Vitamin D and chronic diseases: the current state of the art

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REVIEW ARTICLE

Vitamin D and chronic diseases: the current state of the art

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Abstract The objective was to provide the current state of the art regarding the role of vitamin D in chronic diseases (osteoporosis, cancer, cardiovascular diseases, dementia, autism, type 1 and type 2 diabetes mellitus, male and female fertility). The document was drawn up by panelists that provided their contribution according to their own scientific expertise. Each scientific expert supplied a first draft manuscript on a specific aspect of the document's topic that was subjected to voting by all experts as "yes" (agreement with the content and/or wording) or "no" (disagreement). The adopted rule was that statements supported by ≥75 % of votes would be immediately accepted, while those with <25 % would be rejected outright. Others would be subjected to further discussion and subsequent voting, where ≥67 % support or, in an eventual third round, a majority of ≥50 % would be needed. This document finds that the current evidence support a role for vitamin D in bone health but not in other health conditions. However, subjects with vitamin D deficiency have been found to be at high risk of developing chronic diseases. Therefore, although at

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the present time there is not sufficient evidence to recommend vitamin D supplementation as treatment of chronic diseases, the treatment of vitamin D deficiency should be desiderable in order to reduce the risk of developing chronic diseases.

Keywords Vitamin D · Musculoskeletal disorders · Cancer · Cardiovascular diseases · Dementia · Autism · Diabetes mellitus · Hypogonadism · Fertility · PCOS · Environment · Lifestyle · Endometriosis

Introduction

The physiological role of vitamin D is to regulate calcium and phosphorus homeostasis and to preserve bone health (Holick 2007; Holick and Chen 2008). However, a growing body of research both from animal and human studies suggests that vitamin D may also be important for a variety of non-skeletal actions that may contribute to the pathogenesis of a wide range of acute and chronic diseases (Muscogiuri et al. 2014). Lack of vitamin D has been implicated in the pathogenesis of several acute and chronic illnesses including musculoskeletal disorders (Ooms et al. 1995), type 1 diabetes (Bierschenk et al. 2009), type 2 diabetes (Pittas et al. 2007), male hypogonadism (Blomberg Jensen 2012), polycystic ovary syndrome (PCOS) (Thomson et al. 2012), cancer (Grant 2016), autism (Saad et al. 2015), dementia (Annweiler et al. 2015) and cardiovascular diseases (Pilz et al. 2013). Of particular interest is the issue of the possible involvement of vitamin D in the management of these diseases. Thus, it appeared appropriate to gather a selected international panel of independent scientific experts in order to develop an evidence-based review that provides the current state of the art on vitamin D status in these diseases.

Methodology

Panelists provided their contribution to this document on their own responsibility. Each scientific expert supplied a first draft manuscript on a specific aspect of the review's topic. Articles were individually retrieved by each panelist up until March 2016, by search in PubMed (MEDLINE), EMBASE and Cochrane Library using at least one of the following terms: vitamin D, cardiovascular diseases, autism, musculoskeletal disorders, type 1 diabetes, type 2 diabetes, male hypogonadism, sperm, testosterone, PCOS, endometriosis, female fertility, osteoporosis cancer, autism and dementia supplemented by references included in the retrieved articles, meta-analyses and reviews. Studies were excluded if they were not in English. All manuscripts were then exchanged and discussed among all panelists by e-mail. Each statement was subjected to voting by all experts as "yes" (agreement with the content and/or wording) or "no" (disagreement).Adopted rule was that statements supported by $\geq$75 % of votes would be immediately accepted, while those with <25 % would be rejected outright. Others would be subjected to further discussion and subsequent voting, where $\geq$67 % support or, in an eventual third round, a majority of $\geq$50 % would be needed (Fig. 1). Lastly, the statements were distributed to the experts by e-mail for final comments. Only suggestions for improvements of clarity of wording or addressing redundancies were considered, while any changes to the meaning were not accepted.

However, several problems arose from the reviewing process, such as the different baseline vitamin D concentrations, the variability in vitamin D formulations and doses, the concomitant use of vitamin D with other medications, the extreme variability of the duration of the treatment, the heterogeneity of the methods to define the primary outcome and the usually small number of patients studied.

