British Journal of Nutrition (2022), 127, 556–562 doi:10.1017/S0007114521001185
© The Author(s), 2021. Published by Cambridge University Press on behalf of The Nutrition Society

Adjunctive vitamin A and D for the glycaemic control in patients with concurrent type 2 diabetes and tuberculosis: a randomised controlled trial

Ke Xiong, Jinyu Wang and Aiguo Ma*

Institute of Nutrition and Health, School of Public Health, Qingdao University, Qingdao, Shandong 266071, People's Republic of China

(Submitted 8 September 2020 – Final revision received 20 March 2021 – Accepted 29 March 2021 – First published online 6 April 2021)

Abstract

The objective of this study is to investigate the effects of vitamin A, D and their interaction on the glycaemic control in patients with both diabetes and tuberculosis. Tuberculosis infection and its treatment induce hyperglycaemia and complicate the glycaemic control in patients with diabetes. A randomised controlled trial with a 2 × 2 factorial design was conducted in a tuberculosis-specialised hospital in Qingdao, China. A total of 279 patients who have both diabetes and tuberculosis were included in this analysis. The patients received standard anti-tuberculosis treatment alone (control group), or together with a dose of vitamin A (600 μg RAE/d) or vitamin D (10 μg/d) or a combination of vitamin A (600 μg RAE/d) and vitamin D (10 μg/d) for 2 months. The effects of the intervention on fasting plasma glucose and 2-h postprandial blood glucose were investigated by ANCOVA. The analysis was adjusted for baseline values, age, sex, smoking, drinking and antidiabetic treatment as covariates. No significant effect was observed for vitamin A and D supplementation on fasting plasma glucose, 2-h postprandial blood glucose, BMI and related blood parameters. No interaction was observed between vitamin A and D supplementation for these endpoints. Vitamin A and D supplementation showed a null effect on the glycaemic control for patients with concurrent diabetes and tuberculosis. Future work should evaluate the effect of vitamin A and D supplementation on insulin-related indices for these patients and investigate the effect of vitamin D receptor genotypes.

Key words: **Vitamin A: Vitamin D: Fasting plasma glucose: Postprandial blood glucose: Randomised controlled trial**

WHO estimated that there were 10 million new incidences of tuberculosis worldwide in 2017, in which 0·79 million had concurrent diabetes[1]. Patients with diabetes are three times more likely to have tuberculosis[2]. Syal *et al.* observed a significant reduction of the gene expression level of retinol X receptor and a corresponding significant increase of the gene expression level of tryptophan-aspartate containing coat protein in type 2 diabetes patients *v.* healthy subjects[3]. The presence of tryptophan-aspartate containing coat protein was shown to stabilise phagosome and thus help the survival of pathogenic mycobacteria[4].

The combination of tuberculosis and diabetes also complicates the treatment of these two diseases. Patients with diabetes had a higher risk of treatment failure, death and relapse for tuberculosis treatment[5], possibly due to reduced concentrations of tuberculosis drugs, high rates of drug-resistant tuberculosis, low treatment compliance or an altered immune response[6]. On the other hand, tuberculosis infection leads to impaired glucose tolerance[7]. The drugs for tuberculosis treatment may induce hyperglycaemia. Rifampin and isoniazid, the major antibiotics for tuberculosis treatment, can accelerate the clearance of antidiabetic drugs, augment the intestinal absorption of glucose and impair insulin secretion[8]. The optimal treatment strategy for concurrent tuberculosis and diabetes is not known[6]. Insufficient micronutrient intake is typical for tuberculosis patients[9], while nutritional intervention is effective in reducing fasting plasma glucose[10]. Adjunctive nutritional therapy may be a potential area to explore for managing concurrent tuberculosis and diabetes.

In recent years, the effect of vitamin D on diabetes and glycaemic control has received substantial interest. Two meta-analyses of randomised controlled trials (RCT) reported a significantly lowering effect of vitamin D supplementation on fasting plasma glucose and insulin resistance in patients with diabetes[11,12]. A recent large RCT including 2423 participants with prediabetes observed that a daily administration of vitamin D to maintain a serum 25-hydroxyvitamin D level of more than 100 nmol/l was an efficient approach to prevent the development

Abbreviations: RCT, randomised controlled trial; VA, vitamin A group; VAD, vitamin A and D group; VD, vitamin D group.

* **Corresponding author:** Aiguo Ma, email magfood@qdu.edu.cn

https://doi.org/10.1017/S0007114521001185 Published online by Cambridge University Press

of diabetes[13,14]. However, the effects of vitamin D supplementation on diabetic patients with concurrent tuberculosis infection were rarely reported.

