Endocrine Journal

ORIGINAL

Advance Publication
doi:10.1507/endocrj.EJ25-0007

A 10-year observational study of the effects of serum 25OH vitamin D levels on the onset of prediabetes at a preventive medicine research center

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Abstract. We report the findings of a 10-year study that followed the relationship between serum 25-hydroxyvitamin D (25OH vitamin D) levels and the onset of prediabetes, analyzed based on sex. One hundred eighty-seven participants were followed who had a baseline hemoglobin A1c (HbA1c) value below 6.0% and fasting plasma glucose level below 100 mg/dL. The cut-off values for vitamin D concentration were 27.7 ng/mL for men and 17.1 ng/mL for women, based on the receiver operating characteristic curve. The prediabetes incidence was significantly higher in women with a vitamin D concentration ≤17.1 ng/mL [HR = 7.08 (2.08–24.2), $p = 0.002$] than in men with a concentration ≤27.7 ng/mL [HR = 2.30 (0.63–8.35), $p = 0.21$], based on the cumulative incidence function curve. Multivariate analysis revealed that an abdominal circumference ≥90 cm and 25OH vitamin D concentration ≤17.1 ng/mL were independent, significant and intervenable risk factors for prediabetes in women. Low levels of vitamin D in women can be a predictive factor in the development of diabetes after 10 years.

Key words: Vitamin D, Prediabetes, Abdominal circumference

Introduction

Vitamin D is a fat-soluble vitamin that is produced by the body on exposure to sunlight or can be ingested orally, and it is involved in calcium absorption in bone metabolism. It has long been associated with osteoporosis and fractures. In recent years, insufficient vitamin D intake has been reported to increase the incidence of diabetes and is inversely correlated with body mass index (BMI). It is also associated with glucose metabolism. However, controversial views exist regarding whether vitamin D supplementation can reduce the incidence of diabetes. These analyses were conducted by men and women together, and we have reported that risk factors for the development of diabetes vary between men and women [1, 2]. To date, sex differences are believed to exist in the onset of many diseases. A speculated mechanism is that many of them are associated with female hormones. Calcium handling, including vitamin D and parathyroid hormone (PTH), is associated with insulin secretion and insulin resistance in the point of diabetes onset. Clarifying the association between vitamin D and glucose metabolism is difficult. The measurement of 25OH vitamin D is used to detect vitamin D deficiency. In this study, we report the findings of a 10-year study that followed the relationship between serum 25OH vitamin D levels and the onset of prediabetes, a condition for which early intervention is highly effective, and the effects of insulin secretion remain low in people who underwent health checkups at the Preventive Medicine Research Center at Asahi General Hospital (Chiba, Japan).

Submitted Jan. 17, 2025; Accepted Apr. 28, 2025 as EJ25-0007
Released online in J-STAGE as advance publication Jun. 14, 2025
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Materials and Methods

From July 1, 2012 to April 30, 2013, 262 men and 172 women, whose serum vitamin D concentration was checked, were included from among 2,566 patients who visited the Preventive Medicine Research Center (Fig. 1). Except for 247 people with an observation period <1 year or an HbA1c value ≥6.0%, or fasting plasma glucose (FPG) ≥100 mg/dL, 187 participants with an HbA1c <6.0% and a fasting plasma glucose level of <100 mg/dL at baseline were included. These 187 people were divided by sex, and a cut-off value of 25OH vitamin D was set, based on the receiver operating characteristic (ROC) curve. The day they met the criteria for prediabetes (*i.e.*, HbA1c ≥6.0%) during the 10-year-period was evaluated as an event. We examined the cumulative incidence function method, a competitive risk model. Various factors underwent univariate analysis by using a competitive risk model. Factors that lead to prediabetes in the next 10 years were extracted, and independent risk factors were extracted by using the stepwise method, based on multivariate analysis, and evaluated by using the adjusted hazard ratio (HR).

The reason we focused on the onset of prediabetes in this study was that we believed that intervention at an early stage, when insulin secretion is preserved, would have a more instructive effect. Vitamin D has a dual effect in insulin secretion and insulin resistance; therefore, a small number of people with onset diabetes were observed during the follow-up period. For prediabetes, an HbA1c value of ≥6.0% was used because blood glucose levels during the observation period were not always taken in the early morning and at fasting. Furthermore, some papers [3, 4] report that, compared with FPG, the HbA1c value is a better method for assessing the risk of developing diabetes, which suggests that HbA1c values are more important than FPG values during an observation period.

Fatty liver was diagnosed with abdominal ultrasound echography. Four criteria used for this diagnosis—hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring—were evaluated by hepatologists. Hypertension was diagnosed, based on a systolic blood pressure (SBP) ≥130 mmHg or diastolic blood pressure (DBP) ≥80 mmHg. Obesity was defined as a BMI ≥25 kg/m^2, based on Japanese standard categories. Dyslipidemia was diagnosed, based on low-density lipoprotein cholesterol ≥140 mg/dL, high-density lipoprotein cholesterol <40 mg/dL, or fasting triglyceride (TG) ≥150 mg/dL. Current and past smokers were defined as "smokers" and individuals who had never smoked were defined as "nonsmokers."

The eGFR for men and women was calculated as follows:
Men: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine (mg/dL)$^{-1.094}$ × age (years)$^{-0.287}$.
Women: eGFR (mL/min/1.73 m^2) = 194 × serum creatinine (mg/dL)$^{-1.094}$ × age (years)$^{-0.287}$ × 0.739.

