



DIABETES MELLITUS TYPE 1 AND HYPOVITAMINOSIS D: CURRENT CLINICAL ASSOCIATIONS

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ABSTRACT

Objective: to analyze scientific publications about the relation between hypovitaminosis D and Diabetes Mellitus type 1 (DM1).

Method: Integrative literature review, using the descriptors "Type 1 diabetes mellitus/diabetes mellitus tipo 1" and "vitamin D deficiency/deficiência de vitamina D" connected by the Boolean operator AND in the Pubmed, Lilacs and SciELO databases. Papers published between 2010-2017 was included, available in their entirety in Portuguese, Spanish and English, and the ones that answer this study main question.

Results: From the 237 papers found, just 6 answered this study main question. The hypovitaminosis D is related to DM1 by the following evidences: low sunlight exposure; modulation of the inflammatory response; increase and control of pancreatic secretion; control of autoantibodies in pancreatic islets; expression of C reactive protein in inflammatory processes.

Conclusion: The literature is scarce of publications that establish a relation between hypovitaminosis D and DM1. Experimental and prospective investigations need to be done to solidify the studied theme.

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INTRODUCTION

The hypovitaminosis D has been associated with several autoimmune diseases, mainly with diabetes mellitus (DM), common disease in different populations.

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The vitamin D deficiency (25-OHD) in the organism is highly prevalent in all races, geographic regions, ages and socioeconomic conditions. Studies indicate that low levels of vitamin D are related with pathologic conditions, such as osteomalacia, osteoporosis, osteoporotic fall and fracture (Bolland, 2010; Forouhi, 2008 and Holmes, 2009). Classic studies of epidemiologic design have been associating the deficiency of vitamin D2 (ergocalciferol) to the increased risk of non-skeletal diseases, such as cancer, multiple sclerosis,

diabetes mellitus type 1 (DM1), diabetes mellitus type 2 (DM2), gestational diabetes mellitus and cardiovascular diseases (Forouhi, 2008 and Holmes, 2009). This vitamin belongs to the group of steroids, which has as primary forms the vitamin D2 (ergocalciferol) and the vitamin D3 (colecalciferol). The main functions of these molecules are the regulation of the homeostasis, acting in the kidneys, bones and parathyroid glands, besides of the participation, in an essential way, on calcium and phosphorus absorption in the intestine (Bolland, 2010; Holmes, 2009; Janner, 2010). The identification of behavioral risk factors, such as nutritional ones (vitamin D) plays an important role in the primary prevention of the disease. However, mainly in the Latin America, there is a shortage of studies that establish the relation between hypovitaminosis D, the clinic and metabolic controls and the chronic complications in patients living with diabetes mellitus type 1. The results of this research can collaborate for establishing a relation between hypovitaminosis D with the metabolic control and the chronic complications of diabetes and, this way, corroborate scientifically the researched theme, helping on the formulation of health policies for chronic diseases, construction of guidelines and nutritional-clinic protocols for the prevention of hypovitaminosis D and other metabolic diseases. Finally, it is expected that this study has some multidisciplinary impact in the clinic care and healthcare spheres (Llewellyn, 2010).

MATERIALS AND METHODS

This is an integrative review (IR) where studies of the national and international literatures were selected, demarcating methodological phases, providing a better comprehension for healthcare professionals about the relation between hypovitaminosis D and DM1.

the integrative review: "What is the relation between Hypovitaminosis D and Diabetes Mellitus Type 1?". The searches were held in November of 2017, through the intersection of Descriptors in Healthcare Science (DECS) and its translations following the terms of Medical Subject Headings (MESH): type 1 diabetes mellitus/diabetes mellitus tipo 1, vitamin D deficiency/deficiência de vitamina D. These descriptors were linked by the Boolean operator AND.

