SALIVARY CORTISOL LEVELS AND RESPONSE TO THE REMISSION INDUCTION TREATMENT IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Among children the most common types of cancer are leukemias [1]. Acute leukemias constitute between 30 and 38% of malignant neoplasms in children, corresponding in 80% to Acute Lymphoblastic Leukemia (ALL) and in 20% to Acute Myeloblastic Leukemia (AML), respectively [2].

ALL is a malignant disorder that originates in a single hematopoietic cell progenitor of B or T lymphocytes and is characterized by a loss of differentiation of lymphoid progenitors producing an increase in immature lymphoblastic cells [3]. It has been reported that 60% of ALL cases occur to children under 20 years of age [4].

In Mexico, cancer in children and adolescents is considered a public health problem [5] urging the need that, through the conjunction of knowledge of epidemiology, biochemistry and genomics, new biomarkers can be identified for a more timely diagnosis, more specific treatment or for monitoring the quality of response to treatment (prognosis).

Glucocorticoids, such as prednisone and dexamethasone, play an important role in the ALL treatment. However, high doses of glucocorticoids may cause suppression of the hypothalamic-adrenal-pituitary axis (HPA) [6]. More specifically, steroids are a fundamental drug in the initial phase of the ALL treatment, during the induction, following the Berlin-Frankfurt-Munich protocol (BFM). They are used in a continuous scheme throughout the induction phase that lasts 28 days, at doses between 40 and 60 mg/m^2/day of prednisolone or 10 mg/m^2/day of dexamethasone with gradual decrements [7].

In recent years, the use of saliva samples to determine concentrations of a wide variety of antibodies, drugs, hormones and tumor markers has spread over the world [8,9]. For example, it is well known that the salivary concentrations of free soluble steroids such as cortisol, reflect approximately 10% of plasma concentrations [10]. The alternative to use the saliva as biological fluid to process samples can be very useful for quantify the level of cortisol as a parameter of evaluation of adrenal function in cases of chemotherapy for ALL, a situation so far unpublished in our country.

The appearance and duration of HPA axis suppression after glucocorticoid therapy for childhood ALL is still not clear. In one study it was presented in almost all children in the first days after the glucocorticoid treatment suspension. Most of the children recovered in a few weeks, but few children lasted up to 34 weeks with adrenal insufficiency [11].

The adrenal insufficiency derived from the treatment against ALL is subtle and manifests as deterioration of the cortisol response to stress. The recuperation has marked interindividual variation [12].

The objective of this project was to determine whether there is an augmented risk for a bad evolution as estimated with the basal and after 8 days of the induction treatment cortisol levels.

Material and methods. This was a clinical, prospective and analytical study developed in the Service of Hematology of the Maternal and Child Hospital of ISSEMYM, in Toluca, Mexico.

The protocol was explained to parents of patients with recent ALL diagnosis and to the children themselves, with an age range between 3 and 18 years. Patients who previously were exposed to steroids were excluded from the study.

The sample was not probabilistic, it was at the convenience of the patients who agreed to enter the study in a period of six months to process the samples before the expiration of the kit.

Weight and height were measured to one decimal place while wearing the child was wearing light clothing and without shoes, using a calibrated digital scale with stadiometer (Seca). Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2).

Blood samples were collected to measure glucose (mg/dL), uric acid (mg/dL) (Siemens advia 1800) and hematometry (Sysmex XL 2000). All measurements followed standardized procedures according to International Federation of Clinical Chemistry and Laboratory Medicine (IFCC).

After 8 hours of fasting, saliva samples were taken in a sterile bottle or a tube of 20 cc, which were kept in refrigeration at 4°C until analysis. The first measurement was made at the diagnosis day of ALL and the second after the phase of induction, following the St. Jude chemotherapy protocols. The quantification was performed in the Research Laboratory of Ciprés Grupo Médico S.C. (CGM) using the ELISA kit of Salimetrics (USA).