Vitamin A is well known for its role in embryonic development and is also required for pancreas development[15,16]. Animal studies showed that vitamin A was required for the maintenance of β-cells and insulin secretion[17,18]. Epidemiological studies reported conflicting results on the association between vitamin A and diabetes[19–23]. The largest study including data from over 3000 participants from the US National Health and Nutrition Examination Survey found that an increased level of total serum retinol (free retinol and retinol ester) was associated with a reduced risk of the metabolic syndrome[21]. A case–control study including 233 participants found a lower serum retinol level in patients with diabetes[23]. Clinical trial investigating the effect of vitamin A supplementation on glycaemic control in human is absent.

The aim of our study is to investigate the effect of vitamin A, D and their interaction on glycaemic control in patients with concurrent tuberculosis and type 2 diabetes by a RCT with a 2 × 2 factorial design.

Experimental methods

Ethics

The ethics committee of the Affiliated Hospital of the Medical School of Qingdao University approved the study, which has a registration number of 20115. The conduction of the trial conforms to the Declaration of Helsinki. All participants provided informed consent.

Study design and population

The current study is a *post hoc* analysis of our previous RCT which investigated the effects of adjunctive vitamin A and D on tuberculosis treatment[24]. The previous RCT reported a null effect of adjunctive vitamin A and D on tuberculosis treatment[24]. A significant portion of the included tuberculosis patients had concurrent type 2 diabetes. We used the data to investigate the effects of vitamin A and D supplementation on the glycaemic control in patients with both tuberculosis and type 2 diabetes. The details of the trial design were described previously[24,25] and registered as ChiCTR-TRC-12002546 on the Chinese Clinical Trial Registry.

We conducted the trial at a tuberculosis-specialised hospital in Qingdao city of China. The inclusion criteria were: newly diagnosed pulmonary tuberculosis (<7-d treatment) and HIV negative. The exclusion criteria were: use of vitamin A or D supplements or corticosteroids in the recent month; using immunosuppressive drugs; extrapulmonary tuberculosis; drug-resistant tuberculosis; pregnancy or lactation; baseline plasma Ca > 2·6 mmol/l, creatinine > 250 mmol/l or aspartate aminotransferase > 3 times of the upper limit; having nephrolithiasis, hyperparathyroidism, organ transplantation, hepatic cirrhosis or cancer in the past 5 years[24].

A 2 × 2 factorial design was employed in this study. The sample size calculation was reported in our previous publication[24]. A total of 800 eligible participants were allocated randomly (1:1:1:1) into one of the four groups: (1) the vitamin A (VA) group (n 200), (2) the vitamin D (VD) group (n 200), (3) the vitamin A and D (VAD) group (n 200) and (4) the control group (n 200). An independent researcher used a random-table method to generate the random sequence, employing a permuted block randomisation method. The block size was four[24].

Among all participants, 279 patients who had both diabetes and tuberculosis were included in this study. The primary outcome of the current study was fasting plasma glucose. The secondary outcomes were postprandial plasma glucose (after breakfast, lunch and dinner), BMI and blood parameters.

Procedure

All participants received a standard anti-tuberculosis treatment, which used combinations of isoniazid, rifampicin, pyrazinamide and ethambutol. An additional vitamin A oral capsule (600 μg RAE/d) was provided in a sachet (together with the oral anti-tuberculosis medication) to the VA group. An additional vitamin D oral capsule (10 μg/d) was provided in a sachet to the VD group. An additional vitamin A (600 μg RAE/d) and D (10 μg/d) oral capsule was provided in a sachet to the VAD group. Only the oral anti-tuberculosis medication was provided in a sachet to the control group. The dosage of vitamin A and vitamin D is according to the recommendation by the Chinese Nutrition Society[26].

The baseline clinical assessment included chest radiography, sputum smear, measurement of weight and height. Fasting blood samples were collected and analysed for fasting plasma glucose and related blood parameters. The 2-h postprandial plasma glucose was tested after breakfast, lunch and dinner. The demographic information, including age, education level, marital status, occupation and smoking, was obtained by a questionnaire at baseline. A three-day 24-h dietary recall was conducted at the end of the intervention. The dietary nutrition intake was calculated by the Computer Expert System for Nutrition Treatment (version 10.1) software, which was developed by Qingdao University and reflected the China Food Composition[27]. At the end of intervention, the fasting plasma glucose, the 2-h postprandial plasma glucose, related blood parameters and the weight were measured again.

