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Vitamin D and Diabetes Mellitus: A Review

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Abstract

Vitamin D deficiency and Diabetes are both disorders of high prevalence in the world. Currently, evidences suggest a possible correlation of low levels of vitamin D with the diagnosis of Diabetes Mellitus. Hypovitaminosis D could be associated with insulin resistance and Diabetes Mellitus, which would in part explain mechanisms involved in the pathogenesis of Diabetes. The aim of this work is to discuss the association between Vitamin D and Diabetes, questioning if vitamin D can prevent the settlement of diabetes or slow down its clinical evolution, and improve the pancreatic function, thus providing a better glycaemic control.

Keywords

Vitamin D, Vitamin D Deficiency, Autoimmune Disease, Diabetes Mellitus, Insulin Resistance

1. Introduction

This work intends to show a literary revision about vitamin D and Diabetes Mellitus, and the relationship between these disorders, as well as investigate the hypothesis that vitamin D might prevent the settlement of diabetes or slow down its clinical evolution, and improve the pancreatic function, thus providing a better glycaemic control. Taking into consideration the severe complications associated with the clinical history of diabetes in individuals with an irregular lifestyle, combined with the low vitamin D levels observed in these patients, it is of vital importance to study vitamin D's action on metabolism, and tries to better understand the role of vitamin D in some chronic diseases as Diabetes.

2. Diabetes Mellitus

2.1. Diabetes Classification

There are several types of diabetes mellitus. Currently, the World Health Organization (WHO) and the Ameri-

can Diabetes Association (ADA) classify these types according to the etiology of the disease, and not according to the form of treatment, in: Type 1 diabetes (DM1), autoimmune, idiopathic, Type 2 diabetes (DM2), other specific types of DM and gestational diabetes [1].

2.2. Pathogenesis

The pathogenesis is very complex and involves an interaction between genetic and environmental factors. Among the environmental factors overweigh (IMC ≥ 25 Kg/m^2), a sedentary lifestyle, a diet high in carbohydrates, high blood pressure (PA ≥ 140/90 mmHg), HDL ≤ 35 mg/dL, triglycerides ≥ 150 mg/dL, smoking habits, alcoholism, polycystic ovary syndrome and some types of medications viral infections in genetically susceptible people (HLA system) are important factors associated with diabetes.

In general, this pathogenesis is related to the peripheral insulin resistance and/or the decline of the insulin production.

In DM1, a chronic inflammatory process installs, due to the presence of the T cells infiltration (CD4+ and CD8+), macrophages, lymphocytes B and cells NK in the cells β autoimmune of the cells β, which can be preceded by hyperglycaemia years before and still persists for 10 years after the diabetes diagnosis took place.

2.3. Diagnosis

The classic symptoms of DM (polyuria, polydipsia, polyphagia and weigh loss) are more frequent in DM1 than in DM2. Fifty percent of the cases are asymptomatic or oligosymptomatic (non-specific signs and symptoms: cramps, recurring vulvovaginitis, asthenia) and an important risk factor is obesity. The diagnosis of DM is made through laboratory tests (fasting glycaemia, oral glucose tolerance test and glycatedhaemoglobin) (**Table 1**) [1].

2.4. Treatment and Goals

In pre-diabetic patients it is important to try a lifestyle change (LC), such as following a healthy diet, poor in fat, begin physical and aerobic exercises with duration of 40 minutes to 1 hour - 3 to 5 days a week, cease smoking and do not consume alcohol.

Key results from the Diabetes Prevention Program (DPP) show that following a healthy diet and starting the practice of physical activities reduced in 58% the incidence of cases of DM in pre-diabetic patients. This intervention is considered double as effective than the use of metformin (31%) (A) [1] [2]. The International Diabetes Federation (IDF) only uses medications (orlistat, metformin, pioglitazone) in case of fail in lifestyle changing (LC) fails or the Impaired Glucose Tolerance persists after 6 months of trying [2].

Most cases of Type 2 diabetes are associated with the metabolic syndrome, and therefore it is important to take important measures, such as: a) start LC and treat diabetes with antidiabetics and/or insulin; b) control high blood pressure, dyslipidaemia and obesity, so the treatment is individualized [3]. Type 1 diabetes has an almost total (at least 80%) or total destruction of pancreatic beta cells, and for this reason the patient is uncapable of producing insulin.

