Original Article

The Association of Vitamin K2 Level with the Glycaemic Status in Type 2 Diabetic Patients: A Case-Control Study

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Abstract

Objectives: The target of this work was to investigate vitamin K2 level link to glycaemic status in type 2 diabetes mellitus (T2DM) patients. **Methodology**: Sixty T2DM patients were divided into 30 uncontrolled T2DM (group I), 30 controlled T2DM (group II) patients and 30 non-diabetic subjects as the control group. Vitamin K2 level, fasting insulin, homeostasis model assessment insulin resistance (HOMA-IR), fasting blood glucose (FBG), 2-h postprandial blood glucose (PPG), glycosylated haemoglobin (HbA1c) and fasting lipids were documented. Waist circumference (WC) was measured and body mass index (BMI) was calculated. **Results**: A highly significant difference between groups was observed in vitamin K2 level ($P < 0.001$) being 1.61 ± 0.56 ng/ml, 2.04 ± 0.59 ng/ml and 2.96 ± 0.82 ng/ml for groups I, II and III, respectively. Among diabetics, a negative correlation was reported between serum vitamin K2 and FBG (r -0.428), 2-h PPBG (r -0.319), HbA1c (r -0.268), fasting insulin (r -0.49), HOMA-IR (r -0.5), total cholesterol (T-cholesterol) (r -0.335) and LDL-C (r -0.296) with $P < 0.05$. The receiver operating characteristic (ROC) curve emphasized the utility of the discriminated potentiality of serum vitamin K2 as a biomarker for uncontrolled hyperglycaemia in T2DM. The multivariate linear regression has shown that FBG is the only significant independent predictor of serum levels of vitamin K2. **Conclusions:** In T2DM patients, serum vitamin K2 level was significantly lower, especially with uncontrolled hyperglycaemia. This suggests that vitamin K2 level has an association with the glycaemic status in T2DM.

Keywords: Insulin resistance, type 2 diabetes mellitus, uncontrolled hyperglycaemia, vitamin K2

Introduction

Vitamin K is known to lower the risk of type 2 diabetes mellitus (T2DM) and metabolic syndrome through its ability to improve insulin sensitivity and glucose metabolism.[1-3]

This can be explained by vitamin K2's impact on both osteocalcin (OC) and adiponectin levels and their association with glycaemic control and insulin sensitivity, besides its anti-inflammatory properties and its lipid-reducing effect.[4,5]

The target of this work was to investigate vitamin K2 level impact on the glycaemic status in T2DM patients, as this link was not focussed on by previous literatures, which targeted only on its supplementation.

This study hypothesized that the level of vitamin K2 will be lower for patients with uncontrolled T2DM.

This work investigated serum vitamin K2 levels between the uncontrolled, controlled T2DM patients and the non-diabetics as the primary aim. The secondary aim was to investigate the relation between serum vitamin K2 and insulin resistance, the metabolic parameters, disease duration and the type of anti-diabetic treatment in T2DM patients.

Materials and Methods

This case-control study was conducted from April 2020 to April 2021 on patients visiting the endocrinology outpatient clinic of Kasr El Ainy Hospital of Cairo University. Before starting the research, approval was taken from the research ethics committee of the Faculty of Medicine of Cairo University and registration was done at Clinicaltrial.gov (ID: NCT04387019). A signed informed consent was taken from all participants.

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The study included 90 participants aged 20–65 years, allocated in three groups, 60 patients with T2DM who were subdivided into group I which included 30 uncontrolled T2DM patients with glycosylated haemoglobin (HbA1c) more than 7, in spite of stable treatment regimen for at least 6 months preceding to the index HbA1c,[6] group II which included 30 controlled T2DM patients with HbA1c less than 7, while the control group included 30 non-diabetes mellitus (DM) (group III).

Patients excluded from the research were those with osteoporosis, history of gastrointestinal (e.g., nausea, vomiting or diarrhoea), hepatic (alanine aminotransferase or aspartate aminotransferase >2·0 times the upper limit of normal persistent for 1 week or longer) or cardiovascular disease (congestive heart failure, myocardial infarction, arrhythmia) and subjects who had vitamin K antagonists or vitamin K supplements.

Full medical history was taken from all subjects, emphasizing the age, duration of DM and its treatment. Clinical examination was performed including blood pressure, waist circumference (WC), weight, height and body mass index (BMI) measurement. The obesity was classified according to the World Health Organization (WHO) criteria.[7]

The laboratory investigations included the following: Fasting blood glucose (FBG), 2-h postprandial blood glucose (2-h PPG), fasting lipids {total cholesterol (TC), triglycerides (TAG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C)}, HbA1c, fasting insulin, homeostasis model assessment insulin resistance (HOMA-IR) and vitamin K2 levels were measured.

