Liu, J Hypo Hyperglycemia 2013, 1:1
http://dx.doi.org/10.4172/2327-4700.1000102

Journal of Hypo & Hyperglycemia

Review Article

A SCITECHNOL JOURNAL

Vitamin D and Diabetes Mellitus: What Do We Know?

Jian Liu[1*]

Abstract

Diabetes mellitus, as a common metabolic disease, affects millions people's health worldwide and its incidence is continuing to increase. It is important to find effective measures of prevention and/or intervention for the disease to reduce its impact on the risk for cardiovascular disease – the leading cause of mortality among patients with diabetes mellitus. Apart from its well-known "classic" effect in bone metabolism, vitamin D has received widespread attention for its potential role in the prevention of diabetes mellitus, in particular type 2 diabetes mellitus. A large number of studies have observed a reverse relationship between vitamin D levels and the risk of diabetes mellitus. The results from the studies aiming to reduce risk for diabetes mellitus with vitamin D supplements are mixed though no study reports worsening the disease pathologically after treatment. Most previous studies on the relationship between vitamin D and diabetes mellitus were orientated from the direction of the "non-classic" effect of vitamin D, but the emerging evidence indicates that its "classic" effect on bone metabolism can be the key to understand its risk association with diabetes mellitus.

Keywords

Vitamin D; Diabetes mellitus; Bone metabolism

Abbreviations

$1,25(OH)_2D$: 1,25-dihyroxyvitamin-D; 25(OH)D: 25-dihyroxyvitamin-D; DBP: Vitamin D-Binding Protein; VDR: Vitamin D Receptor; T1D: Type 1 Diabetes Mellitus; T2D: Type 2 Diabetes Mellitus; GDM: Gestational Diabetes Mellitus; HLA: Human Leukocyte Antigen; CVD: Cardiovascular Disease; UVR: Ultraviolet Radiation; EUB: Erythemal Ultraviolet B; NOD: Non-Obese Diabetic; RAS: Renin-Angiotensin System; NHANES: National Health And Nutrition Examination Survey; RCT: Randomized Controlled Trial; RECORD: Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; WHI: Women Health Initiative; HAPO: Hyperglycemia and Adverse Pregnancy Outcome; IFG: Impaired Fasting Glucose

Introduction

Vitamin D

Vitamin D is well known for its primary physiological role of regulation of calcium homeostasis in maintaining bone health. However, growing evidence indicates that vitamin D is also involved in modulating body composition, energy homeostasis, insulin sensitivity, and immune function [1-3]; thus, vitamin D deficiency has been observed to be associated with a broadening field of health problems including certain cancers, cardiovascular disease, and diabetes mellitus [4-7].

There are two sources of vitamin D available for the human body; endogenous synthesis in the skin from exposure to sunlight and exogenous consumption in foods and/or pharmaceutical supplements. The endogenously synthesised vitamin D comprises approximately 80-90% of circulating levels of vitamin D [2]. As expected, season and latitude affect the levels of vitamin D [2,8,9].

The active metabolite of vitamin D in the human body is $1,25(OH)_2D$, which is generated in multiple steps. 25(OH)D is produced first in the liver through D-25 hydroxylase and then further converted to $1,25(OH)_2D$, primarily but not exclusively, in the kidneys by the 25(OH)D-1alpha-hydroxylases [10]. Within the circulation, DBP is the major transport protein for vitamin D metabolites in plasma. $1,25(OH)_2D$ can bind to the intracellular vitamin D nuclear receptors, which present in most tissues and cells of the body [11,12], and then initiate the activations that regulate not only calcium metabolism, but also differentiation and division of various cell types [13]. Although $1,25(OH)_2D$ is the biologically active form of vitamin D, however, serum 25(OH)D concentrations are recommended as the best indicator in reflecting vitamin D levels from either exposure to sunlight or dietary sources [10].

The primarily biological role of vitamin D is known for its regulating function of calcium metabolism to maintain extracellular calcium ion levels within a physiologically acceptable range. Since the physiologically acceptable range of calcium is very tight (8.5–10.2 mg/dL) and the concentration of calcium distribution between outside and inside of the cell is balanced at a vast difference ratio (10000:1), any change that occurs to the range or the balance will cause various disease sequelae [14]. Extreme vitamin D deficiency will result in rickets in children and osteomalacia in adults; while vitamin D deficiency in certain degrees will increase the risk for many metabolic diseases, particularly for diabetes mellitus [11]. The VDR has been found to be expressed in beta cells in pancreatic and other vitamin D related genes such as DBP and D-24-hydroxylase, which degrades the active form of vitamin D into water-soluble inactive forms [15]. Although many epidemiological studies and animal experimental studies have observed a reverse relationship between serum vitamin D levels and the risk of diabetes mellitus, it is not totally understood how vitamin D signaling plays a physiologically important role in beta cells and in the development of diabetes mellitus.

Diabetes mellitus

The increasing prevalence of diabetes mellitus is rising at an alarming rate globally. It is estimated that approximately 346 million people worldwide have diabetes and the incidence is continuing to increase [16]. Diabetes mellitus significantly increases the risk for coronary heart disease, stroke, renal failure, lower limb amputations, and visual impairment and blindness. People with diabetes mellitus require at least two to three times higher the health-care resources, which may account for up to 15% of national health care budgets [17]. Three main types of diabetes mellitus are recognized, i.e., T1D, T2D

***Corresponding author:** Jian Liu, PhD, Department of Community Health Sciences, Brock University, 500 Glenridge Ave. St. Catharines, OntarioL2S 3A1, Canada, E-mail: jliu@brocku.ca

Received: December 15, 2012 **Accepted:** January 27, 2013 **Published:** February 05, 2013

doi:http://dx.doi.org/10.4172/2327-4700.1000102

and GDM. The vast majority of the diabetic patients (90 – 95%) are with type 2 diabetes.

Type 1 diabetes mellitus: T1D, previously known as juvenile diabetes or insulin-dependent diabetes mellitus, is usually diagnosed in children and younger adults. The incidence of T1D is increasing in children and youth by about 3% (range 2–5%) per annum with approximately 76,000 children aged less than 15 years annually developingT1D worldwide [18]. The increase has been observed in countries with both high and low prevalence, particularly with a steeper increase in some of the low-prevalence countries [19]. The incidence rates of T1D vary between countries with countries such as China reporting the lowest incidence rates (about 0·57cases per 100,000 population younger than 18 years of age per year) to rates roughly 30 times higher in the UK (18–20 per 100,000 per year) to almost 100-fold higher (about 48–49 per 100,000 per year) in Finland and Sardinia [20]. T1D is seen predominantly in children younger than 15~ years of age with a significant trend towards decreasing age at presentation [18].

