the presence of hyperglycemic complaints can decrease the EQ-5D score by 0.071 to 0.09 units [25]. Finally, our data provided indirect evidence that fear of hypoglycemia and its awareness are not major determinants of QoL in patients on CSII. Probably, this finding could be attributed to CGMS use, which seem to attenuate the fear of hypoglycemia.

In conclusion, our findings suggest that better metabolic control and better quality of life seem to be directly related. Achieving a better glycemic control could positively impact the QoL of these individuals. Prevention of hypoglycemia remains a major challenge in daily diabetes management. Although the physical aspects of the disease are important in determining QoL in patient with T1DM, further research on psychosocial aspects of everyday life, such as employment limitations, sexual life, physical activity, psychological well-being, sleep, and disease acceptance is needed to determine an overall evaluation of the QoL of patients with T1DM. Further studies must be carried out in order to elucidate whether CSII contributes to improvement in the QoL of people with T1DM.

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SUMMARY

WHICH FACTORS MAY AFFECT THE QUALITY OF LIFE IN PATIENTS WITH TYPE 1 DIABETES MELLITUS USING THE MEDTRONIC VEO CONTINUOUS SUBCUTANEOUS INSULIN INFUSION PUMP?

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Continuous Subcutaneous Insulin Infusion (CSII) is considered an effective therapeutic approach to the treatment of patients with Type 1 Diabetes Mellitus (T1DM). Literature offers limited information regarding the quality of life (QoL) in patients using CSII. The aim of the study was to investigate the impact of diabetes related factors on the QoL of patients with T1DM on CSII treatment, in a Greek urban population. A cross-sectional study was conducted on 80 patients with T1DM using CSII. [(Mean±SD) age: 35.9±11.4 years, duration of diabetes: 24.2±10.3 years, BMI: 24.6±3.5kg/m^2, duration of Insulin pump use: 7.1±3.9 years, HbA1c: 7.7±1.1%, gender: 37 males-43 females)]. QoL was assessed using the patient self-administered EuroQol EQ 5D validated in Greek. Correlation and regression analyses were performed to examine the relationship between EQ index - EQ VAS scores and diabetes related factors. Hypoglycemia Awareness was measured using Clarke and Gold Score questionnaires, Hypoglycemic Episodes were expressed as number of episodes per week and the Fear of Hypoglycemia was measured using the worry subscale of the Hypoglycemia Fear Survey (HFS-W). Results were as follows: Gold score: 2.8±1.5, Clarke score: 2.8±2.1, Hypoglycemia Fear Score: 20.6±11.2, Number of hypoglycemic Episodes per week: 4.3±2.9, VAS score: 68.7±18.1, EQ index: 0.79±0.24. In univariate analyses QoL was negatively correlated with Hypoglycemic episodes, HbA1c, Hypoglycemia Fear Score and Hypoglycemia Awareness status. After regression analysis, only HbA1c and the number of hypoglycemic episodes per week remained independently related to QoL scores. Prevention of hypoglycemia and glycemic control should be emphasized in order to improve QoL in patients with T1DM with CSII.

Keywords: quality of life, Type 1 diabetes mellitus, continuous subcutaneous insulin infusion pumps, hypoglycemia unawareness.

РЕЗЮМЕ

ОЦЕНКА КАЧЕСТВА ЖИЗНИ БОЛЬНЫХ САХАРНЫМ ДИАБЕТОМ ТИПА 1, НАХОДЯЩИХСЯ НА НЕПРЕРЫВНОЙ ПОДКОЖНОЙ ИНФУЗИИ ИНСУЛИНА

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На сегодняшный день непрерывная подкожная инфузия инсулина (CSII) является эффективным методом лечения больных сахарным диабетом типа 1. В литературе редко встречается оценка влияния такого метода лечения пациентов на качество их жизни.

Целью исследования явилась оценка качества жизни больных сахарным диабетом типа

1, находящихся на непрерывной подкожной инфузии инсулина.