Sampling was done as follows: 5 ml of fasting (12–16 h) venous blood was collected by venipuncture and split into two parts: The first part was 2 ml of blood added to a tube containing ethylenediaminetetraacetic acid (EDTA) for determination of HbA1c with cation exchange resin. The second part was 3 ml of blood left in plastic serum tubes and was stored at −80°C for fasting insulin and vitamin K2 assessment. Vitamin K2 was measured in serum using vitamin K2 ELISA kit, Catalog, Catalog #: SEH4127s. The spectrophotometric absorbance was assessed at 450 nm in accordance with the manufacturer's commands.

Fasting serum insulin was measured utilizing radio immuno assay.[8] Insulin resistance was estimated according to the HOMA-IR applying the following equation: HOMA-IR = FBG (mg/dl) × fasting serum insulin (μIU/ml)/405[12]. HOMA-IR cutoff value used was 2.7 (>2.7 was considered insulin resistant and <2.7 was considered insulin sensitive).[9]

The investigators who performed the clinical examination and laboratory work were masked from patients' groups (diabetic or non-diabetic).

Statistical approaches

The information was coded and submitted utilizing version 26 of the Statistical Package for the Social Sciences (SPSS) (IBM Corp., Armonk, NY, USA). Data were summed by applying the mean and standard deviation for quantitative variables and categorical factors by using frequencies (number of cases) and relative frequencies (percentages). On comparing the groups, contrasts between two groups were carried out utilizing the unpaired t-test while analysis of variance (ANOVA) with several post hoc comparisons when distinguishing higher than two groups.[10] The Chi-squared test was performed to distinguish categorical data. Instead, the exact test was applied when the expected frequency was lesser than 5.[11] Correlations were made applying the Pearson correlation coefficient between quantitative variables.[12] The receiver operating characteristic (ROC) curve was created with an area under curve analysis executed to identify the favoured cutoff value of vitamin K2 for the determination of uncontrolled DM. Linear regression analysis was performed to find independent forecasters of vitamin K2.[13] *P* values below 0.05 were statistically significant.

Sample size

The sample size was calculated utilizing the G power software version 3.1.9.4. Analysis was done on vitamin K level in the controlled and uncontrolled T2DM patients and control as the primary outcome. The authors performed a pilot study on 45 (15 patients per group) that showed mean vitamin K2 levels of 1.6 ng/ml, 2 ng/ml and 2.8 ng/ml for the uncontrolled, controlled T2DM and control, respectively. By using a type I error of 0.05, power of 98% and an effect size of 0.5, a number of 30 patients for each group was calculated.

Results

Ninety-nine patients were enrolled in this study, 5 refused to participate, 4 blood samples were spoiled and only 90 patients completed the analysis (30 patients in each group). The basic characteristics of the study population are given in Table 1.

The mean serum vitamin K2 level in uncontrolled T2DM patients was significantly lower compared to controlled T2DM patients and the controls ($P < 0.001$) [Table 1].

There was a significant difference ($p < 0.001$) between uncontrolled T2D patients and controls, and uncontrolled and controlled diabetes with regard to vitamin K2 levels and age, weight, BMI, WC, FBG, 2-h PPG, HbA1c, fasting insulin, HOMA-IR, T-cholesterol, TAG, HDL-C and LDL-C.

By generating a ROC curve, it was found that an area under the curve of 0.687 and cutoff value of 1.9685, sensitivity would be 86.2% and specificity would be 53.3% with 95% CI 0.551 to 0.823 and *P* value = 0.014. These results emphasize the usefulness of the discriminated ability of serum vitamin K2 as a biomarker for uncontrolled hyperglycaemia in patients with T2DM.

In all patients, a negative correlation between vitamin K2 and FBG, 2-h PPBG, HbA1c, fasting insulin, HOMA-IR, T-cholesterol and LDL-C was found [Table 2, Figure 1].