Individuals with T1D do not produce insulin in their body, which is believed to be the result of autoimmune processes between genetic and environmental factors. The variation of HLA genes is considered to contribute approximately 50% of the total genetic susceptibility to T1D [21]. Pathologically, T1D is a condition in which pancreatic cell destruction leads to absolute insulin deficiency. Two subtypes have been identified in T1D; type 1A, which includes the common, immune-mediated forms of the disease [22,23]; and type 1B, which is far less frequent, has usually unknown causes, and occurs mostly in individuals of Asian or African descent who have varying degrees of insulin deficiency between sporadic episodes of ketoacidosis [24]. The exact mechanism of the disease is not totally understood, but the consensus is that the majority of the patients with T1D acquire the disease as a result of autoimmune destruction of insulin-producing beta cells of the pancreas [20,22]. It is believed that several genetic and environmental risk factors are involved in the development of T1D.

Type 2 diabetes mellitus: T2D prevalence has been increasing dramatically worldwide in both genders during last three decades, but this increase is more dramatically seen in women (the prevalence of diabetes mellitus for women was increased 23% from 7.5% in 1980 to 9.2% in 2008; and for men by 18% from 8.3% in 1980 to 9.8% in 2008) [25]. Although originally described as a lifelong disease mainly occurring among the elderly adults, T2D (also known as adult-onset diabetes or non-insulin-dependent diabetes mellitus) is now observed to affect younger adults and even children. With the rise of overweight and obese individuals and the changing of life style, concern has risen about a global T2D epidemic [26]. It has been projected that the number of people with diabetes worldwide will increase from 171 million in 2000 to 366 million by 2030 with a noticeable increase from the developing countries. For instance, the number of people with T2D in China will have more than doubled from 20.7 million in 2000 to 42.3 million in 2030, which is a much faster rate than that in United States and Canada (19.7 million in 2000 to 33.9 million in 2030) [27]. Individuals with T2D usually have adverse lipid profiles and are at a significant risk of increased mortality from CVD [28].

In contrast to T1D, people with T2D are believed to have insulin insensitivity, initially with compensatory increase in insulin secretion, but the beta-cells in the pancreas may fail to keep up with the increased workload resulting in a relative insulin insufficiency and eventually the development of T2D. Although insulin insensitivity and beta-cell dysfunction are critical to the development of impaired glucose tolerance and T2D, the exact mechanisms are complicated and not well understood. There is a genetic basis for the dysfunction in both parameters, but environmental factors are undoubtedly to play a major role in its process. Vitamin D deficiency has been suggested to be one of the environmental factors and its relationship with the risk of T2D has been primarily investigated by a number of studies in humans [29].

Gestational diabetes mellitus: GDM is hyperglycaemia with onset or first recognition during pregnancy. Although the symptoms of GDM are similar to T2D, it is often diagnosed through prenatal screening, rather than reported symptoms. Women with GDM are at a great increased risk of developing T2D in comparison to those women without GDM [30].

Since lack of uniform standards in glucose tolerance testing for pregnant women in many countries there is not an accurate estimation of the global incidence of GDM [31]. The prevalence rates estimated in certain areas, such as Europe and China, were between 2.0 and 6.0% [32,33]. However, an international multicenter study of GDM conducted in a heterogeneous, multinational, multicultural, and ethnically diverse cohort with approximately 25,000 women in the third trimester of gestation found that about 18% (range 9.3 – 25.5%) of the pregnancies were affected by GDM after performing a 75-g oral glucose tolerance test [34]. It has been observed that GDM is more frequent in certain ethnic groups than in the general population. In general, white women have a lower incidence than black women; while Asian women have the highest rate [35].

Although usually an increase in the concentration of pregnancy hormones leads to a change of metabolism pattern of the body and may reduce tissues sensitivity to insulin, for some women pregnancy is a trigger for a series of metabolic imbalances that lead to a diabetic state. These women may have already been genetically vulnerable. In addition, when environmental factors, such as diet, obesity, depression, etc. are present these women may increase the likelihood of developing diabetes [36]. It has also been suggested that vitamin D deficiency may play a role for the occurrence of GDM [37].

Vitamin D Deficiency and Diabetes Mellitus

Vitamin D deficiency definition

Currently, no standard definition of optimal vitamin D status exists and there is a considerable controversy on the definition of vitamin D deficiency. The recently updated position statement from the Institutes of Medicine suggests that vitamin D as serum 25(OH) D with levels less than 30 nmol/L (12 ng/mL) is considered as deficiency; and less than 50 nmol/L (20 ng/mL) but higher than 30 nmol/L as inadequacy in regard to bone health [38]. However, many others believe that a much higher level of vitamin D may be needed to maintain overall health beyond just bone health [1], particularly when examining vitamin D levels and its risk association with diabetes mellitus and other chronic diseases. There is, currently, consideration of the widespread prevalence of hypovitaminosis D, as it may affect people worldwide, particularly the children and the elderly [1,2].

Vitamin D deficiency and type 1 diabetes mellitus

The seasonal pattern of the incidence of T1D has been observed by many epidemiological studies in different countries, regions, and ethnicity groups [39-42]. The incidence of T1D seems to peak more in the winter season than other seasons in many countries

located in both the northern and the southern hemispheres [41]. Since the primary source of circulating vitamin D in humans is largely derived from processes initiated by UVR exposure, which is in nature inversely associated with latitude, several studies have reported a latitudinal gradient for the prevalence of T1D [43-45]. In Newfoundland, Canada, one of the highest documented incidences of T1D worldwide, the results of ecological analysis have suggested a link between T1D risk and limited UVB exposure [46]. Data from 51 regions worldwide was used to examine the relationship between UVB irradiance and age-standardised incidence rates of T1D in children and indicated that the incidence of T1D was greater at higher latitudes [47]. Many observational studies have also showed that a lower level of serum vitamin D or vitamin D deficiency is very common among those newly diagnosed T1D patients in children, adolescents, and young adults [48-52].

NOD mice have been used as models in animal experimental studies to examine vitamin D deficiency and the risk of diabetes. The results from most of the studies, except for one [53], supported what has been observed from human's studies. NOD mice that are genetically predisposed to develop insulitis and T1D had the disease developed earlier when growing in a vitamin D depleted environment [54]. When the active metabolites of vitamin D were administrated in early life of these mice, it significantly decreased the risk of developing T1D [55,56]. Those treated with vitamin D had much higher levels of serum calcium [56]. The results from mice lacking VDR seemed to be more complicated. In comparing to NOD mice without VDR knockout, those VDR knockout NOD mice were not different in glucose homeostasis and incidence of diabetes [57,58]. However, those VDR knockout mice significantly increased mRNA expression and protein production from the local pancreatic islet RAS; while pre-treatment with 1,25(OH) could prevent and reverse the increase in the RAS component formation and improve insulin secretion. This formation is induced by high glucose concentrations in isolated mouse islets [57]. Furthermore, when those VDR knockout mice were fed a standard diet, the capacity of islet-cells to produce and/or secrete insulin was severely impaired by the hypocalcaemia, but it could be normalized with feeding a high-lactose calcium rescue diet [59]. This suggests that the effect of vitamin D on diabetes may, at least in part, be mediated through the role of calcium.

