нию квадратичной регрессии. Сгенерированный прогноз детской инвалидности вследствие эпилепсии соответствует уравнению как линейной, так и квадратичной регрессии.

რეზიუმე

ბავშვთა ასაკის ეპილეფსიის ეპიდემილოგიის ასაკობრივი და გენდერული ასპექტები და მათი პროგნოზი

[1]ო.სუხონოსოვა, [23]ო.ტოპორკოვა

[1]ხარკოვის დიპლომისშემდგომი განათლების სამედიცინო აკადემია; [2]ხარკოვის ბავშვთა საავადმყოფო №5; [3]ხარკოვის საერთაშორისო უნივერსიტეტი, უკრაინა

კვლევის მიზანს წარმოადგენდა ბავშვთა ასაკის ეპილეფსიის ეპიდემიოლოგიური მაჩვენებლების (გავრცელებადობა, ავადობა, ინვალიდობა) ასაკობრივი და გენდერული მახასიათებლების განსაზღვრა დაავადების განვითარების ზუსტი პროგნოზის შედგენისათვის.

ხარკოვის ოლქში მცხოვრებ ბავშვებსა და მოზარდებში ჩატარებულია ეპილეფსიის ეპიდემიოლოგიური მონიტორინგი: სკოლამდელი ასაკის ბავშვები (6 წლამდე) – 337 (33,14%), სასკოლო ასაკის ბავშვები (7-14 წელი) – 414 (40,7%) და მოზარდები (15-17 წელი) – 266 (26,16%).

გაანალიზებულია გავრცელებადობა, ავადობა, ინვალიდობა და პირველადი ინვალიდობა ეპილეფსიის შედეგად 2006-2020 წწ. პერიოდში, შედგენილი და აპრობირებულია ზემოაღნიშნული მაჩვენებლების პროგნოზი 2016-2020 წწ. მონაცემების მიხედვით.

ეპილეფიის გავრცელებადობის და ავადობის დაგენერირებული პროგნოზი ბავშვთა ასაკის მოსახლეობაში შეესაბამება მრავლობითი რეგრესიის განტოლებას, ბავშვთა ასაკის ინვალიდობისა კი - როგორც ხაზოვანი, ასევე, მრავლობითი რეგრესიის განტოლებას.

INFLUENCE OF VITAMIN D ON HUMAN HEALTH (REVIEW)

Jachvadze M., Cholokava N., Gogberashvili K.

Tbilisi State Medical University, Department of Pediatrics, Georgia

Vitamin D deficiency remains a significant global, public health problem despite the availability of supplementation and numerous published guidelines for its prevention. It can have a major impact on the health of infants, children, and adolescents, with ramifications that persist into adulthood. Features of vitamin D deficiency and osteomalacia include: 1) hypocalcemic seizures and tetanic spasms; 2) life-threatening hypocalcemic, cardiomyopathy; 3) bone pain and muscle weakness; 4) limb and pelvic deformities; 5) failure to thrive; 6) developmental delay; and 7) dental anomalies. Rickets, because of vitamin D deficiency can also lead to death from heart failure caused by hypocalcemic cardiomyopathy, even in developed countries [2,8,22]. In addition, narrowing of the pelvic outlet after nutritional rickets in childhood can result in obstructed labor and maternal and fetal death [10,35]. The objective of present study was to assess the associations between vitamin D concentrations and respiratory diseases in a large and rapidly expanding literature.

Material and methods. Observational studies and numerous randomized trials were selected according the key words: vitamin D, the hypovitaminosis D, respiratory diseases. Data sources: - Medline, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, ClinicalTrials.gov, and the International Standard Randomized Controlled Trials Number registry from 2011 to 2021.