Statistical analysis

We used the Fine and Gray model to examine the effects of vitamin D concentration on the onset of prediabetes. Factors were extracted and multivariate analysis was conducted to evaluate the independence of each factor. In multivariate analysis, factors were selected by

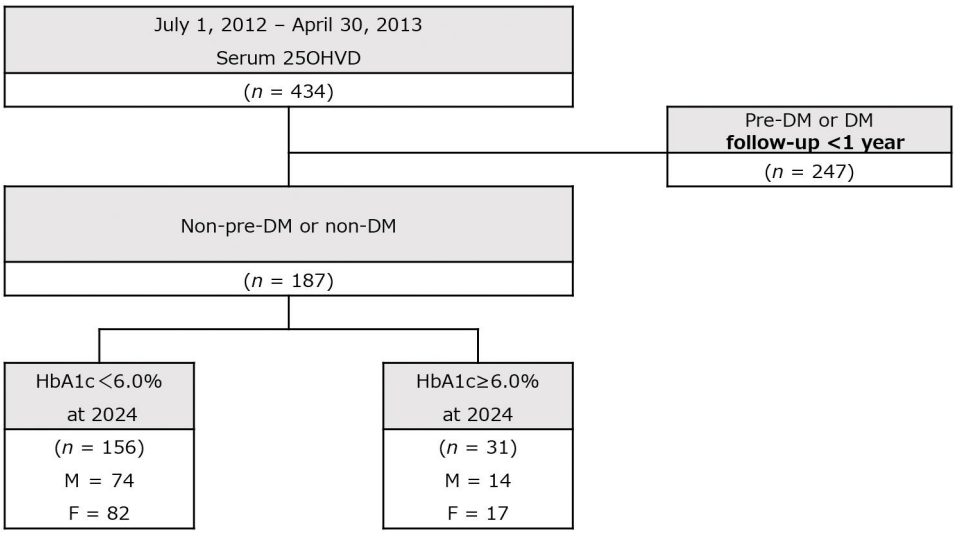


Fig. 1 From July 2012 to April 2013, 434 men and women who requested vitamin D measurement were included from among 2,566 patients who were examined by the Preventive Medicine Research Center of our hospital (Asahi General Hospital, Chiba, Japan). Abbreviations: 25OHVD, 25OH vitamin D; DM, diabetes mellitus; HbA1c, hemoglobin A1c; M, male; F, female

using the stepwise method.

Approval of the research protocol

The protocol for this research project has been approved by the ethics committee of Asahi General Hospital (Chiba, Japan), which approved the study on May 16, 2023 (approval no. 2023051615). We confirm that all procedures were followed in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Declaration of Helsinki guidelines (as revised in Fortaleza, Brazil in October 2013).

Informed consent

We applied the opt-out method to obtain informed consent for this study.

Results

Fig. 1 shows the flow diagram of this study. Table 1 shows the baseline characteristics of participants, based on the appearance of new-onset prediabetes during the 10-year period. Sex differences were observed. Significant differences existed for postprandial plasma glucose concentration, HbA1c, obesity, fatty liver, and the 25OH vitamin D serum concentration in women with the onset of prediabetes, compared with non-prediabetes. However, a significant difference existed only for the HbA1c value in men at baseline. In women, the HbA1c level significantly differed by 0.25% between the participants who were prediabetic and the participants who were not prediabetic at baseline. However, the difference in HbA1c between the two groups widened after the observation period (5.91% ± 0.18% *vs.* 5.53% ± 0.26%, $p < 0.001$) and the difference between the two groups was 0.28 ± 0.19 *vs.* 0.15 ± 0.22 ($p < 0.05$). This finding may be because of the effects of decreased vitamin D over the course of the period.

The cut-off value of 25OH vitamin D for the onset of diabetes in men, based on the ROC curve, was 27.7 ng/mL (Fig. 2A). The cumulative incidence function curve revealed that the ≤27.7 ng/mL group developed prediabetes during the 10 years but without a significant difference [HR = 2.30 (0.63–8.35); $p = 0.21$] (Fig. 2B).

The cut-off value on the ROC curve was 17.1 ng/mL for women. At 10 years, the prediabetes incidence was significantly higher in the ≤17.1 ng/mL group, based on the cumulative incidence function curve [HR = 7.08 (2.08–24.2); $p = 0.002$] (Fig. 2C, D).

We analyzed the significant factors for the onset of prediabetes in women. The univariate analysis of the competitive risk model revealed that obesity, abdominal circumference ≥90 cm, and serum 25OH vitamin D concentration ≤17.1 ng/mL were significant (Table 2). These factors were selected by using the stepwise method. Multivariate analysis revealed abdominal circumference ≥90 cm and 25OH vitamin D ≤17.1 ng/mL were the independent risk factors in women. However, in men, we could not select factors by using the stepwise method. Therefore, we chose three factors with small *p*-values. No risk factors for developing diabetes could be identified, even with multivariate analysis.

Discussion

Vitamin D is involved in metabolic processes in many tissues in humans and is believed to be involved in various diseases and health maintenance. In recent years, vitamin D has been associated with the risk of osteoporosis and fractures and has been associated with chronic kidney disease and cognitive function [3-5]. Vitamin D has also been associated with arteriosclerosis, severity of autoimmune diseases and COVID-19 infection, cardiovascular disease, and mortality, and it has a profound effect on the whole body [6-8].