Table 1: Comparison of parameters among the studied groups

Variable		Group-I		Group-II		Group-III		*P*
		Count	%	Count	%	Count	%	
Sex	Male/Female	8/22	26.7/73.3	4/26	13.3/86.7	4/26	13.3/86.7	0.296
TTT	Insulin	21	70.0	7	23.3	0	0.0	< 0.001
	OHD	4	13.3	18	60.0	0	0.0	
	Mixed insulin-OHD	5	16.7	5	16.7	0	0.0	
BP	Normal	20	66.7	24	80.0	29	96.7	0.012
	HTN	10	33.3	6	20.0	1	3.3	
		Mean	SD	Mean	SD	Mean	SD	
Age (years)		50.13	10.15	52.13	10.14	36.30	8.10	< 0.001
Disease duration (years)		11.73	6.04	5.77	4.35	.	.	< 0.001
Weight (kg)		89.50	18.73	78.67	15.70	74.63	15.39	0.003
Height (cm)		161.60	8.83	157.67	8.42	162.27	8.20	0.082
BMI (kg/m^2)		34.27	6.84	31.55	6.24	28.52	6.42	0.004
WC (cm)		111.27	13.54	104.80	14.42	95.83	11.51	< 0.001
FBG (mg/dl)		232.33	72.50	132.33	34.28	95.53	7.77	< 0.001
2-h PPG (mg/dl)		276.33	53.89	165.00	33.94	161.80	12.54	< 0.001
HB A 1c (%)		8.61	0.83	6.32	0.39	5.01	0.27	< 0.001
Fasting insulin (µIU/ml)		24.63	6.37	13.4	3.2	10.3	1.51	< 0.001
HOMA-IR		15.14	8.2	4.62	2.2	2.44	0.52	< 0.001
T-cholesterol (mg/dl)		216.63	23.09	193.63	42.13	192.37	23.60	0.004
TAG (mg/dl)		207.77	34.06	201.83	55.50	160.47	37.93	< 0.001
HDL-C (mg/dl)		38.69	10.54	45.10	7.49	51.50	9.28	< 0.001
LDL-C (mg/dl)		125.73	17.84	115.60	12.27	106.50	9.19	< 0.001
Vitamin K2 (ng/ml)		1.61	0.56	2.04	0.59	2.96	0.82	< 0.001

*Parameters are described as numbers, percent, mean±SD, *P<0.05 is significant, TTT, treatment, BP, blood pressure OHD, oral hypoglycaemic drugs, HTN, hypertension, WC, waist circumference, BMI, body mass index, FBG, fasting blood glucose, 2-h PPG, 2 hours postprandial blood glucose, HbA1c, glycated haemoglobin, HOMA-IR, homeostasis model assessment insulin resistance, T-cholesterol, total cholesterol, HDL-C, high-density lipoprotein cholesterol, LDL-C, low-density lipoprotein cholesterol

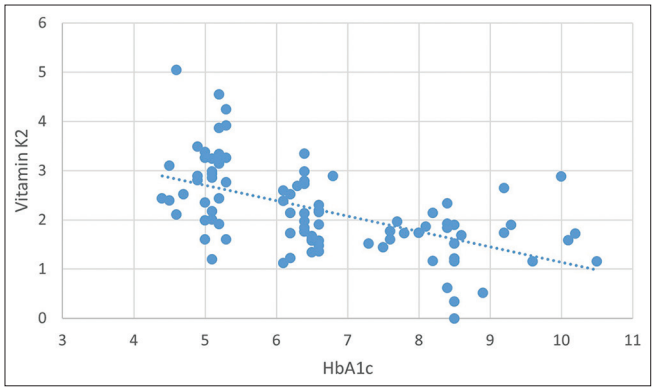

Figure 1: Correlation between vitamin K2 and HbA1c in all cases

Among uncontrolled T2DM patients, a negative correlation was observed between vitamin K2 and fasting insulin and HOMA-IR with $P < 0.05$. Also, a negative correlation between vitamin K2 and T-cholesterol was reported among controlled diabetics. In addition, a negative correlation was observed between vitamin K2 and age among controls ($P < 0.05$) [Table 2].

By multivariate linear regression between vitamin K2 and FBG, 2-h PPBG, HbA1c, fasting insulin, HOMA-IR, T-cholesterol, LDL-C, age, disease duration age, weight, height, BMI and WC, the only significant independent predictor of vitamin K2 was FBG [Table 3].

Gender effect on vitamin K2 levels between groups showed significant difference as regard vitamin K2 levels in males between diabetics and control and also, in females between diabetics and controls. While there was an insignificant difference as regard vitamin K2 levels between males and females of the same group in the three groups.