Vitamin D and osteoporosis

Current recommendations

Vitamin D supplementation is highly recommended for the treatment of osteoporosis. For adults aged 50 and older, the National Osteoporosis Foundation of the USA has recommended intake is 800–1000 international units (IU) per day (Cosman et al. 2014). In order to prevent osteoporosis-related fractures, vitamin D 700–800 IU/day should be complemented with calcium, using a dose of 1000–1200 mg/day of elemental calcium (Bischoff-Ferrari et al. 2005; Boonen et al. 2007).

Evidence

Vitamin D treatment has been reported to reduce loss of bone mass in women (Ooms et al. 1995; Macdonald et al. 2013). In order to identify the most effective vitamin D dose to preserve bone mass, a one-year randomized double-blind controlled trial comparing high-dose vitamin D3 (6500 IU/day) with the standard dose (800 IU/day) has been performed in vitamin D replete postmenopausal women with a BMD T score ≤ -2.0 in either lumbar spine (L2-4) or total hip. No difference in terms of efficacy has been found between the two doses (Grimnes et al. 2012).

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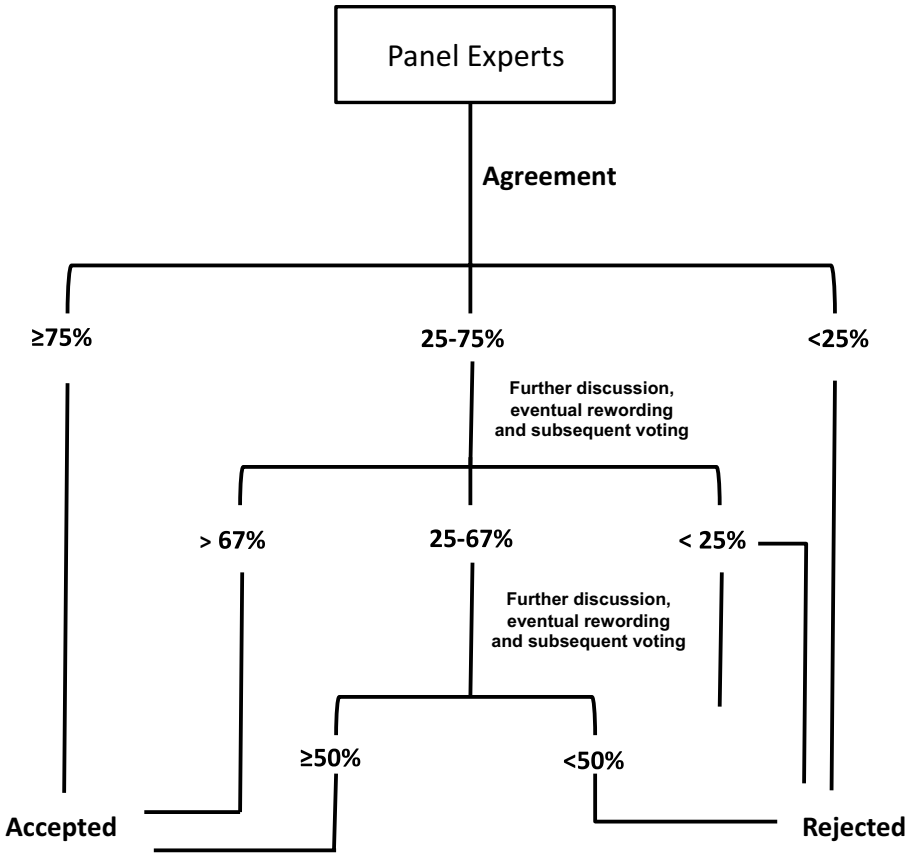

Fig. 1 Procedure for the selection and approval of the statements. Statements supported by ≥75 % of votes would be immediately accepted, while those with <25 % would be rejected outright. Others would be subjected to further discussion and subsequent voting, where ≥67 % support or, in an eventual third round, a majority of ≥50 % would be needed

In terms of bone fragility, vitamin D supplemented study participants over 65 years of age showed lower fracture outcomes as compared to non-supplemented ones. Furthermore, fracture prevention was achieved in both institution and community dwellers on vitamin D supplements (Bischoff-Ferrari et al. 2012).

A significant reduction in hip and non-vertebral fractures has been reported in a meta-analysis of studies performed in postmenopausal women supplemented with vitamin D at doses of 700–800 IU/day (Bischoff-Ferrari et al. 2005). A pooled analysis of studies comparing fracture prevention in individuals on vitamin D alone as compared to those on vitamin D and calcium has concluded that vitamin D and calcium in tandem was a prerequisite for fracture prevention, while solely vitamin D supplementation did not demonstrate this effect (Boonen et al. 2007; Group D 2010).