- Establishment of the criteria for inclusion and exclusion of studies/sampling or literature search: The criteria for inclusion and exclusion of the studies were: scientific research available on-line in their entirety or in articles shape; published in the last five years (2011-2016), in Portuguese, English or Spanish. Were excluded articles with no relation with the proposed theme, studies not available gratuitously in their entirety in the consulted electronic bases, published in other languages except Portuguese, English and Spanish and studies with a methodological design that doesn't allow the identification of the proposed theme.
- Definition of the data to be extracted from the selected studies / characterization of the studies: There were extracted data such as Title of the Study; Authors; Year of Publication; Journal where the paper was published, City and Country of origin of the study; research Aims, studied Sample, applied Methodology and the main results obtained.
- Evaluation of the studies included in the Integrative Review: the selected studies were analyzed considering the accuracy and the characteristics of them aiming to find the main contributions around the theme;
- Interpretation of the results: the comparison of the data was proceeded utilizing other authors conclusions in the

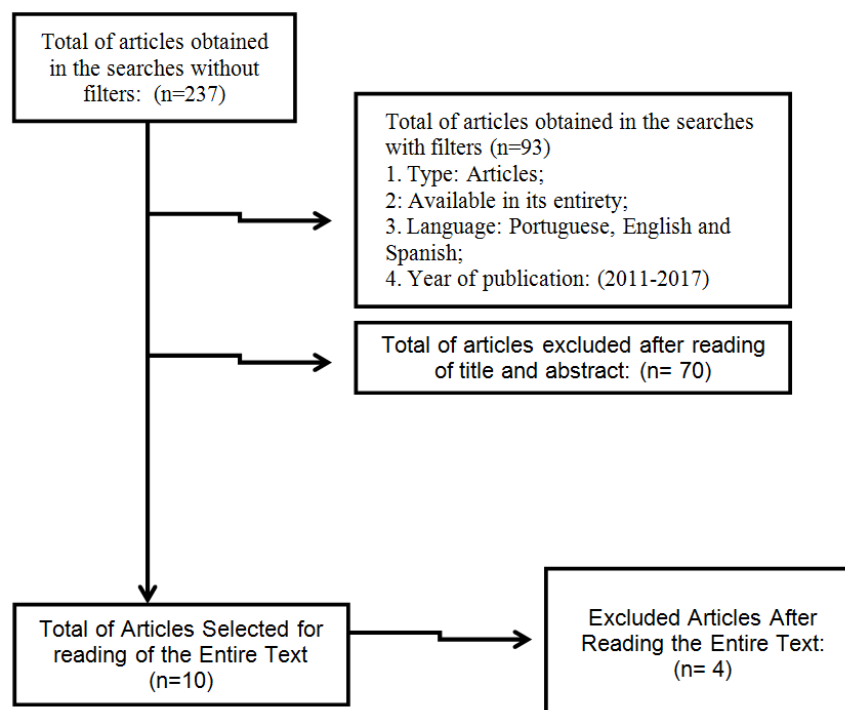


Figure 1. Flow chart of the methodological phases of the selection of articles for this study

The review was structured in 6 stages in order to increase the accuracy of the study (Mendes, 2008)

- Identification of the theme and selection of the hypothesis or research question for the elaboration of

literature, with delimitations of the conclusions and inferences of the researches. For the findings discussion in the study, the hypovitaminosis D was utilized as the category of analysis, articulating the interpretation with

the theorists who link its relation to Diabetes Mellitus Type 1.

- The Integrative Review Presentation: this integrative review is showed through a figure of tables, in a way that makes it clear, concise and objective according to its main results.

RESULTS

Using the methodology and descriptors aforesaid, there were found 237 articles. After the application of the inclusion and exclusion criteria, just as the reading of the titles and abstracts and the exclusion of duplicated papers, the sample of this study was composed of 6 articles, as demonstrated in Above Figure 1.

The Table 1 shows the intersection of descriptors used, the number of found articles and the number of included articles. In Table 2 the data referred to the articles included in this study can be observed (E1, E2, E3, E4, E5 and E6), presented duo the title, authors, year of publication and journal where they were published. In Table 3 the results that characterize the study of this review are showed, including the city and country where they were developed, the main objective of the study, the analyzed sample, methodology applied and the main found results.