Discussion

This case-control study targets to evaluate the association of serum vitamin K2 level and the glycaemic condition in T2DM patients. Previous studies found that supplementation with vitamin K2 decreased T2DM risk by enhancing glucose metabolism and sensitivity to insulin. Additionally, the research found that serum carboxylated OC levels, a vitamin K-dependent protein, were accompanied by improvement of glycaemic status and insulin sensitivity. However, no previous studies targeted the association of serum vitamin K2 level and glycaemic control in patients with T2DM.

Table 2: Correlation between vitamin K2 and other measured parameters in the studied groups

Variable	Vitamin K2 (ng/ml)									
	Group-I		Group-II		Group-III		Group I and II (Diabetic cases)		All groups	
	Correlation coefficient (*r*)	*P*	Correlation coefficient (*r*)	*P*	Correlation coefficient (*r*)	*P*	Correlation coefficient (*r*)	*P*	Correlation coefficient (*r*)	*P*
Age (Years)	0.204	0.288	0.105	0.582	-0.412-	0.024	0.169	0.201	-0.357	<0.001
Disease duration (Years)	-0.020-	0.919	0.070	0.712			-0.168-	0.202	-0.4719	<0.001
Weight (kg/m^2)	-0.105-	0.589	-0.075-	0.695	-0.233-	0.215	-0.187-	0.157	-0.309	0.004
Height (cm)	-0.074-	0.702	-0.006-	0.977	-0.177-	0.349	-0.124-	0.351	0.0078	0.94
BMI (kg/m^2)	-0.090-	0.642	-0.067-	0.723	-0.151-	0.426	-0.140-	0.289	-0.312	0.003
WC (cm)	-0.134-	0.487	0.129	0.496	-0.261-	0.163	-0.072-	0.587	-0.354	0.0006
FBG (mg/dl)	-0.360-	0.055	-0.171-	0.366	-0.350-	0.058	-0.428-	0.001	-0.576	<0.0001
2-h PPG (mg/dl)	-0.194-	0.313	0.094	0.620	-0.162-	0.391	-0.319-	0.014	-0.473	<0.0001
HbA1c (%)	0.060	0.759	0.163	0.389	0.090	0.635	-0.268-	0.040	-0.5569	<0.0001
Fasting insulin (µIU/ml)	-0.45-	0.01	-0.17-	0.37	-0.08-	0.66	-0.49-	0.005	-0.585	<0.0001
HOMA-IR	-0.46-	0.01	-0.21-	0.27	-0.19-	0.31	-0.5-	0.0049	-0.555	<0.0001
T-cholesterol (mg/dl)	0.068	0.725	-0.428-	0.018	-0.170-	0.370	-0.335-	0.010	-0.333	0.0013
TAG (mg/dl)	0.201	0.296	0.144	0.448	-0.065-	0.735	0.128	0.332	-0.233	0.03
HDL-C (mg/dl)	0.004	0.982	0.091	0.633	0.233	0.215	0.151	0.255	0.412	<0.0001
LDL-C (mg/dl)	-0.147-	0.447	-0.301-	0.106	-0.212-	0.260	-0.296-	0.023	-0.444	<0.0001

*P<0.05 is significant, WC, waist circumference, BMI, body mass index, FBG, fasting blood glucose, 2-h PPG, 2 hours postprandial blood glucose, HbA1c, glycated haemoglobin, HOMA-IR, homeostasis model assessment insulin resistance, HDL-C, high-density lipoprotein cholesterol, LDL-C, low-density lipoprotein cholesterol, *r*, Correlation coefficient

Table 3: Multivariate regression analysis between vitamin K2 and other measured parameters in DM

Model		Unstandardized coefficients		Standardized coefficients	*t*	*P*	95.0% Confidence interval for B	
		B	Std. error	Beta			Lower bound	Upper bound
Vitamin K2	(Constant)	2.463	0.191		12.899	<0.001	2.081	2.845
	FBG	-0.003-	0.001	-0.428-	-3.576-	0.001	-0.005-	-0.002-

a. Dependent variable: vitamin K2

Our results supported our hypothesis that in subjects with T2DM, vitamin K2 levels were lower than controls and in patients with uncontrolled T2DM, levels of vitamin K2 were significantly lower than in patients with controlled T2DM. A negative correlation was observed among the uncontrolled T2DM patients between vitamin K2 level and fasting insulin and HOMA-IR supporting the relation of vitamin K2 level with insulin resistance. Also, a negative correlation was observed among diabetic patients between vitamin K2 and FBG, 2-h PPBG, HbA1c, T-cholesterol, LDL-C, fasting insulin and HOMA-IR. Also, the results confirmed the ability of serum vitamin K2 to be used as a biomarker for uncontrolled hyperglycaemia in T2DM. FBG was found as the only significant independent predictor for serum vitamin K2 levels.

