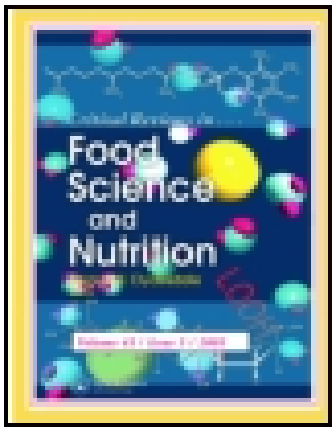

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Vitamin D Status and Glucose Metabolism in Youth

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Vitamin D Status and Glucose Metabolism in Youth

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Abstract

This study aimed to review and synthesize the available scientific evidence on the relationship between serum 25(OH)D concentrations and glucose metabolism among adolescents. A total of 19 studies were included. Many studies did not find a relation between 25(OH)D concentrations and insulin sensitivity, but most studies have shown that vitamin D status influences glucose dysregulation in youth due to particularities of this life stage. Considering the prevalence of vitamin D deficiency and insufficiency were high among adolescents, the importance for vitamin D status correction in this young group, in which chronic diseases are not expected but getting every day more common, is mandatory.

Key words: adolescent; vitamin D; insulin; glucose.

Introduction

The role of vitamin D (25 hydroxyvitamin D) in glucose homeostasis, pancreatic ß-cell function and insulin secretion and sensitivity has been investigated since the identification of vitamin D receptor in pancreas (Pechakara & Pittas, 2008). Additionally, *in vitro* studies have shown that vitamin D enhances insulin stimulated glucose transport and up-regulates transcription of the insulin receptor gene (Maestro et al., 2000; Maestro et al., 2002).

Adiposity is inversely related to serum vitamin D concentrations (Cheng et al., 2010). Accordingly, vitamin D deficiency is highly prevalent among obese children and adolescents (Smotkin-Tangorra et al., 2007; Rajakumar et al., 2008; Alemdazeh et al., 2008).

Glucose tolerance, insulin secretion, insulin sensitivity and body fat mass are strongly related physiological traits. Insulin has a major impact on body composition and body growth in youth (Veldhuis et al., 2005). Type 2 diabetes (DM2), a disease that used to be common only among adults and elderly, nowadays also affects children and adolescents. Fazeli Farsani et al. (2013), in a systematic review with 37 population-based studies in children and adolescents, found a range of 0ï 330 per 100,000 persons/years for DM2 incidence rates, and 0ï 5,300 per 100,000 persons for DM2 prevalence rates over the world. The lowest incidence rates were observed in European countries, while United States showed the highest. These data make clear how disturbances on insulin secretion and consequences on glucose metabolism are now a concerning health issue among youth.

Considering that adolescence is a crucial period for prevention of chronic diseases and that vitamin D insufficiency has been highly observed among this population, this study aimed to

review and synthesize the recent available scientific evidence on the relationship between serum vitamin D concentrations and insulin sensitivity among adolescents.

Methods

A review of literature from the last six years was made. The search included the original studies published from July 2007 to July 2013 that evaluated the relationship between serum vitamin D concentrations and insulin sensitivity among adolescents. Observational epidemiological studies and clinical trials (randomized or not, controlled or not) were accepted.

The search strategy of the original studies was designed to be used in PubMed database, and adapted to 4 other databases (Lilacs, SciELO, Scopus and Science Direct). The following search limits were considered: human studies, published in any language and date of publication from July 2007 to July 2013. Three sets of intersection of bibliographic search terms were combined: population (adolescent, adolescence, youth), vitamin D (hydroxyvitamin D, 25(OH)D, calcitriol, 25-hydroxyvitamin D) and outcome (insulin, glucose, glycemic).

Articles were rejected on initial screening if authors determine, based on the analysis of the title and summary, inadequate inclusion criteria or presence of any of the exclusion criteria for the review. Furthermore, articles with incomplete methodology were also excluded. In cases of uncertainty or disagreement, the full text was consulted to confirm their eligibility. In order to complement the search in bibliographic databases, lists of references of included articles were consulted to identify any possible relevant study previously unidentified.

The search strategy found 124 non-duplicate articles, and the vast majority was located through the first appointment made at PubMed (117 articles). At the end, 19 original studies that presented the outcomes measures of interest were selected.

The included studies were conducted in countries around the world, being most North-Americans (n = 11), 2 Europeans, 5 Asians and 1 South-American. Associations between serum vitamin D and glucose and/or insulin concentrations were investigated in 18 cross-sectional studies. One study investigated the vitamin D supplementation effects on insulin sensitivity. Studies characteristics, as design, country and population are shown in **Table 1**.

Some of the studies (n=7) that have evaluated vitamin D concentrations in adolescents also included children in their analysis. Although the target of this review was the subjects from 10 to 19 years old, we opted to maintain the studies that also analyzed younger subjects.