At this time, we focused on the relationship between serum vitamin D concentration and the onset of prediabetes related to glucose intolerance. Previous reports on vitamin D and glucose metabolism have focused on the relationship between serum vitamin D concentration and the onset of diabetes, and whether vitamin D supplementation improves glucose tolerance. The results of these issues are controversial clinically [9-11]. The relationship between glucose tolerance and vitamin D is very complicated *in vivo*, including its effect *via* serum calcium, and it is associated with insulin sensitivity, insulin secretion, and obesity, *etc*. The finding that insulin secretion and insulin sensitivity are important factors associated with the onset of diabetes is well-known. In particular, the importance of factors related to sex differences in insulin sensitivity is well recognized, although individual differences exist. Men and women are different with regard to sex hormones, fat accumulation, and insulin resistance; therefore, considering the onset of diabetes separately between men and women seems necessary [12-14].

Regarding sex differences in the incidence of diabetes, adiponectin has been reported to have a stronger antidiabetic effect in women, and the action of vitamin D through its anti-inflammatory effects may be important [15-17]. The finding that osteocalcin may be involved in the relationship between adiponectin and glucose metabolism has been reported, and this molecule and vitamin D may be involved [18-23].

With regard to the development of diabetes, vitamin D

Table 1 Baseline characteristics of patients, based on 10-year new-onset of prediabetes

Parameter	Total	Incident Prediabetes		*p* value	Men	Incident Prediabetes		*p* value	Women	Incident Prediabetes		*p* value
		No	Yes			No	Yes			No	Yes	
n	187	156	31		88	74	14		99	82	17	
Sex: Men (%)	88 (47.1)	74 (47.4)	14 (45.2)	0.846								
Age (years)	57.76 ± 9.39	57.51 ± 9.61	59.06 ± 8.21	0.400	57.44 ± 10.18	57.09 ± 10.20	59.29 ± 10.22	0.463	58.05 ± 8.67	57.88 ± 9.09	58.88 ± 6.43	0.666
Obesity, *n* (%)	37 (19.8)	28 (17.9)	9 (29.0)	0.215	26 (29.5)	22 (29.7)	4 (28.6)	1.000	11 (11.1)	6 (7.3)	5 (29.4)	0.020
Abdominal circumference (cm)	80.34 ± 9.40	80.04 ± 9.29	81.82 ± 9.95	0.336	84.26 ± 8.60	84.36 ± 8.84	83.71 ± 7.43	0.799	76.85 ± 8.71	76.15 ± 7.89	80.26 ± 11.63	0.076
Hypertension, *n* (%)	42 (22.5)	34 (21.8)	8 (25.8)	0.640	25 (28.4)	21 (28.4)	4 (28.6)	1.000	17 (17.2)	13 (15.9)	4 (23.5)	0.484
Dyslipidemia, *n* (%)	10 (5.3)	10 (6.4)	0 (0.0)	0.374	8 (9.1)	8 (10.8)	0 (0.0)	0.346	2 (2.0)	2 (2.4)	0 (0.0)	1.000
Smoking habit, *n* (%)	185 (98.9)	154 (98.7)	31 (100.0)	1.000	87 (98.9)	73 (98.6)	14 (100.0)	1.000	98 (99.0)	81 (98.8)	17 (100.0)	1.000
FPG (mg/dL)	91.93 ± 4.84	91.67 ± 4.96	93.19 ± 3.98	0.110	93.01 ± 4.45	92.78 ± 4.44	94.21 ± 4.44	0.272	90.96 ± 4.98	90.67 ± 5.21	92.35 ± 3.46	0.207
PPG (mg/dL)	146.3 ± 28.6	143.7 ± 28.5	159.2 ± 25.5	0.006	145.5 ± 29.0	143.8 ± 29.2	154.7 ± 27.3	0.195	147.0 ± 28.3	143.7 ± 28.1	162.8 ± 24.1	0.011
HbA1c (%)	5.42 ± 0.23	5.38 ± 0.21	5.61 ± 0.18	<0.001	5.39 ± 0.22	5.35 ± 0.21	5.56 ± 0.20	0.001	5.44 ± 0.23	5.40 ± 0.22	5.65 ± 0.16	<0.001
eGFR (mL/min/1.73 m^2)	76.86 ± 12.26	77.37 ± 12.70	74.30 ± 9.49	0.205	77.93 ± 12.07	78.69 ± 12.36	73.91 ± 9.77	0.176	75.91 ± 12.41	76.17 ± 12.96	74.63 ± 9.54	0.643
Uric acid (mg/dL)	5.05 ± 1.23	5.06 ± 1.23	4.98 ± 1.25	0.736	5.75 ± 1.13	5.79 ± 1.13	5.53 ± 1.18	0.437	4.43 ± 0.96	4.41 ± 0.93	4.53 ± 1.15	0.644
AST (IU/L)	22.74 ± 6.10	22.55 ± 6.27	23.71 ± 5.14	0.336	22.61 ± 6.83	22.27 ± 6.85	24.43 ± 6.65	0.281	22.86 ± 5.41	22.80 ± 5.73	23.12 ± 3.57	0.829
ALT (IU/L)	19.83 ± 8.85	19.40 ± 8.44	22.00 ± 10.60	0.135	21.27 ± 10.42	20.91 ± 10.02	23.21 ± 12.58	0.450	18.55 ± 6.99	18.04 ± 6.47	21.00 ± 8.92	0.112
Fatty liver	33 (17.6)	26 (16.7)	7 (22.6)	0.443	20 (22.7)	18 (24.3)	2 (14.3)	0.509	13 (13.1)	8 (9.8)	5 (29.4)	0.044
Ca (mg/dL)	9.30 ± 0.31	9.31 ± 0.31	9.26 ± 0.30	0.361	9.27 ± 0.32	9.28 ± 0.31	9.24 ± 0.34	0.635	9.33 ± 0.30	9.34 ± 0.30	9.28 ± 0.28	0.400
IP (mg/dL)	3.38 ± 0.47	3.37 ± 0.48	3.45 ± 0.43	0.361	3.10 ± 0.39	3.07 ± 0.38	3.27 ± 0.42	0.076	3.63 ± 0.39	3.64 ± 0.39	3.60 ± 0.38	0.726
25OHVD (ng/mL)	21.56 ± 8.10	22.03 ± 8.04	19.21 ± 8.16	0.077	25.02 ± 8.61	25.25 ± 8.56	23.80 ± 9.11	0.568	18.49 ± 6.21	19.12 ± 6.29	15.43 ± 4.87	0.025