Results and discussion. Vitamin D is a steroid that regulates the function of around 200 genes in the human body. It's status depends on the amount of vitamin D produced in the skin through the ultraviolet radiation and received with food [37].Thus, the time, geographical location, skin color, age affects the formation of vitamin D in the skin. As for the nutritional deficit,vitamin D content in food is too small and insufficient to cover demands [10,12,41]. The term 'vitamin D' is used for two different forms which are found in nature: vitamin D_3 (cholecalciferol) from animal sources and vitamin D_2 (ergocalciferol) from plants. Vitamin D3 to be converted into an active form−1,25(OH)2D, must undergo two processes of hydroxylation in the body. At the first stage of hydroxylation in the liver by the action of 25-hydroxylase (CYP2R1), 25-hydroxyvitamin D [25(OH)D, also called calcidiol is formed. While the second hydroxylation in the kidneys by the action of CYP27B1 (1α-hydroxylase), leads to formation of the biologically active form, 1,25(OH)2D - calcitriol - the bioactive hormonal form of vitamin D [10,16,20]. Calcitriol is able to regulate calcium-phosphorus balance in various pathways, first stimulating calcium and phosphorus absorption by enterocytes. When dietary calcium intakes are inadequate, calcitriol interacts with the vitamin D receptor (VDR) expressed on osteoblasts, bringing osteoclasts precursors to maturation and promoting calcium and phosphorus absorption by bone tissue. Calcitriol acts synergistically with parathormone (PTH) that acts in bone stimulating calcium absorption by the osteoclasts, and in the kidney where it promotes calcium reuptake in the tubules, phosphorus excretion, and vitamin D conversion into its active hormone form [41].

Vitamin D status is defined by the measurement of 25(OH)D concentrations. This term refers to both its circulating forms, the $25(OH)D_3$ and $25(OH)D_2$, the last from plant dietary sources.

$1,25(OH)_2D$ measurement does not reflect vitamin D status, owing to the short half-life (4–6 h) and the lower concentration (pg/ml vs. ng/ml). $1,25(OH)_2D$ levels are reduced only when 25(OH)D levels are below 4 ng/ml. The measurement of 25(OH)D is difficult due to its lipophilic nature, the binding to vitamin D binding protein, the different circulating forms that also include epimers and isobars, and the standardization. In particular, the 24,25-dihydroxyvitamin D may represent up to 10–15% of the total quantity of 25(OH)D [41]. According to the latest guidelines (10, 17,19,41), there are 25-hydroxyvitamin D (25 [OH] D) determinations: 21-29 ng/ml (52.5-72.5 nmol/l) - diagnosed as vitamin D insufficiency, and if its concentration <20 ng/l (<50 nmol/l) - vitamin D deficiency. Consequently, the sufficient concentration of vitamin D is 31 -60 ng/ml (according to the American Pediatric Academy 31-100 nmol/l) [10,27]. According to the recommendations of the World Health Organization, the American Pediatric Academy and the American Endocrinologists' Society, it is recommended the prophylactic daily dose of Vitamin D - 400 IU/day in breastfed and supplementary fed infants up to 1 year of age. On the other hand, WHO recommends the extension of breastfeeding up the age of 2, but there is nothing about vitamin D supplementation. From 1 year to 18 years, it is recommended for 600 IU/day, in adults - 19-50 years of age 1500-2000 IU day [27]. Adolescents are at increased risk for vitamin D deficiency [12,28,29,40], thus the Society for Adolescent Health and Medicine recommended continuous vitamin D supplementation (600 IU daily for healthy adolescents, and at least 1000 IU daily for adolescents at risk for vitamin D deficiency or insufficiency) in addition to vitamin D received through the diet or via sun exposure [44,45,49].

Despite the high account of sunny days during the year, the southern European and Asian countries – Turkey, Greece, Egypt, Saudi Arabia, India, Japan [1,19,36,45,49] is registered with D Vitamin's low rate compared to the developed northern countries. It is noted that the level of vitamin D depend more on countries economical level than geographical location and physical factors. D hypovitaminosis is more characteristic for developing countries where it is prolonged breastfeeding without vitamin D supplementation, the government does not regulate support with vitamin D, the population awareness about this problem is very low.[5,9,32,42].