Vitamin D deficiency and insufficiency

Most studies evaluated serum 25(OH)D concentrations among children and adolescents, which is a commonly used marker of vitamin D status, since it represents both endogenous synthesis from the skin and dietary/supplements intake (Ganji et al., 2011). However, it is important to note that not all studies have used the same cutoff points that determine vitamin D insufficiency and vitamin D deficiency.

The vitamin D deficiency, usually but not always defined as serum 25(OH)D <50 nmol/L, has been shown to be common in healthy adolescent populations, with a higher prevalence in African American youth and during winter months (Holick, 2007; Rajakumar et

al., 2005; Alemzadeh et al., 2008). In a recent study with adolescents, 31.5% had vitamin D <50 nmol/L (deficient) and 48.3% had vitamin D from 50 to 75 nmol/L (insufficient) (Ford et al., 2011). Among the included studies, however, vitamin D deficiency varied from 11.2% to 100%.

Impaired glucose metabolism in youth

Glucose homeostasis is affected by different complex metabolic events that correlate and occur simultaneously. Despite the influence of 25(OH)D concentrations ï which will be better described below ï , other factors such as increased body weight can unbalance the physiological equilibrium between insulin activity in the peripheral tissues and ß-cell function.

Impaired fasting glucose and impaired glucose tolerance are the beginning of the spectrum of altered glucose metabolism that drives to type 2 diabetes development, and seems to be similar among youth and adults. ß-cell failure can be caused either by a functional defect, in which the cell gets unable to secrete adequate amounts of insulin in response to physiologically elevated blood glucose, or by a progressive reduction of ß-cell mass (Giannini & Caprio, 2013).

Adiposity is a strong determinant of insulin sensitivity and secretion (Goran et al., 2003), especially fat subdivision: visceral adiposity, as well as intra-myocellular and liver fat, characterize a significant increase in the risk of developing insulin resistance in obese children and adolescents (Weiss et al., 2003). Many studies also support that obesity in early life is associated with type 2 diabetes development at childhood, as also with increased risk of diabetes in later life (Giannini & Caprio, 2013).

In a study with children and adolescents from 8 to 18 years old, Tfayli et al. (2010) found that insulin sensitivity decreased as fasting plasma glucose increased even within the normal reference range, but insulin secretion did not increase sufficiently to maintain the glucose disposition index, what suggests that the impairments in insulin sensitivity and ß-cell response leading to diabetes may be evident at plasma glucose levels within the normoglycemic range. Insulin sensitivity results were also consistent with data from studies with adults, which have used different fasting plasma glucose categories.

Although the mechanisms of impaired glucose metabolism seem to be the same between youth and adults, some studies suggest that glucose dysregulation in youth may advance faster than in adults, possibly due to factors of pubertal development. Despite several other independent risk factors (such as ethnicity and genetic factors) and the transient pubertal insulin resistance (that seems to be a natural phenomenon necessary for growth and maturation, and reverses with time), it is suggested that youth may have a failure in the ß-cell compensatory response to insulin resistance (an inability to adequately compensate through increased ß-cell secretion) (Goran et al., 2003).

The growth hormone, which is high during this phase and declines with completion of puberty, could also play a role, once its administration to nonï deficient adolescents is associated with deterioration in insulin action (ADA, 2000).

When considering an adolescent with a genetic predisposition for insulin resistance compounded with environmental risk exposure, the additional charge of the transient pubertal insulin resistance may tip the balance from a state of compensated hyperinsulinemia with normal

glucose tolerance, to inadequate insulin secretion and glucose intolerance that are maintained beyond puberty and can reach type 2 diabetes diagnosis (ADA, 2000).

Finally, physical inactivity and dietary factors should be also considered as contributors to impaired fasting glucose and impaired glucose tolerance. Such conditions have been reported as severely inadequate around the world. Otherwise, it is believed that physical activity may decrease the risk for DM2 through associated or even independent factors such as improvement in peripheral insulin resistance, improvement in cardiovascular fitness or by promoting weight loss and visceral fat reduction (Duncan et al., 2003; Giannini & Caprio, 2013).

Regarding diet, a low-glycemic index diet with a greater amount of fibers and minimally processed whole grain products are shown to decrease glycemic and insulin responses, as well as higher intake of polyunsaturated fat (Hu et al., 2001).

Vitamin D status and glucose metabolism in youth

There is a recent increase in researching the effects of vitamin D status on glucose metabolism in adults, and such interest is now also extended to younger populations.