Remarks

The discrepancies in design and execution mode of the different trials do not facilitate head to head comparison of the results. Differences in regard to the mode of vitamin D delivery, i.e., oral or intramuscular, the dosing regimen, the study population, compliance assessment may prevent to draw definitive conclusions. Since most studies assessed efficacy of vitamin D along with calcium, the effect of vitamin D alone on bone health is difficult to estimate (Levis and Theodore 2012; Avenell et al. 2009; Bischoff-Ferrari 2012).

Vitamin D and cancer

Current recommendations

There are no current recommendations for vitamin D supplementation for preventing and/or treating cancer. Evidence coming from RCTs suggest that 25-hydroxyvitamin D [25(OH)D] concentration above 75 nmol/L may prevent cancer and improve survival after diagnosis (Grant 2016). To achieve this concentration, 1000–2000 IU/day vitamin D3 may need to be taken, depending on a number of individual and environmental factors (Holick et al. 2011).

Evidence

The evidence for a link of vitamin D and cancer comes from single-country geographical ecological studies, observational studies of cancer incidence and survival according to solar UVB dose or exposure, serum 25(OH)D concentrations, studies of mechanisms and clinical trials of vitamin

D supplementation. Perhaps the strongest evidence derives from the ecological studies. Such studies have found significant inverse correlations between solar UVB doses and incidence and/or mortality rate for 15–20 types of cancer. The findings from several mid-latitude countries are generally consistent with each other; other risk-modifying factors have been accounted for in many of these studies, and no mechanism other than vitamin D production has been suggested to explain these findings (Moukayed and Grant 2013). Both case–control and cohort studies have looked at cancer incidence with according to 25(OH)D concentrations. Such studies nearly always find an inverse correlation between 25(OH)D concentration and incidence of colorectal cancer (Grant 2015). Case–control studies consistently find an inverse correlation between 25(OH)D concentration measured near the time of cancer diagnosis and the prevalence of breast cancer; however, most prospective studies do not find such significant correlations (Grant 2015). The first trial to report a beneficial effect of vitamin D3 supplementation on cancer was one conducted on postmenopausal women living in Nebraska. They were given 1100 IU/day vitamin D3 and/or 1500 mg/day calcium or placebo (Lappe et al. 2007). The mean 25(OH)D concentration in those taking vitamin D3 rose from 72 to 96 nmol/L. Between the ends of the first and fourth years, those taking vitamin D3 plus calcium had significantly lower relative risk of incident cancer than those taking calcium alone.

Another trial that found a beneficial effect of vitamin D and calcium supplementation (400 IU/day vitamin D3 plus 1500 mg/day calcium) was the Women's Health Initiative, but only in those women who were not taking vitamin D or calcium prior to enrollment. In those women, supplementation significantly decreased the risk of total breast and invasive breast cancers by 14–20 % and non-significantly reduced the risk of colorectal cancer by 17 %" (Bolland et al. 2011). The mechanisms whereby vitamin D reduces the risk of cancer include reducing inflammation, effects on cellular differentiation, progression and apoptosis, while those increasing survival include reduced angiogenesis around tumors and reduced metastasis (Moukayed and Grant 2013; Fleet et al. 2012). Based on all the available evidence, UVB exposure and vitamin D may play important roles in reducing the incidence of many types of cancer and increasing survival after onset (Grant 2016).

Remarks

Data coming from prospective cohort studies had the main limitation that 25(OH)D concentrations were measured at the time of enrollment while cancer incidence was investigated for anywhere from three to about 20 years after enrollment, during which time 25(OH)D concentrations change. Clinical trials of vitamin D for cancer prevention have generally not been properly designed. They are largely based on the guidelines for pharmaceutical drugs, which assume that the only source of the agent is in the trial, and that there is a linear dose–response relation. Neither assumption is satisfied for vitamin D trials. Such clinical trials should start with an understanding of the 25(OH)D concentration-health outcome relation, measure 25(OH)D concentrations at baseline, enroll people with low 25(OH)D concentrations, supplement with enough vitamin D3 to advance 25(OH)D concentration along the relation, then measure achieved 25(OH)D.

Vitamin D and cardiovascular diseases

Current recommendations

There are no current recommendations regarding to vitamin D supplementation as therapy to prevent and/or cure cardiovascular diseases (CVD).

