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Vitamin D deficiency as a risk factor of type 2 diabetes in children and adolescents

Niski poziom witaminy D u dzieci i młodzieży jako czynnik sprzyjający rozwojowi cukrzycy typu 2

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ABSTRACT

Obesity is a global problem, more and more children have a weight above the norm. Obesity is related to circulatory system and metabolic disorders. Relations between obesity and metabolic disorders are known, however factors affecting the risk of such syndromes may extend beyond mentioned relations. Existence of vitamin D receptors in many of body cells, especially in pancreas islets of Langerhans indicates the possibility of significant role played by vitamin D in glucose homeostasis. Several epidemiological studies have reported that low 25-hydroxy vitamin D levels, the most common vitamin D indicator in plasma, very frequent in obese children, is correlated with insulin resistance. Moreover, mechanism of vitamin D is associated both with calcium level in tissues, that regulate insulin synthesis and insulin secretion, and direct secretion of pancreatic beta cells. Parathormone PTH, often defined as obesity indicator, is also crucial. Its high level indicates the risk of metabolic disorders. There is no doubt that reducing of body mass together with complementation of vitamin D insufficiency is the best solution for obese children to decrease the risk of incidence and limit the consequences of type 2 diabetes, one of most common civilization disease.

Key words: diabetes mellitus, type 2, obesity abdominal, vitamin D deficiency

STRESZCZENIE

Otyłość jest problemem na poziomie globalnym i dotyczy w coraz większym stopniu dzieci. Prowadzi do wielu chorób, w tym głównie związanych z układem krążenia i zaburzeniami metabolicznymi. Zależności pomiędzy otyłością a chorobami metabolicznymi są powszechnie znane, jednak okazuje się, że czynniki wpływające na ryzyko zachorowalności mogą wykraczać poza wspomniane zależności. Obecność receptorów witaminy D w wielu komórkach ciała, w tym w obszarze trzustkowych wysp Langerhansa, wskazuje na możliwą istotną rolę tej witaminy w przemianach, które warunkują zachowanie właściwej glikemii. Wiele badań wskazuje, że niski poziom 25 hydroksywitaminy D, często spotykany u dzieci z nadwagą, jest skorelowany ze zwiększoną insulinoopornością. Mechanizm działania witaminy D jest nie tylko związany z regulacją poziomu wapnia w tkankach, ale także wiąże się z bezpośrednim wydzielniczym działaniem trzustkowych komórek beta, czyli regulacją syntezy i sekrecji insuliny. Nie bez znaczenia jest stężenie parathormonu PTH, często nazywanego wyznacznikiem otyłości, którego wysoki poziom świadczy o możliwym ryzyku zachorowania na choroby metaboliczne. Wątpliwości nie budzi fakt, iż obniżenie masy ciała wraz z uzupełnieniem niedoborów witaminy D u dzieci otyłych jest właściwym sposobem zminimalizowania ryzyka zachorowania lub ograniczenia skutków jednej

Udział współautorów / Participation of co-authors: A – przygotowanie projektu badawczego/ preparation of a research project; B – zbieranie danych / collection of data; C – analiza statystyczna / statistical analysis; D – interpretacja danych / interpretation of data; E – przygotowanie manuskryptu / preparation of a manuscript; F – opracowanie piśmiennictwa / working out the literature; G – pozyskanie funduszy / obtaining funds

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z najczęstszych chorób cywilizacyjnych naszych czasów, cukrzycy typu 2.