A peripheral blood count of less than 1000 absolute blasts after a week of prednisone was defined as a good response to treatment; higher values or death were defined as bad response.

The values were expressed as mean and standard deviation (SD). The Mann-Whitney U test was used to compare the variables values per gender or type of evolution. Spearman correlation was performed among the variables age, BMI, uric acid, glucose, leukocytes, platelets, cortisol at the time of diagnosis and at 8 after the beginning of induction therapy. According to the patients' evolution, Receiver Operating Characteristic (ROC) curves were made for salivary cortisol levels and uric acid. The SPSS ver. 22 statistical software package (IBM Corp., Armonk, NY, USA) was used. A P value of ≤ 0.05 was considered statistically significant in all tests.

This study was approved by the ethics committee of the Maternal and Child Hospital of ISSEMYM (code: 1-19). All of the procedures were conducted in accordance with the Declaration of Helsinki and the General Health Law of Mexico. Informed consent was obtained from the children's parents and verbal informed assent, from the students. The identity of the patient was respected and kept in privacy.

Results and discussion. We included 20 patients who were measured salivary cortisol at the time of their diagnosis and 8 days after starting steroid treatment. Between the studied patients we found that 9 (45%) were girls and 11 (55%) were boys; as shown in graph 1, the age range was between 4 and 14 years, with an average of 108.7 months (9 years). Table 1 shows the general characteristics of the population of this study.

Table 1. General characteristics of the patients

Variable	Mean	Standard Deviation
Age (years)	108,7	60,6
BMI (kg/m^2)	17,0	4,4
Uric acid (mg)	5,5	2,3
Glucose (mg)	91,3	15,0
Leukocytes (x 10^9/L)	24,526	50,551
Platelets (x 10^9/L)	80,611	49,334
Basal cortisol (µg/dL)	0,1039	0,175
Cortisol after induction (µg/dL)	0,2424	0,562

Correlations were made of the response to treatment with the following variables: age, BMI, uric acid, glucose, leukocytes, platelets, cortisol at the time of diagnosis and at 8 days after having started the induction therapy. Through the Spearman correlation the only ones that showed statistical significance in a positive sense were age with BMI ($r^2 = 0,590$, $p = 0,013$), uric acid with leukocyte number ($r^2 = 0,503$, $p = 0,028$) and in a negative sense BMI with the leukocytes' count ($r^2 = -0,551$, $p = 0,022$).

When comparing the variables between genders, the only significant difference was that for erythrocytes (Table 2); meanwhile, there were no any difference between the two types of responses to the induction treatment (Table 3) of the variables analyzed, even in this case the percentage of blasts was similar in the two groups (8,56 in the Bad Response Group and 9,2 in the Good Response Group). Notwithstanding, it was found that salivary cortisol levels had a greater area under the curve (AUC) than uric acid levels as predictors of a poor response to the induction to remission (Fig.).

Table 2. Variables comparison between gender

Variable	Girls (N = 9) Mean (SD)	Boys (N = 11) Mean (SD)	P
Age (months)	88,2 (52,9)	125,4 (63,6)	0,269
BMI (kg/m^2)	16,1 (3,56)	18,03 (5,30)	0,5
Uric acid (mg/dL)	5,27 (1,88)	5,71 (2,70)	0,901
Erythrocytes (x 10^9/L)	2,28 (0,75)	3,11 (0,89)	0,036
Glucose (mg/gL)	87 (10,72)	94,81 (17,49)	0,402
Hb (g/dL)	7,3 (2,37)	9,68 (2,81)	0,087
Leukocytes (x 10^9/L)	9,36 (5,63)	36,931 (66,73)	0,879
Neutrophils (x 10^9/L)	,865 (1,080)	2,291 (2,091)	0,087
Platelets (x 10^9/L)	91,555 (44,384)	69,666 (54,152)	0,309
Basal cortisol (µg/dL)	0,0624 (0,06)	0,137 (0,22)	0,518
Cortisol after induction (µg/dL)	0,150 (0,24)	0,334 (0,78)	0,229