Statistical analysis

The analysis was conducted by the SPSS software (version 25.0). The significance was detected at a 5 % level. The differences of continuous variables were compared using a t test or a Mann–Whitney U test. The differences of categorical variables were compared using a χ^2 test. The 2 × 2 factorial design has two allocations: vitamin A and vitamin D allocation. The influence of one allocation on continuous outcomes was evaluated by ANCOVA with baseline value, sex, age, smoking, drinking, antidiabetic treatment and another allocation as covariates.

Results

A total of 800 patients were enrolled into this study from October 2012 to March 2015 (Fig. 1). Among the included patients, thirty-

https://doi.org/10.1017/S0007114521001185 Published online by Cambridge University Press

British Journal of Nutrition

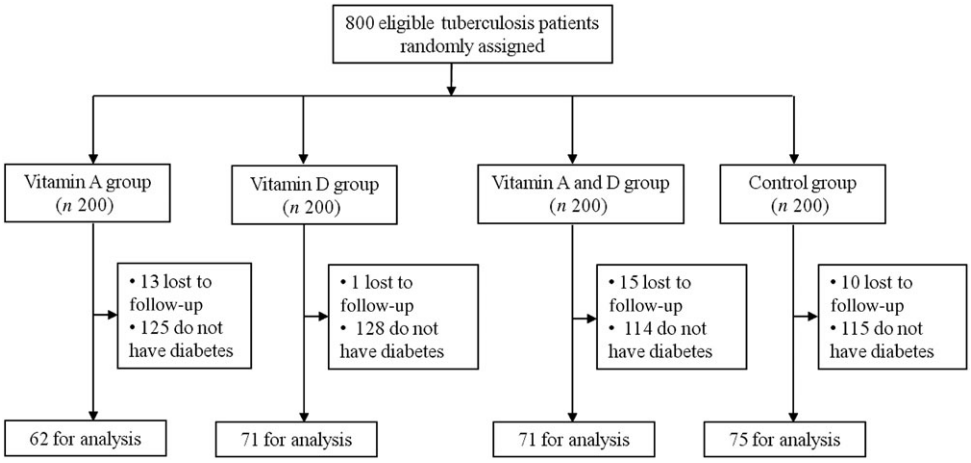

Fig. 1. Trial flow.

nine patients were lost to follow-up. Four hundred eighty-two patients did not have diabetes and were excluded from the current analysis. The remaining 279 patients were included in this analysis with sixty-two patients in the VA group, seventy-one patients in the VD group, seventy-one patients in the VAD group and seventy-five patients in the control group. In order to take advantage of the efficiency of a 2 × 2 factorial design for studying main effects, the VA group and the VAD group were combined as the with-vitamin A group, and the VD group and the control group were combined as the non-vitamin A group, to investigate the effects of vitamin A supplementation. Similarly, the VD group and the VAD group were combined as the with-vitamin D group, and the VA group and the control group were combined as the non-vitamin D group, to investigate the effects of vitamin D on glycaemic control.

Most demographic characteristics were comparable between the with-vitamin A group and the non-vitamin A group, and between the with-vitamin D group and the non-vitamin D group (Table 1). More patients in the non-vitamin A group had insulin injection instead of oral hypoglycaemics as their antidiabetic treatment than those in the with-vitamin A group. More patients in the with-vitamin D group had lifestyle adjustment as their antidiabetic treatment than those in the non-vitamin D group. The non-vitamin A group had slightly more participants consuming alcohol compared with the with-vitamin A group (5 % *v.* 0 %). And, the non-vitamin D group had more participants smoking cigarettes compared with the with-vitamin D group (12 % *v.* 5 %). According to the three-day 24-h dietary recall, the median retinol equivalent intake was 424·6 ug/d, which was insufficient. No significant difference was observed for the energy, protein, carbohydrate, fat, dietary fibre and retinol equivalents intake either between the with-vitamin A group and the non-vitamin A group, or between the with-vitamin D group and the non-vitamin D group (Table 2).

The mean fasting plasma glucose among all patients was significantly reduced after the intervention period (mean difference (MD): −1·6 (95 % CI −2·0, −1·1), $P < 0·001$). The mean fasting plasma glucose at Month Two was 8·0 mmol/l in the with-vitamin D group and 8·1 mmol/l in the non-vitamin D group (adjusted MD: −0·1 (95 % CI −0·8, 0·6), $P = 0·70$) (Table 3). The mean fasting plasma glucose at Month Two was 8·2 mmol/l in the with-vitamin A group and 7·9 mmol/l in the non-vitamin A group showing no significant difference between the two groups (adjusted MD: 0·3 (95 % CI −0·4, 1·0), $P = 0·37$) (Table 4). No interaction was observed between the vitamin A and D intervention (interaction coefficient: −1·3 (95 % CI −2·7, 0·1), $P = 0·07$).

