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Research Article

The Effects of Vitamin K2 (Menaquinone-7) on the Leptin and Adiponectin Levels in Overweight/Obese Type 2 Diabetes Patients: A Randomized Clinical Trial

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a prevalent disease with metabolic consequences. Lower levels of adiponectin and higher levels of leptin were reported in T2DM. This study aimed to evaluate the effect of menaquinone-7 (MK-7) supplementation on adiponectin and leptin in overweight/obese T2DM patients.

Methods: Sixty men and women with T2DM and 27 ≤ body mass index < 35 kg/m^2, participated in this double-blind placebo-controlled randomized clinical trial for 12 weeks. The subjects were allocated into intervention (200 µg/day MK-7) or placebo groups. Three-day food records, anthropometrics and physical activity were assessed and fasting blood samples were collected at the pre- and post-intervention. Serum adiponectin, leptin, fasting blood sugar (FBS) and fasting insulin (FI) were measured and adiponectin to leptin ratio (A/L ratio) was calculated.

Results: MK-7 decreased fasting blood sugar (P: 0.018) and fasting insulin (P: 0.012), according to a within group analysis of the 45 patients who finished the research. Fasting blood sugar (P: 0.024) and leptin levels (P: 0.032) were lower in the MK-7 group, but there were no significant changes between the groups in terms of adiponectin or the adiponectin to leptin (A/L) ratio.

Conclusion: Current study showed that MK-7 supplementation could lead to significant reduction in leptin and FBS, but it has no effect on the adiponectin and A/L ratio in overweight/obese T2DM patients.

Introduction

Type 2 diabetes mellitus (T2DM) is a widespread disease which is defined by chronic elevated blood glucose level.[1,2] Hyperglycemic hyperosmolar syndrome (high blood osmolarity without ketosis) and hypoglycemia are acute complications of T2DM and microvascular complications (nephropathy, neuropathy and retinopathy) or macrovascular complication (coronary heart disease, peripheral vascular disease and stroke) are its chronic complications.[3] Global prevalence of T2DM has an increasing trend,[1] as 463 million reported T2DM patients in 2017 had shown 25% increase since 1995.[4] In 2017, it was estimated that 7.3 percent of Iranians have type 2 diabetes, which is a 57 percent increase from 1990.[4] Complications of diabetes mellitus are correlated with body weight status, and rising body mass index (BMI) has been linked to a higher risk of T2DM complications.[5]

Different approaches are being used to control the T2DM, such as diet therapy, regular exercise, lifestyle changes, regular blood glucose monitoring and finally medication or insulin therapy.[6,7] Vitamin supplementation was used to control T2DM and its complications. Many studies have reported the beneficial effects of vitamin K to decrease T2DM risk as it is effective to improve the insulin sensitivity, glucose metabolism, dyslipidemia, inflammation and oxidative stress.[3,8,9]

Vitamin K, a fat soluble vitamin and gamma glutamyl carboxylase cofactor, has 3 different forms: K1 (phylloquinone), K2 (menaquinone) and K3 (menadione). Phyloquinone is found in green leafy vegetables and specific vegetable oils. Menaquinone is in some animal or bacterial fermentation products, whereas menadione is the synthetic form.[10-12]

The United States Institute of Medicine recommends 90-120 µg/day vitamin K (menaquinone or phylloquinone) as its adequate intake for adults.[12] Menaquinone (MK-n) exists in different forms which MK-4 and MK-7 are the most common ones.[3] According to a research, MK-7 is more effective at protein carboxylation, has a longer half-life, and is more readily absorbed by tissues than

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phylloquinone. It also achieves higher and more stable blood levels than K1.[13] Due to its increased absorption rate, bioavailability, and half-life, certain investigations revealed that MK-7 had the same effects on glucose metabolism at lower doses than MK-4.[3,14]

Adipokines are bioactive molecules derived from fat tissue which are important to regulate the appetite, metabolism, insulin activity and inflammation.[15] Adiponectin and leptin are the most known adipokines that show opposite effects on insulin function and inflammation.[16] Compared to healthy adults, lower levels of adiponectin and higher levels of leptin were reported in T2DM patients.[17,18] Adiponectin to leptin ratio (A/L) is a good index to evaluate the insulin resistance and antidiabetic treatment efficacy in T2DM patients.[19,20] In addition, earlier research shown that this ratio may be a more accurate predictor of insulin resistance than HOMA-IR (homeostatic model assessment insulin resistance index), QUICKI (quantitative insulin sensitivity check index), McAuley index, and the ratio of glucose to insulin in the fasting state.[21]