Data from the National Health and Nutrition Examination Survey (NHANES), a longitudinal follow-up study, including individuals from 12 to 17 years showed that, after adjustments, insulin concentrations were 24% lower among males with serum vitamin D Ó 75 nmol/L in comparison to those with serum 25(OH)D concentrations < 50 nmol/L ($p = 0.003$). In this study, 25(OH)D concentrations were inversely associated with glucose concentrations between Mexican-American boys, but not among girls (Ford et al, 2011).

Parikh et al. (2012), reassessing data from NHANES, conducted a multiple linear regression analysis which showed that in the lowest tertile of serum 25(OH)D, adolescents presented a significant increase in homeostatic model assessment-insulin resistance (HOMA-IR) and fasting glucose concentrations. Meanwhile, an analysis of three cycles from NHANES (2001-2002, 2003-2004, and 2005-2006) with adolescents from 12 to 19 years old (n = 5,867) found an inverse association between serum 25(OH)D and HOMA-IR, but not with fasting plasma glucose.

Studying African-American obese adolescents, Ashraf et al. (2009) found that whole body insulin sensitivity index (WBISI) was significantly lower among the 25(OH)D deficient group. This study also showed a tendency for higher fasting glucose and higher 2-hour insulin concentrations among the 25(OH)D deficient group. Other investigators have shown similar results, with significant inverse associations between vitamin D status and fasting glucose concentration, insulin concentration and/or HOMA-IR (Delvin et al., 2010; Johnson et al., 2010; Garanty-Bogacka et al., 2011; Kelly et al., 2011; Ashraf et al., 2011).

Expected associations were reported through different parameters when evaluating the relationship between vitamin D status and glucose metabolism during adolescence, as glycated hemoglobin (Alemzadeh et al. 2008; Williams et al 2011) and insulin sensitivity (Alemzadeh et al. 2008; Rajakumar et al 2012). However, findings are inconsistent among studies. Poomthavorn et al. (2012) found no relationship between serum 25(OH)D and HOMA-IR, WBISI, fasting plasma glucose, fasting insulin or 2-hour plasma glucose in Thai obese adolescents. Moreover, no correlations with glucose tolerance, insulin sensitivity or insulin secretion were observed by Ferrarezi et al. (2012) with Brazilian obese adolescents, and neither by Erdönmez et al. (2011)

with children and adolescents from Turkey. Besides an ethnic component was considered in the above mentioned studies, the differences regarding the latitude, zenith angle of the sun and sun exposure habits could have some influence in the observed results.

Furthermore, many studies included children in their analysis (which means non-pubertal subjects), which may impact differently the studied metabolic pathways. Khadgawat et al. (2012), evaluating the influence of puberty on glucose metabolism in obese individuals from 6 to 17 years old, reported an inverse relationship between 25(OH)D and HOMA-IR only in post-pubertal ones.

Better understood in adulthood, the relationship between 25(OH)D concentrations and glucose metabolism is not well explored among the youth, since the consequences of an altered glucose metabolism and insulin resistance or sensitivity in this period are mild. There are, however, possible evidences by which 25(OH)D insufficiency and/or deficiency could contribute to insulin resistance. First, there are gene polymorphisms of vitamin D receptor (VDR), vitamin D binding protein (DBP) and vitamin D 1Ŭhydroxylase (CYP1alpha), that could modify insulin secretion leading to insulin resistance and deregulation of glucose homeostasis (Oh & Barrett-Connor, 2002; Thrailkill, 2011; Malecki, 2003).

Second is the immune regulatory function of vitamin D, given that almost every cell of the immune system expresses VDR. Studies supported the role of 25(OH)D and calcitriol as anti-inflammatory agents. Calcitriol could inhibit T-cell proliferation, and as also can be produced by activated macrophages (Chagas et al., 2012).

In chronic inflammation, calcitriol could inhibit the release of the TNFŬ from the macrophages by regulating the activity of the NF-əƃ (Teegarden & Donkin, 2009) as well as suppress the expression of Toll like receptor 2 and 4 proteins, reducing the release of cytokines.

Lastly, disturbances on calcium-PTH axis can be mentioned. Hypocalcemia can lower glucose-stimulated insulin secretion in ƃ-cells (Yamaguchi et al., 2011). Higher PTH levels reduces insulin sensitivity and glucose uptake by liver, muscle and adipose cells (Harkness & Cromer, 2005).

Although obesity is an important determinant of both inadequate vitamin D status and abnormal glucose homeostasis, the relationship between these parameters was still significant when models were adjusted by adiposity parameters (Delvin et al., 2010; Johnson et al., 2010; Garanty-Bogacka et al., 2011; Kelly et al., 2011). In accordance, circulating 25(OH)D was negatively associated with glucose and HOMA-IR after adjusting by percent of body fat, season, sexual maturation, age and sex in American black and white adolescents living in Augusta, GA (33º North Latitude) (Parikh et al., 2012).