It is essential to individualize the treatment towards diabetes, especially in children, older patients and patients with kidney failure, who are more predisposed to recurring or asymptomatic hyperglycaemia.

3. Vitamin D

3.1. Pathophysiology

Vitamin D is naturally found as ergocalciferol (vitamin D2) in edible fungus, while colecalciferol (vitamin D3) is synthesized in the skin through sun light, and is available through fish oils extracted from fish found in cold and deep water such as tuna and salmon [4] [5]. It is estimated that 80% - 90% of vitamin D in the body are produced through skin synthesis, and the remaining by the ingestion of foods and supplements of this vitamin [6].

Ergocalciferol and the colecalciferol are biologically inactive and potentially equivalent, and they have the same ways of metabolization. During sun light exposure, the UVB radiation (290 - 315 nm) is absorbed by the 7-dehydrocholesterol in the plasmatic membrane of the epidermal keratinocytes (Malpighi layer) and the dermal fibroblast. The energy is absorbed resulting in the reorganization of the double connections and opened of

Table 1. Diagnosis of diabetes mellitus—according to ADA.

Category	Fasting glycemia	OGTT 75 mg*	Casual glycemia	Glycated hemoglobin
Normal blood glucose	<100	<140		≤5.6%
Pre-diabetes	>100 a < 126	≥140 a < 200		5.7 a 6.4%
Diabetes mellitus	≥126	≥200	≥200+ symptoms	≥6.5%
Gestational diabetes	≥92 a < 126 2 occasions	JJ: ≥92 1h: ≥180 2h: ≥153		≥6.5% 2 occasions

*to be requested between 24 and 28 weeks of pregnancy.

its B ring to form pre-vitamin D3. Once formed, vitamin D3 quickly suffers rearrangement of its double connections to form vitamin D3, which is thermodynamically more stable. Vitamin D that comes from foods and supplements is absorbed by the small intestine and makes its way to the blood stream, to be gathered with colecalciferol (vitamin D3) which comes from the epidermis [7].

This vitamin circulates in the blood stream linked to the protein (DBP) and 2 mitochondrial cytochrome P-450 enzymes to the liver, where it suffers hydroxylation by the 25-hydroxylase enzyme of the carbon 25 (CYP27B1), giving rise to 25-hydroxy vitamin D or calcidiol [25(OH)D], a molecule found inactive in higher levels in the blood stream, and with a half-life of 2 weeks. The 25-hydroxy vitamin D is transported to the cell of the proximal renal tubules, as well as to other tissues, by the DBP protein, where the conversion to 1,25-dihydroxyvitamin D or calcitriol [1,25(OH)2D] occurs, through the action of the renal enzyme 1 α-hydroxylase (CYP27B1) [7].

The 1,25 (OH)2D stimulates the absorption of calcium and phosphorus, gathering them secreted by syntheses of 25-hydroxy vitamin D and 1,25(OH)2D, inappropriate homeostasis of the calcium (only 10% to 15% of the calcium and 60% of the phosphorus from the diet is absorbed) and a constant elevation of levels of PTH (secreted by the parathyroid), which stimulate the production of 1,25(OH)2D in the renal level, resulting in a condition of secondary hyperparathyroidism, with increases bone remodelling and leads to a decrease in bone mass. Adequate levels of vitamin D increase the absorption of calcium and phosphorus up to 30% - 40% and 80% respectively [8].

There are 36 different tissues in the body able to interact with the physiology of vitamin D, which means, the biological effects of the active form of the calcitriol mediated by the presence of the 1 α-hydroxylase enzyme (CYP27B1) and receptors of vitamin D (VDR) works in these target-tissues. They are, among others: the kidneys, bones, parathyroid gland, intestines, the heart, placenta, liver, breast, pancreatic beta cells, the thyroid gland, immunologic system cells, the brain, adrenal glands, ovaries and testicles [9]-[11]. This fact revolutionized the understanding of the role of Vitamin D at various levels of the human body, once these cells are capable to convert the inactive 25-hydroxy vitamin D into 1,25-hydroxy vitamin D in an autocrine and paracrine way [9]. These data support the recent hypothesis that vitamin D deficiency could be associated to the pathophysiology of different diseases, although no concrete causal effect has been established so far [12].