Values are presented as the mean ± the standard deviation.

Abbreviations: FPG, fasting plasma glucose; PPG, postprandial glucose; HbA1c, hemoglobin A1c; eGFR, estimated glomerular filtration rate; AST, aspartate aminotransferase; ALT, alanine aminotransferase; Ca, calcium; IP, inorganic phosphate; 25OHVD, 25-hydroxyvitamin D

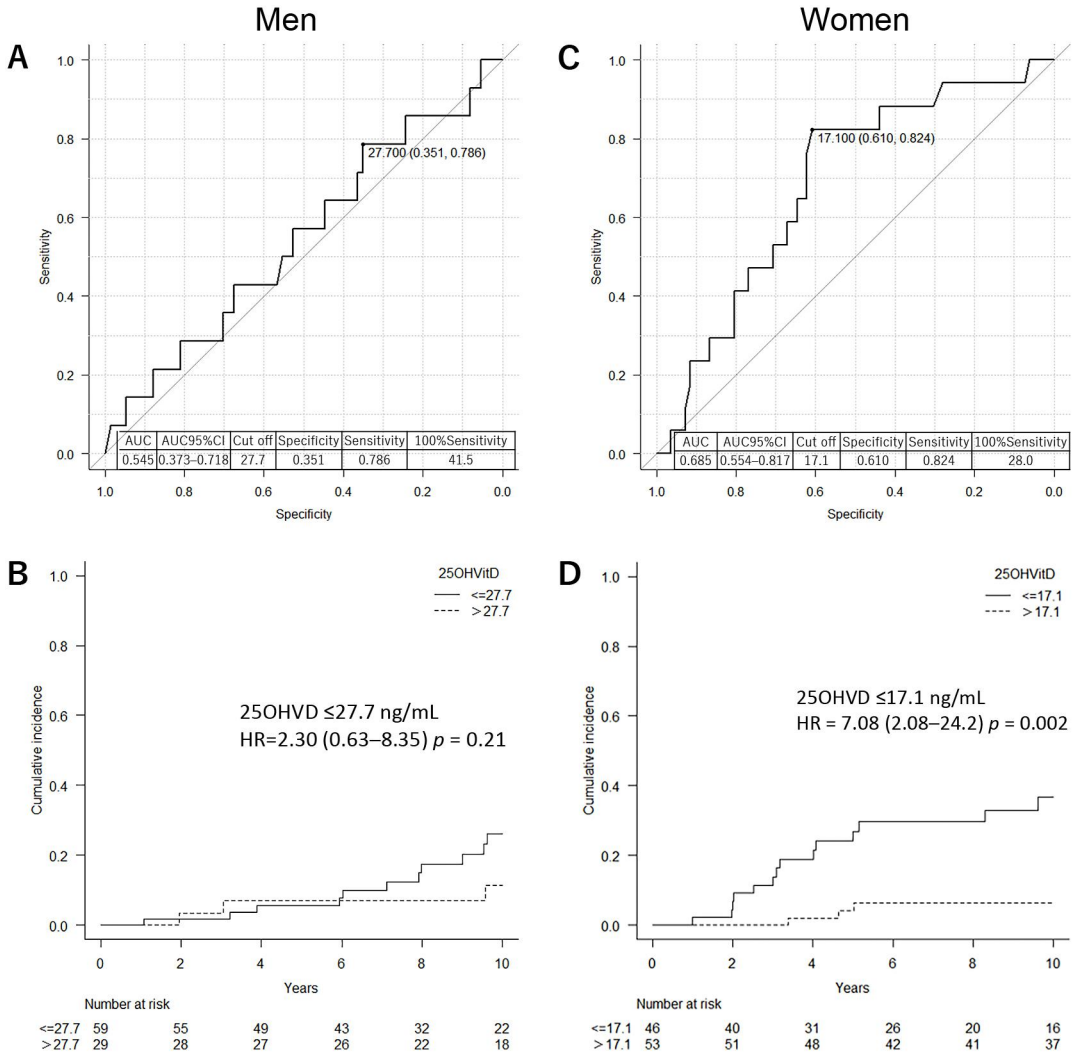


Fig. 2 The cut-off value for the onset of diabetes in men, based on the ROC curve, is 27.7 ng/mL (Fig. 2A). The cumulative incidence function curve shows that the ≤27.7 ng/mL group developed prediabetes over 12 years, but without a significant difference [HR = 2.30 (0.63–8.35); p = 0.21; Fig. 2B]. However, based on the ROC curve, the cut-off value is 17.1 ng/mL for women. The prediabetes incidence is significantly higher in the ≤17.1 ng/dL group at 10 years, based on the cumulative incidence function curve [HR = 7.08 (2.08–24.2); p = 0.002; Fig. 2C, D].