The mean postprandial glucose values among all patients were significantly reduced after the intervention period. The MD for 2-h postprandial plasma glucose after breakfast, lunch and dinner were −3·0 mmol/l ($P < 0·001$), −2·9 mmol/l ($P < 0·001$) and −1·8 mmol/l ($P < 0·001$), respectively. No significant difference between the with-vitamin A group and the non-vitamin A group, or between the with-vitamin D group and the non-vitamin D group, was observed for the 2-h postprandial blood glucose after breakfast, lunch and dinner. Similarly, no significant interaction was observed between the vitamin A and D supplementation. Comparisons were also made among the VA, VD, VAD and control groups. Using the control group as the reference, no significant difference was observed for the VA, VD and VAD groups for the fasting plasma glucose and the 2-h postprandial blood glucose after breakfast, lunch and dinner (Table A1).

At Month Two, the BMI was similar between the non-vitamin D group and the with-vitamin D group, and between the non-vitamin A group and the with-vitamin A group (Table 3). The blood cell counts, erythrocyte sedimentation rate and Hb were also similar between the groups. In addition, when comparisons were made among the VA, VD, VAD and control groups, no significant difference was observed for the VA, VD and VAD groups *v.* the control group for all the blood parameters (Table A1). No serious adverse events were reported. Non-serious adverse events were summarised in our previous manuscript[24].

Discussion

We adopted a 2 × 2 factorial design to investigate the vitamin A, D supplementation and their interaction on glycaemic control in patients with both tuberculosis and diabetes. We first report here

British Journal of Nutrition

https://doi.org/10.1017/S0007114521001185 Published online by Cambridge University Press

Table 1 Baseline characteristics by treatment allocation
(Mean values and standard deviations; numbers and percentages)

	Non-Vitamin A*			With Vitamin A				Non-Vitamin D			With Vitamin D			
	n	Values	% or SD	*n*	Values	% or SD	*P*	*n*	Values	% or SD	*n*	Values	% or SD	*P*
Age (years)	146	53·5	11·6†	133	54·3	12·9	0·59	137	53·3	13·0	142	54·5	11·4	0·42
Sex	146			133			0·31	137			142			0·91
Male		130	89 %‡		113	85 %			119	87 %		124	87 %	
Female		16	11 %		20	15 %			18	13 %		18	13 %	
BMI (kg/m2)	139	22·4	3·2	125	22·2	3·4	0·59	132	22·4	3·2	132	22·2	3·3	0·61
Education completed	146			133			0·76	137			142			0·54
None		4	3 %		5	4 %			5	4 %		4	3 %	
Primary school		21	14 %		23	17 %			19	14 %		25	18 %	
Class VII–IX		65	45 %		49	37 %			62	45 %		52	37 %	
Class X–XII		36	25 %		36	27 %			31	23 %		41	29 %	
Diploma or higher		20	14 %		20	15 %			20	15 %		20	14 %	
Marital status	146			133			0·46	137			142			0·13
Single		9	6 %		7	5 %			12	9 %		4	3 %	
Married		130	89 %		124	93 %			121	88 %		133	94 %	
Widowed		3	2 %		1	1 %			1	1 %		3	2 %	
Divorced		4	3 %		1	1 %			3	2 %		2	1 %	
Occupation	146			133			0·14	137			142			0·64
Unskilled worker or farmer		46	32 %		58	44 %			47	34 %		57	40 %	
Professional		20	14 %		13	10 %			15	11 %		18	13 %	
Retired		26	18 %		29	22 %			30	22 %		25	18 %	
Unemployed		25	17 %		14	11 %			18	13 %		21	15 %	
Student		1	1 %		0	0 %			1	1 %		0	0 %	
Other		28	19 %		19	14 %			26	19 %		21	15 %	
Outdoor activity (more than 2 h/d)	139	32	23·0 %	124	27	21·8 %	0·81	132	29	22·0 %	131	30	22·9 %	0·86
Presently smoke cigarettes	146	11	8 %	133	12	9 %	0·65	137	16	12 %	142	7	5 %	0·04
Presently consume alcohol	146	7	5 %	133	0	0 %	0·01	137	5	4 %	142	2	1 %	0·23
Baseline sputum smear	144			132			0·53	136			140			0·28
<3 acid-fast bacilli per high-power field		72	50 %		61	46 %			70	51 %		63	45 %	
≥3 acid-fast bacilli per high-power field		72	50 %		71	54 %			66	49 %		77	55 %	
Number of patients with cavities	146	87	60 %	131	76	58 %	0·79	137	83	61 %	140	80	57 %	0·56
Fasting plasma glucose (mmol/l)	133	10·0	3·7	123	10·1	4·1	0·91	124	10·4	4·5	132	9·7	3·2	0·18
2-h postprandial plasma glucose after breakfast (mmol/l)	134	15·0	5·5	122	13·8	5·8	0·09	126	14·7	6·1	130	14·2	5·2	0·48
2-h postprandial plasma glucose after lunch (mmol/l)	133	13·3	4·8	118	13·3	5·0	0·93	125	13·3	5·2	126	13·3	4·6	0·95
2-h postprandial plasma glucose after dinner (mmol/l)	130	12·9	4·5	120	13·1	5·1	0·81	122	13·2	5·2	128	12·7	4·3	0·41
Antidiabetic medication	139	112	81 %	124	98	79 %	0·76	132	110	83 %	131	100	76 %	0·16
Antidiabetic treatment	139			124			0·03	132			131			0·04
Insulin injection		67	48 %		48	39 %			62	47 %		53	41 %	
Oral hypoglycaemics		27	19 %		43	35 %			41	31 %		29	22 %	
Oral hypoglycaemics and insulin injection		12	9 %		5	4 %			5	4 %		12	9 %	
Lifestyle adjustment		33	24 %		28	23 %			24	18 %		37	28 %	