In general, the effects of vitamin D in the immunologic system are the increase of innate immunity, associated with a multifaceted regulation of acquired immunity [13].

In a 2012 randomized double-blind clinical study, the use of 2000UI of colecalciferol during 18 months in 38 patients with Type 1 diabetes DM1 and a recent diagnosis, a protective immunologic effect was found, which included a larger number of T regulator cells and a reduced beta cell function loss. These results are not enough to establish an association, but raise relevant questions regarding the pathofisiology of the disease [9].

3.2. Diagnosis

As there are many causes to vitamin D deficiency, it is suggested to request tests from all patients at risk, such as: 1) those in use of chronic glucocorticoids; 2) those with autoimmune diseases (rheumatoid arthritis, asthma, lupus, DM1); 3)menopause; 4) history of osteopenia and/or osteoporosis; 5) intestinal dysfunction (celiac disease, previous bariatric surgery); 6) cold geographic region. The Canadian Pediatric Society recommends periodic tests to measure levels of 25-hydroxy vitamin D and calcium for pregnant women and breastfeeding mothers [11].

The calcidiol is the metabolite which circulates in large quantity and has half-life of 2 weeks, therefore is considered the best indicator to evaluate vitamin D status [9] [13] [14].

There is no consensus about the exact cutoff level that should define a "sufficiency" regarding vitamin D levels [14]. There is a reverse correlation between PTH and 25-hydroxy vitamin D values, that means an increase in PTH as a biomarker reflects a low physiologic level of vitamin D. Therefore, to prevent vitamin D deficiency or to maintain a calcium homeostasis, it was suggested that the best cutoff of 25-hydroxy vitamin D would be 30 ng/mL (75 nmol/L), that means, the qualitative fundament is to consider as appropriate a level of vitamin D capable of maintaining the PTH in normal concentrations [12].

The laboratorial reference value can be expressed in ng/mL or nmol/L. In order to obtain nmol/L from ng/mL it is necessary to multiply the value in ng/mL by 2.5 times [14]. The maximum limit of normality was not defined yet, but some literature reports in the literature show intoxication by vitamin D based on hypercalciuria, regarding levels above 140 ng/mL of vitamin D [5]. According to Griz, an intoxication might occur if the level of vitamin D would be higher than 150 ng/mL [8].

3.3. Treatment and Goals

It is not recommended to prescribe vitamin D supplementation to the whole population. Those who would benefit from supplementation are patients at risk for hipovitaminosis D, as described before, and those with clinic contraindications to sun exposure, such as patients with skin cancer, transplanted or those with lupus [14]. There are still uncertainties about the ideal dosage to maximize the skeletal muscle health, and the formation of bone mass, as well as the exact dose to be used in order to increase the serum vitamin D levels above 30 ng/mL [4]. However, many authors report that higher levels are necessary in order to obtain healthy bones in diabetic patients, those with cancer and other immune diseases [7].

As already seen, vitamin D has the function not only to develop and maintain bone tissue health, the normal homeostasis of the calcium and phosphorus but also to act in the differentiation and proliferation of cells, notably on hormonal secretion (example: insulin), on the immune system (e.g.: lupus, rheumatoid arthritis, diabetes, asthma) and on chronic diseases (DM2, HAS, obesity), although no evidence confirms its efficacy in treating such disorders, but simply describe associations with these diseases.

In Brazil, the most available form of vitamin D for treatment, maintenance and prevention of DM is colecalciferol (vitamin D3), which is considered a more effective metabolite, and has an extended half-life, while ergocalciferol (vitamin D2) shows a short half-life (4 - 6 hours) and laboratory tests do evaluate their level isolated, but combined. Calcitriol and other active analogues of vitamin D, such as paricalcitol and dexercalciferol are used only in special cases, such as in acquired and genetic disorders of vitamin D, phosphate metabolism extreme bad absorption and IRC [14].