Table 3. Variables comparison per response to the treatment

Variable	Bad response (N = 6)	Good response (N = 14)	P
Age (months)	107,93 (62,75)	110,50 (60,92)	0,967
BMI (kg/m^2)	17,28 (4,57)	1,36 (0,198)	0,571
Uric acid (mg/dL)	5,93 (2,36)	4,65 (2,23)	0,219
Erythrocytes (x 10^9/L)	2,48 (0,85)	3,31 (0,83)	0,069
Glucose (mg/gL)	90,28 (11,06)	93,66 (22,98)	0,804
Hb (g/dL)	7,90 (2,76)	10,26 (2,44)	0,083
Leukocytes (x 10^9/L)	20,400 (44,547)	34,151 (66,27)	0,804
Neutrophils (x 10^9/L)	1,361 (1,523)	2,321 (2,411)	0,364
Platelets (x 10^9/L)	79,461 (47,760)	83,600 (59,036)	0,921
Basal cortisol (µg/dL)	0,0756 (0,0766)	0,169 (0,30)	0,773
Cortisol after induction (µg/dL)	0,251 (0,633)	0,216 (0,36)	0,926
Blasts (%)	8,56 (15,57)	9,2 (9,89)	

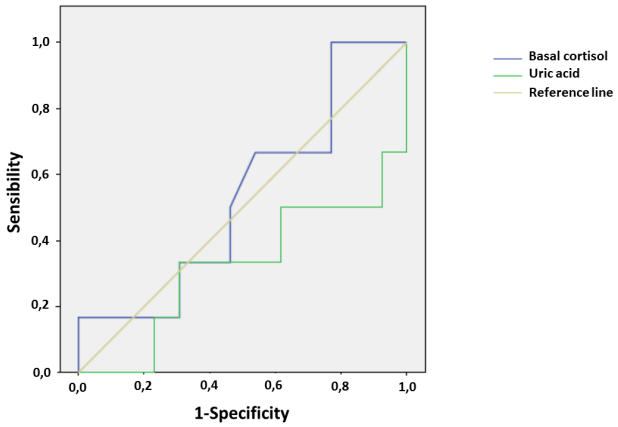

Fig. ROC curve of basal salival cortisol and uric acid as predictors of a poor response to the induction to remission

A higher incidence of adverse effects, especially sepsis and septic shock, had been expected, in relation to the use of dexamethasone in chemotherapy schemes against ALL; and these events are principally diagnosed during the maintenance phase [13]. The explanation of these undesired and feared side effects could be by the HPA suppression caused by dexamethasone; decreasing in a drastic way the cortisol production, which in turn represents an insufficient response to stress, which would generate an impact in the immune system with an inadequate host response to infections. This situation constitutes and remains a cause of mortality and morbidity in children treated with ALL [14]. However unexpectedly in our pilot study, the level of cortisol after 8 days of the beginning of the induction phase was on average higher than the baseline.

In the studied population of this survey the basal cortisol was reported higher than normal reference ranges for healthy children [15,16] and this time of measure was related to a worse response to the treatment of induction to remission. It has been described that the use of dexamethasone is correlated in an important way to adverse events, being the main complications fever, neutropenia and infection. In fact, infections cause 68% of the deaths in the period of induction to remission; in some studies it is reported that the most frequent site is in the colon, due to colitis neutropenia; however, others report some cases due to respiratory infections, infections associated with catheters, infections in the nervous system and even nosocomial infections without known initial focus [17,18].

Logically speaking the higher basal cortisol levels of the patients with ALL would be associated with a greater response to stress [19,20], that is, with a greater attack to the patient's general condition at the time of starting chemotherapy. It calls the attention that the few studies analyzing the salivary cortisol levels in patients treated for ALL have focused the main issue after the induction phase but the basal levels have not been studied and probably they can reflect the degree of the stressful condition attacking the child's organism.