Для этого отобраны 80 больных сахарным диабетом типа 1 (37 мужчин и 43 женщины), проживающих в г. Афинах, для проведения перекрестного анализа. Средний возраст пациентов составил 35.9±11.4 лет, длительность сахарного диабета типа 1 – 24.2±10.3 года, индекс массы тела - 24.6±3.5 кг/м^2, длительность использования инсулиновой помпы – 7.1±3.9 лет, показатель HbA1c – 7.7±1.1%.

Для оценки качества жизни пациентов использован утвержденный в Греции опросник самооценки – EuroQol EQ 5D. Проведен корреляционный и регрессионный анализ EQ индекса – EQVAS шкалы с факторами, связанными с диабетом. Оценка гипогликемии проводилась по вопроснику Clarke и Gold Score. Подсчитывалось количество эпизодов гипогликемии в течение недели. Проведена оценка страха гипогликемии (Hypoglycemia Fear Survey - HFS-W шкала): Gold Score - 2.8±1.5, Clarke Score - 2.8±2.1, Hypoglycemia Fear Score - 20.6±11.1. Эпизоды гипогликемии в течение недели - 4.3±2.9, VAS Score – 68.7±18.1, EQ индекс – 0.79±0.24. Унивариационный анализ показал отрицательную корреляцию между качеством жизни и эпизодами гипогликемии, HbA1c, страхом и осведомленностью о гипогликемии. Регрессионный анализ выявил связь качества жизни только с HbA1c и эпизодами гипогликемии в течение недели. Полученные в результате проведенного исследования данные диктуют необходимость строгого контроля за гликемией и гипогликемией для повышения качества жизни больных сахарным диабетом типа 1, находящихся на непрерывной подкожной инфузии инсулина.

რეზიუმე

ინსულინის უწყვეტი კანქვეშა ინფუზიით მკურნალობაზე მყოფი შაქრიანი დიაბეტი ტიპი 1-ით პაციენტების ცხოვრების ხარისხის შეფასება

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ინსულინის უწყვეტი კანქვეშა ინფუზია (CSII) ეფექტური მიდგომაა შაქრიანი დიაბეტი ტიპი 1-ის მქონე პაციენტების სამკურნალოდ. მონაცემები თუ როგორ მოქმედებს CSII პაციენტის ცხოვრების ხარისხზე ლიტერატურაში საკმაოდ მწირია.

კვლევის მიზანს წარმოადგენდა ინსულინის უწყვეტი კანქვეშა ინფუზიით მკურნალობაზე მყოფი პაციენტების ცხოვრების ხარისხის შესწავლა, რისთვისაც შერჩეული იყო 80 შაქრიანი დიაბეტით ტიპი 1-ით პაციენტი (37 კაცი, 43 ქალი), მცხოვრები ქ. ათენში. ჩატარდა ჯვარედინი კვლევა. პაციენტების საშუალო ასაკი შეადგენდა 35.9±11.4 წ., დიაბეტის ხანგრძლივობა - 24.2±10.3 წ., სხეულის მასის ინდექსი - 24.6±3.5 კგ/მ^2, ინსულინის ტუმბოს მოხმარების ხანგრძლივობა - 7.1±3.9 წ., HbA1c - 7.7±1.1%. ცხოვრების ხარისხის შეფასება ხორციელდებოდა საბერძნეთისთვის დამტკიცებული თვითშეფასების კითხვარით - EuroQol EQ 5D. კორელაციური და რეგრესიული ანალიზის მეშვეობით შეფასდა EQ ინდექსს, EQ VAS სკალას და დიაბეტთან დაკავშირებულ ფაქტორებს შორის კავშირი. ჰიპოგლიკემიის ამოცნობა მოხდა Clarke და Gold Score კითხვარებით; ჰიპოგლიკემიის ეპიზოდები აღირიცხა, როგორც კვირის მანძილზე ჰიპოგლიკემიის რაოდენობა, ხოლო ჰიპოგლიკემიის შიშის შეფასება