The current recommendation from US "Food and Nutrition Board" is that both pregnant and nonpregnant individuals aged from 0 to 50 years of age should consume 200 IU of vitamin D daily as individual intake [10]. For each additional 100 UI of vitamin D ingested orally per day, an increase of about 1 ng/mL of 25-hydroxy vitamin D results [7]. The dosage and duration of treatment varies according to the degree of deficiency, aiming to reach levels equal or over 30 ng/mL). If the patient is an infant, or in an obese adult, user of anticonvulsivant drugs, glucocorticoids, antifungals, ketoconazole or antiretroviral therapy for HIV, this patient should receive at least between 2 to 3 times more vitamin D according to the age, with a minimum of 6.000 to 10.000 UI/per day, and a and maintenance therapy of 3.000 to 6.000 UI/ per day [4].

The Canadian Academy of Pediatrics recommends the use of an additional 2.000 UI/per day during pregnancy and breastfeeding. According to the American College of Obstetricians and Gynecologists, when there is a diagnosis of deficit of vitamin D during pregnancy, an extra 1.000 - 2.000 UI/per day should be prescribed [15].

After a 6 - 8 week treatment for vitamin D deficiency, it is recommended to request new laboratory tests to evaluate the levels of 25-hydroxy vitamin D, to prescribe a "maintenance dose" and to continue with the changes in lifestyle. Attention should be given to avoid a hypervitaminosis D (25-hydroxy vitamin D > 100 ng/mL + hyperkalaemia and hyperphosphatemia with symptoms of tiredness, nausea and vomit). In patients who take 1,25(OH)D, it is suggested to monitor the levels of 25-hydroxy vitamin D and calcium, to prevent hyperkalaemia [4].

4. Relationship between Vitamin D and Diabetes Mellitus

4.1. Pathophysiology

Some specific mechanisms have been extensively investigated on the perspective of clarifying the function of

vitamin D on insulin secretion and action. The association between vitamin D and diabetes mellitus is explained by the following: a) the discovery of receptors of vitamin D (VDR) and 1α-hydroxylase enzyme inside beta cells; b) calcium-linking protein vitamin D-dependent (DBP) in the pancreatic tissue; and c) increase in the association between acquired and innate immunity [16].

The 1α-hydroxylase enzyme, within beta cells, converts 25-hydroxy vitamin D into 1,25(OH)2D, which is connected to the VDR's, which will form the heterodimer VDR/RXR (retinoid x receptor). After the translocation to the core of the cell, the complex is connected to VERE (vitamin D's element of response) in the promoter of the gene of the insulin and will activate the transcription of the insulin's gene, which will promote the cell's proliferation, differentiation and the immunomodulation [7] [17]. Recently, studies have suggested that a polymorphism of the RVD gene can confer genetic protection against DM1, and the polymorphism of the CYP27B1 gene has influence in the susceptibility for the DM1 [9] [11].

While in Type 1 diabetes a chronic inflammatory process occurs due to the presence of infiltration of the T(CD4+ and CD8+) cells, macrophages, lymphocytes B and NK cells in the beta cells of the pancreas, the insulitis as mentioned before. The macrophages and the dendritic cells secrete IL-12 which promotes the differentiation of the Th0 cells in Th1, stimulation those to secrete IFN-γ and IL-2 induces the migration of the T cytotoxic CD8+ cells, which are specifically against the auto antigens of the beta cells which in association with the class I molecules, cause the destruction of the beta cells through the mediated apoptosis by Fas and the release of perforin and granzyme. IL-1β, IFN-γ and TNF-α will stimulate this destruction of the cells. In vitamin D, the dendritic cells exposed to 1,25(OH)2D characterize by the reduced levels of the expression of the complex MHC Type II and co-stimulating molecules (CD40, CD80, CD86) which promotes a reduction of the presentation of antigens and a diminished secretion of IL-12, but an increase in production of IL-10, promoting, afterwards, the differentiation of lymphocytes Th2. The effects of 1,25(OH)2D on the acquired specific antigenic immunologic response, characterized preferably by the inhibition of the proliferation of lymphocytes T, especially the T cells helper 1 (Th1). Besides, the profile of cytokines of the human T cells treated with 1,25(OH)2D was compatible with of the Th2 cells , therefore the conclusion that vitamin D in vitro promote the change of the T cells, Th1 to Th2 has been reached [9]. That is, the usage of 1,25(OH)2D or analogs inhibits the secretion of cytokines pro-inflammatory Th1 (IL-2, interferon-γ, tumour necrosis factor α), Th9 (IL-9) and Th22 (IL-22) and promote the production of anti-inflammatory cytokines Th2 (IL-3, IL-4, IL-5, IL-10), inhibits the maturation of the dendritic cells and modulates the development of lymphocytes CD4 [7] avoiding stress in the beta cells, avoiding this way apoptosis in the beta cells [9].

