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Vitamin D – skin synthesis revisited

Nowe spojrzenie na syntezę skórną witaminy D

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S u m m a r y

Almost all cells and organs of human body are using the active form of vitamin D as a co-regulator of many important physiological pathways and as an enhancer of their normal actions. Proper supplementation with vitamin D counteracts rickets and osteomalacia, and decreases the probability of such problems as such problems as certain kinds of cancer, kidney and heart diseases, diabetes, high blood pressure, obesity, fractures, osteoporosis, dental problems, respiratory tract infections, and central nervous system malfunctions. Among our body cells the keratinocytes stand out as those who confer the full spectrum of metabolic reactions concerning vitamin D from its synthesis to conversion into active metabolites and inactivation. This special position of keratinocytes stems from their location and function as a boundary layer between the human body and the environment. Cutaneous synthesis is an important factor in supplementation of our body with vitamin D. Current belief is that poor vitamin D status does not let our body systems work efficiently. Therefore maintaining of the proper vitamin status with the highest possible and safe use of sun rays is essential.

S t r e s z c z e n i e

Prawie wszystkie komórki naszego ciała wykorzystują aktywną postać witaminy D jako regulatora wielu ważnych szlaków fizjologicznych i jako stymulatora ich aktywności fizjologicznej. Właściwe zaopatrzenie w witaminę D zapobiega krzywicy i osteomalacji oraz zmniejsza prawdopodobieństwo wystąpienia różnego rodzaju nowotworów oraz szeregu problemów, takich jak choroby nerek, serca, cukrzyca, złamania, nadciśnienie, otyłość, problemy dentystyczne, osteoporoza, infekcje dróg oddechowych czy zaburzenia działania centralnego układu nerwowego.

Spośród wszystkich komórek, keratynocyty wyróżniają się, posiadając pełny zestaw przemian metabolicznych dotyczących witaminy D, począwszy od jej syntezy, a kończąc na aktywnych metabolitach i ich inaktywacji. Ta specjalna rola keratynocytów wynika z ich funkcji i lokalizacji jako warstwy granicznej pomiędzy ludzkim ciałem a otoczeniem. Skórna synteza jest ważnym elementem w zaopatrzeniu naszego organizmu w witaminę D. Zgodnie z aktualnymi poglądami żaden z układów naszego ciała nie może pracować z maksymalną wydajnością przy niedostatecznym stanie zaopatrzenia w witaminę D. Zatem utrzymanie właściwego poziomu witaminy D z możliwie dużym, ale bezpiecznym udziałem promieni słonecznych wydaje się konieczny.

Conflict of interest
Konflikt interesów
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According to current views vitamin D should be regarded as a factor which is necessary but not sufficient for normal course of the key cellular biochemical pathways. Vitamin D is thought to be an enabler: its presence is necessary for the cellular processes to happen, but is neither their stimulant nor their cause. Therefore low level of vitamin D supplementation although not a direct cause of pathology or dysfunction – is regarded as a factor disturbing the cellular response to intra- and extracellular signals. It is now known that virtually all human body cells and tissues feature vitamin D receptors (VDR). Most cells have also capability of conversion of 25-hydroxyvitamin D [25(OH)D] to its active form 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. Cellular "in situ" activation of vitamin D gives the tissues an opportunity to use vitamin D in accordance to their needs. Thus with insufficient vitamin D supplementation, none of our body's systems can work with optimum efficiency. On account of that vitamin D insufficiency being on most cases a result of low level of skin synthesis stimulation, is inevitably observed in wide range of diseases and

dysfunctions (1). Modern human ancestors evolving in equatorial Africa gained the capability of constitutive production of melanin in their epidermal cells, to protect against burns and DNA damage by strong ultraviolet (UV) radiation (2, 3). Concomitantly with settling in the regions of higher latitudes a devolutional loss of this capability took place in favor to a mechanism of the UV induced melanin synthesis (4).

Another interesting adaptation to lower lighting conditions was a change of the availability of a substrate for the fotochemical reaction which is 7-dehydrocholesterol (7DHC), by tuning the activity of 7DHC dehydrogenase (DHCR7) converting 7DHC into cholesterol. In process of genetic adaptation to lower lighting conditions the variability due to single nucleotide polymorphism of the DHCR7 gene (DHCR7) played a significant role. Another interesting feature of DHCR7 is it's inhibition by vitamin D. Therefore one of the responses the insolation is drop of the cholesterol synthesis and providing a substrate for the synthesis of vitamin D (5-9).