DISCUSSION

After a rigorous evaluation in the literature about the relation between DM1 and hypovitaminosis D, there were found 10

Table 1. Result of the bibliographic search according to the database, descriptors, number of found articles and number of excluded articles after reading the title, subject and entire text

Data Base	Descriptors	NumberofArticles	IncludedPapers
PUBMED	Type 1 diabetes mellitus AND vitamin D deficiency	105	4
BVS	Diabetes mellitus tipo 1AND Deficiência de vitamin D	50	0
SCIELO	Type 1 diabetes mellitus AND vitamin D deficiency	79	2
	Diabetes mellitus tipo 1AND Deficiência de vitamin D	0	0
	Type 1 diabetes mellitus AND vitamin D deficiency	3	0
Total of the Research		237	6

Table 2. Selected articles, categorized in number of the study and classified in type of study, authors, year and journal of publication

Number	Title	Authors, year	Journal
E1	Lower vitamin D status is more common among Saudi adults with diabetes mellitus type 1 than in non-diabetics.	Al-Daghri NM, Al-Attas OS, Alokail MS, Alkharfy KM, Yakout SM, Aljohani NJ, Al Fawaz H, Al-Ajlan AS, Sheshah ES, Al-Yousef M, Alharbi M, 2014.	BMC Public Health
E2	Vitamin D status in diabetic Egyptian children and adolescents: a case-control study	Azab SF, Saleh SH, Elsaeed WF, Abdelsalam SM, Ali AA, Esh AM, 2013	Italian Journal of Pediatrics
E3	Hypovitaminosis D in children with type 1 diabetes mellitus and its influence on biochemical and densitometric parameters.	Vojtková J, Ciljaková M, Vojarová L, Janíková K, Michnová Z, Sagiová V, 2012.	Acta Médica
E4	Low vitamin D levels correlate with the pro inflammatory state in type 1 diabetic subjects with and without microvascular complications.	Devaraj S, Yun JM, Duncan-Staley CR, Jialal I, 2011.	American Journal Clinical Pathology
E5	Prevalence of vitamin D deficiency in pre-type 1 diabetes and its association with disease progression.	Raab J, Giannopoulou EZ, Schneider S, Warncke K, Krasmann M, Winkler C, Ziegler AG, 2014.	Diabetologia Journal
E6	Low levels of vitamin D in North Indian children with newly diagnosed type 1 diabetes.	Borkar VV ¹ , Devidayal, Verma S, Bhalla AK, 2010.	Pediatric Diabetes

Table 3. Characteristics of the selected studies according to the location, objective, sample, methodology applied and the main results

Numberofthestudy	City, Country	Objective	Sample	Methodology	MainResults
E1	Riyadh, Saudi Arabia	To evaluate the levels of vitamin D in adults Saudi carriers of DM1	120 pacientes.	Experimental, Case-control	Hypovitaminosis D bigger in group case DM1 + low sun exposure
E2	Zagazig, Egypt	To Evaluate the levels of vitamin D in children and teenagers Egyptian carriers of DM1	120 patients	Experimental, case-control	Vitamin D acts as modulator of autoimmune inflammatory response of DM1
E3	Martins, Slovakia	To stablish the relation between hypovitaminosis D and biochemical and densitometric parameters with children carriers of DM1	58 patients	Transversal, Quantitative, Analytical.	Vitamin D is associated with the increase and control of the pancreatic secretion of insulin
E4	Sacramento, USA	To relate hypovitaminosis D with DM1 and to relate DM1 with microvascular complications.	86 patients	Experimental, Case-control	Correlation between hypovitaminosis D and higher levels of C-Reactive Protein
E5	Neuherberg, Germany	To relate hypovitaminosis D with the progression of DM1 and the deficiency of autoantibodies in pancreatic islets	3140 patients	Cohorte, Prospective	Hypovitaminosis D is not associated to the progression of DM1, but it is related to the presence of autoantibodies in pancreatic islets
E6	Chandigarh, India	To evaluate the levels of vitamin D in children with and without DM1	100 patients	Case-control, Cohorte	Hypovminosis D is evident in the DM1 group and not evident in control group

articles, which after a critical analysis just 6 were chosen according to the objective of this paper. This fact emphasizes and proves the recent findings about the relation between hypovitaminosis D, DM1 and the information and publication deficits regarding the theme, highlighting that most of the publications discuss only DM2. The analysis of the type of publication showed up that none of the studies were published in the same journals and that 50% of them were published in English journals. The study E1 was published in BMC Public Health, the study E2 in Italian Journal of Pediatrics and the study E5 was published in the Diabetology Journal, both with head offices in England. Regarding the research design, it is identified that 50% of the articles had the same methodology, which the studies E1, E2 and E4 all were experimental, case-control, the study E3 was designed as a transversal, quantitative and analytical, the study 5 prospective of the type cohort and the E6 was designed as case-control and cohort.