Results from several cohort or population-based case-control studies with vitamin D supplements supported the link between vitamin D deficiency and the risk of T1D, though some others did not. The results from a birth-cohort study of northern Finland indicated that taking vitamin D in early life could reduce the risk for T1D in later life. Approximately 12,000 Finnish children enrolled at a 1966 baseline. During an approximately 30 years follow-up, it was found that those children with suspected rickets during their first year of life had a 3-times higher risk of developing T1D later in life; while those who received at least 2000 IU/day of vitamin D during their first year of life reduced risk of developing T1D later in life by 88% [60]. A case–control study from a nested cohort conducted in Norway found that cod liver oil supplementation in infancy or during maternal pregnancy was associated with a lower risk of T1D [61,62]; and, further, that children from mothers with lower levels of serum 25(OH)D during pregnancy were at increased risk of T1D [63]. However, the results from two other studies showed that either maternal intake of vitamin D during pregnancy [64] or during infancy did not affect the risk of T1D [65], though both of these studies had no information on the fetal and/or maternal level serum 25(OH)D.

The distribution of the VDR gene and its relationship with T1D in human has also been examined by several studies though the results are inconsistent. For instance, a recently case-control study conducted in a group of Turkish patients with T1D found that bone turnover markers, such as osteocalcin and C telopeptide, and bone mineral density were significantly lower in patients with T1D, but that the VDR gene polymorphisms, Bsm1, Fok 1, Apa1, and Taq1 showed no difference between those cases and controls [66]. A similar result has been reported from a previous meta-analysis, which showed no association between VDR gene polymorphisms and T1D risk [67]. However, another meta-analysis conducted with the similar data suggested that the risk association of the VDR polymorphisms genes with T1D might be affected by the levels of winter UVR. Therefore, the involvement of VDR variants in the etiology of T1D could not be excluded [68].

Vitamin D deficiency and type 2 diabetes mellitus

The seasonal pattern for the risk of T2D does not appear as that for T1D, though a few of studies have shown seasonal variations of concentrations of pre-prandial glucose and HbA1c in T2D patients with levels higher in winter and lower in summer [69,70].

However, a number of observational studies have shown a reversed risk association of T2D with vitamin D in the relationship between higher levels of intake vitamin D and/or calcium and a lower T2D risk or that between lower levels of serum 25(OH)D and an increased risk for incident T2D [71-75]. The results from some other studies were not in favor of this link [76-78]. For instance, lower serum 25(OH) levels might be associated with the increased risk of incident T2D in men [73], but not in old women [78]. The ethnicity background seems to affect this association too; a reversed relationship between serum 25(OH)D and risk of T2D has been observed in New Zealand Polynesians and Caucasians, but those Polynesians had much lower levels of 25(OH)D [74]. Similarly, results from an analysis of the third NHANES showed a reversed relationship between serum 25(OH) D levels and T2D risk among Mexican-Americans and Hispanic Whites, but not in non-Hispanic blacks [75]. The results from another analysis conducted among middle-aged Caucasian men and women indicated that individuals with serum 25(OH)D levels >80 nmol/L were half as likely to have diabetes in comparison to those with levels <37 nmol/L [79].

In addition, central adiposity status is considered as an important factor to confound the risk association of T2D with vitamin D because patients with T2D often coexist with central adiposity [80,81]. Obese adults are more likely to be at high risk for vitamin D deficiency as body fat may sequester the fat-soluble vitamin [1]. Similar phenomena were also observed among children and adolescents who lived in different regions (e.g., 40.4 degree of N in Pittsburgh [82] and 33 degree of Nin Atlanta [83]) of the United States and Italy [84], but not among children and adolescents living the Bangkok (13 degree of N) [85] or adolescent girls in Beijing (40 degree of N), China [86]. Regardless of the obesity status, however, the mean levels of serum 25(OH) D for those children and adolescents in Bangkok were approximately 70 nmol/L; while for those girls in Beijing nearly 90% of them had serum 25(OH)D levels of <50 nmol/L, measured in winter time. This may suggest that obesity status may not be the issue as the majority of these subjects had either relatively high levels or relatively low levels of serum 25(OH)D. This question needs to be further explored. This may partially explain why in some studies adjustment for variables related to obesity (e.g., body mass index)

doi:http://dx.doi.org/10.4172/2327-4700.1000102

the reversed risk association of T2D with serum 25(OH)D levels still persisted [75,79], but in others were diminished [76].

A number of interventional studies have been conducted to examine whether vitamin D supplement can reduce the risk of T2D, but the results are mixed. For instance, a double-blind, RCT was conducted among 314 older Caucasians without diabetes showed that in comparison to those in a placebo group, those in the experimental group with daily intake 700 IU of vitamin D_3 and 500 mg of calcium for three years prevented increases in plasma glucose and insulin resistance among patients with impaired fasting glucose [7]. Patients with T2D in another two RCTs also showed that patients who consumed a vitamin D_3 fortified yogurt drink (1,000 IU/day) with either 500 mg/day or less calcium in comparison to patients who consumed plain yogurt improved glycemic status, lipid profile and endothelial biomarkers [87,88]. However, the results from two large-scale RCTs, the RECORD and the WHI, did not show benefits of daily intake of vitamin D_3 (800 IU/day alone or in combination with 1,000 mg/day of calcium in the RECORD or 400 IU/day with 1,000 mg/day of calcium in the WHI) in the prevention of the development of T2D [89,90]. Several small RCT's results suggested that significant vitamin D supplementation (either in a single dose of 100,000 IU or 40,000 IU/week for 6 months) on patients with T2D did not improve their glycemic status [91-93], but it might improve systolic blood pressure and endothelial function in a short term [92,94]. However, no study has shown worsening pathology of T2D while taking vitamin D.

Vitamin D deficiency and gestational diabetes mellitus

The prevalence rates of GDM vary by region, but are not affected by latitude. A review done by the Vitamin D and Lifestyle Intervention for Gestational Diabetes Mellitus Prevention research group indicated that although the prevalence rates differed by regions in Europe (ranges 2.0–6.0%), the lower prevalence rates of GDM were in the Northern or Atlantic seaboard parts of Europe (< 4%); while the higher prevalence rates (> 6%) predominated in the South or Mediterranean seaboard regions [32]. The results from the HAPO study also showed that the frequency of GDM was not affected by the latitude, for example, those higher than 25% of GDM included those results from Bellflower, USA (33 degree of N) and Singapore (1 degree of N); while those results lower than 12% were from Barbados (13 degree of N) and Beersheba (31 degree of N) [34]. However, whether the incidence of GDM differed by season seems unknown.

The results in regard to the relationship between vitamin D deficiency and GDM risk appear mixed with some of them in favor of it [95-97] and others not [98,99]. However, vitamin D deficiency (defined as <50 nmol/L) or insufficiency (<75~80 nmol/L) seems very prevalent in pregnant women [37,100-102]. The levels of serum 25(OH)D have been observed to be inversely associated with levels of HbA1c among women with GDM and this relationship seemed not to be affected by other known risk factors [103]. In addition, vitamin D deficiency has been linked to adverse outcomes of pregnancy, such as preeclampsia [78,98] and small-for-gestational-age babies [104], but this is beyond the scope of our focus here and will be given more detail discussion in other section.