* Non-vitamin A group is the combination of vitamin D group and control group; With-vitamin A group is the combination of vitamin A group and vitamin A and D group; Non-vitamin D group is the combination of vitamin A group and control group; With-vitamin D group is the combination of vitamin D group and vitamin A and D group.
† Numerical variables are presented as mean values and standard deviations unless noted otherwise.
‡ Categorical variables are presented as number of patients in a specific category and percentages.

https://doi.org/10.1017/S0007114521001185 Published online by Cambridge University Press

Table 2. Daily dietary intake (three-day 24-h recall) of participants*
(Mean values and standard deviations)

	Non-Vitamin A (*n* 129)		Vitamin A (*n* 125)		Non-Vitamin D (*n* 122)		Vitamin D (*n* 132)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Energy (kcal)	1477·2	451·2†	1474·9	470·0	1526·3	488·9	1429·7	427·5
Protein (g)	65·3	22·7	64·5	19·0	65·6	21·8	64·2	20·1
Carbohydrate (g)	211·0	71·9	215·5	72·0	222·3	75·4	204·8	67·5
Fat (g)	41·3	22·3	39·4	24·3	41·6	24·2	39·3	22·3
Dietary fibre (g)	12·1	6·5	11·1	6·7	12·0	6·2	11·2	6·9
Retinol equivalent (ug), median (IQR)	407·1	291·5	432·3	277·9	396·6	295·6	430·2	233·3

* The difference between the groups (non-vitamin A *v.* vitamin A group, or non-vitamin D *v.* vitamin D group) was tested by a *t* test for normal data and a Mann–Whitney *U* test for non-normal data.
† Data are presented as mean values and standard deviations unless noted otherwise.

Table 3. Effects of vitamin D allocation on BMI, glycaemic and blood parameters
(Mean values and standard deviations)

	Non-Vitamin D†			With Vitamin D†					
	n	Mean	SD	*n*	Mean	SD	Adjusted mean difference*	95 % CI	*P**
BMI (kg/m2)	132	22·5	0·1	131	22·4	0·1	−0·1	−0·2, 0·004	0·06
Fasting plasma glucose (mmol/l)	110	8·1	0·7	111	8·0	0·7	−0·1	−0·8, 0·6	0·70
2-h postprandial plasma glucose after breakfast (mmol/l)	103	11·1	1·0	91	11·2	1·0	0·1	−1·1, 1·2	0·93
2-h postprandial plasma glucose after lunch (mmol/l)	102	10·0	0·9	89	10·3	0·9	0·3	−0·6, 1·3	0·51
2-h postprandial plasma glucose after dinner (mmol/l)	102	10·3	0·9	88	10·3	1·0	−0·1	−1·1, 0·9	0·89
Total erythrocyte counts (10^{12}/l)	117	4·4	0·2	119	4·6	0·2	0·1	−0·1, 0·3	0·18
Erythrocyte sedimentation rate (mm/h)	99	36·5	7·0	109	32·7	7·2	−3·8	−11·1, 3·5	0·31
Hb (g/l)	118	132·8	3·9	119	135·2	4·0	2·4	−2·0, 6·8	0·28
Total leucocyte counts (10^9/l)	119	6·3	0·4	119	6·4	0·5	0·1	−0·4, 0·5	0·84
Blood neutrophil counts (10^9/l)	103	4·4	0·4	96	4·5	0·5	0·1	−0·4, 0·6	0·65
Blood lymphocyte counts (10^9/l)	91	1·5	0·1	95	1·5	0·1	−0·03	−0·1, 0·1	0·67
Blood monocyte counts (10^9/l)	84	0·2	0·04	90	0·2	0·04	−0·03	−0·1, 0·01	0·14