Finally, it is mandatory to analyze the rates of infection and mortality in every Hematology Service, to decide whether prophylactic antibiotic therapy in thus patients with adverse risk factors or a lower dose of steroids to reduce the risk of adrenal-immune suppression that leads to severe infections could be plausible.

A limitation of this study is the small number of patients included, for what we consider to keep on this research line in a wider population parameters, adding more variables such as cortisol in blood to perform a correlation with salivary cortisol, and with a with closer and long-term follow-up.

Conclusions. In this first approach, basal salivary cortisol had a larger area under the curve in the ROC curve as predictor of a bad response than uric acid, situation that still needs future studies. The option to measure salivary cortisol offers great advantages that should be explored in terms of its clinical utility to check the ACTH-cortisol axis in patients with ALL who receive chemotherapy avoiding the stress of venipuncture.

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REFERENCES

1. Hernández AQ, Beatriz A, Sumano R, Solís RMÁ, Vallejo MV. Neoplasias malignas en los niños del Hospital General de Oaxaca, entre 1999 y 2011. // Rev Mex Pediatr. 2013;80(4):136–141.
2. Saletta F, Seng MS, Lau LMS. Advances in paediatric cancer treatment. // Transl Pediatr. 2014;3(2):156-82.
3. Paul S, Kantarjian H, Jabbour EJ. Adult Acute Lymphoblastic Leukemia. // Mayo Clin Proc. 2016;91(11):1645-66.
4. Kaushansky K, Lichtman MA, Prchal JT, Levi MM, Press OW, Burns LJ, et al. Williams Hematology. 6th ed. New York: McGraw-Hill; 2016. 2528 p.
5. Jiménez-Morales S, Hidalgo-Miranda A, Ramírez-Bello J. Acute lymphoblastic leukemia: a genomic perspective // Bol Med Hosp Infant Mex. 2017;74(1):13-26.
6. Rensen N, Gemke RJ, van Dalen EC, Rotteveel J, Kaspers GJ. Hypothalamic-pituitary-adrenal (HPA) axis suppression after treatment with glucocorticoid therapy for childhood acute lymphoblastic leukaemia. // Cochrane Database Syst Rev. 2017;11:CD008727.
7. Perdomo I, Linares A, Acevedo L, Coll M. Supresión del eje hipotálamo-hipófisissuprarrenal después de la quimioterapia de inducción en niños con leucemia linfoide aguda. // Iatreia. 2016;29(1):18-26.
8. Aguilar Cordero MJ, Sánchez López AM, Mur Villar N, García García I, Rodríguez López MA, Ortegón Piñero A, et al. Salivary cortisol as an indicator of physological stress in children and adults; a systematic review. // Nutr Hosp. 2014;29(5):960-8.
9. Fujii T, Schug J, Nishina K, Takahashi T, Okada H, Takagishi H. Relationship between Salivary Oxytocin Levels and Generosity in Preschoolers. // Sci Rep. 2016;6:38662.
10. Vining RF, McGinley RA, Symons RG. Hormones in saliva: mode of entry and consequent implications for clinical interpretation. // Clin Chem. 1983;29(10):1752-6.
11. Gordijn MS, Gemke RJ, van Dalen EC, Rotteveel J, Kaspers GJ. Hypothalamic-pituitary-adrenal (HPA) axis suppression after treatment with glucocorticoid therapy for childhood acute lymphoblastic leukaemia. // Cochrane Database Syst Rev. 2012;(5):CD008727.
12. Salem MA, Tantawy AA, El Sedfy HH, El Laboudy MA, Toaima DN, Mahmoud NH, et al. A prospective study of the hypothalamic-pituitary-adrenal axis in children with acute lymphoblastic leukemia receiving chemotherapy. // Hematology. 2015;20(6):320-7.
13. Te Poele EM, de Bont ESJM, Marike Boezen H, Revesz T, Bökkerink JPM, Beishuizen A, et al. Dexamethasone in the maintenance phase of acute lymphoblastic leukaemia treatment: is the risk of lethal infections too high? // Eur J Cancer. 1990. 2007;43(17):2532-6.
14. Shulman DI, Palmert MR, Lawson Wilkins Drug and Therapeutics Committee. Adrenal insufficiency: still a cause of morbidity and death in childhood. // Pediatrics. 2007;119(2):e484-494.
15. Törnhage CJ. Reference values for morning salivary cortisol