With a sufficient level of 25-hydroxy vitamin D > 30 ng/mL, occurs the decrease of 1,25(OH)2D3 and the PTH induces the entrance of calcium in the cells core in the muscular tissues, adipose tissue and pancreatic cells (via the calcium canal), which stimulate signal transduction and activation of the glucose 4 transporter (GLUT4) for better insulin response [16].

The contribution of vitamin D to the metabolism of the glucose also implicates modifications in the concentration extra and intracellular of calcium in the pancreatic beta cells. The secretion of insulin is a calcium-dependent process mediated by 1,25(OH)2D3 and by the PTH. In case of 25(OH)D deficiencies and consequently the increase of PTH, it seems to promote reduction in the secretory capacity of the cells. This deficiency also can cause difficulties to the capacity of the beta cells in converting the pro-insulin into insulin, and also increase apoptosis of these cells into DM2 [18].

4.2. Treatment and Goals

Diabetes and hypovitaminosis D are frequent clinical situations around the world; therefore, lots of efforts have been made in the implementation of methods for monitoring and development of effective therapies for their control.

Vitamin D seems to have a role in the pathophysiology of Diabetes through the immunomodulatory and anti-inflammatory form, reducing insulin resistance, increasing insulin secretion and decreasing autoimmune insulitis, consequently reducing the risk of DM1 and DM2. It is possible, therefore, that the supplementation of vitamin D in an early phase could offer protection against the development of DM.

To date, the exact impact of vitamin D works in the pathophysiology of DM is unclear. New studies based on a larger groups of patients are necessary to show whether the administration of 25-hydroxy vitamin D or 1,25(OH)2D would significantly reduce the risk of DM1, or contribute to the preservation of adequate levels of

C peptide after diagnosis (17). As the exact cutoff value of vitamin D3 to protect against de development of DM, if it exists, is not known, most authors suggest that 25-hydroxy vitamin D levels should stay above 30 ng/mL, without a specific consequence in mind besides keeping it within the "normal" range.

5. Discussions and Results

Vitamin D is a steroid hormone and has two forms: vitamin D3 (colecalciferol), which is produced in 80% - 90% of the cases by skin absorption of the UVB, and vitamin D2 (ergocalciferol), produced by plants and fish. Known actions of it are in bone metabolism, in the kidneys and the parathyroid glands. In recent years a theoretical possibility of anti-inflammatory and immunomodulatory effects was raised in the medical literature.

Diabetes is a metabolic disease due to progressive destruction of beta cells in the pancreas. The pancreas is responsible for the production of insulin. Autoimmune and environmental factors are proved to be associated with its development. Diabetes prevalence is in a rise, specifically Type 2 diabetes, due to the obesity epidemic, the ageing of populations, and a sedentary lifestyle. There are many types of diabetes mellitus described through different ethiologies. Its treatment should be individualized. A high incidence of microvascular (diabetic nephropathy, diabetic neuropathy, diabetic retinopathy, diabetic foot) and macrovascular complications (acute myocardial infarction, stroke, thrombosis, peripheral arterial disease) have an important impact on life expectancy and on quality of life of diabetic patients. Antidiabetic drugs and lifestyle changes are associated with a better control of the progression of DM2 and its complications, as the key parts of its treatment.

Vitamin D deficiency and Diabetes are two endemic disorders, showing high prevalences in the world. Hypovitaminosis D has possibly become endemic due to the use of sunscreen, protective clothing and hats; to the increase of obesity, to the inappropriate ingestion of foods rich in vitamin D (fungis and fish) and to ageing.