The incidence of DM1 has been related to the latitude in several epidemiologic studies, which indicate that this factor explains 40% of the risk variation for DM1 in childhood. Evaluating the sample of articles obtained in this IR, it is observed that all of the studies were performed in countries from the north hemisphere with latitude above the tropic of cancer (Moraes, 2010; Mulligan, 2010 and Tahrani, 2010). In Europe, North and South Americas, Australia and China the DM1 increases proportionately to the latitude. Possibly the explanation for this event is linked to the level of vitamin D synthesized and metabolized by the solar radiation (Mulligan, 2010 and Pittas, 2010). The incidence of DM1 follows a global distribution pattern inverse to the quantity of UVB rays, in other words, the bigger is the latitude and the distance from the equatorial line, the smaller is the quantity of radiation UVB and the bigger is the number of cases of DM1 of this etiology (Mulligan, 2010; Pittas, 2010 and Chua, 2011). The literature also indicates a seasonal pattern of the disease where most of the diagnosed cases in children occur in autumn and wintertime and a smaller number of cases are diagnosed in spring and summertime. This pattern indicates a smaller number of DM1 with higher dairy temperatures and hours of sunlight, showing a strong relation with the levels of plasmatic vitamin D (Tahrani, 2010; Chua, 2011 and Devaraj, 2011). Regarding the values for detection of hypovitaminosis D, although it is still divergent in the literature, a general agreement shows that levels of 25-OHD under 50 nmol/L are enough for generating an increasing PTH and loss of bone mass.

The deficiency would be grave when the serum level of 25-OHD were under 25 nmol/L (10 ng/mL) (Devaraj, 2011; Hamed, 2011 and Sales, 2011). This way, it would be interesting to analyze individually the studies included in this RI. The study E1 has evaluated 120 adults, which 60 of them were diagnosed with DM1 and 60 were healthy people compounding the control-group, creating a relation between the deficiency of vitamin D in these two groups the following results could be found: The levels of 25-OHD were $33,4 \pm 1,6$ nmol/L in the group-control and $28,1 \pm 1,4$ nmol/L in the DM1 group. These results can be compared to other studies that show the increasing of the risk of DM1 with deficiency of vitamin D (Kordonouri, 2011 and Sales, 2011). The prevalence of vitamin C deficiency was bigger in the study E1 than in previous occidental studies comparing individuals with DM1 (Sales, 2011; Salvodelli, 2011; Diretrizes da Sociedade Brasileira de Diabetes, 2011; Sperling, 2011; American Diabetes Association, 2012). The nature of the low levels of

vitamin D in adults with DM1 is important because it can potentially clarify the mechanisms of autoimmune destruction of beta cells (Salvodelli, 2011; Diretrizes, 2011; American Diabetes Association, 2013). The study E2 got a sample of 120 individuals between 6 and 16 years old, which 80 of them were diagnosed with DM1 and 40 were healthy young people (group-control). The levels of 25-OHD showed that 44 diabetic people (55%) presented deficit of vitamin D and 36 cases (45%) showed normal levels, with an average of $24,7 \pm 5,6$ for 25-OHD. In the group-control 12 individuals (30%) have presented deficit of vitamin D and 28 individuals (70%) have presented normal rates with an average of $26,5 \pm 4,8$ nmol/L de 25-OHD. Comparing the results obtained in E2 with the literature some divergences with other researches can be observed, once that the differences between the levels of vitamin D in the diabetic group was not significantly lower than in the group-control (Diretrizes da Sociedade Brasileira de Diabetes, 2011; American Diabetes Association. 2013 and Kapellen, 2012). The study E3 has been performed with 58 individuals with DM1 from 9 to 19 years old, with the focus in compare the hypovitaminosis D occasioned by DM1 with biochemical and densitometric parameters, which 37 (63,69%) individuals has presented high levels of 25-OHD. Studies has been reporting that the supplementation of magnesium can increase the bones mineral density.