Abbreviation: 25OHVD, 25OH vitamin D

may be involved in glucose metabolism in terms of insulin synthesis and insulin secretion in pancreatic β cells [24-26]. Vitamin D receptors are also expressed on pancreatic β cells and are involved in the regulation of glucose metabolism [25]. No definitive views exist on the effects of vitamin D supplementation on glucose metabolism and obesity, with studies currently reporting effective and ineffective results [10, 27-30].

Some reports [31, 32] indicate that vitamin D supplementation effectively improves insulin sensitivity in obese people. One report [33] indicates that insulin secretion improved but insulin sensitivity did not change after 3 months. In addition, vitamin D has an effect on inhibiting the onset of type 2 diabetes in adults and the elderly, and it is effective in improving plasma glucose level and insulin sensitivity in healthy individuals and in people with metabolic syndrome [34, 35]. However, many reports indicate that it is not effective [36-38]. This inconsistency in the evaluation of vitamin D replacement therapy suggests that results vary, depending on the participants, dosage, and duration, and that the action of vitamin D is more complicated. Perhaps most importantly, the results of these trials may vary, depending on the duration of vitamin D administration, the proportion of participants with diabetes, ratio of male to female participants, whether vitamin D deficiency is included in the population, and differences in dietary habits between countries and in methods for assessing sensitivity. Vitamin D is stored in adipose tissue, and the degree of visceral fat accumulation affects serum vitamin D

Table 2 Univariate and multivariate Fine and Gray analysis findings with regard to the onset of prediabetes

Men	Univariate analysis			Multivariate analysis					
	HR	HR 95%CI	*p* value	aHR	HR 95%CI	*p* value	aHR	HR 95%CI	*p* value
Age ≥60 y	0.92	(0.32–2.61)	0.880	1.03	(0.30–3.53)	0.960			
Obesity (BMI ≥25)	0.96	(0.31–2.97)	0.940	1.08	(0.16–7.21)	0.940			
Abdominal circumference ≥85 cm	0.90	(0.32–2.52)	0.840	1.05	(0.21–5.35)	0.950			
Hypertension	2.25	(0.63–7.99)	0.210	1.83	(0.60–5.61)	0.290	2.03	(0.61–6.79)	0.250
Dyslipidemia	1.58	(0.44–5.66)	0.480	1.79	(0.48–6.60)	0.380			
ALT ≥30 IU/mL	1.06	(0.28–4.06)	0.930	1.46	(0.32–6.53)	0.620			
Fatty liver	0.50	(0.12–2.01)	0.330	0.36	(0.05–2.45)	0.300	0.50	(0.12–2.08)	0.340
25OH vitamin D ≤27.7 (ng/mL)	2.30	(0.63–8.35)	0.210	2.19	(0.51–9.48)	0.300	2.22	(0.60–8.26)	0.230
Women	Univariate analysis			Multivariate analysis					
	HR	HR 95%CI	*p* value	aHR	HR 95%CI	*p* value	aHR	HR 95%CI	*p* value
Age ≥60 y	0.80	(0.31–2.08)	0.650	1.28	(0.45–3.62)	0.640			
Obesity (BMI ≥25)	3.95	(1.44–10.8)	0.008	1.48	(0.40–5.50)	0.550			
Abdominal circumference ≥90 cm	4.80	(1.75–13.2)	0.002	2.26	(0.50–10.2)	0.290	3.51	(1.24–9.96)	0.018
Hypertension	1.64	(0.41–6.49)	0.480	1.79	(0.52–6.14)	0.360			
Dyslipidemia	0.92	(0.11–7.38)	0.940	0.00	(0.00–0.00)	0.000			
ALT ≥30 IU/mL	2.44	(0.68–8.82)	0.170	1.69	(0.44–6.44)	0.450			
Fatty liver	2.60	(0.99–6.86)	0.053	0.87	(0.17–4.42)	0.870			
25OH vitamin D ≤17.1 ng/mL	7.08	(2.08–24.2)	0.002	7.12	(2.08–24.4)	0.002	6.21	(1.76–21.9)	0.005

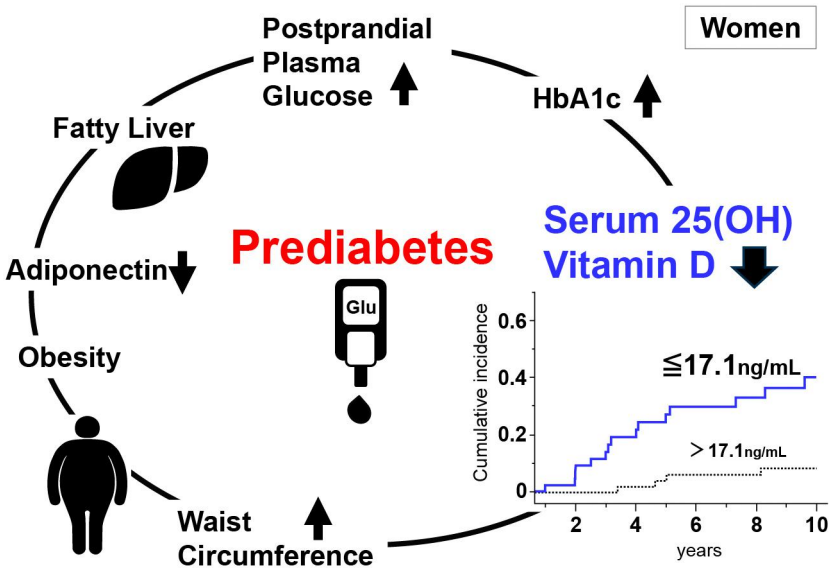
aHR, adjusted hazard ratio; HR, hazard ratio; CI, confidence interval; BMI, body mass index; ALT, alanine aminotransferase; 25OH vitamin D, 25 hydroxyvitamin D