Hypovitaminosis D is also associated with insulin resistance and to diabetes mellitus, that is, vitamin D seems to affect the glucose homeostasis. Vitamin D inhibits the inflammatory responses caused by cytokines, diminishes stress in beta cells, which in turn avoids pancreatic apoptosis cellular. Along with these discoveries on a cellular level, there are possibilities that vitamin D could have a role on the prevention of the beginning of insulin resistance.

Currently, the primary prevention of DM1 is the stimulation of the use of breastfeeding and vitamin D supplementation, and also the exposition to sunlight daily. For Type 2 diabetes, a different approach is necessary, regarding a change in lifestyle: starting physical exercises and a healthy diet aiming to avoid obesity, sedentary lifestyle, avoid smoking and ingestion of alcohol and blood pressure control. These measures are focused on patients at risk of developing diabetes, particularly pre-diabetic patients.

Regarding secondary prevention, there are evidences that the strict metabolic control has an important role in the prevention of the appearance or progression of its complications, as shown by the DCCT Trial for Type 1 diabetes, and the United Kingdom Prospective Diabetes Study (UKPDS), regarding Type 2 diabetes DM2.

6. Conclusions

A relevant association between Diabetes Mellitus and vitamin D levels has been documented in several studies, without a clear clinical meaning or practical use so far.

There are multiple controversies in the literature about the desirable cutoff values of 25(OH) vitamin D, regarding the definitions of "insufficiency", "deficiency", "sufficiency" and "over dosage".

A specific dose of vitamin D supplementation to be prescribed for populations in general is not available to date, due to the presence of individual factors such as different levels of sunlight exposure, geographic location and skin pigmentation.

The possible benefits of the ingestion of vitamin D in pregnant women are still unclear, regarding the possibility of vitamin D supplementation to prevent gestational diabetes mellitus, and whether keeping normal vitamin D serum levels in newborns (up to one year of age) could work to prevent Type 1 diabetes.

Studies show that vitamin D not only is associated with prevention of autoimmune diseases and chronic diseases, but can be also part of their treatment, in the future. It is unknown whether the cutoff value of 25(OH). Vitamin D is enough to prevent and/or to treat chronic diseases. Hypovitaminosis D is a risk factor for autoimmune diseases, chronic diseases and some types of cancers.

There is currently no strong evidence that confirms the role of vitamin D in the prevention or treatment of diabetes. In other words, the importance and benefits of vitamin D supplementation are still not clear for human health.

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References

[1] Araújo, S., Araújo, A., Gerhardt, N. and Ortiz, C.D.V.A. (2014) Diretrizes da Sociedade Brasileira de Diabetes: 2013-2014—Sociedade Brasileira de Diabetes. Organização José Egidio Paulo de Oliveira, Sérgio Vencio, AC Farmacêutica, São Paulo.

[2] Lamounier, R.N. and Laura, M.W. (2013) Pré-diabetes/Diagnóstico e Tratamento. 5 Edition, Capítulo 53, Doenças do Pâncreas Endócrino, Guanabara Koogan, Rio de Janeiro, 668-674.

[3] Vilar, L., Júnior, R.M.M., Almeida, S.L. and Forti, A. (2013) Endocrinologia Clinica. 5 Edition, Capítulo 6, Tratamento Farmacológico do Diabetes tipo 2, Guanabara Koogan, Rio de Janeiro, 633-637.

[4] Dasa, M. (2012) Um Novo Guideline e suas Implicações Práticas. *Revista Inovar Saúde*, **17**, 12-15.

[5] Castro, L.C.G. (2011) O Sistema Endocrinológico Vitamina D. *Arquivos Brasileiros de Endocrinologia & Metabologia*, **55**, 566-575.

[6] Schuch, N.J. (2011) Relação entre a Concentração sérica da Vitamina D, Polimorfismo no Gene VDR e Sindrome Metabólica em Indivíduos Adultos. In: EdUSP (São Paulo), Ed., *Programa de Pós-graduação em Nutrição em saúde Pública*, Faculdade em Saúde Pública, Universidade de São Paulo, São Paulo-SP, 12-103.