Despite intense focus around the role of vitamin D status in health and disease, there has been a worldwide failure to implement public health guidance and eradicate the most severe manifestations of vitamin D and calcium deficiency in most vulnerable population – childhood because of several barriers - such as reluctance of mothers to give their children daily supplementation, lack of knowledge about vitamin D actions and the risk of nutritional rickets, lack of awareness by health care professionals, assumption that both breast milk and formula milk provide sufficient vitamin D intake [40,42,48]. According the literary data, this problem is especially serious for developing countries [1,34,35,45].

It is known that Vitamin D deficiency in children causes rickets, at adult age develops osteoporosis on the basis of hypocalcemia. According to data received in recent years, it is confirmed the role of D3 vitamin deficiency in the development of other pathological conditions such as retardation in linear growth, obesity, diabetes, chronic fatigue syndrome, neuro-degenerative diseases, tumors, autoimmune, cardiovascular diseases [2,10,22,28]. Different data were published in the British Journal BMJ and American Osteopathic Association [27,46]. Vitamin D is not considered to have impact on human health, but the authors recommending to continue research in this direction. According authors conclusion, although vitamin D is thought to influence many disease processes, the evidence is currently insufficient to support supplementation to enhance extraskeletal benefits. The umbrella review of vitamin D research revealed some evidence for decreased risk of colorectal cancer, nonvertebral fractures, cardiovascular disease prevalence, hypertension, ischemic stroke, high body mass index, metabolic syndrome, type 2 diabetes, small for gestational age–birth, and gestational diabetes mellitus [46]. On the other hand, the overview of the literature conducted by PubMed MEDLINE and Cochrane Database Systematic Review published in Mayo Clinic Proceedings confirms the multiple functions of Vitamin D rather than influence on skeletal health. It was noted the effect of hypovitaminosis D on progression of acute and chronic infections, development of autoimmune, endocrine diseases, as well as its impact on the epigenetic programming of the fetus [21]. However, while recent data suggest a possible role of vitamin D in the pathogenesis of several pathological conditions, including infectious and autoimmune diseases, the actual impact of vitamin D status on the global health of children and adolescents, other than bone, remains a subject of debate [4,40,46].

Vitamin D has complex immunoregolatory properties by modulating both innate and adaptive immunity and regulating the inflammatory response. Vitamin D affects B lymphocytes proliferation, differentiation and antibody secretion, as well as a T-cell shift from Th1 to Th2 phenotype and thus limits the potential tissue damage associated with Th1 cellular immune responses. Vitamin D affects the differentiation of Treg cells, its participation in the development of autoimmune diseases. $1,25(OH)_2D_3$ operates on the synthesis of pro-and anti-inflammatory cytokines, the production of the interleukins - such as IL-1, IL-6, IL-8, IL-12 and TNFα [15,16,30]. On the other hand, the immune system cells react to vitamin D through appropriate receptors (VDR) and participate in its synthesis. Based on the above, the plasma concentration of vitamin D is important for outcome of several diseases and pathological conditions at all stages of life [15,16,30]. A relationship between vitamin D status and the incidence or the severity of respiratory infections in children has been confirmed in many observational studies [4,11,18,24,26,33,51].

Hypovitaminosis D has a high prevalence worldwide at any ages. In pediatrics, US data derived by the National Health and Nutrition Examination Survey cohort indicate a prevalence ranging 9–18%, and 51–61% of vitamin D deficiency and insufficiency [32]. A recent meta-analysis was conducted on all the cohort studies of the European population, basing also on a pediatric population of 14971 subjects (1–18 years) [6]. The Authors applied the Vitamin D standardization Program and developed protocols for standardizing existing 25(OH)D values from national health/nutrition surveys. The prevalence according to age (1–6 years, 7–14 years, and 15–18 years) ranged 4–7%, 1–8%, and 12–40%, respectively, suggesting that particular attention should be kept not only in infants but also in adolescents. Nonwhite subjects and those living at relatively mild-latitude countries (47–60° N) had a higher prevalence range (5–20%) than southern countries. Limitations of the study include the fact that some of the studies mainly included children aged 7–11 years, and that vitamin D supplements, food fortification or sun awareness campaigns could have influenced the estimates. Data from Italian pediatrics are only limited being represented by the Roma cohort (12.5–17.5 years) included in the HELENA study [6]. Particularly, vitamin D status should be monitored at least yearly in subjects that require supplementation during the whole

year because affected from pathological conditions or receiving drugs affecting vitamin D metabolism [41].