Data coming from RCT suggest that 25(OH)D concentrations above 50 nmol/L are sufficient to meet the vitamin D requirements in 97.5 % of the population (Ross et al. 2011). Under circumstances of no sunlight exposure supplementation of 800 IU vitamin D per day are required to achieve 25(OH)D levels above 50 nmol/L (Cashman 2015).

Evidence

The association between CVD and 25(OH)D is based on a considerable amount of longitudinal and cross-sectional observational studies (Pilz et al. 2013). Such studies have reported associations between serum 25(OH)D levels and cardiovascular risk, in particular stroke, myocardial infarction, heart failure and the ensuing CV mortality (Pilz et al. 2013). These epidemiological studies are despite careful adjustments, could be limited by residual confounding and reverse causation. Stronger evidence for a causal link between vitamin D and CVD comes from Mendelian randomization studies (Wang et al. 2010) and from case reports of children with rickets (Yilmaz et al. 2015). In these pediatric cases, left ventricular hypertrophy and heart failure resolved with vitamin D supplementation (Yilmaz et al. 2015). This is in line with an increasing body of evidence that especially patients with heart failure might benefit from vitamin D supplementation (Pilz et al. 2013).

Clinical trials of vitamin D supplementation for CVD prevention have nevertheless so far reported mostly negative results (Ford et al. 2014). Meta-analyses of RCTs showed no consistent effect on endothelial function, blood pressure, LV function, myocardial infarction, stroke or CV mortality (Pilz et al. 2013; Ford et al. 2014; Norman and Powell 2014). The vast majority of these RCTs (Pilz et al.

2012) have, however, not included sufficient participants in whom an effect would be most expected, i.e., individuals with vitamin D deficiency and at increased CVD risk.

Mechanistically the potential causal link is likely based on direct effects of vitamin D on the vitamin D receptor found on the vasculature and the myocardium (Yilmaz et al. 2015). Vitamin D receptor (VDR) knock-out animals and cell-based models have indicated that vitamin D is involved cellular cholesterol efflux, anti-inflammatory actions, the RAAS, parathyroid hormone (PTH) and fibrosis (Pilz et al. 2013; Norman and Powell 2014). Fibrotic remodeling of the myocardium and the vasculature is a major determinant of CVD progression, and vitamin D has repeatedly been implicated as a protective factor through suppression of matrix metalloproteinases and FGF-23 (Pilz et al. 2013; Norman and Powell 2014). Elevated PTH is considered to be a hallmark of vitamin D deficiency and may contribute to onset and progression of CVD (Pilz et al. 2013). Nevertheless, there is conflicting data in regard to lipid levels, with some studies even reporting adverse effects of vitamin D (Kelishadi et al. 2014).

Remarks

The epidemiological studies assessing the association between vitamin D and CVD may, despite careful adjustments, be limited by residual confounding and reverse causation. RCTs have so far not reported a consistent beneficial effect of vitamin D supplementation on hard CVD endpoints. It must, however, be acknowledged that there was a very high heterogeneity between the included RCTs and the number of patients at elevated risk suffering from vitamin D deficiency is too small to allow final conclusions.

Vitamin D and dementia

Current recommendations

Although determining a "cognition-based reference value" for optimal 25(OH)D concentration remains under debate, it appears that people with 25(OH)D < 25 nmol/L exhibit greater risks of dementia than those with 25(OH)D > 25 nmol/L, and even more compared to those with 25(OH)D > 75 nmol/L (Annweiler and Beauchet 2014). A supplementation plan designed to achieve a final 25(OH)D concentration of more than 75 nmol/L seems thus desirable to prevent the onset of dementia in healthy population and cognitive decline in patients with dementia. People can take 1000–5000 IU/day vitamin D3 depending on a number of individual and environmental factors.

Evidence

Vitamin D is involved in both neurophysiology (synthesis of neurotransmitters and neurotrophins) and neuroprotection (anti-inflammatory and antioxidant effects, clearance of amyloid-beta peptide) (Kalueff and Tuohimaa 2007). Hypovitaminosis D can be considered as a risk factor for cognitive decline and dementia, as supported by observational prospective longitudinal studies in humans reporting greater cognitive decline and increased dementia risk following hypovitaminosis D (Annweiler et al. 2015; Llewellyn et al. 2010).