* The influence of vitamin D allocation was tested by ANCOVA and adjusting baseline values, age, sex, antidiabetic treatment, smoking, drinking and vitamin A allocation as covariates.
† Numerical variables are presented as mean and standard deviations.

Table 4. Effects of vitamin A allocation on BMI, glycaemic and blood parameters
(Mean values and standard deviations)

	Non-Vitamin A‡			With Vitamin A‡						
	n	Mean	SD	*n*	Mean	SD	Adjusted mean difference*	95 % CI	*P**	$P_{for\ interaction}$†
BMI (kg/m^2)	139	22·4	0·1	124	22·4	0·1	0·02	−0·1, 0·1	0·80	0·36
Fasting plasma glucose (mmol/l)	116	7·9	0·6	105	8·2	0·7	0·3	−0·4, 1·0	0·37	0·07
2-h postprandial blood glucose after breakfast (mmol/l)	102	10·9	1·0	92	11·3	1·0	0·4	−0·7, 1·5	0·50	0·56
2-h postprandial blood glucose after lunch (mmol/l)	101	10·0	0·9	90	10·3	0·9	0·4	−0·6, 1·3	0·47	0·85
2-h postprandial blood glucose after dinner (mmol/l)	100	10·0	0·9	90	10·6	1·0	0·7	−0·3, 1·7	0·18	0·53
Total erythrocyte counts (10^{12}/l)	125	4·5	0·2	111	4·5	0·2	−0·1	−0·3, 0·1	0·36	0·33
Erythrocyte sedimentation rate (mm/h)	108	35·4	6·8	100	33·8	7·3	−1·6	−9·0, 5·7	0·66	0·37
Hb (g/l)	125	134·1	3·8	112	134·0	4·1	−0·1	−4·5, 4·4	0·98	0·71
Total leucocyte counts (10^9/l)	126	6·4	0·4	112	6·3	0·5	−0·1	−0·6, 0·4	0·68	0·22
Blood neutrophil counts (10^9/l)	106	4·5	0·4	93	4·4	0·4	−0·1	−0·6, 0·5	0·77	0·50
Blood lymphocyte counts (10^9/l)	97	1·5	0·1	89	1·5	0·1	0·03	−0·1, 0·2	0·68	0·11
Blood monocyte counts (10^9/l)	92	0·2	0·04	82	0·2	0·04	−0·02	−0·1, 0·02	0·31	0·12

* The influence of vitamin A intervention was tested by ANCOVA and adjusting baseline values, age, sex, antidiabetic treatment, smoking, drinking and vitamin D allocation as covariates.
† The interaction between vitamin A and D was tested by ANCOVA and adjusting baseline values, age, sex, antidiabetic treatment, smoking, drinking, vitamin A allocation and vitamin D allocation as covariates.
‡ Numerical variables are presented as mean values and standard deviations.

British Journal of Nutrition

https://doi.org/10.1017/S0007114521001185 Published online by Cambridge University Press

a null effect of daily administration of 2000 IU vitamin A or 400 IU vitamin D on the glycaemic control (fasting plasma glucose and 2-h postprandial glucose) of patients with both tuberculosis and diabetes during their 2-month intensive-phase tuberculosis treatment.

Previous studies have suggested a beneficial effect of vitamin D on glycaemic control. *In vitro* and animal studies indicated that vitamin D may stimulate insulin secretion and improve insulin sensitivity in peripheral tissues[28–30]. A recent meta-analysis including twenty RCT concluded an improvement in insulin resistance and fasting plasma glucose by the supplementation of vitamin D in patients with diabetes[14]. This meta-analysis found that the lowering effect on fasting plasma glucose only exited in the subgroup with a vitamin D intervention dosage higher than 2000 IU/d. The lower intervention dosage in our study (400 IU/d) could be part of the reasons for the null effect which was observed in our study. The second reason for the observed null effect could be the combination of diabetes and tuberculosis, which complicates the glycaemic control. Third, vitamin D receptor plays an important role in the modulation of insulin secretion and sensitivity by vitamin D. The interaction between vitamin D and vitamin D receptor genotype among the patients may affect the results. We did not have enough budge to evaluate this.