It is wellknown the ancient method - heliotherapy (treatment with sun rays) for tuberculosis disease. They thought that the sun's rays directly killed the tuberculosis mikobacteria. Successfully was used fish oil (rich with vitamin D) in treatment of tuberculosis and to reduce the morbidity. Now it is known, that vitamin D is involved in the correct functioning of the immune system. On other hand, activation of tuberculosis process depends on immune system insufficiency [13,23,52]. According the authors data, the prevalence of vitamin D deficiency in pulmonary tuberculosis cases is very high. Hypovitaminosis D was associated with more severe clinical symptoms, higher sputum smear positivity, and extensive lesions in chest radiograph among pulmonary tuberculosis patients [52].

During last years appeared data from controlled trials where there are confirmed D hypovitaminosis correlations with infections. The systemic review of the randomized controlled trials and meta-analysis showed the effectiveness of vitamin D supplementation for reducing morbidity with respiratory diseases, but because of few materials statistically reliable data were not received [4,11]. Consequently, the authors are recommending to continue and extend the research, using vitamin D in the treatment of infections. At the same time, there are a lot of data about vitamin D status positive correlations with the upper respiratory infections morbidity [16,21,26,30,33,34,51]. There are new data where low 25(OH)D levels are associated with a rise in hospital admissions or oral steroids treatment in asthma patients. A meta-analysis showed a significant association between vitamin D supplementation and reduction of asthma exacerbations (17% vs. 46%, $p<0.029$) [3,14, 25,47].

In literary sources, the impact of Vitamin D is considered to influence the duration and severity of pneumonia. The authors note that in the cases of severe and complicated pneumonia, the concentrations of vitamin D was significantly lower than in control cases [20,24,38,51]. It is considered recommendations to add vitamin D for treatment severe pneumonia. Viral and bacterial pneumonia kills more children than any other illness, accounting for 19% of all deaths in children less than five years of age worldwide; and under-nutrition, which includes vitamin D insufficiency/deficiency, has been implicated in 53% of all these deaths [WHO, 2017].

Interest in the potential for vitamin D supplementation to reduce the risk of acute respiratory infections (ARIs) has increased since the emergence of the COVID-19 pandemic. During the 2020s Coronavirus pandemic (COVID-19 disease) caused by the new Coronavirus (SARS - CoV-2) conducted clinical trials have been confirmed the effect of vitamin D on severity and duration of coronaviral pneumonia, development of acute respiratory distress syndrome [7]. According to their data, the involvement of calcitriol in the management of the disease reduces the need for intensive treatment by activation the vitamin D receptor (VDR). It reduces cytokin/chemokine storm, stimulates neutrophil activity, has a definite impact on increased coagulation processes. The relevance of these findings to COVID-19 is not yet confirmed and requires further investigation [50].

The aim of present study was to reveal associations between vitamin D concentrations and respiratory diseases in a large and rapidly expanding literature. The results of our study show that the vitamin D deficiency and rickets still remains an under-recognized clinical problem. The literature review revealed the lack of knowledge about vitamin D actions and the risk of nutritional rickets, lack of awareness by health care professionals, assumption that both breast milk and formula milk provide sufficient vitamin D intake [40,42,48]. According the literary data, this problem is especially serious for developing countries [1,34,35,45]. On the other hand, the last years literary data show that there is solid evidence that vit D supplementation can reduce the rates of infections in pediatric population [4,11]. There are a lot of data about vitamin D status positive correlations with the upper and lower respiratory infections morbidity [16,21, 24,26,30,33,34,38,51]. It is also the growing evidence for a beneficial role of supplementation in preventing autoimmune disorders and asthma exacerbations. But most of researchers have concluded that clinically useful effect remains uncertain and requires confirmation in farther well designed randomized controlled trials.