concentrations in healthy school-aged children. // J Pediatr Endocrinol Metab. 2002;15(2):197-204.
16. Rolfsjord LB, Bakkeheim E, Berents TL, Alm J, Skjerven HO, Carlsen K-H, et al. Morning Salivary Cortisol in Young Children: Reference Values and the Effects of Age, Sex, and Acute Bronchiolitis. // J Pediatr. 2017;184:193-198.e3.
17. Prucker C, Attarbaschi A, Peters C, Dworzak MN, Pötschger U, Urban C, et al. Induction death and treatment-related mortality in first remission of children with acute lymphoblastic leukemia: a population-based analysis of the Austrian Berlin-Frankfurt-Münster study group. // Leukemia. 2009;23(7):1264-9.
18. Aguilar-Hernández M, Fernández-Castillo G, Núñez-Villegas NN, Pérez-Casillas RX, Núñez-Enríquez JC. Leading causes of death during the induction therapy in pediatric patients with acute lymphoblastic leukemia. // Rev Med Inst Mex Seguro Soc. 2017;55(3):286-91.
19. Gunnar MR, Bruce J, Hickman SE. Salivary cortisol response to stress in children. // Adv Psychosom Med. 2001;22:52-60.
20. Jessop DS, Turner-Cobb JM. Measurement and meaning of salivary cortisol: a focus on health and disease in children. // Stress. 2008;11(1):1-14.

SUMMARY

SALIVARY CORTISOL LEVELS AND RESPONSE TO THE REMISSION INDUCTION TREATMENT IN CHILDREN WITH ACUTE LYMPHOBLASTIC LEUKEMIA

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Cancer in children, and mainly the acute lymphoblastic leukemia (ALL), is considered as one of the leading public health problems in Mexico. Glucocorticoids used to treat ALL may cause suppression of the hypothalamic-pituitary-adrenal axis. The aim of the present study was to determine whether cortisol levels in saliva of the patients with ALL are related to the response to the remission induction therapy.

The authors have conducted a clinical, prospective and comparative study. The Mann-Whitney U test was used to compare the variables values by gender or type of evolution. According to the patients' evolution, ROC curves were made for salivary cortisol levels and uric acid. An absolute value of 1000 blasts in peripheral blood count after a week of prednisone regimen was defined as a satisfactory response to the treatment.

Review of the data has shown that area under the salivary cortisol levels' curve (AUC) was greater than that under the uric acid levels', as a predictor of a poor response to the remission induction. There were no statistically significant gender-associated differences in any variables except in erythrocytes.

High levels of cortisol in saliva at the time of diagnosis of ALL seem to be of bad prognosis of the response to the remission induction therapy.

Keywords: acute lymphoblastic leukemia, prognosis, saliva cortisol, steroid.