The prevalence of hypovitaminosis D is high enough in people with dementia to justify measurement vitamin D in this population and to correct deficiency (Annweiler et al. 2015). Vitamin D likely explains, at least in part, the diversity of symptoms in dementia because hypovitaminosis D impairs the many organs other than the brain,and is associated with numerous co morbidities (Annweiler et al. 2015).

Few controlled trials are available. Some cognitive benefits were observed following 4 weeks of supplementation, with particularly marked improvements in executive functions and information processing speed (Annweiler and Beauchet 2013).

Remarks

The serum 25(OH)D concentration can not be used as a biomarker of dementia because hypovitaminosis D is common in older adults and not specific enough for dementia screening/diagnosis, or for evaluating the response or tolerance of medical treatment (Annweiler et al. 2015). Most trials that assessed the effect of vitamin D on dementia, and *a fortiori* the inconclusive ones, have generally not been properly designed. Vitamin D treatment may fail to have an effect on the onset and/or progression of dementia if lower doses are used, if participants are sufficient at baseline, if controls are treated, and if RCT 25(OH)D concentration is not measured before and on treatment in trials (Annweiler and Beauchet 2014; Annweiler and Beauchet 2013).

Vitamin D and autistic spectrum disorder

Current recommendations

The treatment with vitamin D of children with autism spectrum disorder (ASD) currently is not recommended. However, current evidence suggests that 25(OH)D levels should be at least 100 nmol/L to have a beneficial effect in children with ASD (Saad et al. 2015).

Evidence

A 3-month Egyptian study of 70 subjects affected by ASD matched with 42 healthy controls, found that serum 25(OH)D levels were inversely correlated with severity on the Childhood Autism Rating Scale (CARS) with ($R = 0.5$ and $P < 0.001$) (Meguid et al. 2010). An open-label trial of high-dose vitamin D (300 IU/kg/day up to a maximum of 5000 IU/day) in 83 of those 122 ASD subjects found, on a per protocol analysis, significant clinical improvement (mean CARS went from 37 to 30) (Saad et al. 2015) Approximately 75 % of supplemented ASD children improved ($P < 0.05$) with no evidence of toxicity. In fact, the highest 25(OH)D level in these children after 3 months of 300 IU/kg/day was 113 nmol/L. The subjects with ASD whose final 25(OH)D was >100 nmol/L had the most robust improvement on the CARS (Saad et al. 2015).

In another open-label study, 37 children aged 3–11 years with ASD were treated for 3 months with large bolus doses (150,000 IU/month given intramuscularly) together with 400 IU/day orally by the same research group that authored the case report referred to above (Feng et al. 2016). They found significant vitamin D treatment effects in ASD on standardized rating scales, again with no evidence of toxicity (Feng et al. 2016). The mean concentrations of the treatment group were 21 41 ng/ml at baseline and after 3 months of treatment, respectively, the highest level being 55 ng/ml. Significant improvement was found with the Autism Behavior Checklist ($P = 0.038$) and the CARS ($P = 0.016$) (Feng et al. 2016).

The first and only RCT of 109 ASD children aged 3–10 years by an Egyptian group using 300 IU/kg/day up to max of 5000 IU/day of vitamin D has been submitted for publication to the Journal of Child Psychology and Psychiatry (Saad et al. 2016, in press). In this study, all autistic children with 25(OH)D < 50 nmol/L were excluded from the study for ethical reasons and treated with vitamin D. Baseline 25(OH)D of the 109 study children (mean age 5.4 years) was around 68 nmol/L in both arms of the study. After the 4-month study duration, mean 25(OH)D in the treatment group was 47 ng/ml, while unchanged in the placebo arm. The highest 25(OH)D obtained in the "high dose" arm was 55 ng/ml. In a per protocol analysis, the total CARS scores significantly decreased (improved) in the vitamin D group, while they remained unchanged in the placebo group (mean CARS ± SD; 30.3 ± 6.1 vs. 36.4 ± 6.0; $P \leq 0.001$, respectively), again with no evidence of toxicity (Saad et al. 2016, in press). Younger children responded better than older children. In terms of prevention, an open-label study of infants born to mothers who already had one child with ASD, found 5000 IU/day of vitamin D given to the pregnant mothers and 1000 IU/day to the newborn child up to the age of 3 years reduced subsequent ASD incidence to 5 % instead of the 20 % which is the rate consistently reported in the literature for mothers who already had one or more autistic child (Stubbs et al. 2016).