განხორციელდა Hypoglycemia Fear Survey (HFS-W) სკალით: Gold score=2.8±1.5, Clarke score=2.8±2.1, Hypoglycemia Fear Score=20.6±11.2 ქულა. ჰიპოგლიკემიის ეპიზოდებმა კვირის მანძილზე შეადგინა 4.3±2.9, VAS score=68.7±18.1, EQ ინდექსი =0.79±0.24. უნივარიაციული ანალიზით გამოვლინდა უარყოფითი კორელაციური კავშირი ცხოვრების ხარისხსა და ჰიპოგლიკემიის ეპიზოდებს, HbA1c, ჰიპოგლიკემიის შიშის სკალას და ჰიპოგლიკემიის ცნობიერების სტატუსს შორის. რეგრესიულმა ანალიზმა გამოავლინა, რომ ცხოვრების ხარისხთან დამოუკიდებელ კავშირში იყო მხოლოდ HbA1c და ჰიპოგლიკემიის ეპიზოდები კვირის მანძილზე.

ჩატარებული კვლევის შედეგად მიღებული მონაცემები მიუთითებს ჰიპოგლიკემიასა და გლიკემიაზე მკაცრი კონტროლის ჩატარების აუცილებლობაზე CSII-ზე მყოფი შაქრიანი დიაბეტი ტიპი 1-ით პაციენტების ცხოვრების ხარისხის გაუმჯობესებისათვის.

THE ROLE OF PSYCHOLOGICAL FEATURES IN MANAGEMENT OF PATIENTS WITH TYPE 1 DIABETES (CASE REPORT)

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Diabetes management (and also self-management) is often associated with patient's psychological features. Sometimes patients do not want to follow doctor's recommendations: inject insulin, measure blood glucose with sufficient frequency and keep measurements in the target range. Moreover, some psychological problems, including fear of hypoglycemia, fear of chronic complications, diabetes burnout syndrome, may interact with poor adherence [1,2].

Case presentation: A 45-year-old Caucasian male consulted our clinic with classic symptoms of diabetes, which appeared after significant stress. Patient had no familial history of diabetes mellitus and had been diagnosed with type 1 diabetes at the age of 27. At the admission to the hospital the blood glucose value was 14 mmol/l, patient had normal vital signs, but he complained of severe weakness, excessive thirst, weight loss (almost 15 kilos per month) and dry mouth. The patient was put on basal-bolus insulin therapy. The first doctor who diagnosed the disease has advised the patient that high blood glucose will result in chronic complications and the most important in the management was to avoid hyperglycemia. Though, from the first day of diagnosis patient decided that glycemic control should be tough and blood glucose range can't go above acceptable values. As a note, the patient did not get any structured education, nor at the onset of diabetes, neither subsequently.

For the next 11 years the patient tried to achieve constant glucose values less than 5 mmol/l. It resulted in very frequent episodes of hypoglycemia, including severe hypoglycemia - sometimes more than 5-6 times per week (more than 15 per month) that required hospitalization. Last hospitalization was 7 years ago.

For the last 6 years the patient has been trying to achieve glucose values less than 6 mmol/l, the duration of levels higher than 7 mmol/l have lasted no longer than 3 minutes per year. Patient has been using only insulin syringes because he did not trust insulin pen and insulin pumps. He's

been measuring blood glucose more than 40 times per day (since the onset of the disease) using usual test-strips and visual test-strips BetaCheck. Sometimes he used CGM Dexcom in cases when he wanted to check accuracy of insulin doses. He does not have family and is convinced that people with diabetes are disabled and shouldn't have children. During the whole course of the disease his HbA_{1c} level has been ≤5.2% (once), and the last HbA_{1c} was 2.9%. He does not have any diabetes related long-term complications.

Discussion and conclusions: Psychological state of patients with diabetes or any other chronic disease can influence management of the disease, but on the other hand can lead to asocialization, difficulties in establishing close relationships or starting a family and to the decreasing quality of life.

