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Vitamin D deficiency: A review of the relationship between vitamin Deficiencies somedisease as Obesity, Diabetes and Cardiovascular in Al-Muthanna Province - Iraq

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Abstract

Vitamin D deficiency is pandemic, and has been implicated in a wide variety of disease such obesity, diabetes and cardiovascular. Recent studies have found a relationship between vitamin D deficiency and an increase in the weight of people, it showed the presence of an enzyme responsible for the formation of vitamin D and the efficacy of metabolism , The lower action of this enzyme leads to a lack of vitamins and hence the low level of metabolic activity in people.Vitamin D deficiency predisposes individuals to type 1 and type 2 diabetes, and receptors for its activated form 1α,25-dihydroxyvitamin D3 have been identified in both beta cells and immune cells. The researchers shown role in the development of type 2 diabetes through impair insulin synthesis and secretion in humans andanimal models. Also , epidemiological studies suggest a link between vitamin D deficiency in early life and the later onset of type 1 diabetes. Also, several studies have reported that vitamin D deficiency is associated with increased risk of cardiovascular disease, including hypertension, heart failure and ischemic heart disease.

Keywords: Vitamin D; Obesity , Diabetes , Cardiovascular.

1. Introduction

The term vitamin D refers to the product that is in food (vitamins D2 and D3) and is synthesized in the skin under the influence of UVB radiation (vitamin D3), whereas the metabolically active molecule is referred to as 1,25 (OH)2D3[13]. Vitamin D is a fat-soluble vitamin known as calciferol. The two major forms of this vitamin are vitamin D2 (ergocalciferol) and vitamin D3 (cholecalciferol). Vitamin D is the only vitamin that can be manufactured by the body and therefore is sometimes referred to as a hormone as well as a vitamin[9] . The sun (UV-B irradiation) triggers a reaction in the skin that converts pro vitamin D to active vitamin D3 which is then transported to the liver and kidneys for further processing , but theexcess vitamin D is stored in fat tissue[28]. Our diet is another source of vitamin D as it can be absorbed through our intestine, Vitamin D is found naturally in a few products such as dairy products , Cheese , Butter , Cream ,Fortified milk , Fish (Salmon, mackerel, sardines, herring, tuna) , Fish oils , Egg yolks , Oysters ,Fortified cereal, Fortified juices[9].some researchers have recommended to be taken Vitamin D supplements that contain either cholecalciferol (vitamin D3) or ergocalciferol (vitamin D 2) with meals because the oily or fatty foods will cause the release of bile into the stomach which will increased absorption of the vitamin. Some studies indicate that vitamin D3 may work more efficiently and be superior to vitamin D2 [28].

Measuring Vitamin D levels

The level of vitamin D in our blood is measured by a 25(OH) D level and it is believed that a sufficient level of this vitamin in the blood ranges between 30-60 ng/ml [27].

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Vitamin D insufficiency:25(OH)D levels of 20 to 30 ng/mlVitamin D deficiency: 25(OH)D levels of below 20 ng/ml

Vitamin D toxicity: 25(OH)D levels of over 150 ng/ml

Vitamin D deficiency

There are certain groups of people that have an increased risk for vitamin D deficiency. These groups include[40]:-

1- Solely breast-fed infants older than 2 months of age

2- Individuals older than 50 years of age

3- Persons living in residential care facilities

4- Persons with problems absorbing fat, which includes those with:

Cystic fibrosis -

- Crohn's disease

- Celiac disease

- Some liver diseases

5- Persons with kidney disease, especially those requiring dialysis

6- Persons that have had gastric bypass surgery

7- Darker-skinned individuals

8- Persons using sunscreen (SPF8 or higher)

9- Obese individuals

10- Persons treated with certain drugs that may interfere with absorption or activity of the vitamin:

- Anti seizure drugs such as phenytoin, phenobarbital, and carbamazepine.
- Drugs used to treat tuberculosis such as isoniazid and rifampin.
- Other drugs including corticosteroids, theophylline (an asthma drug).

Chronic severe vitamin D deficiency in infants and children causes abnormal bones and it leads to rickets. While in adults, that causes muscle weakness, bone pain and osteoporosis and due to much higher risk for fractures especially in the elderly[5].

Vitamin D and Obesity

Obesityispandemic, defined by the World Health Organization as a body mass index (BMI) of 30 kg/m2 or more, affecting on the substantial numbers of people in most developed nations [17].overweight is included BMI (25–29.9), approximately 14 million Australians and 70% of Americans aged over 60, are obese or overweight [2]. Older people that suffering excess body fat accumulation face increased risk for coronary heart disease, hypertension, metabolic syndrome, osteoarthritis, diabetes mellitus, and other co-morbidities [8]. It is necessary to identify obesity risk factors, especially those that can be easily treated. In the published literaturethey found association between increasing BMI and lower serum 25-hydroxyvitamin D (25D) concentrations [8]. Early, thestudiesreported an association between obesity and low serum 25D concentrations, as well as high concentrations of parathyroid hormone (PTH) and 1,25-dihydroxyvitamin D (1,25D)[3]. Also been reported that body fat content is inversely related to serum 25D concentration, and that this associations is stronger than those between 25D and BMI and body weight [2]. The association between reduced 25D concentrations and obesity is well-established, therefore the mechanisms for the lower 25D concentrations are not fully described, and there is uncertainty as to what the health consequences of these lower concentrations mightbe[10].