While there are few studies on the effects of vitamin K in adiponectin and leptin levels,[14,22-25] there are limited evidence in T2DM cases.[10,26] Rasekhi *et al.*[26] showed that phylloquinone supplementation increased adiponectin in prediabetic women. In an animal model of diabetes, Hussein *et al.*[10] demonstrated that vitamin K2 boosted adiponectin expression. After three months of supplementing obese mice with menaquinone, Kim *et al.*[27] saw a substantial drop in leptin levels. Vitamin K2 supplementation, as MK-7, enhanced adiponectin in postmenopausal women, according to research by Knapen *et al.*[25] In the literature review, only five studies assessed the effect of vitamin K, as MK-7, on the adiponectin or leptin levels which none of them was conducted in the patients with diabetes.[14,23,25,28,29]

There are not enough data about the effects of vitamin K on the adiponectin and leptin levels in the patients with T2DM and adiponectin and leptin changes are common in overweight/obese T2DM patients as many other metabolic consequences. Additionally, MK-7 has distinct qualities including its biological effects and bioavailability. Therefore, the present study's objective was to assess how menaquinone as MK-7 affected the levels of adiponectin and leptin as well as the A/L ratio in individuals with overweight or obesity-related type 2 diabetes.

Methods

Subjects

This study was a parallel double-blind placebo-controlled randomized clinical trial which was performed in T2DM patients. Sixty men and non-postmenopausal women aged 20-55 years with BMI from 27 to 35 kg/m^2 who received anti-diabetic drugs for at least six months before participating entered to the study. People who received insulin, contraceptives, corticosteroids, anticoagulant drugs like warfarin and coumarin, hormones, any dietary supplements or weight lowering drugs for three months before recruiting and who were in different conditions like pregnancy, lactation, menopause, presence of vascular, cardiac, bone, thyroid, parathyroid, intestine, kidney, liver, inflammatory or infectious diseases, polycystic ovary syndrome, rheumatoid arthritis, malignancies and experience of recent surgery or smoking were excluded from study. This paper is a supplement to a previously published research,[30] focusing on adiponectin and leptin levels that have not been previously mentioned. Before the start of the trial, all participants were informed of the protocol and signed a written permission form. They were permitted to exit the research at any moment without providing an explanation. The study was approved by the ethics committee of Tabriz University of Medical Sciences, Tabriz, Iran (Ethics code: IR.TBZMED.REC.1399.096) and registered by the Iranian Registry of Clinical Trials (IRCT20100123003140N22).

Randomization, blinding and study procedure

A blinded assistant used RAS (Random Allocation Software) for allocating participants into two groups (1:1) and sealed and opaque envelopes with successive numbering were used for allocation concealment. Menaquinone-7 and placebo capsules (Nanochemia, Karaj, Iran) were in the same shape and color with the same container labeling. All participants and researchers were blind to participant allocation. After a 12-hour overnight fast, blood samples were taken from the qualified individuals who had been diagnosed with T2DM by an endocrinologist.[30]

Intervention

According to the published recommendations, standardized dietary advices were given to all participants.[31] After being randomly assigned to either the intervention or placebo groups, the patients in the placebo group received cornstarch capsules with their main meal for 12 weeks whereas those in the intervention group got 200 µg/d of MK-7 capsules. They were followed-up by phone call weekly and visiting every three weeks.[30]

Assessment of physical activity and dietary intake

The patients' nutritional intake and physical activity levels were estimated using the three-day food diary and the international physical activity questionnaire-short form (IPAQ-SF), respectively. The validity and reliability of IPAQ-SF, which evaluates the intensity and duration of physical activity in last seven days, was previously studied by BashiriMoosavi *et al.*[32] Metabolic equivalents of different types of physical activities were multiplied by weekly duration of that activity and participants were categorized as low (<600 MET), moderate (600-3000 MET) and high (≥3000 MET) by MET-minutes/week. At the start and conclusion of the trial, participants in both groups were instructed to fill out the three-day food records immediately after eating for three separate days (a weekend and two weekdays). Researchers checked entered information by a face-to-face interview, and obtained dietary information was examined using Nutritionist IV

software (First Databank, San Bruno, California, USA), which was customized for Iranian foods.[30]