РЕЗЮМЕ

УРОВЕНЬ КОРТИЗОЛА В СЛЮНЕ И ОТВЕТ НА ТЕРАПИЮ ИНДУКЦИИ РЕМИССИИ ПРИ ОСТРОМ ЛИМФОБЛАСТНОМ ЛЕЙКОЗЕ У ДЕТЕЙ

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Раковые заболевания среди детей, и в основном острый лимфобластный лейкоз (ОЛЛ), считается одной из ведущих проблем общественного здравоохранения в Мексике. Глюкокортикоиды, используемые при лечения ОЛЛ, могут вызывать подавление гипоталамо-гипофизарно-надпочечниковой оси. Целью настоящего исследования явилось определение связи уровня кортизола слюны пациентов с ОЛЛ с ответом на индукцию ремиссии. Проведено клиническое, проспективное и сравнительное исследование. U-критерий Манна-Уитни использовался для сравнения значений переменных по половому или эволюционному признакам. В соответствии с эволюцией заболевания построены кривые ROC для уровней слюнного кортизола и мочевой кислоты. Абсолютное значение 1000 бластов в подсчете периферической крови после недельного режима преднизона определено как удовлетворительный ответ на лечение. Обзор данных показал, что площадь под кривой показателей слюнного кортизола (AUC) была больше, чем под кривой показателей мочевой кислоты, что является прогностическим показателем неблагоприятного ответа на индукцию ремиссии. Не было статистически значимых различий ни по одной переменной, кроме эритроцитов при контрастировании по половому признаку.

Присутствие высоких уровней кортизола в слюне при диагностировании ОЛЛ, очевидно, является признаком неблагоприятного ответа на терапию индукции ремиссии.

რეზიუმე

კორტიზოლის დონე ნერწყვში და პასუხი რემისიის ინდუქციის თერაპიაზე მწვავე ლიმფობლასტური ლეიკოზის დროს ბავშვებში

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ონკოლოგიური დაავადებები ბავშვებში, ძირითადად კი – მწვავე ლიმფობლასტური ლეიკოზი, საზოგადოებრივი ჯანდაცვის ერთ-ერთ წამყვან პრობლემად ითვლება მექსიკაში. მწვავე ლიმფობლასტური ლეიკოზის სამკურნალოდ გამოყენებულმა გლუკოკორტიკოიდებმა, შესაძლოა გამოიწვიონ ჰიპოთალამუსურ-ჰიპოფიზურ-თირკმელზედა ჯირკვლის ღერძის დათრგუნვა.

წინამდებარე კვლევის მიზანს წარმოადგენდა პაციენტების ნერწყვში კორტიზოლის დონის კავშირის შეფასება რემისიის ინდუქციის თერაპიასთან მწვავე ლიმფობლასტური ლეიკოზის დროს.

ჩატარებულია კლინიკური, პროსპექტული და შედარებითი კვლევა. მან-უიტნის U-კრიტერიუმი გამოიყენებოდა ცვლადი მაჩვენებლების შედარებისათვის გენდერული ან ევოლუციური ნიშნებით. დაავადების ევოლუციის შესაბამისად, ნერწყვში კორტიზოლის და შარდმჟავას დონეებისათვის აგებულ იქნა ROC-მრუდები. პრედნიზონის ერთკვირიანი რეჟიმის შემდეგ პერიფერიული სისხლში 1000 ბლასტის აბსოლუტური მაჩვენებელი შეფასდა, როგორც დამაკმაყოფილებელი პასუხი მკურნალობაზე. მონაცემების ანალიზმა აჩვენა, რომ ფართობი ნერწყვის კორტიზოლის მრუდის ქვეშ (AUC) მეტია, ვიდრე შარდმჟავას მრუდის ქვეშ, რაც რემისიის ინდუქციაზე არაკეთილსაიმედო პასუხის პროგნოზულ მაჩვენებელს წარმოადგენს. სტატისტიკურად სარწმუნო განსხვავება დადგენილი არ იქნა არც ერთი ცვლადის მიმართ, გარდა ერითროციტების გენდერული ნიშნით კონტრასტირებისა.

ნერწყვის კორტიზოლის მაღალი მაჩვენებლები მწვავე ლიმფობლასტური ლეიკოზის დიაგნოსტიკისას, როგორც ჩანს, რემისიის ინდუქციის თერაპიაზე არაკეთილსაიმედო პასუხს წარმოადგენს.