Vitamin D, Bone Size and Diabetes Mellitus

Bone size and diabetes mellitus

Although VRD is present in most tissues and cells in the body, suggesting that vitamin D may have been involved in a wide range of biological actions, its role on calcium/phosphate homeostasis to maintain bone health is considered as the primary and classic function. Interestingly, the relationship between bone size and diabetic risk has long been noticed. For example, the standing height, leg length, the ratio of leg length/height, and femur bone length are all observed to have a negative association with the risk of T2D, GDM, and glucose intolerance [94,105-109]. However, in one study this negative relationship was only observed in white but not in black individuals [94]. Bone size and its risk for T1D appear not as sound as that for T2D because most incident T1D patients are still growing children and adolescents [110]. Among T1D adults, however, it has been found that short stature is associated with microvascular complications [111]. One explanation for this observed relationship is that these components of stature are indicators of factors acting during early childhood that affect the risk of developing diabetes in later life.

The new findings in bone metabolism suggest that bone is a critical endocrine organ and the molecular products from bone metabolism are involved in the global regulation of energy metabolism [112]. Osteocalcin, an osteoblast-specific protein during bone remodeling, is identified as a common link between bone and glucose metabolism in animal studies [113,114]. It was found in mice that osteocalcin can not only cause beta cells in the pancreas to release more insulin, but simultaneously, it can also direct fat cells to release more adiponectin, which increases sensitivity to insulin. The results from human studies, however, are mixed and depend on the type of diabetes and the stage. For instance, the low levels of osteocalcin at the baseline among normal males were observed to be associated with an increased risk for incident T2D in a nested case-control study [115]. Several studies have observed lower levels of osteocalcinin T1D patients with complications [116] and male T2D patients [117]. While for pregnant women, the levels of osteocalcin were higher in women with GDM than those without and it was suggested that osteocalcin may enhance insulin secretion in insulin resistance status [118].

Serum 25(OH)D levels, femur bone size and type 2 diabetes mellitus

It would be too simple to consider that the bone size in the observed risk relationship with diabetes was just a proxy indicator of nutritional factors on early childhood development based on the emerging evidence. Osteocalcin may be the key to explain the observed relationship between bone size and the risk for diabetes, but no study so far has been done to examine the relationship between osteocalcin and bone size.

However, using the data from the NHANES, we explored the relationship between serum 25(OH)D levels, femur bone size and T2D and found that the serum levels of 25(OH)D and all variables related to diabetes mellitus were negatively related to the gender-specific quintiles of femur bone lengths (Table 1) after adjustment for age, ethnicity, smoking, family history of diabetes, family income and waist circumference [119].

When analysis was conducted among those without T2D, we also found that the odds ratios of IFG (fasting glucose between 5.6 mmol/L and 6.9 mmol/L [120]) for quintiles 2–5 of femur bone lengths in comparison to the reference (quintile 1) were 0.94 (0.68, 1.31), 0.82 (0.59, 1.13), 0.76 (0.55, 1.05), and 0.63 (0.45, 0.86), respectively (p for trends <0.001).

VDR gene polymorphisms are found to have a link to adult height

Table 1: Adjusted# mean levels of vitamin D and other variables related to diabetes by quintile of femur bone length, the National Health and Nutrition Examination Survey (2001-2002, 2003-2004).

			Femur length quintiles			
	Q1	Q2	Q3	Q4	Q5	p-value for trends*
Males						
Range of femur length (cm)	31.0~	39.4~	41.2~	43.0~	45.0~53.4	
Serum 25-OH-vitamin D (ng/ml, mean)	23.7	24.2	24.6	25.0	25.4	c
Fasting plasma glucose (mg/dL, mean)	110.7	108.6	106.5	104.4	102.3	a
Fasting insulin (uu/ml, mean)	11.2	10.8	10.3	9.9	9.4	c
Glycohemoglobin: (%, mean)	5.67	5.61	5.56	5.51	5.45	a
Diabetes (%)	11.9	10.0	8.4	7.0	5.8	a
Females						
Range of femur length (cm)	26.4~	35.8~	37.7~	39.4~	41.1~50.9	
Serum 25-OH-vitamin D (ng/ml, mean)	22.6	23.2	23.8	24.4	25.0	b
Fasting plasma glucose (mg/dL, mean)	102.7	101.2	99.8	98.3	96.8	a
Fasting insulin (uu/ml, mean)	10.4	9.9	9.4	8.9	8.4	a
Glycohemoglobin: (%, mean)	5.61	5.55	5.49	5.44	5.38	a
Diabetes (%)	8.3	6.9	5.8	4.9	4.1	c
*a: <0.001, b: <0.01, c:< 0.05						

Adjusted for age, current cigarette smoking, ethnicity, blood relatives with diabetes, family annual income and waist circumference. [Reproduced with permission from J. Liu: Appl Physiol Nutr Metab 36: 264-270 (2011) NRC Research Press].

[121]. It is believed that adequate intake of vitamin D will help not only children to reach their genetically programmed height and peak bone density but also will help adults to prevent osteoporosis [122]. To maintain bone health, theoretically, taller adults may need more vitamin D than their shorter counterparts due to their longer bones that requiring more calcium. Since VDR is also found in beta cells, the active role of vitamin D in the functional regulation of the endocrine pancreas is confirmed [123]. Therefore, if there is no restriction of the intake of vitamin D, the serum level of 25(OH)D in adults should reflect an ideal level to meet the physiological needs for both bone calcium homeostasis and glucose metabolism. However, in reality, the serum level of 25(OH)D may be lower than the ideal level in many adults because of inadequate intake of vitamin D levels from either exposure to sunlight or dietary sources [124,125].

It is unclear how bone size in adults and vitamin D levels influence diabetic risk development. However, VDR is also expressed in osteoblasts and regulates the expression of several genes in this cell, including osteocalcin [126]. Although no data has showed how serum levels of osteocalcin are related to adults' stature, the level of serum osteocalcin is recommended as one of the indicators in treatment monitoring of osteoporosis [127]. In normal children, the serum levels of osteocalcin increase as they grow and the peak value of it occurs when they reach puberty [128,129]. The observed negative diabetic risk associations with bone size in adults may be due to the capability of producing osteocalcin which is affected by vitamin D. Poor nutrition, including inadequate intake of vitamin D in early childhood, affects children's growth, which may not only let the children have short bone size or short stature, but may also influence their glucose metabolic pathway. Those with serious deficiency of vitamin D may develop diabetes at an earlier age as shown by those Finnish children in whom those with suspected rickets during their first year of life had a 3-times higher risk of developing T1D later on [60]. However, this novel hypothesis needs to be further studied.

Conclusion

Emerging evidence suggests that vitamin D and diabetes mellitus are linked by biological associations. However, no clear evidence indicates a causal relationship between vitamin D deficiency and diabetes mellitus. In particular, the results from vitamin D supplementation studies are mixed and inconsistent, although no study has shown worsening of the pathology. Most previous studies on vitamin D and diabetes were orientated from the direction of its "non-classic" effect of vitamin D, but the emerging evidence suggests that its "classic" effect, on bone metabolism and via bone mediation, a newly recognized endocrine organ likely involved in energy metabolism and linked to the development of diabetes, may inform the direction of future research.