Our findings can be explained by vitamin K's impact on both OC and adiponectin levels and their association with glycaemic control and insulin sensitivity, besides, its anti-inflammatory properties through the inactivation of the tumour necrosis factor-κB (NF-κB) signalling pathway and its lipid-lowering effects.[4]

OC is a type of vitamin K-dependent protein, formed by osteoblasts. The recognition site of propeptide in uncarboxylated OC is necessary for binding to glutamate carboxylase (GGCX) to undergo an unusual post-translational alteration. Following carboxylation, the propeptide is extracted and the matured carboxylated OC is released.[14] The γ-carboxyglutamic (Gla) remnants in OC enhance the proliferation of ß-cell, secretion and sensitivity of insulin by motivating islet ß-cells.[15]

It was hypothesized that the impact of adiponectin and OC augmented insulin sensitivity. Adiponectin augments insulin sensitivity through enhanced fatty acid oxidation and suppression of hepatic glucose development.[16]

The impact of vitamin K intake was assessed for sensitivity to insulin and glycaemic state by Beulens *et al*.[2] They studied the bond of dietetic phylloquinone (vitamin K1) and menaquinone (vitamin K2) supplementation with T2DM hazard in a prospective cohort study that included a broad sample of 38,094 adult Dutch males and females. Their findings

showed a 7% reduction in T2DM risk for each 10-µg rise in vitamin K2 intake.

Choi *et al*.[17] also demonstrated an association between insulin sensitivity and vitamin K2 intake of 30 mg for 4 weeks among healthy young men. In their study, supplementation with vitamin K2 was noticed to be related to an improved index of insulin sensitivity ($P = 0.01$) with no impact of placebo treatment on the index. Manna *et al*.[5] suggested that vitamin K1 and vitamin K2 intake were essential to lower T2DM hazard and suggested that vitamin K2 played an extra advantageous role than vitamin K1 in insulin sensitivity and metabolism of glucose.

The negative correlation between vitamin K2, T-cholesterol and LDL-C among diabetic cases can be explained by vitamin K2 mediated increased adiponectin level which enhances sensitivity to insulin through augmented oxidation of fatty acids and lessened the accumulation of fat and serum TAG. It's also possible that vitamin K2 decreases the resistance to insulin through effective lipid-lowering. Tschritter *et al*.[18] reported that lower plasma adiponectin levels have been observed in fatty participants relative to thin subjects. Moreover, in obesity, the level of adiponectin was downregulated and positively correlated with insulin sensitivity.

Based on recent new perspectives into the control of lipid metabolism, vitamin K2 supplementing is considered one of the possibly groundbreaking therapeutic methods to treat insulin resistance and decrease the T2DM hazard.[3,4]

The higher BMI, WC and lipid profile found in T2DM than controls can be explained by that obesity is accompanied by higher lipid deposition in non-adipose tissues such as skeletal muscle, liver and ß-cells of the pancreas. In pancreatic ß-cells, short-term fatty acid exposure triggers protein kinase C (PKC) and induces insulin exocytosis directly. While long-term free fatty acid excess (FFA) contributes to dampened glucose-motivated insulin secretion. On the one side, the increased supply of fatty acids in the skeletal muscle contributes to reduced glucose oxidation. In exchange, glucose-6-phosphate accumulation limits insulin-stimulated glucose uptake.[4]

Study limitations

The lack of enough previous studies to compare the results of this work was the most important limitation. Also, further studies should be undertaken for the evaluation of vitamin K2 supplementation's role in uncontrolled T2DM.

Conclusion

The study concluded that vitamin K2 levels were lower than controls in subjects with T2DM and vitamin K2 levels were significantly lower in patients with uncontrolled T2DM than in patients with controlled T2DM. A negative significant correlation was observed among diabetic patients between vitamin k2, FBG, 2-h PPBG, HbA1c, fasting insulin, HOMA-IR, T-cholesterol and LDL-C. Also, the ROC curve emphasized the utility of the discriminated potential of serum vitamin K2 as a biomarker for uncontrolled hyperglycaemia in T2DM patients. FBG was found to be the only significant independent predictor for serum vitamin k2 levels. These results raise the concern about the relationship between vitamin K2 level and the glycaemic state in T2DM.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

The author notes that there is no contradiction of interest in stating that the impartiality of the study published may be prejudicing it.

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