ReducedActivationand/orIncreasedCatabolism

Vitamin D acts to limit production of its precursor, early studies suggested that 1,25D concentrations were elevated in obese individuals, it was thought that this may lower 25D levels[14]. Given that further, larger studies have suggested that 1,25D concentrations tend to be lower in obese individuals, this feedback mechanism is unlikely to be relevant[39]. Adipose tissue (AT) in obese women expresses the enzymes for both the formation of 25D and its active

metabolite, 1,25D and for degradation of vitamin D [11]. Subcutaneous Adipose tissue has also been found to have lower expression of one of the enzymes responsible for 25-hydroxylation of vitamin D (CYP2J2), as well as a tendency toward a decreased expression of the 1-α hydroxylase[30]. These data suggest that both 25-hydroxylation and 1-α hydroxylation are impaired in obesity. In vitro studies have demonstrated that 1,25D inhibits adiposeness and induces adipocyte apoptosis [14]. Under normal physiological conditions the serum 1,25D concentration is tightly regulated, but there can be significant differences between 1,25D concentrations within different tissues owing to in situproduction[15].There is also evidence that weight loss leads to increased 25D concentrations, which may in turn provide additional protection against chronic disease[15].

Table (1.1): WHO Classification of under and overweight in adults according to BMI.

Classification	BMI (kg/M2)	Risk of Comorbidities
Underweight	<18.5	Low
Healthy Weight	18.5-24.9	Average
Overweight	25.0-29.9	Increased
Obese Class I	30.0-34.9	Moderate
Obese Class II	35.0-39.9	Severe
(Obese Class III (Morbid)	>40.0	Very Severe

Obesity has been suggested to be a risk factor for vitamin D deficiency, The inverse association between higher body fat and lower vitamin D levels has been attributed to sequestration of the fat-soluble vitamin within the plentiful adipose tissue[9]. National population-based dataare lacking of the prevalence risk factors for vitamin D deficiency among over weight and obese children. Identifying vitamin D deficiency in these children may be particularlyimportant for their skeletal and cardiovascular health[15]. The research suggests that vitamin D deficiency increases the risk of these conditions Fractures, Blount disease, and slipped capital femoral epiphysis are more common in obese children[15]. Cardiovascular disease risk factors and impaired glucose homeostasis also are associated with vitamin D deficiency , these are more common in overweight and obese children[9]. Theprevalenceof vitamin D deficiency among children classified into clinically useful BMIpercentilecategories (overweight, obese,andseverelyobese)mayinform the need for screening and treatment ofvitaminDdeficiencybyprimarycare physicians[27].

Vitamin D and diabetes

The discovery of receptors for 1α,25-dihydroxyvitamin D3 (1,25(OH)2D3)that activated form of vitamin D, in tissues with no direct role in calcium and bone metabolism (e.g. pancreatic beta cells and cells of the immune system),It showed the physiological role of this molecule[23]. An increased of type 2 diabetes has been described in vitamin D-deficient individuals [16]. Also insulin synthesis and secretion have been shown to be impaired in beta cells from vitamin D-deficient and glucose tolerance is restored when vitamin D levels return to normal[21]. The determined of receptors for 1,25(OH)2D3 in cells of the immune system led to experiments in animal models of type 1 diabetes in which the giving of high doses of 1,25(OH)2D3 was shown to prevent type 1 diabetes mainly through immune regulation[21]. It has been demonstrated that 1,25(OH)2D3 is one of the most powerful blockers of dendritic cell differentiation and that it directly blocks IL-12 secretion, Lymphocyte proliferation is inhibited and regulator cell development is enhanced [23]. The role of vitamin D in type 1 and type 2 diabetes is clear, and it is possible applications of the molecule or its synthetic analogues in clinical disease[26].