During embryonic development, vitamin A is essential for pancreas differentiation, β-cell formation and maturation[15,16]. Recent studies found that vitamin A was also required for β-cell maintenance and insulin secretion in adult mice[17,18]. Epidemiological studies reported an inverse association between the serum retinol concentration and diabetes risk[21–23]. However, our RCT observed a null effect of vitamin A supplementation on glycaemic control for patients with concurrent diabetes and tuberculosis. To our knowledge, the current trial is one of the first RCT to investigate the effect of vitamin A supplementation on glycaemic control.

Although no significant effect of vitamin A and D supplementation was observed on the glycaemic control of patients with both diabetes and tuberculosis in the current work, the simultaneous antidiabetic treatment significantly reduced the fasting plasma glucose and postprandial glucose among the patients after the intervention period.

Our study has several strengths. First, the incidence rate for concurrent diabetes and tuberculosis was low. We recruited 279 patients with both tuberculosis and diabetes and conducted one of the largest RCT for the effect of vitamin intake on this population. Second, we adopted a 2×2 factorial design, which allowed us to efficiently investigate the effects of vitamin A, D and their interaction.

A few limitations of our study should be acknowledged. First, due to insufficient blood samples, we were unable to analyse the effects of vitamin A and D supplementation on other relevant parameters (e.g. insulin and inflammation factors). Second, no placebo was used in our study. Initial survey suggested a low acceptance rate of placebo in our patients. We decided to use blank control to improve the enrolment and compliance. Third, the 2-month duration of the study did not allow us to evaluate the long-term effects on glycaemic control. Fourth, the sample sizes for fasting plasma glucose and postprandial glucose were reduced due to insufficient blood samples for some participants.

In conclusion, the adjunctive supplementation of vitamin A and D did not significantly improve the glycaemic control for the patients with both tuberculosis and diabetes. Future work should evaluate the effects of adjunctive vitamin A and D on insulin-related indices of patients with both tuberculosis and diabetes, as well as the effects of vitamin D receptor genotypes on the results.

Acknowledgements

This work was funded by the National Natural Science Foundation of China (A. M., grant number 81172662). The funder had no role in the design, analysis or writing of this article.

K. X.: conceptualisation, methodology, formal analysis and writing-original draft preparation. J. W.: methodology, formal analysis and writing-review and editing. A. M.: writing-review and editing, project administration and funding acquisition.

There are no conflicts of interest.

Supplementary material

For supplementary material referred to in this article, please visit https://doi.org/10.1017/S0007114521001185

References

1. World Health Organization (2018) *Global Tuberculosis Report 2018*. Geneva: WHO.
2. Jeon CY & Murray MB (2008) Diabetes mellitus increases the risk of active tuberculosis: a systematic review of 13 observational studies. *PLoS Med* **5**, 1091–1101.
3. Syal K, Srinivasan A & Banerjee D (2015) VDR, RXR, Coronin-1 and Interferonγ Levels in PBMCs of Type-2 Diabetes Patients: molecular Link between Diabetes and Tuberculosis. *Indian J Clin Biochem* **30**, 323–328.
4. Anand PK & Kaul D (2005) Downregulation of TACO gene transcription restricts mycobacterial entry/survival within human macrophages. *FEMS Microbiol Lett* **250**, 137–144.
5. Baker MA, Harries AD, Jeon CY, *et al.* (2011) The impact of diabetes on tuberculosis treatment outcomes: a systematic review. *BMC Med* **9**, 1–5.
6. Riza AL, Pearson F, Ugarte-Gil C, *et al.* (2014) Clinical management of concurrent diabetes and tuberculosis and the implications for patient services. *Lancet Diabetes Endocrinol* **2**, 740–753.
7. Oluboyo PO & Erasmus RT (1990) The significance of glucose intolerance in pulmonary tuberculosis. *Tubercle* **71**, 135–138.
8. Niazi AK & Kalra S (2012) Diabetes and tuberculosis: a review of the role of optimal glycemic control. *J Diabetes Metab Disord* **11**, 28.
9. Xiong K, Wang J, Zhang J, *et al.* (2020) Association of dietary micronutrient intake with pulmonary tuberculosis treatment failure rate: a cohort study. *Nutrients* **12**, 2491.
10. Xiong K, Wang J, Kang T, *et al.* (2020) Effects of resistant starch on glycaemic control: a systematic review and meta-analysis. *Br J Nutr* 1–29.
11. George PS, Pearson ER & Witham MD (2012) Effect of vitamin D supplementation on glycaemic control and insulin resistance: a