[7] Ramalho, A.O. (2013) A influência da vitamina D na patogênese da diabetes mellitus tipo 1. In: Centro Hospitalar do Porto, Ed., *Mestrado Integrado em Medicina*, Instituto de Ciências biomédicas Abel Salazar, Universidade do Porto, Porto, 1-39.

[8] Griz, L.H.M. (2013) Deficiência de Vitamina D em Mulheres Portadoras de Diabetes Mellitus tipo 2 na pós-menopausa. In: Biblioteca do Centro de Pesquisas Aggeu Magalhães, Ed., *Curso de Doutorado em Saúde Pública*, Centro de Pesquisa Aggeu Magalhães, Fundação Oswaldo Cruz, Recife-PE, 12-72.

[9] Lopes, P.M.A. (2014) O Papel da Vitamina D nas Doenças Autoimunes Sistêmicas. In: Centro Hospitalar do Porto, Ed., *Mestrado Integrado em Medicina*, Instituto de Ciências biomédicas Abel Salazar, Universidade do Porto, Porto, 1-16.

[10] Mulligan, M.L., Felton, S.K., Riek, A.E. and Bernal-Mizrachi, C. (2010) Implication of Vitamin D Dificienty in Pregnacy and Lactatin. *American Journal of Obstetrics & Gynecology*, **202**, 429.e1-429.e9.

[11] Kuelie, T., Groff, A., Redmer, J., Hounshell, J. and Scrager, S. (2009) Vitamina D: Uma Revisão Baseada em Evidência. *Journal of the American Board of Family Medicine*, **22**, 698-706.

[12] Borges, J.M. (2014) Suplementação com Vitamina D: Uma revisão sistemática. In: UFBA/SIBI/Bibliotheca Gonçalo Moniz, Ed., *Conclusão do curso de Medicina*, Faculdade de Medicina da Bahia, Universidade Federal da Bahia, Salvador-BA. 3-27.

[13] Marques, C.D.L., Dantas, A.T., Fragoso, T.S. and Duarte, A.L.B.P. (2010) A Importância dos Níveis de Vitamina D nas Doenças Autoimunes. *Revista Brasileira de Reumatologia*, **50**, 67-80. http://dx.doi.org/10.1590/S0482-50042010000100007

[14] Moeda, S.S., Borba, V.Z.C., Camargo, M.B.R., Silva, D.M.W., Borges, J.L.C., Bandeira, F. and Castro, M.L. (2014) Recomendações da Sociedade Brasileira de Endocrinologia e Metabolismo (SBEM) para o Diagnóstico e Tratamento da Hipovitaminose D. *Arquivos Brasileiros de Endocrinologia & Metabologia*, **58**, 411-433. http://dx.doi.org/10.1590/0004-2730000003388

[15] Pereira, M.V. and Solé, D. (2015) Deficiência de Vitamina D na Gravidez e o seu Impacto sobre o Feto, o Recém Nascido e na Infância. *Revista Paulista de Pediatria*, **33**, 104-113. http://dx.doi.org/10.1016/j.rpped.2014.05.004

[16] Schuchu, N.J., Garcia, V.C. and Martini, L.A. (2009) Vitamina D e Doenças Endocrinometabólicas. *Arquivos Brasileiros de Endocrinologia & Metabologia*, **53**, 625-633. http://dx.doi.org/10.1590/S0004-27302009000500015

[17] Griz, L.H.M., Bandeira, F., Andrade, M., Gabbay, M.A.L., Dib, A.S. and Carvalho, E.F. (2014) Vitamin D and Diabetes Mellitus: An Update 2013. *Arquivos Brasileiros de Endocrinologia & Metabologia*, **58**, 1-8. http://dx.doi.org/10.1590/0004-2730000002535

[18] Linhares, E.V.L. (2012) Determinação da Vitamina D e sua ralação com a resistência à Insulina em Pacientes Diabéticos Tipo 2. Dissertação, Programa de Pós-graduação em Alimentos e Nutrição, Universidade do Piauí, Terezina-PI. 11-48.