concentrations. One study, conducted in the United States on individuals aged 12–19 years old, reported a negative correlation between visceral fat accumulation and serum vitamin D level, which was only observed in women [39]. Similar reports, which used a small number of participants, have also indicated a negative correlation between obesity, visceral fat accumulation, and vitamin D level; in addition, different effects of vitamin D supplementation between men and women has been reported [40]. In our report, the rate of obesity was higher in the group that had prediabetes at baseline, and the waist circumference tended to be slightly larger, but without a significant difference. In addition, in the multivariate analysis 10 years later, waist circumference was a significant risk factor (HR. 3.51), whereas vitamin D concentration was a major risk factor (HR = 6.21). We believe that serum vitamin D concentration has an extremely strong influence on glucose metabolism and the onset of prediabetes. In addition, racial differences have previously been indicated with regard to visceral fat and subcutaneous fat accumulation [41]. We examined the relationship between baseline vitamin D concentrations, waist circumference, and BMI, but we found no correlation. However, whether this finding was because of racial differences is unclear.

A common suggestion seems to be that people with vitamin D deficiency or vitamin D depletion should be actively supplemented with natural forms and levels controlled to the extent that they do not become excessive. Based on our results, scientists may find different results if they analyze them separately for men and women.

A recent detailed review article was published on the efficacy of vitamin D and vitamin D replacement therapy for various diseases [42]. According to this article, many of these studies were short-term and the participants were diverse, and no definite opinion exists regarding the effects of vitamin D supplementation. A meta-analysis of active vitamin D supplementation for an average of 3 years, from prediabetes to the onset of diabetes, suppressed the incidence of diabetes [43]. In addition, a systematic review and meta-analysis studies have also reported that it was effective in preventing the development of diabetes [44-46]. According to the meta-analyses, vitamin D can be used safely, except in cases of kidney damage, and it is generally recommended for preventing the onset of diabetes.

In Japan, a study utilizing the glucose tolerance test was also conducted on people with diabetes, who had



Graphical Abstract

taken active vitamin D supplementation for 3 years, revealed no improvement in glucose metabolism markers, compared with a placebo [47]. Although this report is a valuable paper in this area, the outcome varies, depending on lifestyle. Further research will be necessary because the participants already had diabetes, the observation period of 3 years was relatively short, and the serum vitamin D level status was unknown. In addition, we believe that the issue regarding the deterioration of glucose metabolism caused by a shortage of vitamin D and the prevention of prediabetes or diabetes by vitamin D supplementation may have to be considered separately. Another review paper on vitamin D and diseases was just recently published. This paper reported the existence of papers focusing on the progression from prediabetes to diabetes—for example, vitamin D deficiency increases this progression, whereas vitamin D supplementation suppresses it [11, 48, 49]. Our research showed that vitamin D is important, but sex differences exist. In our study, we also examined the development of prediabetes before diabetes; therefore, few reports exist to date. Our report also suggested that it takes longer to go from normal glucose tolerance to prediabetes in low vitamin D groups, and the effects of vitamin D supplementation are expected to take at least 3 years or more. As described previously, we believe that targeting the onset of prediabetes should be an intervention applied at a time when it is most effective, and the analysis of the onset in women, with a focus on sex differences, provided new findings that differ from those of previous analyses.

This study had some limitations. First, it was a one-center study and the number of cases was not large. Second, obtaining information on lifestyle habits was not possible during the follow-up. Third, although early intervention was the goal, blood glucose measurement during follow-up was not always done on fasting in the morning; therefore, abnormalities in glucose metabolism were evaluated only *via* HbA1c levels. Furthermore, we excluded patients with prediabetes, based on the HbA1c and FPG levels at baseline; therefore, we may have missed individuals who were already prediabetic. Fourth, genetic polymorphisms in genetic background such as vitamin D receptors in the participants could not be examined.

In summary, we reported that low levels of vitamin D in women can be a predictive factor in the development of diabetes after 10 years. Furthermore, vitamin D is involved in various diseases and will be an important indicator of lifestyle intervention in women (Graphical Abstract). In the future, the issue regarding whether these diseases can be prevented when providing supplementation for hypovitaminosis needs to be clarified.

Acknowledgements

We thank all staff in the Clinical Research Support Center (Chiba, Japan) for their participation.

Disclosure

Authors KO, RO, YSuzuki, JO, and NH examined the participants and wrote the manuscript. KT, YI, YE, HS, SW, KK, and SY reviewed the manuscript and contributed to the discussion. YSakuma and YSato helped in the analytical assistance. All authors approved the final version of the manuscript. NH (corresponding author)

had full access to all data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Conflict of Interest

None of the authors has any potential conflicts of interest associated with this research.