Acknowledgement

Thanks to Dr. Brian Jeynes for his help in editing this manuscript.

References

1. Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, et al. (2011) Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 96: 1911-1930.
2. Mithal A, Wahl DA, Bonjour JP, Burckhardt P, Dawson-Hughes B, et al. (2009) Global vitamin D status and determinants of hypovitaminosis D. Osteoporos Int 20: 1807-1820.
3. Wolden-Kirk H, Overbergh L, Christesen HT, Brusgaard K, Mathieu C (2011) Vitamin D and diabetes: its importance for beta cell and immune function. Mol Cell Endocrinol 347: 106-120.
4. Anderson JL, May HT, Horne BD, Bair TL, Hall NL, et al. (2010) Relation of vitamin D deficiency to cardiovascular risk factors, disease status, and incident events in a general healthcare population. Am J Cardiol 106: 963-968.
5. Garland CF, Comstock GW, Garland FC, Helsing KJ, Shaw EK, et al. (1989) Serum 25-hydroxyvitamin D and colon cancer: eight-year prospective study. Lancet 2: 1176-1178.
6. Garland FC, Garland CF, Gorham ED, Young JF (1990) Geographic variation in breast cancer mortality in the United States: a hypothesis involving exposure to solar radiation. Prev Med 19: 614-622.
7. Pittas AG, Harris SS, Stark PC, Dawson-Hughes B (2007) The effects of calcium and vitamin D supplementation on blood glucose and markers of inflammation in nondiabetic adults. Diabetes Care 30: 980-986.
8. van der Mei IA, Ponsonby AL, Engelsen O, Pasco JA, McGrath JJ, et al. (2007) The high prevalence of vitamin D insufficiency across Australian

populations is only partly explained by season and latitude. Environ Health Perspect 115: 1132-1139.

9. Pettifor JM, Moodley GP, Hough FS, Koch H, Chen T, et al. (1996) The effect of season and latitude on in vitro vitamin D formation by sunlight in South Africa. S Afr Med J 86: 1270-1272.
10. Holick MF (2009) Vitamin D status: measurement, interpretation, and clinical application. Ann Epidemiol 19: 73-78.
11. Adams JS, Hewison M (2010) Update in vitamin D. J Clin Endocrinol Metab 95: 471-478.
12. Holick MF (2007) Vitamin D Deficiency. N Engl J Med 357: 266-281.
13. Nagpal S, Na S, Rathnachalam R (2005) Noncalcemic actions of vitamin D receptor ligands. Endocr Rev 26: 662-687.
14. Fujita T (2000) Calcium paradox: consequences of calcium deficiency manifested by a wide variety of diseases. J Bone Miner Metab 18: 234-236.
15. Bikle D (2009) Nonclassic actions of vitamin D. J Clin Endocrinol Metab 94: 26-34.
16. WHO (2011) Diabetes.
17. WHO (2011) Global status report on noncommunicable diseases 2010.
18. IDF (2009) Diabetes in the Young: a Global Perspective. IDF Diabetes Atlas.
19. Aanstoot HJ, Anderson BJ, Daneman D, Danne T, Donaghue K, et al. (2007) The global burden of youth diabetes: perspectives and potential. Pediatr Diabetes 8: 1-44.
20. Daneman D (2006) Type 1 diabetes. Lancet 367: 847-858.
21. Risch N (1987) Assessing the role of HLA-linked and unlinked determinants of disease. Am J Hum Genet 40: 1-14.
22. Concannon P, Rich SS, Nepom GT (2009) Genetics of Type 1A Diabetes. N Engl J Med 360: 1646-1654.
23. Devendra D, Liu E, Eisenbarth GS (2004) Type 1 diabetes: recent developments. BMJ 328: 750-754.
24. Abiru N, Kawasaki E, Eguch K (2002) Current knowledge of Japanese type 1 diabetic syndrome. Diabetes Metab Res Rev 18: 357-366.
25. Danaei G, Finucane MM, Lu Y, Singh GM, Cowan MJ, et al. (2011) National, regional, and global trends in fasting plasma glucose and diabetes prevalence since 1980: systematic analysis of health examination surveys and epidemiological studies with 370 country-years and 2·7 million participants. Lancet 378: 31-40.
26. Zimmet P, Alberti KG, Shaw J (2001) Global and societal implications of the diabetes epidemic. Nature 414: 782-787.
27. Hossain P, Kawar B, El Nahas M (2007) Obesity and diabetes in the developing world--a growing challenge. N Engl J Med 356: 213-215.
28. Liu J, Sempos C, Donahue RP, Dorn J, Trevisan M, et al. (2005) Joint distribution of non-HDL and LDL cholesterol and coronary heart disease risk prediction among individuals with and without diabetes. Diabetes Care 28: 1916-1921.
29. Osei K (2010) 25-OH vitamin D: is it the universal panacea for metabolic syndrome and type 2 diabetes? J Clin Endocrinol Metab 95: 4220-4222.
30. Bellamy L, Casas JP, Hingorani AD, Williams D (2009) Type 2 diabetes mellitus after gestational diabetes: a systematic review and meta-analysis. Lancet 373: 1773-1779.
31. Ben-Haroush A, Yogev Y, Hod M (2004) Epidemiology of gestational diabetes mellitus and its association with Type 2 diabetes. Diabet Med 21: 103-113.
32. Buckley BS, Harreiter J, Damm P, Corcoy R, Chico A, et al. (2012) Gestational diabetes mellitus in Europe: prevalence, current screening practice and barriers to screening. A review. Diabet Med 29: 844-854.
33. Zhang F, Dong L, Zhang CP, Li B, Wen J, et al. (2011) Increasing prevalence of gestational diabetes mellitus in Chinese women from 1999 to 2008. Diabet Med 28: 652-657.
34. Sacks DA, Hadden DR, Maresh M, Deerochanawong C, Dyer AR, et al. (2012) Frequency of gestational diabetes mellitus at collaborating centers based on IADPSG consensus panel-recommended criteria: the Hyperglycemia and Adverse Pregnancy Outcome (HAPO) Study. Diabetes Care 35: 526-528.
35. Reece EA, Leguizamón G, Wiznitzer A (2009) Gestational diabetes: the need for a common ground. Lancet 373: 1789-1797.
36. Lain KY, Catalano PM (2007) Metabolic changes in pregnancy. Clin Obstet Gynecol 50: 938-948.
37. Dror DK (2011) Vitamin D status during pregnancy: maternal, fetal, and postnatal outcomes. Curr Opin Obstet Gynecol 23: 422-426.
38. Ross AC, Taylor CL, Yaktine AL, Del Valle HB (2011) Dietary Reference Intakes for Calcium and Vitamin D. National Academies Press.
39. Fleegler F, Rogers KD, Drash A, Travis LB, Rosenbloom AL (1978) The season and diabetes. Pediatrics 61: 325.
40. Kahn R, Anderson JE (2009) Improving diabetes care: the model for health care reform. Diabetes Care 32: 1115-1118.
41. Moltchanova EV, Schreier N, Lammi N, Karvonen M (2009) Seasonal variation of diagnosis of Type 1 diabetes mellitus in children worldwide. Diabet Med 26: 673-678.
42. Weets I, Truyen I, Verschraegen I, Van der Auwera B, De Schepper J, et al. (2006) Sex- and season-dependent differences in C-peptide levels at diagnosis of immune-mediated type 1 diabetes. Diabetologia 49: 1158-1162.
43. (1988) Geographic patterns of childhood insulin-dependent diabetes mellitus. Diabetes Epidemiology Research International Group. Diabetes 37: 1113-1119.
44. (2000) Variation and trends in incidence of childhood diabetes in Europe. EURODIAB ACE Study Group. Lancet 355: 873-876.
45. Staples JA, Ponsonby AL, Lim LL, McMichael AJ (2003) Ecologic analysis of some immune-related disorders, including type 1 diabetes, in Australia: latitude, regional ultraviolet radiation, and disease prevalence. Environ Health Perspect 111: 518-523.
46. Sloka S, Grant M, Newhook LA (2010) The geospatial relation between UV solar radiation and type 1 diabetes in Newfoundland. Acta Diabetol 47: 73-78.
47. Mohr SB, Garland CF, Gorham ED, Garland FC (2008) The association between ultraviolet B irradiance, vitamin D status and incidence rates of type 1 diabetes in 51 regions worldwide. Diabetologia 51: 1391-1398.
48. Borkar VV, Devidayal, Verma S, Bhalla AK (2010) Low levels of vitamin D in North Indian children with newly diagnosed type 1 diabetes. Pediatr Diabetes 11: 345-350.
49. Cooper JD, Smyth DJ, Walker NM, Stevens H, Burren OS, et al. (2011) Inherited variation in vitamin D genes is associated with predisposition to autoimmune disease type 1 diabetes. Diabetes 60: 1624-1631.
50. Littorin B, Blom P, Schölin A, Arnqvist HJ, Blohmé G, et al. (2006) Lower levels of plasma 25-hydroxyvitamin D among young adults at diagnosis of autoimmune type 1 diabetes compared with control subjects: results from the nationwide Diabetes Incidence Study in Sweden (DISS). Diabetologia 49: 2847-2852.
51. Pozzilli P, Manfrini S, Crinò A, Picardi A, Leomanni C, et al. (2005) Low levels of 25-hydroxyvitamin D3 and 1,25-dihydroxyvitamin D3 in patients with newly diagnosed type 1 diabetes. Horm Metab Res 37: 680-683.
52. Svoren BM, Volkening LK, Wood JR, Laffel LM (2009) Significant vitamin D deficiency in youth with type 1 diabetes mellitus. J Pediatr 154: 132-134.
53. Hawa MI, Valorani MG, Buckley LR, Beales PE, Afeltra A, et al. (2004) Lack of effect of vitamin D administration during pregnancy and early life on diabetes incidence in the non-obese diabetic mouse. Horm Metab Res 36: 620-624.
54. Giulietti A, Gysemans C, Stoffels K, van Etten E, Decallonne B, et al. (2004) Vitamin D deficiency in early life accelerates Type 1 diabetes in non-obese diabetic mice. Diabetologia 47: 451-462.
55. Mathieu C, Waer M, Laureys J, Rutgeerts O, Bouillon R (1994) Prevention of autoimmune diabetes in NOD mice by 1,25 dihydroxyvitamin D3. Diabetologia 37: 552-558.
56. Zella JB, McCary LC, DeLuca HF (2003) Oral administration of 1,25-dihydroxyvitamin D3 completely protects NOD mice from insulin-dependent diabetes mellitus. Arch Biochem Biophys 417: 77-80.