Impact of personal characteristics of this patient aggravated difficulties of late onset of the disease. It is more difficult to accept the disease when personality had been formed.

Not only the patient's attitude to the management of the disease can play the role. It is very important to take into account doctor's communication and counseling skills. Because of the doctor's warning about the risk of long-term complications associated with high blood glucose levels, the patient chose to live in constant hypoglycemia.

Successful management of diabetes is also based on a regular structured education. Many studies have shown advantages of continuous education in diabetes control, maintaining blood glucose and HbA_{1c} goals. Lack of education at the beginning of the disease, on the background of strict goals in blood glucose levels lead to unfavorable behavior and restricted acceptance of any kind of education except the personal.

The fear of possible long-term complications of diabetes due to decompensated glucose levels can form obsessive-compulsive complex. The sequence of obsessive thoughts about the fear of long-term complications of diabetes is followed by compulsive actions of endless blood glucose measurement resulting in frequent episodes of severe hypoglycemia. It is well known that frequent episodes of severe hypoglycemia are life-threatening complication of diabetes, which can affect diabetes control, lead to unpredictable glucose levels, omitting of symptoms of hypoglycemia and recurrent hypoglycemia [4]. Moreover, it may cause mental disorders, cognitive impairments and even abuse of low blood sugars.

Psychosocial environment and patient's communication skills also suffer because of overly stringent diabetes self management. The patients considers his contacting the other people as problematic opening up of close relationship connected with his beliefs about diabetes [5]. The examples are as follows: «People with diabetes are an encumbrance», «Nobody needs a partner with diabetes», «Healthy people will always prefer healthy partners for the family building and having children».

According to this patient's psychological condition, he requires regular visits to doctor. At present, the main goal is to interrupt endless blood glucose measurements, shift the focus of attention from numbers to understanding the dynamic changes of blood glucose (trends) due to using continuous glucose monitoring more frequently. The doses of insulin should be corrected according to his body weight and demands.

Moreover, the patient should get structured education course, perhaps individually or with the support of peers. He needs qualified psychological help to improve the quality of life, to overcome the fear of possible long-terms complications, as the key for resolving the obsessive-compulsive complex, to relieve depression and diabetes burning out symptoms and, if necessary, to start antidepressant medications and to improve socialization.

It is very important to remember that individual approach should be applied to each patient [6,7]. Doctors should understand the value of conversation with patient. Doctor's education during university or postgraduate course should include the course of psychological communications and counseling skills. Primarily, leading the patients (especially after diagnosis), recognizing patients' psychological types, knowledge about cooperation with different patients, motivational interview and a subsequent professional burning out prevention.

An abundant amount of studies confirm advan-

tages of structured education in diabetes control. In Russia there is a problem for the patients to obtain sufficient attainments. Schools of diabetes are organized but are not always available for patients with diabetes.

Compensation of diabetes can be improved meaningfully if we take into consideration psychological features of the patients and work in cooperation with psychologists, as a united diabetes team. Patients with diabetes need help in each special situation: at the beginning of the disease, during pregnancy, in case of difficulties in the family, after diabetic ketoacidosis, after episodes of severe hypoglycemia and etc…

Interestingly, we as specialists, know enough about fear of hypoglycemia [8,9] but we do not emphasize the fear of hyperglycemia or chronic complications, that, per se, can lead to frequent episodes of severe hypoglycemia, like in our case.

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SUMMARY

THE ROLE OF PSYCHOLOGICAL FEATURES IN MANAGEMENT OF PATIENTS WITH TYPE 1 DIABETES (CASE REPORT)

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Studies have shown that effective diabetes management (and also self-management) can delay or prevent the micro- and macrovascular complications. But sometimes the way of achieving optimal glycemic control can affect quality of patient's life resulting in different fears and other psychological problems.

Our clinical case demonstrates type 1 diabetes (T1D) patient with frequent episodes of hypoglycemia, including severe hypoglycemia, and various psychosocial problems. It confirms the importance of doctor's communication skills and necessity of constant collaboration with psychologist in organization of diabetes care.