Blood sampling and biochemical measurements

Seven milliliters of blood were collected after a 12-hour overnight fasting at pre- and post-intervention. Serum adiponectin and leptin were measured by double-antibody sandwich ELISA (enzyme-linked immunosorbent assay) method with human adiponectin and leptin Elisa kits (Eastbiopharm, Hangzhou, china). The kits sensitivity for adiponectin and leptin were 0.11 mg/L and 0.021 ng/ml,respectively. Adiponectin to leptin ratio was calculated by dividing adiponectin amount by leptin amount. Moreover, serum fasting blood sugar (FBS) and serum fasting insulin (FI) were measured by enzymatic (Pars Azmoon, Tehran, Iran) and sandwich ELISA (enzyme-linked immunosorbent assay, Monobind, Lake Forest, CA, USA) methods, respectively.[30]

Anthropometric indices

A qualified nutritionist pre- and post-treatment took all measures. BMI was calculated after measuring the subject's height (with a precision of 0.1 cm without shoes) and weight (with a precision of 0.1 kg while wearing light clothes using a Seca scale).[30] Moreover, bioelectrical impedance analysis (BIA) was used to assess body fat percentage.

Sample size and statistical methods

The sample size was estimated based on mean and standard deviation (SD) of adiponectin in a similar study which was published in 2015[26] and the result was 17 per group considering 95% power with a 5% risk of type 1 error which was increased to 23 per group according to predicted 25% attrition rate. Based on the protocol approach, statistical analysis was performed. Using the Kolmogrov-Smirnov test and descriptive indices, the normality of quantitative data was confirmed. For reporting normally and non-normally distributed values, respectively, mean with SD and median with minimum and maximum were employed. Number (percent) was used to represent qualitative characteristics. Independent sample t-test or Mann-Whitney was used to assess the differences among the groups at baseline and Chi-squared or Fisher exact test was used to determine those differences in qualitative variables. The within-group changes were assessed by Paired sample t-test and Wilcoxon signed-rank test for normally and non-normally distributed variables respectively. An analysis of covariance (ANCOVA) adjusting for baseline values and potential confounders (glycemic indices and changes of dietary vitamin K intake) was used to compare among the