Conclusion. The systemic review of the randomized controlled trials and meta analysis showed the effectiveness of vitamin D supplementation for reducing morbidity with respiratory diseases. But most of researchers have concluded that data remain uncertain and requires confirmation in farther well designed randomized controlled trials.

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SUMMARY

INFLUENCE OF VITAMIN D ON HUMAN HEALTH (REVIEW)

Jachvadze M., Cholokava N., Gogberashvili K.

Tbilisi State Medical University, Department of Pediatrics, Georgia

Objectives - the associations between vitamin D concentrations and respiratory diseases have been assessed in a large and rapidly expanding literature.

Observational studies and numerous randomized trials. Data sources: - Medline, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, ClinicalTrials.gov, and the International Standard Randomized Controlled Trials Number registry from 2011 to 2021. Vitamin D plays an essential role in maintaining bone health through regulating calcium concentrations in the body. The development of vitamin D deficiency is associated with deteriorating bone health and in severe cases, hypocalcemia, rickets, and osteomalacia in children and adults. Those at greatest risk of vitamin D deficiency include patients with chronic illnesses (e.g., chronic kidney disease, cystic fibrosis, asthma, and sickle cell disease), dark-pigmented skin, poor nutrition, and infants who are exclusively breastfed.

The primary source of vitamin D is sunlight exposure with nutritional intake. However, the composite literature is often confusing and has led to heated debates about the optimal concentrations of vitamin D and related guidelines for supplementation. According to the last period of research, the impact of vitamin D is actively discussing the correct functioning of the immune system. It is established that it participates in the formation of the innate and adaptive immune response. In last years appeared data from controlled trials where there are confirmed D hypovitaminosis correlations with infections. The systemic review of the randomized controlled trials and meta analysis showed the effectiveness of vitamin D supplementation for reducing morbidity with respiratory diseases. In literary sources, the impact of Vitamin D is considered to influence the duration and severity of pneumonia. The authors note that in the cases of severe and complicated pneumonia, the concentrations of vitamin D was significantly lower than in control cases. It has been proposed that the activation of the vitamin D receptor (VDR) signaling pathway may generate beneficial effects in ARDS caused by SARS-CoV-2 with decreasing the cytokine/chemokine storm, regulating the renin-angiotensin system, modulating neutrophil activity.

The systemic review of the randomized controlled trials and meta analysis showed the effectiveness of vitamin D supplementation for reducing morbidity with respiratory diseases. But most of researchers have concluded that data remain uncertain and requires confirmation in farther well designed randomized controlled trials.

Keywords: vitamin D, the hypovitaminosis D, respiratory diseases.

РЕЗЮМЕ

ВЛИЯНИЕ ВИТАМИНА D НА ЗДОРОВЬЕ ЧЕЛОВЕКА (ОБЗОР)

Джачвадзе М.В., Чолокава Н.Н., Гогберашвили К.Я.

Тбилисский государственный медицинский университет, департамент педиатрии, Грузия

Цель исследования - анализ данных об ассоциации между концентрацией витамина D и различными заболеваниями у детей.

Проанализированы результаты многочисленных рандомизированных исследований и клинических наблюдений, посвященных влиянию различной концентации витамина D на здоровье человека. С этой целью просмотрены публикации базы данных Medline, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, ClinicalTrials.gov за 2011-2021 гг. Витамин D выполняет значимую роль в поддержании здоровья костной системы путем регулирования концентрации кальция в организме. Дефицит витамина D связан с ухудшением минеральной плотности костей, способствует развитию гипокальциемии и рахита у детей и остеомаляции у взрослых. Гиповитаминоз D чаще встречается у пациентов с хроническими заболеваниями (хронические заболевания почек, цистический фиброз, астма и серповидноклеточная анемия), у лиц с темным пигментом кожи

и у младенцев, которые длительное время находятся только на грудном вскармливании. Основным источником витамина D является солнечный свет и питание. Однако единого мнения об оптимальных концентрациях витамина D крови и соответствующих руководств по питанию в литературных источниках не имеется. На сегодняшний день в проводимых исследованиях активно обсуждается воздействие витамина D на функционирование иммунной системы. Установлено, что витамин D участвует в формировании врожденного и адаптивного иммунного ответа. Согласно множеству научных источников, адекватные концентрации витамина D выполняют значимую роль в формировании костной системы в младенческом возрасте, а также в защите от аутоиммунных заболеваний. В условиях вспышки коронавирусной инфекции содержанию витамина D придается особое значение. Выявлено, что активация рецептора витамина D (VDR) оказывает положительный эффект в лечении SARS-COV-2, уменьшая шторм цитокина/хемокина и модулируя активность нейтрофилов.