Another element of the system of the keratinocyte response to UV radiation is cytochrome P450 CYP11H1, converting vitamin D_3 to noncalcemic secosteroids like $20(OH)D_3$ and $20,23(OH)_2D_3$. Together with side-products of the previtamin D production (lumisterol, tachysterol), and $25(OH)D_3$ made by CYP27A they form a UV sink supplemental to the melanin, protecting cellular DNA (8).

Keratinocytes also play an important role in protecting of the human organism from harmful environmental factors such as pathogen microorganisms. Active form of vitamin D namely $1,25(OH)_2D_3$ which in keratinocytes comes from $25(OH)D_3$ produced "in situ" within the same cell, acting through the VDR induces synthesis of a specific protein cathelicidin with bactericidal properties. It is quite obvious that the vitamin D metabolic pathway activated by the UV radiation is responsible for first line of defence against the environmental pathogens. The system is activated by the TLR (toll-like) receptors located on the cellular surface. Cathelicidin as a natural antibiotic is involved in the inborn resistance system as it is present in macrophages, fibroblasts, epithelial cells and many others. Thus ineffective skin synthesis of vitamin D is correlated with the general drop in resistance (10, 11).

Epidermal vitamin D receptors enable the cells to show an autocrine response to produced in the same cells active form of vitamin D – $1,25(OH)_2D$. It is already known that an array of important skin functions is regulated by an active form of vitamin D and (or) it's receptor. Among them are inhibition of proliferation, inducing of differentiation, impermeable barrier formation, inducing of the inborn resistance, suppression of carcinogenesis and regulation the hair follicle cycle (12).

Epithelial cells because of their placement are especially vulnerable to the mutagenic and carcinogenic action of the UV rays. One of the constituent of their defence system is the full metabolic cycle of vitamin D enabling the keratinocytes to make the active form of vitamin D from 25(OH)D made in the same cells. $1,25(OH)_2D_3$ together with it's receptor also present in the keratinocytes, are showing remarkably pleiotropic action in cooperation with calcium sensing receptor (CaSR). It was found, that mice devoid of VDR and CaSR a spontaneous carcinogenesis takes place in the keratinocytes, even in the absence of such stimuli like UV or the chemical carcinogens (8). Active form of vitamin D together with it's receptor redirect the intracellular β-catenin to make complexes with the E-cadherin, which together with the calcium ions reduces the probability of the malignant transformation to occur. At the same time the Wnt signal pathway is switched to reduced proliferation, and reduction of some cyclins involved in epithelial cells proliferation (12, 13).

This is supported by the results of the research showing that higher vitamin D supplementation levels were attributable to lower rates of different types of cancers. New study involving more than 300 000 pancreas cancer cases in patients from 172 countries located at various latitudes revealed that the lowest rates (1/100 000) were present in countries with the top insolation (UVB intensity, providing for clouding), whist in the countries with the lowest insolation the frequency was about 10 times higher in women and in men. Similar dependence was found also for multiple myeloma (14-18).

Positive effects of an increased exposition to UVB with reference to the risk of other internal organ cancers are also known, and the risk also increases with the latitude. This was found for the colon cancers, breast cancers, as well as for pancreas, bladder, ovaries, brain and kidneys (14). In the United States mortality due to 15 cancers in Caucasians was found to be inversely proportional to the intensity of the available UVB. Similar dependencies were shown for different Asiatic and European countries (1).

Skin vitamin D synthesis appears as a valuable and difficult to replace activity of the human body. It is quite obvious now, that although the general level of vitamin D supplementation of the human organism can be effectively adjusted with food supplements, the epidermal vitamin D metabolism together with its important implications will not function without access to ultraviolet rays.

CONCLUSIONS

Like other micronutrients, vitamin D is a necessary but not sufficient factor for key cell-biologic processes. It must be present for those processes to take place. Thus low vitamin D status does not so much cause disease or dysfunction: it impairs cellular response to both internal and external signals. It is now recognized that essentially every tissue and cell in the body has vitamin D receptors. Furthermore, most cells also have the capability

of converting 25(OH)D to its active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], and most of our daily vitamin D consumption occurs in this way. This conversion in the cell allows each tissue to use vitamin D as it is needed. It also follows that, in the absence of sunlight and vitamin D, none of our body systems can work at their optimal potential (1).

Take home messages:

1. Looking after the proper supplementation of the organism in vitamin D, will increase the chance to maintain the good state of health.
2. This should be achieved with the highest possible use of insolation.
3. Sensible use of the available sunrays does not conflict with the protection against skin cancers.

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