Vitamin D and type 2 diabetes

VitaminDdeficiencywaslinkedtotype2diabetes in humans many years ago [4]. These observations were confirmed inanimalmodels,whichdetermined that pancreatic insulin secretion is inhibited by vitamin D deficiency [23]. Several reports have ascribed an active role to vitamin D in the functional regulation of the endocrine pancreas, particularly the beta cells[4]. Not only are receptors for 1,25(OH)2D3 found in beta cells but the effector part of the vitamin D

pathway is also present in the form of vitamin D-dependent calcium-binding protein, also known as calbindin-D28k [33]. The expression of calbindin-D28K has been shown to protect beta cells from cytokine-mediated cell death [29]. Several studies have demonstrated a link between VDR gene polymorphisms and type 2 diabetes, although the findings differ from one population to another[26]. A study in Bangladeshi Asians demonstratedthattheApaIRFLPinfluencesinsulinsecretioninresponsetoglucose[24].Whileassociations between the VDR ApaI RFLP and higher fasting plasma glucose levels and glucose intolerance were observed in a community-based study of older adults without known diabetes [24]. More recently, genotyping for TaqI, ApaI, BsmI and FokIRFLPs revealed that the BsmI RFLP is associated with high fasting glucose levels in young males with low physical activity[25].

Vitamin D and type 1 diabetes

Several epidemiological studies have described correlation between geographical latitude and theincidenceoftype1diabetes,andaninversecorrelationbetween monthly hours of sunshine and the incidence of diabetes[20]. A seasonALpatternofdiseaseonsethasalsobeendescribedfor type 1 diabetes, once again suggesting an inverse correlation between sunlight and the disease[16]. Vitamin D is an obvious candidate as a mediator of this sunshine effect[41]. Dietary vitamin D supplementation is often recommended in pregnant women and in children to prevent vitamin D deficiency[32]. Cod liver oil taken during the first year of life,its reduced the riskof childhood-onsettype1 diabetes [32].Also, a multicentercase-control study also showed an association between vitamin D supplementation in infancy and a decreased risk of type 1 diabetes [35]. A further study found that an intake of 2,000 IU of vitamin D during the first year of life decrease the risk of developing type 1 diabetes, and showed that the incidence of childhood diabetes was three times higher in subjects with suspected rickets [12]. More recently, the Diabetes Autoimmunity Study in the Young (DAISY) reported that the presence of islet auto-antibodies in offspring was inversely correlated with maternal dietary vitamin D intake during pregnancy [1]. It remains to be determined whether these observations are the result of supplementation of vitamin D to supraphysiological levels, or are simply the result of the prevention of vitamin D deficiency[7]. Observations in animal models suggest the latter, since regular supplements of vitamin D in neonatal and early life offered no protection against type 1 diabetes in nonobese diabetic (NOD) mice or in BioBreeding (BB) rats, whereas the prevalence of diabetes is doubled in NOD mice rendered vitamin D-deficient in early life[19]. The results of genetic studies investigating a possible relationship between VDR polymorphisms and type 1 diabetes are highly confusing: a clear correlation exist in some populations whereas no correlation can be found in others [22].

VitaminDandCardiovascularDiseaseVitamin D as a direct factor on cardiac tissues and the vasculatureduringafew in vitro and in vivo studies, especially in response to injury[34]. They demonstrated that matrix metalloproteinase (MMP) that contribute to aberrant cardiomycet remodeling in response to injury and atherosclerosis[38]. Vitamin D receptor have impaired cardiac relaxation and contractility and develop left ventricularhypertrophy and Clinical studies have evaluated the role of vitamin D directly on the vasculature[17]. A crosssectional study of subjects with ESRD demonstrated a significant positive correlation between vitamin D and arterial compliance that's measured by brachial artery flow mediated dilation and a negative correlation between aortic pulse wave velocity, both findings indicating decreased vascular compliance[18]. Vitamin D (1,25-hydroxyvitamin D) inhibited pro-fibrotic markers in vitro using mesenchyme multipotent cells, suggesting that vitamin D may also have a direct effect on the vasculature in response to injury[6]. Also, diabetic patients that ingested a large dose of vitamin D (100,000 IU) had significant improvement in endothelial function measured by flow mediated dilation and decrease in blood pressure[36]. Finally, a recent randomized controlled trial of vitamin D supplementation on people with heart failure and demonstrated significant reductions in inflammatory cytokines involved in the pathophysiology of heart failure[31].

Conclusion

Vitamin D insufficiency is very common in the world . Several recent studies have demonstrated association between vitamin D insufficiency and risk of injury of obesity, diabetes and cardiovascular disease. It showedassociation between reduced 25D concentrations and obesity they can be determined by a volumetric dilatational model. Thus, the obese individuals requires higher doses from vitamin D than the general population. Also, showed evidence exists that vitamin D deficiency arecauses damages to beta cells function and leads to glucose intolerance in animal and humans thus the individuals are suffering predisposes to type 2 diabetes. They found Vitamin D deficiency in early life predisposes humans then development of autoimmune diabetes.A major conclusion that can be drawn from the studies includes that vitamin D deficiency is not only effect on calcium and bone, but also for glucose metabolism. Finally, Several studies have suggested that vitamin D deficiency predisposes individuals to increased risk of incident hypertension, ischemic heart disease, sudden cardiac death or heart failure.

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