Słowa kluczowe: cukrzyca typu 2, otyłość brzuszna, niedobór witaminy D

The growing number of consumed calories in diet, lack of physical activities and a sedentary lifestyle are main factors leading to overweight and obesity, which have recently been recognized as a worldwide epidemic. World Health Organization estimated that in 2008 overweight and obesity posed a threat to 1,5 billion people all over the world. Taking into consideration the growing number of overweight children the problem applies also to adolescents [1]. In the USA the frequency of overweight occurrence among children aged between 2 and 19 increased from 4% in 1960s to 14% in 2000, and by 17% from 2000 to 2010 [2]. According to the publication within the project HEPS (Healthy Eating and Physical Education in Schools) from 2010 nowadays in Europe one to four children suffers from overweight. In Poland approx. 18% of children are overweight, whereas 5 years ago the figure reached 11-12% [3]. Overweight and obesity among children lead not only to health disorders and psychological problems, but also affect the state of health in the further stages of the child's development. Approximately from 50 to 80% teenagers remain overweight once they reach puberty [4]. Health problems such as circulatory system disorders and diabetes mellitus type 2 are closely related to obesity. The number of diabetes incidence is rapidly growing. Currently, in the USA 1,9 million new cases are diagnosed every year and the disease has been recognized as the fifth among the most frequent causes of death in this country [5]. According to the statistics published by International Diabetes Federation (IDF), approx. 285 million people suffer from diabetes and by the year 2025 the number will have grown to over 380 million. It is estimated that nowadays 2 million people are affected by diabetes, which makes 6,54% of the population. Among children aged under 15 the figure is estimated to 17,7 cases per 100 000 inhabitants [6]. In spite of the fact that new methods of treatment of diabetes and its complications are being constantly improved preventive actions are favoured. Epidemiological statistics show that 9 to 10 incidences are related to unhealthy eating habits and lifestyle, the change of which can minimize the risk of new cases. The main social factor which can be brought under control is obesity, although in many cases reaching and maintaining the right body mass is not easy in the long term. In the USA 41 million people are at risk of developing diabetes caused by obesity [7]. The modern lifestyle predisposes more children to the risk than in the past.

The resent research indicates the contribution of vitamin D in the pathogenesis of metabolic changes observed among obese children and adults leading to the developing of diabetes type 2. Overweight children live a sedentary lifestyle. Being rarely outdoors their body exposure to the sunlight is limited. Furthermore, the consumption of unhealthy food might cause the deficiency of mineral elements and vitamins.

The latest findings also suggest that overweight children often skip breakfast as one of the main meals or replace dairy products with sweetened beverages [8,9,10]. These factors carry the considerable risk of developing deficiency of vitamin D, especially that its bioavailability is limited due to the considerable amount of body fat and its sedimentation in the fat tissue [11]. The body fat distribution plays a vital role in bioavailability of vitamin D. Fat subcutaneous tissue might store more vitamin D synthesized in cutis in comparison with the amount of vitamin D gained from diet. Wortsman et al. indicated that obese people showed lower by 57% concentration of 25(OH)D in blood than non-obese people after 24 hours from being exposed to UV–B and the synthesis of vitamin D, whereas the concentration of vitamin D in the form of its progenitor 7-Dehydrocholesterol reached the similar level in the both groups [12]. The vitamin D receptors are located in over 30 tissues and body organs, also enzymes facilitating the hydroxylation of vitamin D into 1,25-dihydroksycholekalcyferol are found not only in the liver and renal tubules, but also in entrecotes, in the cells of the prostate gland, mammilla, microphage, osteogenic cells, the connective tissue and in the immune system. They were also detected in the cardiac muscle, blood vessels, brain, pancreas, adrenal gland, pituitary gland, oxybutynin, striated muscles and beta cells of the pancreatic islets of Langerhans [13]. Owing to the fact that vitamin D receptors are so widespread a lot of research is undertaken to estimate the potential role of vitamin D in pathogenesis of development of metabolic syndrome and diabetes type 2. The detection of VDR in the cells of beta-pancreas led to the hypothesis that 1,25 (OH) 2D-VDR plays the vital role as a transcriptional factor in the control of insulin releasing. The presence of 1 alfa-hydroxylase in the beta-cells may indicate the role of the local production of vitamin D and its potential impact on the secretory activity of beta-cells through affecting the balance between inner and outer cellular condensation of calcium ions in the pancreas beta-cells influencing the insulin releasing. Having its receptors in great number located in various tissues, vitamin D may also have an impact on their insulin resistance. It directly influences insulin receptors expression in the target cells, strengthens insulin action in response to glucose transport [14]. Considering its role in controlling the condensation of inner and outer cellular calcium, vitamin D may also affect transmission of insulin signal