Keywords: type 1 diabetes, severe hypoglycemia, fear of hypoglycemia, psychological support.

РЕЗЮМЕ

РОЛЬ ПСИХОЛОГИЧЕСКИХ ОСОБЕННОСТЕЙ ПАЦИЕНТА В МЕНЕДЖМЕНТЕ САХАРНОГО ДИАБЕТА ТИПА 1 (КЛИНИЧЕСКИЙ СЛУЧАЙ)

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Множество исследований подтвердили, что эффективный контроль сахарного диабета (а также самоконтроль) может отсрочить или даже предотвратить развитие микро- и макрососудистых осложнений диабета. Однако иногда способ достижения желаемого гликемического контроля влияет на качество жизни пациента, приводя к возникновению различных страхов и других психологических нарушений. Описан клинический случай пациента с высоким показателем гипогликемии, в том числе тяжелой, и рядом психосоциальных проблем, которые являются как причиной, так и следствием сложившейся ситуации. Необходимо помнить, что не только успешная компенсация заболевания, но и психологическое здоровье пациента во многом зависит от навыков общения доктора с пациентом. Работа в команде «пациент-доктор-психолог» необходима как в дебюте заболевания, так и при возникновении сложных ситуаций в жизни пациента: при наступлении беременности, конфликтов в семье, после эпизода диабетического кетоацидоза, перенесенной тяжелой гипогликемии.

რეზიუმე

ფსიქოლოგიური მახასიათებლების როლი შაქრიანი დიაბეტი ტიპი 1-ით პაციენტის მენეჯმენტში (კლინიკური შემთხვევა)

მ. დუნიჩევა, ტ.ზაგოროვსკაია,
ე. პატრაკეევა

რეპროდუქტოლოგიის და ოჯახის დაგეგმარების ცენტრი, რუსეთი

კვლევებით დამტკიცებულია, რომ დიაბეტის ეფექტური მართვა (და თვითმართვა) აფერხებს მიკრო- და მაკროსისხლძარღვოვანი გართულებების ჩამოყალიბებას. თუმცა, გარკვეულ პირებში ოპტიმალური გლიკემიის სამიზნე მაჩვენებლების მიღწევის გზამ შესაძლოა იმოქმედოს ცხოვრების ხარისხზე და გამოიწვიოს სხვადასხვა სახის ფობიების ან რიგი ფსიქოლოგიური პრობლემების ჩამოყალიბება.

წარმოდგენილი კლინიკური შემთხვევა ეხება შაქრიანი დიაბეტი ტიპი 1-ის მქონე პაციენტს, რომელსაც აღენიშნებოდა ჰიპოგლიკემიის და მათ შორის მწვავე ჰიპოგლიკემიის ხშირი ეპიზოდები და ასევე სხვადასხვა სახის ფსიქოლოგიური პრობლემები. მისი ფსიქო-ემოციური ფონიდან გამომდინარე, შეიქმნა მკურნალობის სქემაში ფსიქოლოგის მუდმივი ჩართვის აუცილებლობა.

მიზანშეწონილია როგორც დაავადების დებიუტში, ისე პაიცენტის ცხოვრებაში რთული სიტუაციების შექმნის დროს მკურნალობა ჩატარდეს სქემით „პაციენტი-მკურნალი-ექიმი-ფსიქოლოგი“.

TYPE 2 DIABETES MELLITUS AND CEREBRAL SMALL VESSEL DISEASE (CASE REPORT)

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A 70-year-old right-handed woman with poorly controlled type 2 diabetes and hypertension was referred to our hospital with sudden-onset left-sided weakness and difficulty with walking and balance. The patient was evaluated in the presence of her son, who provided most of the medical history. She was talking to her son at their home when her son noticed that her speech was slurred and balance was disturbed. She was not moving her left arm and leg properly. Her son has been concerned about her short-term memory problems for the past 10 months. The patient had a fall 10 months ago; after that, she started to ask the same questions over and over. There was another fall 4 months ago and also an episode of dizziness 2 months ago. Consequent to these incidents, her son has noticed further decline in her cognition. She also developed mild speech and swallowing difficulty, emotional incontinence as well as urinary urgency and occasional urinary incontinence.