Studies that have evaluated the benefits of vitamin D supplementation on insulin and glucose metabolism during adolescence are scarce. Ashraf et al. (2011), after evaluating the relationship between 25(OH)D and the components of metabolic syndrome in obese adolescents, supplemented a subgroup of 14 deficient girls. Authors observed a trend for improvement in fasting glucose.

Belenchia et al. (2013) supplemented 35 obese vitamin D deficient adolescents with 4000 IU/day or placebo for 6 months. The supplemented group significantly increased 25(OH)D concentration, fasting insulin and HOMA-IR, suggesting that the correction of an inadequate

25(OH)D concentration may be important to the standard treatment of obesity and its associated insulin resistance. These results indicate that effects of vitamin D supplementation in glucose metabolism should be further investigated during adolescence, irrespective of geographical localization, sexual maturation, body fat, race and physical activity.

Since some of the differences observed between the studies (such as age, 25(OH)D measurement method and study design) could lead to different results, more prospective interventional controlled studies with different ethnicities, adequate sample size and vitamin D dosage and also greater power test are greatly needed to yield stronger results. Studies using gold-standard techniques to assess insulin resistance as well as 25(OH)D concentration would also bring valuable insights.

Indeed, because vitamin D insufficiency is nowadays a public health concern in many countries, and the prevalence of disturbances of glucose metabolism does not stop increasing, it would be prudent to maintain an adequate concentration of circulating vitamin D. This can be achieved by encouraging not only an active and outdoor lifestyle, but also a balanced diet, composed by foods naturally rich in vitamin D together with fortified foods, if available. When such condition is not achieved, then the vitamin D supplementation should be considered.

Conclusions

In summary, this review showed most evidences that vitamin D status could influences glucose dysregulation that is worsen during adolescence due to factors such as pubertal development and transient pubertal insulin resistance, as well as inadequate physical activity and

dietary habits. The vitamin D status may affect the secretion of pancreatic insulin through their effects on vitamin D metabolism-related genes, immune regulatory function and chronic inflammation. In addition, decreased 25(OH)D concentrations cause alterations in calcium-PTH axis, leading to the speculation that PTH may mediate the effects of vitamin D on insulin sensitivity and glucose tolerance.

Finally, considering the elevated prevalence of 25(OH)D insufficiency and deficiency among adolescents, in which chronic diseases are not expected but getting every day more common, the vitamin D status correction in this young group could contribute to a better health status during older ages.

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Table 1. Included studies: study design, country, population, sex, age and sample size.

Authors and year of publication	Study Design	Country	Population	Sex	Age	N
Alemzadeh R et al., 2008	Cross-sectional	USA	obese	M/F	6 to 17	127
Ashraf AP et al., 2009	Cross-sectional	USA	obese	F	mean = 14±2	51
Ashraf AP et al., 2011	Cross-sectional / Supplementation trial	USA	obese	F	mean = 14±2	80
Boucher-Berry C et al., 2012	Cross-sectional	USA	normal weight, overweight and obese	M/F	11 to 14	106
Delvin EE et al., 2010	Cross-sectional	Canada	normal weight, overweight and obese	M/F	9, 13 and 16	1745
Erdönmez D et al., 2011	Cross-sectional	Turkey	normal weight and obese	M/F	11 to 18	301
Ferrarezi DA et al., 2012	Cross-sectional	Brazil	obese	M/F	7 to 16	319
Ford ES et al., 2011	Cross-sectional	USA	normal weight, overweight and obese	M/F	12 to 17	1941
Ganji V et al., 2011	Cross-sectional	USA	normal weight, overweight and obese	M/F	12 to 19	5867
Garanty-Bogacka B et al., 2011	Cross-sectional	Poland	obese	M/F	10 to 18	64
Johnson MD et al., 2010	Cross-sectional	USA	normal weight, overweight and obese	M/F	2 to 18	302
Kelly A et al., 2011	Cross-sectional	USA	normal weight and obese	M/F	4 to 18	85
Mutlu A et al., 2011	Cross-sectional	Turkey	type 1 diabetes	M/F	2 to 20	120
Parikh S et al., 2012	Cross-sectional	USA	normal weight, overweight and obese	M/F	14 to 18	701
Poomthavorn P et al., 2012	Cross-sectional	Thailand	normal weight, overweight and obese	M/F	mean = 11.2 ± 2.6	179
Rajakumar K et al., 2012	Cross-sectional	USA	normal weight and obese	M/F	8 to 18	183
Shin YH et al., 2012	Cross-sectional	South Korea	normal weight and overweight	M/F	12 and 13	188
Williams DM et al., 2011	Cross-sectional	UK	normal weight, overweight and obese	M/F	12 to 19	740-5609
Belenchia AM et al., 2013	Randomized controlled trial	USA	obese	M/F	mean = 14 ± 3	35