57. Cheng Q, Li YC, Boucher BJ, Leung PS (2011) A novel role for vitamin D: modulation of expression and function of the local renin-angiotensin system in mouse pancreatic islets. Diabetologia 54: 2077-2081.

58. Gysemans C, van Etten E, Overbergh L, Giulietti A, Eelen G, et al. (2008) Unaltered diabetes presentation in NOD mice lacking the vitamin D receptor. Diabetes 57: 269-275.

59. Driver JP, Lamont DJ, Gysemans C, Mathieu C, Serreze DV (2011) Calcium insufficiency accelerates type 1 diabetes in vitamin D receptor-deficient nonobese diabetic (NOD) mice. Endocrinology 152: 4620-4629.

60. Hyppönen E, Läärä E, Reunanen A, Järvelin MR, Virtanen SM (2001) Intake of vitamin D and risk of type 1 diabetes: a birth-cohort study. Lancet 358: 1500-1503.

61. Stene LC, Joner G (2003) Use of cod liver oil during the first year of life is associated with lower risk of childhood-onset type 1 diabetes: a large, population-based, case-control study. Am J Clin Nutr 78: 1128-1134.

62. Stene LC, Ulriksen J, Magnus P, Joner G (2000) Use of cod liver oil during pregnancy associated with lower risk of Type I diabetes in the offspring. Diabetologia 43: 1093-1098.

63. Sørensen IM, Joner G, Jenum PA, Eskild A, Torjesen PA, et al. (2012) Maternal serum levels of 25-hydroxy-vitamin D during pregnancy and risk of type 1 diabetes in the offspring. Diabetes 61: 175-178.

64. Marjamäki L, Niinistö S, Kenward MG, Uusitalo L, Uusitalo U, et al. (2010) Maternal intake of vitamin D during pregnancy and risk of advanced beta cell autoimmunity and type 1 diabetes in offspring. Diabetologia 53: 1599-1607.

65. Simpson M, Brady H, Yin X, Seifert J, Barriga K, et al. (2011) No association of vitamin D intake or 25-hydroxyvitamin D levels in childhood with risk of islet autoimmunity and type 1 diabetes: the Diabetes Autoimmunity Study in the Young (DAISY). Diabetologia 54: 2779-2788.

66. Gogas Yavuz D, Keskin L, Kıyıcı S, Sert M, Yazıcı D, et al. (2011) Vitamin D receptor gene BsmI, FokI, ApaI, TaqI polymorphisms and bone mineral density in a group of Turkish type 1 diabetic patients. Acta Diabetol 48: 329-336.

67. Guo SW, Magnuson VL, Schiller JJ, Wang X, Wu Y, et al. (2006) Meta-analysis of vitamin D receptor polymorphisms and type 1 diabetes: a HuGE review of genetic association studies. Am J Epidemiol 164: 711-724.

68. Ponsonby AL, Pezic A, Ellis J, Morley R, Cameron F, et al. (2008) Variation in associations between allelic variants of the vitamin D receptor gene and onset of type 1 diabetes mellitus by ambient winter ultraviolet radiation levels: a meta-regression analysis. Am J Epidemiol 168: 358-365.

69. Liang WW (2007) Seasonal changes in preprandial glucose, A1C, and blood pressure in diabetic patients. Diabetes Care 30: 2501-2502.