from one of its receptors causing the decrease in the activity of glucose transporter GLUT 4 [15]. Insulin resistance and secretion of pancreas beta-cells disorder have a significant impact on developing glucose intolerance and diabetes type 2. Both genetic and sociocultural factors play the vital role in developing these disorders. Many research findings demonstrate that obesity is connected with the low level of 25 (OH)D. Chiu et al. [16] confirmed the existence of interrelation between the concentration of 25(OH)D in serum and the fundamental parameters assessing insulin resistance. They also claimed that 25(OH) D deficiency might have an impact on decrease in the ability of the pancreas beta-cells to compensate in adults. Tzotzas et al. observed the increase in the condensation of 25(OH)D in obese women who had lost weight. Initially, the level of 25(OH)D which the obese women exhibited was lower than the one estimated in the control group with the similar level of parathormone PTH. Having lost 20 kg of weight (10% of the body mass) the women showed increased concentration of 25(OH)D and lower insulin resistance [17]. Reinehr et al. [18] indicated the increase in concentration of 25(OH)D in obese children after the change in their lifestyle that caused the significant loss of weight. Roth et al. [19] investigated the correlation between insulin resistance, concentration of adiponectin and deficiency of vitamin D in children. The research findings confirmed that the low concentration of 25(OH)D is correlated with higher insulin resistance and the level of adiponectin. The significant correlation between 25(OH) D and the level of resistin in obese children was not established. Some research point out the essential role of the level of resistin, which can support the development of insulin resistance and diabetes type 2 in obese people [20]. Statistics illustrating the influence of vitamin D on glucose metabolic disorder found in the literature are contradictory. The majority of the research proves the influence of the deficiency of vitamin D on glucose homeostasis disorders in adults. Some researchers even emphasize the direct correlation between the concentration of 25(OH)D in tissues and the increase in the risk of developing diabetes type 2 [21]. The theory has not been proved in case of children as the research findings are not explicit. Rajakumar et al. investigated the correlation between the amount of vitamin D and the level of abdominal and overall obesity, and the amount of fat in children of the white race and Afro-Americans. It has been established that the low concentration of 25(OH)D is connected with obesity and the lower level of HDL. However, the vitamin D deficiency is also correlated with bigger amount of inner fat tissue especially in children of the white race [22]. Reinehr et al. [18] have not proved whether the level of 25(OH)D and the concentration of PTH play a crucial role in insulin resistance in obese children. Also Creo et al. [23] have not observed the correlation between the level of 25(OH)D and insulin resistance in children aged from 2 to 6 years. Some scientists propose the hypothesis that the low level of vitamin D is interrelated with worse glucose tolerance. Kelly et al [24] stated that the low concentration of 25(OH) D in population of children with higher risk of developing diabetes and with higher level of BMI were related to insulin resistance. Alemzadeh et al. [25] established that deep deficiency of vitamin D in the target group of teenagers was close correlated with insulin resistance. The research undertaken by Olson et al. [26] on a group of children with the appropriate body mass and on a group of obese children show significant negative correlation between the concentration of 25(OH)D in obese children and insulin resistance in tests that measured the indicator HOMA-IR. The research findings by Torun et al. [27] reveal the existence of relation between insulin resistance and BMI, but the relation between insulin resistance and the concentration of 25(OH)D both in children and teenagers was not established. It was stated that there were crucial correlations between the degree of obesity and some biochemical parameters related to insulin resistance, but the level of 25 hydroxyvitamin D did not determine insulin resistance. Reinehr et al. [28] claims that the sufficient loss of body mass bigger than 0,5 BMI in children throughout a year has a deep influence on decrease of insulin resistance. De Las Heras et al. conducted research on the level of 25(OH)D in obese children categorized into three groups. The first group consisted of children with right glucose tolerance, the second of the children at pre-diabetic stage and the third of children suffering from diabetes. No differences in the concentration of 25(OH) D were detected among these groups. Furthermore, there were no significant correlations between the concentration of 25(OH)D and insulin resistance, and the secretory activity of beta-cells [29]. In the majority of research it was assumed that the level of vitamin D was defined only by the concentration of 25(OH)D, whereas the most active metabolite, that influenced the insulin production was calcitriol synthesized as a result of hydroxylation of calcidiol 25(OH)D. It is worth noting that during the diagnostic testing of deficiency of vitamin D, one should not focus on measuring of concentration of the active metabolite 1,25(OH)D as it might lead to the incorrect assessment of the presence of vitamin D in the body, caused by the fact that people with deficiency of vitamin D show the correct or even higher concentration of calcitriol influenced by the higher concentration of PTH [30]. The amount of the hormone produced by parathormone – PTH is significantly correlated with BMI, that is why it can be regarded as an indicator of obesity [31]. Hjelmesaeth et al. [32] have not found any relation between 25(OH)D and a metabolic syndrome, but they have proved the positive correlation between concentration of PTH in the cells, the metabolic syndrome and obesity. The recent research demonstrates that higher level of PTH is