Согласно литературным данным, имеются доказательства, что прием витамина D снижает уровень распространения инфекции в педиатрической популяции. Однако некоторые исследователи утверждают, что положительный эффект витамина D остается неопределенным и требует проведения тщательно спланированных рандомизированных контролируемых исследований.

რეზიუმე

ვიტამინი D-ს გავლენა ადამიანის ჯანმრთელობის მდგომარეობაზე (მიმოხილვა)

მ. ჯაჭვაძე, ნ. ჭოლოკავა, ქ. გოგბერაშვილი

თბილისის სახელმწიფო სამედიცინო უნივერსიტეტი, პედიატრიის დეპარტამენტი, საქართველო

კვლევის მიზანს წარმოადგენდა ვიტამინ D-ს სისხლში კონცენტრაციის გავლენის დადგენა ადამიანის ჯანმრთელობის მდგომარეობაზე.

თანამედროვე მდგომარეობით D ვიტამინის დეფიციტი ითვლება ჯანმრთელობის გლობალურ პრობლემად, მაგრამ ჯანმრთელობის ორგანიზაციებისა და მთავრობების ოფიციალური წარმომადგენლების მიერ მოსახლეობის ინფორმირებულობა ამ პრობლემის შესახებ არაერთგვაროვანია.

ჩატარებულია რანდომიზებული კონტროლირებადი კვლევების, გამოქვეყნებული ლიტერატურული წყაროების, მიმოხილვითი პუბლიკაციების სისტემური შესწავლა Medline, Embase, the Cochrane Central Register of Controlled Trials, Web of Science, ClinicalTrials.gov ელექტრონული ბაზების გამოყენებით 2011-2021 წწ. პერიოდში.

ლიტერატურული მონაცემების ანალიზმა გამოავლინა, რომ ვიტამინი D-ს დეფიციტი იწვევს ჰიპოკალცემიას, რაქიტს, ოსტეომალაციას როგორც ბავშვებში, ისე მოზრდილებში. განსაკუთრებით მაღალია D ვიტამინის დეფიციტის რისკი პაციენტებში ქრონიკული დაავადებებით, ადრეული ასაკის ბავშვებში კვების დეფიციტის და გახანგრძლივებული ექსკლუზიური ძუძუთი კვების დროს. ბოლო პერიოდის კვლევების მიხედვით, აქტიურად განიხილება D ვიტამინის დადებითი გავლენა იმუნური სისტემის ფუნქციონირებაზე. დადგენილია, რომ D ვიტამინი მონაწილეობს თანდაყოლილი და შეძენილი იმუნური პასუხის ფორმირებაზე. რიგ პუბლიკაციებში, კონტროლირებული კვლევებით დადასტურებულია D ჰიპოვიტამინოზის კავშირი ინფექციებით გამოწვეულ ავადობასთან. გაანალიზებულია D ჰიპოვიტამინოზის გავლენა როგორც ბაქტერიული, ისე ვირუსული (SARS-COV-2) პნევმონიის მიმდინარეობის სიმძიმეზე. გამოქვეყნებული ლიტერატურული წყაროების სისტემურმა კვლევამ და მეტაანალიზმა აჩვენა ვიტამინი D-ს გამოყენების ეფექტურობა რესპირატორული ინფექციებით ავადობის შემცირებისათვის პედიატრიულ პაციენტებში. ლიტერატურული მონაცემები D ვიტამინის გავლენის შესახებ არაერთგვაროვანია და ავტორთა აზრით, საჭიროებს კვლევების შემდგომ გაგრძელებას.