70. Ishii H, Suzuki H, Baba T, Nakamura K, Watanabe T (2001) Seasonal variation of glycemic control in type 2 diabetic patients. Diabetes Care 24: 1503.

71. Pittas AG, Dawson-Hughes B, Li T, Van Dam RM, Willett WC, et al. (2006) Vitamin D and calcium intake in relation to type 2 diabetes in women. Diabetes Care 29: 650-656.

72. Kirii K, Mizoue T, Iso H, Takahashi Y, Kato M, et al. (2009) Calcium, vitamin D and dairy intake in relation to type 2 diabetes risk in a Japanese cohort. Diabetologia 52: 2542-2550.

73. Knekt P, Laaksonen M, Mattila C, Härkänen T, Marniemi J, et al. (2008) Serum vitamin D and subsequent occurrence of type 2 diabetes. Epidemiology 19: 666-671.

74. Scragg R, Holdaway I, Singh V, Metcalf P, Baker J, et al. (1995) Serum 25-hydroxyvitamin D3 levels decreased in impaired glucose tolerance and diabetes mellitus. Diabetes Res Clin Pract 27: 181-188.

75. Scragg R, Sowers M, Bell C (2004) Serum 25-hydroxyvitamin D, diabetes, and ethnicity in the Third National Health and Nutrition Examination Survey. Diabetes Care 27: 2813-2818.

76. Grimnes G, Emaus N, Joakimsen RM, Figenschau Y, Jenssen T, et al. (2010) Baseline serum 25-hydroxyvitamin D concentrations in the Tromsø Study 1994-95 and risk of developing type 2 diabetes mellitus during 11 years of follow-up. Diabet Med 27: 1107-1115.

77. Pittas AG, Chung M, Trikalinos T, Mitri J, Brendel M, et al. (2010) Systematic review: Vitamin D and cardiometabolic outcomes. Ann Intern Med 152: 307-314.

78. Robinson CJ, Alanis MC, Wagner CL, Hollis BW, Johnson DD (2010) Plasma 25-hydroxyvitamin D levels in early-onset severe preeclampsia. Am J Obstet Gynecol 203: 366.e1-6.

79. Brock KE, Huang WY, Fraser DR, Ke L, Tseng M, et al. (2011) Diabetes prevalence is associated with serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D in US middle-aged Caucasian men and women: a cross-sectional analysis within the Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial. Br J Nutr 106: 339-344.

80. Qiao Q, Nyamdorj R (2010) Is the association of type II diabetes with waist circumference or waist-to-hip ratio stronger than that with body mass index? Eur J Clin Nutr 64: 30-34.

81. Vazquez G, Duval S, Jacobs DR Jr, Silventoinen K (2007) Comparison of body mass index, waist circumference, and waist/hip ratio in predicting incident diabetes: a meta-analysis. Epidemiol Rev 29: 115-128.

82. Rajakumar K, de las Heras J, Chen TC, Lee S, Holick MF, et al. (2011) Vitamin D status, adiposity, and lipids in black American and Caucasian children. J Clin Endocrinol Metab 96: 1560-1567.

83. Dong Y, Pollock N, Stallmann-Jorgensen IS, Gutin B, Lan L, et al. (2010) Low 25-hydroxyvitamin D levels in adolescents: race, season, adiposity, physical activity, and fitness. Pediatrics 125: 1104-1111.

84. Pacifico L, Anania C, Osborn JF, Ferraro F, Bonci E, et al. (2011) Low 25(OH) D3 levels are associated with total adiposity, metabolic syndrome, and hypertension in Caucasian children and adolescents. Eur J Endocrinol 165: 603-611.

85. Poomthavorn P, Saowan S, Mahachoklertwattana P, Chailurkit L, Khlairit P (2012) Vitamin D status and glucose homeostasis in obese children and adolescents living in the tropics. Int J Obes 36: 491-495.

86. Foo LH, Zhang Q, Zhu K, Ma G, Trube A, et al. (2009) Relationship between vitamin D status, body composition and physical exercise of adolescent girls in Beijing. Osteoporos Int 20: 417-425.

87. Nikooyeh B, Neyestani TR, Farvid M, Alavi-Majd H, Houshiarrad A, et al. (2011) Daily consumption of vitamin D- or vitamin D + calcium-fortified yogurt drink improved glycemic control in patients with type 2 diabetes: a randomized clinical trial. Am J Clin Nutr 93: 764-771.

88. Shab-Bidar S, Neyestani TR, Djazayery A, Eshraghian MR, Houshiarrad A, et al. (2011) Regular consumption of vitamin D-fortified yogurt drink (Doogh) improved endothelial biomarkers in subjects with type 2 diabetes: a randomized double-blind clinical trial. BMC Med 9: 125.

89. de Boer IH, Tinker LF, Connelly S, Curb JD, Howard BV, et al. (2008) Calcium plus vitamin D supplementation and the risk of incident diabetes in the Women's Health Initiative. Diabetes Care 31: 701-707.

90. Avenell A, Cook JA, MacLennan GS, McPherson GC (2009) Vitamin D supplementation and type 2 diabetes: a substudy of a randomised placebo-controlled trial in older people (RECORD trial, ISRCTN 51647438). Age Ageing 38: 606-609.

91. Jorde R, Figenschau Y (2009) Supplementation with cholecalciferol does not improve glycaemic control in diabetic subjects with normal serum 25-hydroxyvitamin D levels. Eur J Nutr 48: 349-354.

92. Sugden JA, Davies JI, Witham MD, Morris AD, Struthers AD (2008) Vitamin D improves endothelial function in patients with Type 2 diabetes mellitus and low vitamin D levels. Diabet Med 25: 320-325.

93. Witham MD, Dove FJ, Dryburgh M, Sugden JA, Morris AD, et al. (2010) The effect of different doses of vitamin D(3) on markers of vascular health in patients with type 2 diabetes: a randomised controlled trial. Diabetologia 53: 2112-2119.

94. Weitzman S, Wang CH, Pankow JS, Schmidt MI, Brancati FL (2010) Are measures of height and leg length related to incident diabetes mellitus? The ARIC (Atherosclerosis Risk in Communities) study. Acta Diabetol 47: 237-242.

95. Clifton-Bligh RJ, McElduff P, McElduff A (2008) Maternal vitamin D deficiency, ethnicity and gestational diabetes. Diabet Med 25: 678-684.

96. Soheilykhah S, Mojibian M, Rashidi M, Rahimi-Saghand S, Jafari F (2010)

Maternal vitamin D status in gestational diabetes mellitus. Nutr Clin Pract 25: 524-527.

97. Poel YH, Hummel P, Lips P, Stam F, van der Ploeg T, et al. (2012) Vitamin D and gestational diabetes: a systematic review and meta-analysis. Eur J Intern Med 23: 465-469.

98. Baker AM, Haeri S, Camargo CA Jr, Stuebe AM, Boggess KA (2012) First-trimester maternal vitamin D status and risk for gestational diabetes (GDM) a nested case-control study. Diabetes Metab Res Rev 28: 164-168.