Funding

This study did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

References

1. Yoshimoto M, Sakuma Y, Ogino J, Iwai R, Watanabe S, *et al.* (2023) Sex differences in predictive factors for onset of type 2 diabetes in Japanese individuals: a 15-year follow-up study. *J Diabetes Investig* 14: 37–47.
2. Sakuma Y, Ogino J, Iwai R, Inoue T, Takahashi H, *et al.* (2021) Hyperferritinemia is a predictor of onset of diabetes in Japanese males independently of decreased renal function and fatty liver: a fifteen-year follow-up study. *J Clin Med Res* 13: 541–548.
3. Rajalakshmi R, Uthaiah CA, Ramya CM, Madhunapantula SV, Salimath PV, *et al.* (2022) Comparative assessment of cognitive impairment and oxidative stress markers among vitamin D insufficient elderly patients with and without type 2 diabetes mellitus (T2DM). *PLoS One* 17: e0269394.
4. Huang B, Wen W, Ye S (2022) Correlation between serum 25-hydroxyvitamin D levels in albuminuria progression of diabetic kidney disease and underlying mechanisms by bioinformatics analysis. *Front Endocrinol (Lausanne)* 13: 880930.
5. Guo J, Mo H, Zuo L, Zhang X (2024) Association of physical activity and vitamin D deficiency with cognitive impairment in older adults: a population based cross-sectional analysis. *Front Nutr* 11: 1390903.
6. Nanri A, Mizoue T, Goto A, Noda M, Sawada N, *et al.* (2023) Vitamin D intake and all-cause and cause-specific mortality in Japanese men and women: the Japan Public Health Center-based prospective study. *Eur J Epidemiol* 38: 291–300.
7. Mercola J, Grant WB, Wagner CL (2020) Evidence regarding vitamin D and risk of COVID-19 and its severity. *Nutrients* 12: 3361.
8. Corrao G, Cantarutti A, Monzio Compagnoni M, Franchi M, Rea F (2022) Change in healthcare during Covid-19 pandemic was assessed through observational designs. *J Clin Epidemiol* 142: 45–53.
9. 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.
10. Pittas AG, Dawson-Hughes B, Sheehan P, Ware JH, Knowler WC, *et al.* (2019) Vitamin D supplementation and prevention of type 2 diabetes. *N Engl J Med* 381: 520–530.
11. Pittas AG, Kawahara T, Jorde R, Dawson-Hughes B, Vickery EM, *et al.* (2023) Vitamin D and risk for type 2 diabetes in people with prediabetes : a systematic review and meta-analysis of individual participant data from 3 randomized clinical trials. *Ann Intern Med* 176: 355–363.
12. Braun AE, Mitchel OR, Gonzalez TL, Sun T, Flowers AE, *et al.* (2022) Sex at the interface: the origin and impact of sex differences in the developing human placenta. *Biol Sex Differ* 13: 50.
13. Tramunt B, Smati S, Grandgeorge N, Lenfant F, Arnal JF, *et al.* (2020) Sex differences in metabolic regulation and diabetes susceptibility. *Diabetologia* 63: 453–461.
14. Hammes SR, Levin ER (2019) Impact of estrogens in males and androgens in females. *J Clin Invest* 129: 1818–1826.
15. Cantorna MT, Zhu Y, Froicu M, Wittke A (2004) Vitamin D status, 1,25-dihydroxyvitamin D3, and the immune system. *Am J Clin Nutr* 80: 1717s–1720s.
16. Du T, Zhou ZG, You S, Lin J, Yang L, *et al.* (2009) Regulation by 1, 25-dihydroxy-vitamin D3 on altered TLRs expression and response to ligands of monocyte from autoimmune diabetes. *Clin Chim Acta* 402: 133–138.
17. Peng Z, Lu Y, Li L, Zhao Q, Feng Q, *et al.* (2013) The draft genome of the fast-growing non-timber forest species moso bamboo (Phyllostachys heterocycla). *Nat Genet* 45: 456–461, 461e1–461e2.
18. Berg AH, Combs TP, Du X, Brownlee M, Scherer PE (2001) The adipocyte-secreted protein Acrp30 enhances hepatic insulin action. *Nat Med* 7: 947–953.
19. Carvallo L, Henriquez B, Olate J, van Wijnen AJ, Lian JB, *et al.* (2007) The 1alpha,25-dihydroxy vitamin D3 receptor preferentially recruits the coactivator SRC-1 during up-regulation of the osteocalcin gene. *J Steroid Biochem Mol Biol* 103: 420–424.
20. 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.
21. Liu E, Meigs JB, Pittas AG, McKeown NM, Economos CD, *et al.* (2009) Plasma 25-hydroxyvitamin d is associated with markers of the insulin resistant phenotype in nondiabetic adults. *J Nutr* 139: 329–334.
22. Park S, Kim DS, Kwon DY, Yang HJ (2011) Long-term central infusion of adiponectin improves energy and glucose homeostasis by decreasing fat storage and suppressing hepatic gluconeogenesis without changing food intake. *J Neuroendocrinol* 23: 687–698.