Her past medical history is notable for 10-year history of type 2 diabetes mellitus, uncontrolled hypertension, and hyperlipidemia. There is no history of recent head trauma, stroke, intracranial surgery, spinal surgery, pericarditis, abnormal bleeding, or any other surgical procedures. She was not on oral anticoagulants. She does not smoke, drink alcohol, or use illicit substances. There is no family history of neurologic diseases, including stroke. On admission, her glucose level was 560 mg/dl, her blood pressure was 185/90, pulse was 90, and respiratory rate was 16. Her oxygen saturation on room air was 99%. Her heartbeat was regular. No bruits were heard over her neck.

Examination

Cranial nerve testing revealed PERRLA (pupils equal, round and reactive to light and accommodation). She had a left facial asymmetry. Blink to threat was decreased on the left. Motor strength was mildly impaired in the left arm and leg. Reflexes were 2/4 on the right and 3/4 on the left. Plantar responses were flexor on the right and extensor on the left. Coordination and gait could not be tested. Sensation was intact. On the Mini-Mental Status Examination the patient scored 21/30 with abnormal clock drawing.

Investigation and diagnosis

A brain MRI scan showed multiple lacunar infarcts in both cerebral hemispheres, leukoaraiosis and microbleeds, thus confirming the diagnosis of cerebral small vessel disease (CSVD). Leukoaraiosis or white matter disease is a descriptive term to denominate the cerebral white matter lesions (WMLs) frequently seen on brain imaging, which are considered to be a radiological sign of tissue damage caused by diabetes and chronic ischemia. Leukoaraiosis and its severity are associated with cognitive decline and a higher risk of stroke. The extent of deep WML is generally rated as mild, moderate and severe according to Fazekas classification. In this case moderate to severe form was reported.

Patients with type 2 diabetes mellitus have an increased risk of cardiovascular (CV) morbidity and mortality. The chronic deleterious effects of hyperglycemia are classically separated into microvascular and macrovascular complications. In addition to the classic target organs of microangiopathy, such as the retina or the kidneys, the brain has also been described more recently as a target organ for diabetic microvascular complications. In our case a brain MRI scan showed distinct lesions, which are mainly caused by and seen in long lasting diabetes and hypertension.

Pathological mechanism is considered to mainly involve arteriosclerosis as a result of lipohyalinosis. Moreover lipohyalinosis, arteriosclerosis, vessel wall leakage and venous collagenosis are recognized microvascular changes and as a small vessel disease.

Occasionally, asymptomatic small subcortical infarcts can be identified by chance on imaging,