independently related to insulin resistance in people with abdominal obesity, which leads to the conclusion that the concentration of PTH has a strong influence on the disease called the metabolic syndrome [33]. Guasch et al. [34] have proved that low concentration of 25(OH)D and the high one of PTH are connected with the higher risk of developing the metabolic syndrome. However, taking into consideration the factor of BMI, the research does not seem to be vital. The majority of studies concerning the influence of the concentration of 25(OH)D on glucose homeostatis uses BMI as the measurement of obesity. But the researchers do not take into consideration the direct measurements of fat tissue or composition of the body mass. Some scientists opt for taking accurate measurements of the amount of fat tissue in the body, as the low concentration of 25(OH)D is often associated with abdominal and overall obesity, which deeply affects the incorrect glucose tolerance and insulin releasing [35]. Moreover, a lot of analyses were conducted on groups consisting of a few members and majority of the research did not examine the influence of calcium, which can have an independent or synergistic with vitamin D impact on reducing the risk of developing diabetes type 2. Researches undertaken by Gagnon et al. were the first ones which were conducted on over 6 500 000 people, which made a significant part of the population. The correlation between the concentration of 25(OH)D and the risk of developing diabetes type 2 was researched through measuring 25(OH) D and assessment of diagnosed and undiagnosed cases of the disease through estimating OGGT. It was proved that high concentration of 25(OH)D determined the lower risk of developing diabetes type 2 after 5 years. Each additional 25 nmol/l 25(OH)D in the blood serum was interrelated with lessening the risk of developing diabetes type 2 by 22-29%. It was also revealed that the increase in the risk of developing the disease is linearly related to the decrease in the content of 25(OH)D and independent of the level of Ca in the diet [36]. The findings support the theory that the mechanism of vitamin D action is not only connected with the regulation of the level of Ca in tissues, which influences the insulin synthesis and secretion, but it also involves releasing the substances from pancreas beta cells [37].The research by Tzozas et al. [17] demonstrated the significant improvement in insulin resistance when being on a diet after four weeks of treatment, whereas the level of 25(OH)D was not sufficient even after 20 weeks of treatment. Reaching the appropriate level of 25(OH)D involves the considerable weight loss and supplementation even after finishing the diet.

The recent research undertaken in Europe and the USA demonstrate the existence of significant vitamin D deficiency both in children and adults. Obese people, that are especially exposed to the risk of developing civilization diseases including diabetes type 2, exhibit the low concentration of 25(OH)D. The research carried out on adults show that the low level of 25(OH)D is correlated with higher insulin resistance, which indicates the higher risk of developing diabetes type 2. In case of overweight children this interrelation has not been proved because the research findings were not explicit. Despite the fact that the mechanism connected with the role vitamin D plays in prevention of diabetes type 2 is well known, maintaining the high level of the concentration of 25(OH)D in the body of children and adolescents is necessary. According to many research findings, the factor that corrects vitamin D deficiency might be 30 minute exposure to the sunlight per 24 hours or oral supplementation of this vitamin.

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