99. Farrant HJ, Krishnaveni GV, Hill JC, Boucher BJ, Fisher DJ, et al. (2009) Vitamin D insufficiency is common in Indian mothers but is not associated with gestational diabetes or variation in newborn size. Eur J Clin Nutr 63: 646-652.

100. Hamilton SA, McNeil R, Hollis BW, Davis DJ, Winkler J, et al. (2010) Profound Vitamin D Deficiency in a Diverse Group of Women during Pregnancy Living in a Sun-Rich Environment at Latitude 32°N. Int J Endocrinol 2010: 917428.

101. Karim SA, Nusrat U, Aziz S (2011) Vitamin D deficiency in pregnant women and their newborns as seen at a tertiary-care center in Karachi, Pakistan. Int J Gynaecol Obstet 112: 59-62.

102. Teale GR, Cunningham CE (2010) Vitamin D deficiency is common among pregnant women in rural Victoria. Aust N Z J Obstet Gynaecol 50: 259-261.

103. Lau SL, Gunton JE, Athayde NP, Byth K, Cheung NW (2011) Serum 25-hydroxyvitamin D and glycated haemoglobin levels in women with gestational diabetes mellitus. Med J Aust 194: 334-337.

104. Leffelaar ER, Vrijkotte TG, van Eijsden M (2010) Maternal early pregnancy vitamin D status in relation to fetal and neonatal growth: results of the multi-ethnic Amsterdam Born Children and their Development cohort. Br J Nutr 104: 108-117.

105. Asao K, Kao WH, Baptiste-Roberts K, Bandeen-Roche K, Erlinger TP, et al. (2006) Short stature and the risk of adiposity, insulin resistance, and type 2 diabetes in middle age: the Third National Health and Nutrition Examination Survey (NHANES III), 1988-1994. Diabetes Care 29: 1632-1637.

106. Brown DC, Byrne CD, Clark PM, Cox BD, Day NE, et al. (1991) Height and glucose tolerance in adult subjects. Diabetologia 34: 531-533.

107. Liu J, Tan H, Jeynes B (2009) Is femur length the key height component in risk prediction of type 2 diabetes among adults? Diabetes Care 32: 739-740.

108. Njølstad I, Arnesen E, Lund-Larsen PG (1998) Sex differences in risk factors for clinical diabetes mellitus in a general population: a 12-year follow-up of the Finnmark Study. Am J Epidemiol 147: 49-58.

109. Sayeed MA, Hussain MZ, Banu A, Rumi MA, Azad Khan AK (1997) Prevalence of diabetes in a suburban population of Bangladesh. Diabetes Res Clin Pract 34: 149-155.

110. Patterson CC, Dahlquist GG, Gyürüs E, Green A, Soltész G (2009) Incidence trends for childhood type 1 diabetes in Europe during 1989-2003 and predicted new cases 2005-20: a multicentre prospective registration study. Lancet 373: 2027-2033.

111. Wadén J, Forsblom C, Thorn LM, Saraheimo M, Rosengård-Bärlund M, et al. (2009) Adult stature and diabetes complications in patients with type 1 diabetes: the FinnDiane Study and the diabetes control and complications trial. Diabetes 58: 1914-1920.

112. Clemens TL, Karsenty G (2011) The osteoblast: an insulin target cell controlling glucose homeostasis. J Bone Miner Res 26: 677-680.

113. Ferron M, Wei J, Yoshizawa T, Del Fattore A, DePinho RA, et al. (2010) Insulin signaling in osteoblasts integrates bone remodeling and energy metabolism. Cell 142: 296-308.

114. Lee NK, Sowa H, Hinoi E, Ferron M, Ahn JD, et al. (2007) Endocrine regulation of energy metabolism by the skeleton. Cell 130: 456-469.

115. Ngarmukos C, Chailurkit LO, Chanprasertyothin S, Hengprasith B, Sritara P, et al. (2012) A reduced serum level of total osteocalcin in men predicts the development of diabetes in a long-term follow-up cohort. Clin Endocrinol 77: 42-46.

116. Paşaoğlu H, Kumandaş S, Keleştimur F (1995) Serum osteocalcin levels in type I diabetes mellitus. Turk J Pediatr 37: 323-329.

117. Kanazawa I, Yamaguchi T, Yamauchi M, Yamamoto M, Kurioka S, et al. (2011) Serum undercarboxylated osteocalcin was inversely associated with plasma glucose level and fat mass in type 2 diabetes mellitus. Osteoporos Int 22: 187-194.

118. Winhofer Y, Handisurya A, Tura A, Bittighofer C, Klein K, et al. (2010) Osteocalcin is related to enhanced insulin secretion in gestational diabetes mellitus. Diabetes Care 33: 139-143.

119. Liu J, Tan H, Jeynes B (2011) Serum 25OH vitamin D level, femur length, and risk of type 2 diabetes among adults. Appl Physiol Nutr Metab 36: 264-270.

120. Rodondi N, Marques-Vidal P, Butler J, Sutton-Tyrrell K, Cornuz J, et al. (2010) Markers of atherosclerosis and inflammation for prediction of coronary heart disease in older adults. Am J Epidemiol 171: 540-549.

121. Xiong DH, Xu FH, Liu PY, Shen H, Long JR, et al. (2005) Vitamin D receptor gene polymorphisms are linked to and associated with adult height. J Med Genet 42: 228-234.

122. Holick MF (2004) Sunlight and vitamin D for bone health and prevention of autoimmune diseases, cancers, and cardiovascular disease. Am J Clin Nutr 80: 1678S-1688S.

123. Lee S, Clark SA, Gill RK, Christakos S (1994) 1,25-Dihydroxyvitamin D3 and pancreatic beta-cell function: vitamin D receptors, gene expression, and insulin secretion. Endocrinology 134: 1602-1610.

124. Zadshir A, Tareen N, Pan D, Norris K, Martins D (2005) The prevalence of hypovitaminosis D among US adults: data from the NHANES III. Ethn Dis 15: S5-97-101.

125. Hyppönen E, Power C (2007) Hypovitaminosis D in British adults at age 45 y: nationwide cohort study of dietary and lifestyle predictors. Am J Clin Nutr 85: 860-868.

126. Lee AJ, Hodges S, Eastell R (2000) Measurement of osteocalcin. Ann Clin Biochem 37: 432-446.

127. Lindsay R, Cosman F (2008) Osteoporosis in: Harrison's Principles of Internal Medicine. McGraw Hill: New York 2397-2408.

128. Kanzaki S, Hosoda K, Moriwake T, Tanaka H, Kubo T, et al. (1992) Serum propeptide and intact molecular osteocalcin in normal children and children with growth hormone (GH) deficiency: a potential marker of bone growth and response to GH therapy. J Clin Endocrinol Metab 75: 1104-1109.

129. Cioffi M, Molinari AM, Gazzerro P, Di Finizio B, Fratta M, et al. (1997) Serum osteocalcin in 1634 healthy children. Clin Chem 43: 543-545.

Author Affiliation

Top

[1]*Department of Community Health Sciences, Brock University, Canada*