Remarks

Well-designed and well-conducted RCTs using high-dose vitamin D [at least 400 IU/kg/day (10 mcg/kg/day) up to 10,000 IU (250 mcg)/day] to treat ASD with careful monitoring are needed. It is unknown if final 25(OH)D levels higher that 100 nmol/L would result in a more consistent treatment effect.

Vitamin D and type 1 diabetes mellitus

Current recommendations

There are no current recommendations to supplement subjects at high risk to develop T1DM or patients who are already affected with vitamin D. Data coming from both observational and RCT studies suggest to avoid vitamin D deficiency in individuals at risk of developing T1DM. Thus, 1500–2000 IU vitamin D daily could be a reasonable amount to prevent vitamin D deficiency and may thus contribute to reduce the burden of type 1 diabetes (Holick et al. 2011). At present evidence lacks to support vitamin D supplementation in vitamin D sufficient subjects in order to prevent T1DM.

Evidence

The evidence for T1DM comes from epidemiological data, small scale supplementation studies and meta-analyses (Mathieu 2015). There seems to be a positive, dose-dependent correlation between vitamin D supplementation in infancy (or even earlier during pregnancy) and a reduced risk of T1D and development of diabetes-related autoimmunity, whereas vitamin D deficiency in early life is clearly associated with a higher risk of T1D later in life (Van Belle et al. 2013). A meta-analysis of data clearly supports supplementation in early infancy irrespective of vitamin D levels and favors higher over lower doses for T1D prevention (Zipitis and Akobeng 2008). It has been shown in observational studies that T1DM patients with good glycemic control had higher 25(OH)D3 levels than T1DM patients with poorer glycemic control (Lamichhane et al. 2015). However, only small studies of interventions with vitamin D (or vitamin D analogues, i.e., alphacacidol) in type 1 diabetes mellitus are available. Overall, these studies use different compounds, different dosing regimens and included different cohorts (T1DM patients vs. latent autoimmune

diabetes of adults (LADA) and have inconsistent results on potential supplementation benefit. Further on the course of the diseases when diabetic complications appear caution is warranted as in a most recent study, symptomatic diabetic neuropathy was associated with low 25(OH)D levels (<50 nmol/L) and also, paradoxically, with even mild elevation of serum vitamin D levels above 100 nmol/L, showing a nonlinear or a U-shaped contribution of vitamin D to symptomatic diabetic neuropathy (Esteghamati et al. 2016).

Remarks

Clinical trials of vitamin D supplementation for T1DM prevention or treatment have generally not been properly designed. It is evident that the initial vitamin D level that demands intervention as well as the choice of the supplement 25(OH)D, active vitamin D, dosage and treatment regimen need clarification as hypercalcemia could be a potential side effect of high doses of active vitamin D, while low doses of regular vitamin D may be inadequate to modify the onset or the progression of the diseases, whereas high doses could potentially aggravate symptoms when diseases complications are present.

Vitamin D and type 2 diabetes mellitus

Current recommendations

Vitamin D supplementation is not recommended for the prevention and treatment of type 2 diabetes mellitus (T2DM). However, current evidence suggests that correcting vitamin D deficiency could be useful in subjects with T2DM. Vitamin D intakes of at least 1500–2000 IU/day for those aged 50–70 years should be recommended to raise the 25(OH)D concentration above 75 nmol/L (Holick et al. 2011). There has been no definitive benefit reported for vitamin D supplementation in subjects with sufficient concentrations vitamin D that are at high risk of, or that already have T2DM.

Evidence

Cross-sectional studies consistently show vitamin D status relates inversely to markers of the risk of later development of T2DM (from infancy, through childhood, adolescence and adult life) and to markers of the metabolic syndrome and of cardiovascular diseases (Boucher 1998). Prospectively, such associations are seen in children and adults, for components of the metabolic syndrome [known to precede T2DM and marking increased risks of cardiovascular diseases in T2DM], including dyslipidemia, increased protein glycosylation, increased arterial stiffness, hypertension and fatty liver. Vitamin D is necessary for adequate insulin release and secretion in response to glucose, reduces the overproduction of tissue-damaging free radicals, and blocks renin production (Li et al. 2002), thereby reducing islet-damaging effects of hyperglycemia with increased insulin resistance, including local pancreatic islet renin-angiotensin system overactivity (Cheng et al. 2013) and potentially reducing blood pressure increases over time. These protective effects reduce pancreatic islet damage, the major factor precipitating T2DM in those with increased insulin resistance (Cheng et al. 2013; Tepper et al. 2016). The benefits of ensuring continued vitamin D repletion also include reductions in hepatic lipid synthesis, normalization of lipid profiles in children (Leung 2016; Hirschler et al. 2014, 2015). Further vitamin D supplementation has been reported to improve the central obesity indices in T2DM subjects in particular in the carriers of the AA genotype of VDR-Cdx-2 (Shab-Bidar et al. 2015).