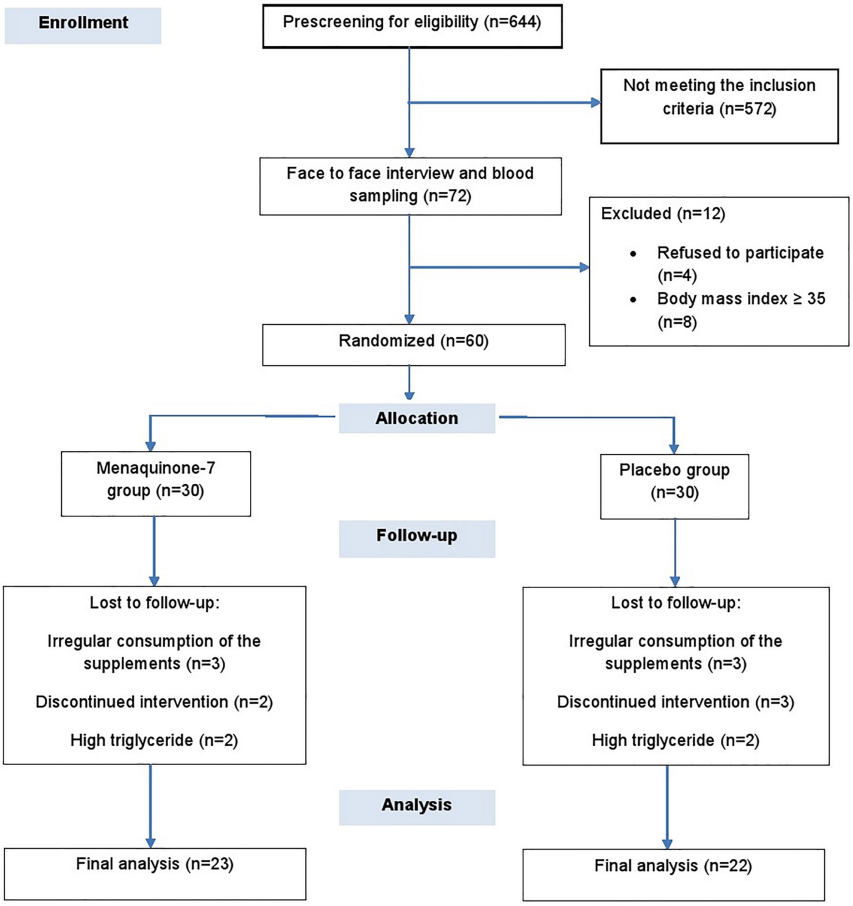

Figure 1. Flow chart of the patient selection process.

groups at the end of the study. Statistically significance level was defined by P-value<0.05 and all statistical analysis were done with SPSS software version 24 (SPSS Inc., IL, Chicago, USA).

Results

At first 644 patients were screened by phone call and verified based on inclusion/exclusion criteria and 72 patients remained after this verification. In face to face meeting, 12 patients were excluded of which 8 patients had BMI>35 and 4 patients refused to participate more. Therefore, 60 patients started the study, and finally 45 patients remained at the end of 12-weeks period (MK-7 group n=23; placebo group n=22). Figure 1 depicts the study's flowchart in detail and lists the number of patients in each group as well as those that were lost to follow-up. Neither study participants who finished it nor those who did not report any negative effects throughout the research's duration.

Demographics characteristics and physical activity

1 shows the demographic features of participants at baseline. Most of the patients were male (16 in MK-7 group and 15 in placebo group) and married (22 in MK-7 group and 21 in placebo group). At baseline, there were no significant variations in the two groups' demographic characteristics. As can be seen in Table 1, there was no significant difference in the two groups' baseline levels of physical activity, and this index remained stable during the course of the research.

Adiponectin, leptin and A/L ratio

As shown in Table 2, there were no significant differences in adiponectin, leptin and A/L ratio among the groups at baseline (P>0.05). After 12-weeks supplementation, adiponectin, leptin and A/L ratio did not change significantly within groups (P>0.05). There were no significant differences in adiponectin and A/L ratio among the groups at the end of study, but leptin was significantly different between two groups adjusting for baseline values and glycemic indices (P:0.032). Even after adjusting for body fat percentage, the mean leptin levels in the MK-7 group were considerably lower than those in the placebo group (P: 0.033). However, after controlling for other confounders including sex, age, and different drugs, no significant effects on adiponectin or leptin were discovered (P>0.05).

Glycemic and anthropometric indices, body fat percentage and dietary intakes

There were no significant differences in body fat percentage, glycemic and anthropometric indices at baseline (P> 0.05, Table 2).Within group analysis showed that FBS and FI

Table 1. Baseline characteristics of the study population.

Variables	Placebo Group (n=22)	MK-7 Group (n=23)	P-value
Age (year) [a]	46.95 (5.25)	45.35 (6.25)	0.357 [c]
Sex [b]			
Male	15 (62.8%)	16 (69.6%)	0.920 [d]
Female	7 (31.8%)	7 (30.4%)	
BMI Category [b]			
Overweight	9 (40.9%)	12 (52.2%)	0.554 [e]
Obese	13 (59.1%)	11 (47.8%)	
Educational level [b]			
<Diploma	10 (45.5%)	9 (39.1%)	
Diploma and Associate	6 (27.3%)	7 (30.4%)	0.912 [d]
≥Bachelor	6 (27.3%)	7 (30.4%)	
Marital Status [b]			
Single	1 (4.5%)	1 (4.3%)	1.000 [e]
Married	21 (95.5%)	22 (95.7%)	
Occupation [b]			
Housewife	13 (59.1%)	15 (65.2%)	
Employed	5 (22.7%)	6 (26.1%)	0.758 [e]
Retired	4 (18.2%)	2 (8.7%)	
Drug History [b]			
Only anti diabetic drugs	3 (13.6%)	8 (34.8%)	
Anti-hyperlipidemia drugs	10 (45.5%)	8 (34.8%)	
Anti-hypertension drugs	3 (13.6%)	3 (13%)	
Both anti-hyperlipidemia and anti- Hypertension drugs	6 (27.3%)	2 (8.7%)	0.175 [e]
Other drugs	0 (0%)	2 (8.7%)	
Physical Activity [b]			
Low	2 (9.1%)	0 (0%)	
Moderate	7 (31.8%)	11 (47.8%)	0.280 [e]
High	13 (59.1%)	12 (52.2%)	

P< 0.05 was considered statistically significant. [a] Mean (standard deviation). [b] Number (%). [c] Based on independent-samples t-test. [d] Based on Pearson Chi-Square test. [e] Based on Fishers exact test.