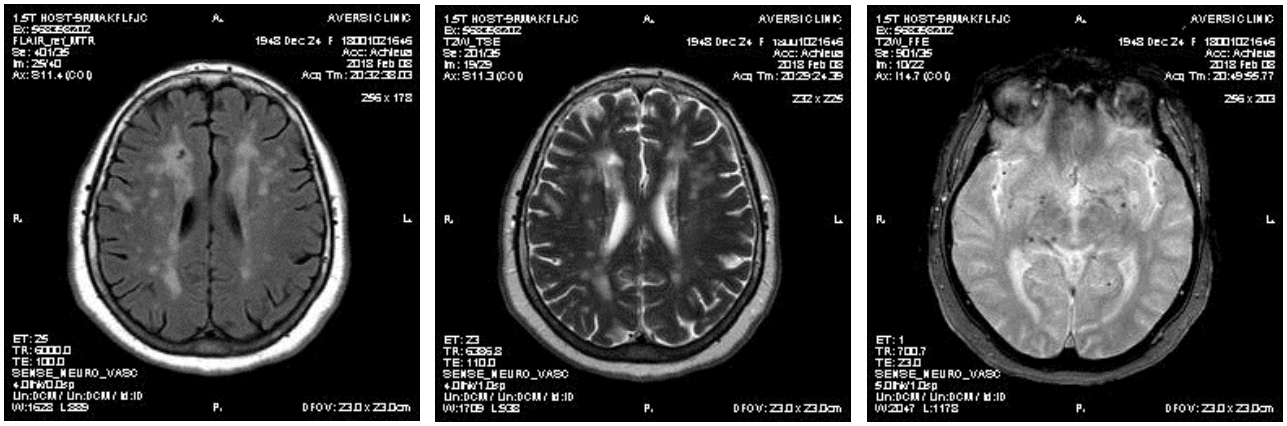

Fig. Brain MRI

and are referred to as silent cerebral infarcts. Silent brain infarction (SBI) on magnetic resonance imaging has been proposed as a subclinical risk marker for future symptomatic stroke. In such cases Diabetes mellitus should be always considered. Early detection and treatment of diabetes favors good outcome.

Our patient has developed lacunar syndrome, pure motor hemiparesis, before admission to the hospital, which is a manifestation of cerebral small vessel disease. Multiple Lacunar infarcts are more frequent in diabetes patients. Also, it has been reported that patients with diabetes and lacunar infarctions are associated with the high recurrence rate of ischemic stroke and worse clinical outcomes.

Moreover the patient had a cognitive impairment, which is cortical-subcortical disconnection syndrome caused by the white matter damage; the latter is a result of cerebral small vessel disease.

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SUMMARY

TYPE 2 DIABETES MELLITUS AND CEREBRAL SMALL VESSEL DISEASE (CASE REPORT)

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Patients with type 2 diabetes mellitus have an increased risk of cardiovascular (CV) morbidity and mortality. Recently, brain has been described also as a target organ for diabetic microvascular complications. Cerebral small vessel disease (SVD) may cause lacunar infarcts and cognitive dysfunction. In our case a brain MRI scan showed distinct lesions, which are mainly caused and seen by long lasting diabetes and hypertension.

Keywords: Cerebral small vessel disease, type 2 diabetes mellitus.

РЕЗЮМЕ

САХАРНЫЙ ДИАБЕТ ТИПА 2 И БОЛЕЗНЬ МЕЛКИХ СОСУДОВ ГОЛОВНОГО МОЗГА (КЛИНИЧЕСКИЙ СЛУЧАЙ)

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Пациенты с сахарным диабетом типа 2 имеют повышенный риск сердечно-сосуди-

стых заболеваний и смертности. С недавнего времени головной мозг описан как орган - мишень микроваскулярных диабетических осложнений. Болезни мелких сосудов головного мозга могут явиться причиной когнитивной дисфункции. В представленном клиническом случае МРТ головного мозга выявила поражения, причинами которых являются длительное течение диабета и гипертония.

რეზიუმე

შაქრიანი დიაბეტი ტიპი 2 და თავის ტვინის წვრილი სისხლძარღვების დაავადება (კლინიკური შემთხვევა)

ს. სოფრომაძე

სამედიცინო ეკოსისტემა *Pineo,* ნევროლოგიის დეპარტამენტი, თბილისი, საქართველო

შაქრიანი დიაბეტი ტიპი 2-ით პაციენტებს მომატებული აქვთ გულ-სისხლძარღვთა დაავადებების განვითარების და სიკვდილობის რისკი. არც თუ ისე დიდი ხანია, რაც თავის ტვინი აღიარებულია დიაბეტის მიკროსისხლძარღვოვანი გართულებების სამიზნე ორგანოდ. თავის ტვინის წვრილი სისხლ-ძარღვების დაზიანება შესაძლოა გახდეს კოგნიტიური დისფუნქციის მიზეზი. წარმოდგენილ კლინიკურ შემთხვევაში მრტ-მ აჩვენა გამოხატული დაზიანებები, რაც უპირატესად გამოწვეულია დიაბეტის ხანგრძლივი მიმდინარეობით და ჰიპერტენზიით.

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