Remarks

Although vitamin D has been demonstrated to have beneficial effect both on insulin action and secretion, current RCT data provide conflicting results. This could explained by the fact that vitamin D supplementation could have a beneficial effect only when the damage of beta cell and/or insulin action is at the beginning. Once that damage has been already established, vitamin D may not be able to reverse it.

Vitamin D and male fertility

Current recommendations

Current recommendations do not support the use of vitamin D supplementation in the treatment of male hypogonadism and male infertility. However, data from cross-sectional studies (Ramlau-Hansen et al. 2011; Hammoud et al. 2012; Yang et al. 2012; Tartagni et al. 2015; Blomberg Jensen et al. 2011) suggest that vitamin D levels higher than 75 nmol/L could potentially reduce the risk of hypogonadism. On the other hand, effect of vitamin D on sperm function has not been assessed in placebo-controlled trials. Cross-sectional studies of this aspect (Lee et al. 2012; Lerchbaum et al. 2014; Tak et al. 2015; Bellastella et al. 2014; Wang et al. 2015) raise the possibility that values of vitamin D higher than 75 nmol/L might improve semen quality.

Evidence

Literature evidence suggests a possible relationship between vitamin D and testosterone levels. In fact, in vitamin D deficient rats, low values of serum testosterone

returned to normal after vitamin D supplementation (Sonnenberg et al. 1986). Also, 1,25-dihydroxyvitamin D3 increases LH-induced testosterone production in both immature and mature ram Leydig cells (Huang et al. 2015).

In humans, cross-sectional studies showed contradictory results. Both positive and lack of association between serum testosterone and vitamin D were found. As a trend, association was mainly found in subjects older than 40 years (Blomberg Jensen 2012).

To the best of our knowledge, there are four different placebo-controlled clinical trials evaluated the effects of vitamin D on testosterone levels. Of these, only one reported a significant increase in total testosterone levels after 3 332 IU daily vitamin D therapy for 1 year (Pilz et al. 2011), whereas two studies did not show any effect with vitamin D dosages of 20,000–40,000 IU per week or 600–1200–2000 IU/die (Jorde et al. 2013; Heijboer et al. 2015). In addition, Scholten and colleagues did not find a significant testosterone change after 4000 IU/die vitamin D supplementation, even if a trend was evident (Scholten et al. 2015).

Experimental studies suggest a possible role of vitamin D in spermatogenesis and sperm maturation in rats (Blomberg Jensen 2012). In rodents, successful mating between a healthy female and a vitamin D deficient male was reduced compared with vitamin D repleted males (Kwiecinski et al. 1989). Moreover, some clinical cross-sectional studies found an association between vitamin D levels and sperm parameters, even if other authors did not confirm this (Ramlau-Hansen et al. 2011; Hammoud et al. 2012; Yang et al. 2012; Tartagni et al. 2015; Blomberg Jensen et al. 2011; Blomberg Jensen et al. 2012; Zhu et al. 2016). Specifically, some authors found a positive association between vitamin D levels and sperm motility and morphology (Blomberg Jensen 2012; Yang et al. 2012), and other ones reported the existence of a relationship between male vitamin D levels and semen ability to begin a pregnancy during cycles of timed vaginal intercourse (Tartagni et al. 2015). On the other hand, other authors suggested an inverse or lack of association between these variables (Ramlau-Hansen et al. 2011; Hammoud et al. 2012). To the best of our knowledge, no clinical trial has ever evaluated the impact of vitamin D administration on sperm function.

Remarks

The populations included in the clinical studies differed in vitamin D and testosterone baseline levels as well as in the treatment period and in clinical status, thus partially justifying the discrepancies of the results. In view of definitive evidence on the potential usefulness of vitamin D supplementation on sperm profile, treatment of male infertility with vitamin D should be considered purely speculative.