Magnesium is absorbed in the small intestine through the passive diffusion, independent of vitamin D, although the DM1 affects negatively the bones density and increase the risk of bones fractures (Griz, 2014 and Griz, 2013). However, when the supplementation of vitamin D is done, the absorption of magnesium is increased (Griz, 2014; Griz, 2013 and Lima, 2010). The article E4 discusses the relation between low levels of vitamin D and DM1 and the relation between DM1 and microvascular complications. The levels of glycated hemoglobin and glucose were higher in the diabetic groups than in the group-control, just as the values of C-reactive protein (CRP). These results corroborate the literature demonstrating evidences of the increase of systemic and cellular inflammations in groups DM1 with hypovitaminosis D, increase of PCR, increase of cytokines and monocytes and the activities of the Natural Killers cells (Griz, 2013&2014; Pludowski, 2013 and Júnior, 2014). The study E5 focus on the relation between hypovitaminosis D in pre-diabetics type 1 and the progression of the disease, and the relation between the deficit of vitamin D and the presence of autoantibodies in the pancreatic islets. Autoantibodies anti-islets cytoplasmic (ICA), autoantibodies anti-insulin (IAA), autoantibodies anti-decarboxylase of glutamic acid (anti-GAD) and autoantibodies associated to insulinoma (IA-2A) are a group of tests that measures autoantibodies associated to diabetes.

These autoantibodies do not cause the diabetes type 1 but they are markers of the immunologic response against the insulin-producing cells (Lima, 2010; Pludowski, 2013; Júnior, 2014; Moeda, 2014). Finally, the study E6 compared the values of vitamin D in diabetic and non-diabetic children from India, where the levels of 25-OHD were significantly lower in the group DM1 than in group-control. This study has obtained results similar to an experiment performed in Italy which has shown that the levels of vitamin D were low in the moment of the diagnosis of DM1 regard to the group-control (Pludowski, 2013). This one compares the seasons with the variable of vitamin D, reporting the no-existence of seasonal variability. The literature reaffirms the findings of high prevalence of

hypovitaminosis D in a population of adults from the same region where the study E6 was performed.²⁸⁻³⁰ However, the high prevalence of hypovitaminosis D conflict with the rates of DM1 in the populations of the studies selected for that RI, which were low when compared with countries where there is a prevalence of vitamin D, suggesting that hypovitaminosis is one among a lot of other factors responsible for the great variations in global rates of DM1 (Kapellen, 2012; Linhares, 2012; Tiwari, 2012; Whitehouse, 2012; Griz, 2014; Pludowski, 2013; Júnior, 2014; Moeda, 2014; Pereira, 2015).

Conclusion

Hypovitaminosis D is a situation associated with several morbidities, mainly the autoimmune ones. This RI has evaluated the relations established in the contemporary literature between the deficit of vitamin D and DM1. The main findings were:

- Relation between hypovitaminosis D and DM1 in groups with low sunlight exposure;
- Vitamin D acting as modulator of autoimmune inflammatory response of DM1;
- Vitamin D related to the increase and control of pancreatic secretion and insulin.
- Hypovitaminosis D acting in inflammatory processes expressing higher levels of reactive C protein;
- Hypovitaminosis D associated with the presence of autoantibodies of pancreatic islets;
- Expression of hypovitaminosis D in groups with established DM1.

The national and international literatures are scarce of productions that establish the relation proposed with the lead question of this integrative review. Most of the studies treat just about DM2, excluding DM1 as focus of the study. It is evident that experimental and prospective types of study are done with the intention of solidify the existent relation between hypovitaminosis D and DM1, since the majority of the studies are impartial under the physiological point of view. It is expected that this results help on the formulation of policies of health faced to chronic diseases and complement the guidelines and clinic and nutritional protocols for the prevention of hypovitaminosis D and consequently helping on reducing cases of DM1 and other autoimmune diseases, influencing positively the quality of life of the ones living with this comorbidity and the spheres of health care.

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