СОВРЕМЕННЫЕ АСПЕКТЫ УЧАСТИЯ ВИТАМИНА D И ЕГО МЕТАБОЛИТОВ В РАЗВИТИИ ОПОРНО-ДВИГАТЕЛЬНОГО АППАРАТА ДЕТЕЙ И ПОДРОСТКОВ (ОБЗОР)

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Исследования биологических свойств и метаболизма витамина Д связаны с его колоссальной ролью в сомато-неврологическом развитии подрастающего поколения. Заинтересованость педиатров [4,29,32] в изучении роли его дефицита вызвана широким распространением гиповитаминоза Д по всему миру среди детей и подростков. Согласно популяционным исследованиям, около 50% проживающего в Европе и США детского населения страдает гиповитаминозом Д. Из них у 61% уровень 25 (ОН) Д не превышает 15-29нг/мл,а у 9% еще намного ниже. В Бразилии Д-дефицит зафиксирован у 14% детей до 10 лет, а у подростков он достиг 24%. В Объединенных Арабских Эмиратах дефицит витамина Д у детей от 8 до 14 лет намного выше в сравнении с детьми от 2 до 7 лет [2,3,6,19].

Метаболические пути и механизмы действия Д-витамина указывают, что его роль не ограничивается только классической функцией (регуляция фосфорно-кальциевого обмена), Являясь стериоидным прегормоном, он превращается в активные метаболиты, которые модулируют экспрессию генов и активность важнейших физиологических систем. Гормонально-активная форма Vitamin-D-receptor-VDR функционирует во всех клеточных системах человеческого организма [8,14,23].

В настоящее время показано, что активность синтеза холекальциферола [7,19] обратнозависима степени пигментации кожи. Таким образом, дети с тёмным цветом кожи чаще относятся к группе риска Д- авитаминоза. Географические и климатические факторы, загрязнение воздуха, сезонность также существенно влияют на синтез витамина Д в организме.

В ходе фотосинтеза (ультрафиолет 280-300 нмк) провитамин Д (7- дегидрохолестерол) превращается в превитамин Д и в дальнейшем (процесс связан с температурой) преобразуется в витамин Д (холекальциферол). Строгая системная регуляция этого процесса (путем трансформации в биологически инертные изомеры: люмистерол, тахистерол) предотвращает развитие 25(ОН)Д3 гипервитаминоза. При нутриентном поступлении Д витамина указанные процессы отсутствуют и избыточная доза витамина Д может вызвать интоксикацию.

В купферовых клетках печени происходит дальнейшее гидроксилирование и образование наиболее активной формы- 1,25(ОН)2Д3.

В настоящее время витамин Д принято рассматривать [24,30] как группу следующих соединений: (Д1)-комплекс эргокальциферола с люмистеролом; (Д2)- эргокальциферол; (Д3)- холекальциферол, носит название «натурального» витамина; (Д4)- дигидротахистерол-провитамин витамина Д3; (Д5) - ситокальциферол; (Д6) - сигма- кальциферол.

Жирорастворимый витамин Д в процессе всасывания в тонком кишечнике переносится по лимфатическим сосудам и попадает в венозную кровь. В тонком кишечнике витамин Д, соединившись с солями жёлчных кислот, образует мицеллы и в качестве микронутриента куммулирует в энтероцитах (пассивная диффузия). При заболеваниях печени и жёлчного пузыря нарушение жёлчной секреции значительно меняет (снижение объёма, но не скорости) характер пассивной диффузии.

Нарушение всасывания витамина Д в желудочно-кишечном тракте может быть также связано со следующими заболеваниями тонкого кишечника: целиакией и муковисцидозом.

Согласно многочисленным исследованиям [24,25], показано, что экспрессия витамина Д осуществляется в костях, почках, поджелудочной железе, поперечно-полосатой и гладкой мускулатуре, клетках головного мозга, органах репродукции и др. Основным механизмом эффекта действия витамина Д являются геномные процессы. Показано, [26], что 7-10% активируемых генов участвуют в регуляции гомеостаза фосфора и кальция, таким образом, кальцитриол выполняет важную роль в профилактике и лечении рахита.

Уровень обеспеченности витамином Д ассоциирован с развитием инфекционных, сердечно-сосудистых, хронических воспалительных, аллергических, аутоиммунных и различных неопластических заболеваний.

В педиатрии витамин Д признан ключевым фактором