British Journal of Nutrition

https://doi.org/10.1017/S0007114521001185 Published online by Cambridge University Press

systematic review and meta-analysis. *Diabet Med* **29**, E142–E150.
12. Li XY, Liu Y, Zheng YD, *et al.* (2018) The effect of vitamin D supplementation on glycemic control in type 2 diabetes patients: a systematic review and meta-analysis. *Nutrients* **10**, 15.
13. Dawson-Hughes B, Staten MA, Knowler WC, *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.
14. Pittas AG, Dawson-Hughes B, Sheehan P, *et al.* (2019) Vitamin D supplementation and prevention of type 2 diabetes. *N Engl J Med* **381**, 520–530.
15. Martin M, Gallego-Llamas J, Ribes V, *et al.* (2005) Dorsal pancreas agenesis in retinoic acid-deficient Raldh2 mutant mice. *Dev Biol* **284**, 399–411.
16. Ostrom M, Loffler KA, Edfalk S, *et al.* (2008) Retinoic acid promotes the generation of pancreatic endocrine progenitor cells and their further differentiation into beta-Cells. *PLoS One* **3**, e2841.
17. Brun P-J, Grijalva A, Rausch R, *et al.* (2015) Retinoic acid receptor signaling is required to maintain glucose-stimulated insulin secretion and β-cell mass. *FASEB J* **29**, 671–683.
18. Trasino SE, Benoit YD & Gudas LJ (2015) Vitamin A deficiency causes hyperglycemia and loss of pancreatic beta-cell mass. *J Biol Chem* **290**, 1456–1473.
19. Krempf M, Ranganathan S, Ritz P, *et al.* (1991) Plasma vitamin A and E in type 1 (insulin-dependent) and type 2 (non-insulin-dependent) adult diabetic patients. *Int J Vitam Nutr Res* **61**, 38–42.
20. Danquah I, Dobrucky CL, Frank LK, *et al.* (2015) Vitamin A: potential misclassification of vitamin A status among patients with type 2 diabetes and hypertension in urban Ghana. *Am J Clin Nutr* **102**, 207–214.
21. Beydoun MA, Shroff MR, Chen X, *et al.* (2011) Serum antioxidant status is associated with metabolic syndrome among US adults in recent national surveys. *J Nutr* **141**, 903–913.
22. Ribel-Madsen R, Friedrichsen M, Vaag A, *et al.* (2009) Retinol-Binding protein 4 in twins regulatory mechanisms and impact of circulating and tissue expression levels on insulin secretion and action. *Diabetes* **58**, 54–60.
23. Erikstrup C, Mortensen OH, Nielsen AR, *et al.* (2009) RBP-to-retinol ratio, but not total RBP, is elevated in patients with type 2 diabetes. *Diabetes Obes Metab* **11**, 204–212.
24. Wang J, Xiong K, Wang Q, *et al.* (2020) Adjunctive vitamin A and D during pulmonary tuberculosis treatment: a randomized controlled trial with a 2×2 factorial design. *Food Funct* **11**, 4672–4681.
25. Xiong K, Wang J, Zhang B, *et al.* (2021) Vitamins A and D fail to protect against tuberculosis-drug-induced liver injury: a post hoc analysis of a previous randomized controlled trial. *Nutrition* **86**, 111155.
26. Chinese Nutrition Society (2013) *Dietary reference intake for Chinese residents 2013*. Beijing: Science Press.
27. Yang Y (2018) *China Food Composition Tables*, 6th ed. Beijing: Peking University Medical Press.
28. Zhou QG, Hou FF, Guo ZJ, *et al.* (2008) 1,25-Dihydroxyvitamin D improved the free fatty-acid-induced insulin resistance in cultured C2C12 cells. *Diabetes Metab Res Rev* **24**, 459–464.
29. Sadek KM & Shaheen H (2014) Biochemical efficacy of vitamin D in ameliorating endocrine and metabolic disorders in diabetic rats. *Pharm Biol* **52**, 591–596.
30. Bland R, Markovic D, Hills CE, *et al.* (2004) Expression of 25-hydroxyvitamin D-3–1 α-hydroxylase in pancreatic islets. *J Steroid Biochem Mol Biol* **89**, 121–125.

British Journal of Nutrition

https://doi.org/10.1017/S0007114521001185 Published online by Cambridge University Press