Vitamin D and female fertility

Current recommendations

To date, the optimal levels of 25(OH)D during the reproductive period are still not clear. The Endocrine Practice Guidelines Committee suggests a daily intake of 1500–2000 IU of vitamin D3 for women between 18 and 70 years of age to raise a blood level of 25(OH)D at least 75 nmol/L. The same recommendations are given for pregnant/lactating women. However, if lactating women chose to not give the infant vitamin D supplementation, they may need to increase their vitamin D supplementation to 4000–6000 IU/day (Holick et al. 2011).

Evidence

The evidence favoring an association between vitamin D levels and female fertility derives from epidemiological studies that showed a seasonal variation in pregnancy rates in Northern countries with a high peak of the conception rate during summer (Rojansky et al. 1992). This event was partially explained by seasonal variation of vitamin D, which may influence endometrial and oocyte development.

In vitro studies have demonstrated that $1,25(OH)_2D_3$ stimulates the ovarian production of progesterone, estradiol and estrone and regulates the anti-Müllerian hormone expression in granulosa cells (Parikh et al. 2010). Moreover, VDR- and 1α-hydroxylase-null mice show uterine hypoplasia, impaired folliculogenesis and anovulation (Lerchbaum and Obermayer-Pietsch 2012).

Several studies have investigated the association between vitamin D and female reproductive disorders, such as polycystic ovary syndrome (PCOS), in vitro fertilization (IVF) outcome and endometriosis. PCOS is the most common endocrine disorder in women in their reproductive age. Observational studies have demonstrated that lower vitamin D levels are related to PCOS symptoms, such as insulin resistance, obesity, menstrual dysfunction, hirsutism and hyperandrogenism (Thomson et al. 2012). However, a meta-analysis has indicated that vitamin D was not different between women with or without PCOS (He et al. 2015). A limited number of studies demonstrated that the supplementation with vitamin D did not improve metabolic and endocrine features in PCOS, except for triglycerides levels and fasting insulin in comparison to placebo group (Thomson et al. 2012; He et al. 2015).

Endometriosis affects 10 % of women in the reproductive age. Observational studies have showed an overexpression of VDR and 1α-hydroxylase in the endometrium of women with endometriosis in comparison to healthy controls (Lerchbaum and Obermayer-Pietsch 2012). Moreover,

vitamin D may mediate the immunological mechanisms involved in the pathogenesis of this disease. However, no association between VDR genetic polymorphisms and endometriosis has been found and results coming from the small number of studies of vitamin D and endometriosis are in contrast. Similarly, observational studies investigating the association between vitamin D levels and IVF outcomes have revealed conflicting results (Lerchbaum and Obermayer-Pietsch 2012).

Remarks

Evidence regarding the association of vitamin D and female fertility is largely based on animal an observational studies rather than intervention trials, except for PCOS. However, the limited number of the intervention studies conducted in PCOS women was not randomized and was conducted in small cohorts of patients. Moreover, the baseline vitamin D levels and the supplementation of vitamin D varied between different studies.

Conclusions

While the majority of observational studies find that serum 25(OH)D concentrations are inversely correlated with incidence of the chronic conditions and diseases discussed in this paper, some have not. Those that did not might have suffered from an inaccurate assessment of the exposure (i.e., vitamin D status) and uncontrolled or residual confounding factors. Almost all observational studies used single measurements of serum 25(OH)D as a proxy of vitamin D status, which may not reflect vitamin D status over long periods, since risk factors for vitamin D deficiency increase with time (aging, declining physical activity and reduced time outside, etc.) and 25(OH)D concentrations vary seasonally. In addition, some study participants may have started taking vitamin D supplements shortly prior to entering the study, thus risk being placed in the incorrect 25(OH)D category based on long-term vitamin D status. There are fewer observational studies on disease progression or survival with respect to 25(OH)D concentrations.

As mentioned in several of the sections, clinical trials for disease prevention or treatment have generally not supported the observational studies. While this finding could be due to problems with the observational studies such as confounding or reverse causality, the more likely reason is poor design of the clinical trials. Therefore, a causal link between vitamin D deficiency and chronic diseases has not been proven and no single recommendation can be provided for or against vitamin D supplementation for prevention or therapy of chronic diseases, outside of osteoporosis. Ongoing and future trials are expected to provide answers as to whether long-term vitamin D repletion holds promise for endocrine health and chronic disease management.

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