23. Maeda N, Takahashi M, Funahashi T, Kihara S, Nishizawa H, *et al.* (2001) PPARgamma ligands increase expression and plasma concentrations of adiponectin, an adipose-derived protein. *Diabetes* 50: 2094–2099.
24. Gao Y, Wu X, Fu Q, Li Y, Yang T, *et al.* (2015) The relationship between serum 25-hydroxy vitamin D and insulin sensitivity and β-cell function in newly diagnosed type 2 diabetes. *J Diabetes Res* 2015: 636891.
25. Park S, Kim DS, Kang S (2016) Vitamin D deficiency impairs glucose-stimulated insulin secretion and increases insulin resistance by reducing PPAR-γ expression in nonobese type 2 diabetic rats. *J Nutr Biochem* 27: 257–265.
26. Gagnon C, Daly RM, Carpentier A, Lu ZX, Shore-Lorenti C, *et al.* (2014) Effects of combined calcium and vitamin D supplementation on insulin secretion, insulin sensitivity and β-cell function in multi-ethnic vitamin D-deficient adults at risk for type 2 diabetes: a pilot randomized, placebo-controlled trial. *PLoS One* 9: e109607.
27. Sato A (2015) The necessity and effectiveness of mineralocorticoid receptor antagonist in the treatment of diabetic nephropathy. *Hypertens Res* 38: 367–374.
28. Belenchia AM, Tosh AK, Hillman LS, Peterson CA (2013) Correcting vitamin D insufficiency improves insulin sensitivity in obese adolescents: a randomized controlled trial. *Am J Clin Nutr* 97: 774–781.
29. Greco EA, Lenzi A, Migliaccio S (2019) Role of hypovitaminosis D in the pathogenesis of obesity-induced insulin resistance. *Nutrients* 11: 1506.
30. Kelishadi R, Salek S, Salek M, Hashemipour M, Movahedian M (2014) Effects of vitamin D supplementation on insulin resistance and cardiometabolic risk factors in children with metabolic syndrome: a triple-masked controlled trial. *J Pediatr (Rio J)* 90: 28–34.
31. von Hurst PR, Stonehouse W, Coad J (2010) Vitamin D supplementation reduces insulin resistance in South Asian women living in New Zealand who are insulin resistant and vitamin D deficient—a randomised, placebo-controlled trial. *Br J Nutr* 103: 549–555.
32. Nagpal J, Pande JN, Bhartia A (2009) A double-blind, randomized, placebo-controlled trial of the short-term effect of vitamin D3 supplementation on insulin sensitivity in apparently healthy, middle-aged, centrally obese men. *Diabet Med* 26: 19–27.
33. Eftekhari MH, Akbarzadeh M, Dabbaghmanesh MH, Hasanzadeh J (2011) Impact of treatment with oral calcitriol on glucose indices in type 2 diabetes mellitus patients. *Asia Pac J Clin Nutr* 20: 521–526.
34. 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.
35. 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.
36. Grant AM, Avenell A, Campbell MK, McDonald AM, MacLennan GS, *et al.* (2005) Oral vitamin D3 and calcium for secondary prevention of low-trauma fractures in elderly people (Randomised Evaluation of Calcium Or vitamin D, RECORD): a randomised placebo-controlled trial. *Lancet* 365: 1621–1628.
37. Tai K, Need AG, Horowitz M, Chapman IM (2008) Glucose tolerance and vitamin D: effects of treating vitamin D deficiency. *Nutrition* 24: 950–956.
38. 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.
39. Li YF, Zheng X, Gao WL, Tao F, Chen Y (2022) Association between serum vitamin D levels and visceral adipose tissue among adolescents: a cross-sectional observational study in NHANES 2011–2015. *BMC Pediatr* 22: 634.
40. Cominacini M, Fumaneri A, Ballerini L, Braggio M, Valenti MT, *et al.* (2023) Unraveling the connection: visceral adipose tissue and vitamin D levels in obesity. *Nutrients* 15: 4259.
41. Rush EC, Scragg R, Schaaf D, Juranovich G, Plank LD (2009) Indices of fatness and relationships with age, ethnicity and lipids in New Zealand European, Māori and Pacific children. *Eur J Clin Nutr* 63: 627–633.
42. Demay MB, Pittas AG, Bikle DD, Diab DL, Kiely ME, *et al.* (2024) Vitamin D for the prevention of disease: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 109: 1907–1947.
43. Lau D (2023) In prediabetes, oral vitamin D reduces progression to new-onset diabetes. *Ann Intern Med* 176: Jc55.
44. Zhang Y, Tan H, Tang J, Li J, Chong W, *et al.* (2020) Effects of vitamin D supplementation on prevention of type 2 diabetes in patients with prediabetes: a systematic review and meta-analysis. *Diabetes Care* 43: 1650–1658.
45. Dawson-Hughes B, Staten MA, Knowler WC, Nelson J, Vickery EM, *et al.* (2020) Intratrial exposure to vitamin D and new-onset diabetes among adults with prediabetes: a secondary analysis from the vitamin D and type 2 diabetes (D2d) study. *Diabetes Care* 43: 2916–2922.
46. Barbarawi M, Zayed Y, Barbarawi O, Bala A, Alabdouh A, *et al.* (2020) Effect of vitamin D supplementation on the incidence of diabetes mellitus. *J Clin Endocrinol Metab* 105: dgaa335.
47. Kawahara T, Suzuki G, Mizuno S, Inazu T, Kasagi F, *et al.* (2022) Effect of active vitamin D treatment on development of type 2 diabetes: DPVD randomised controlled trial in Japanese population. *BMJ* 377: e066222.
48. Giustina A, Bilezikian JP, Adler RA, Banfi G, Bikle DD, *et al.* (2024) Consensus statement on vitamin D status assessment and supplementation: whys, whens, and hows. *Endocr Rev* 45: 625–654.
49. Bouillon R, Manousaki D, Rosen C, Trajanoska K, Rivadeneira F, *et al.* (2022) The health effects of vitamin D supplementation: evidence from human studies. *Nat Rev Endocrinol* 18: 96–110.