Table 2. Comparison of adiponectin, leptin, A/L ratio, glycemic and anthropometric indices among study groups at baseline and at the end of the intervention.

Variables	Placebo Group (n=22)	MK-7 Group (n=23)	MD (95% CI), P
Adiponectin (mg/L)			
Before	10.85 (5.30, 67.20)	14.30 (4.20, 78.70)	0.928 [a]
After	12.75 (4.20, 69.30)	11.50 (1.80, 72.70)	-0.07(-0.26, 0.11), 0.413 [c]
P-value [b]	0.592	0.697	
Leptin (ng/ml)			
Before	2.45 (1.60, 11.90)	2.50 (1.30, 13)	0.251 [a]
After	2.75 (1.40, 12.40)	2.70 (0.60, 12.70)	-0.16 (- 0.31, -0.01), 0.032 [c*]
P-value [b]	0.269	0.322	
A/L ratio (×1000)			
Before	5.27 (2.94, 11.76)	4.83 (1.70, 12.49)	0.318 [a]
After	4.80 (3, 14.14)	5.18 (2.15, 17.97)	0.05 (-0.09, 0.21), 0.453 [c]
P-value [b]	0.306	0.316	
FBS (mmol/L)			
Before	7.74 (2.13)	7.59 (2.80)	0.15 (-1.34, 1.65), 0.838 [d]
After	8.14 (1.82)	6.72 (2.75)	-1.35 (-2.51, -0.18), 0.024 [f*]
MD (95% CI), P [e]	0.39 (-0.76, 1.56), 0.484	-0.87 (-1.57, -0.16), 0.018 *	
FI (µIU/ml)			
Before	14.35 (7.65, 25.52)	15.70 (9.50, 44)	0.286 [a]
After	15.55 (5.67, 29.12)	9.90 (5.40, 15.20)	-5.82 (-15.79, 4.13), 0.241 [g]
P-value [b]	0.783	0.012 *	
Weight (kg)			
Before	85.92 (12.56)	85.73 (11.91)	0.19 (-7.25, 7.64), 0.952 [d]
After	86.50 (12.55)	86.73 (12.58)	-0.52 (-1.95, 0.91), 0.465 [f]
MD (95% CI), P [e]	0.57 (-0.02, 1.17), 0.051	1 (-0.30, 2.30), 0.125	
BMI (kg/m^2)			
Before	30.65 (2.76)	30.30 (2.23)	0.35 (-1.16, 1.88), 0.642 [d]
After	30.91 (2.77)	30.68 (2.97)	-0.18 (-0.76, 0.39), 0.513 [f]
MD (95% CI), P [e]	0.25 (-0.01, 0.52), 0.061	0.37 (-0.14, 0.90), 0.152	
Body Fat (%)			
Before	26.26 (4.91)	25.40 (5.03)	0.86 (-2.24, 3.96), 0.579 [d]
After	27.20 (5.58)	26.47 (4.31)	-0.56 (-1.70, 0.57), 0.319 [f]
MD (95% CI), P [e]	0.10 (-0.60, 0.81), 0.761	0.73 (-0.26, 1.72), 0.141	

Median (min, max) and mean (SD) with mean difference (95% CI) are presented for data not normally and normally distributed respectively. * P< 0.05 was considered statistically significant. [a] P based on Mann–Whitney U-test. [b] P based on Wilcoxon signed-ranked test. [c] P based on analysis of covariance (ANCOVA) adjusted for baseline values and glycemic indices. [d] P based on independent-samples t-test. [e] P based on paired samples t-test. [f] based on analysis of covariance (ANCOVA) adjusted for baseline values and changes of dietary vitamin K intake. [g] P based on Quantile regression adjusted for baseline values and changes of dietary vitamin K intake.
MD, mean difference; CI, confidence interval; A/L ratio, adiponectin to leptin ratio; FBS, fasting blood sugar; FI, fasting insulin; BMI, body mass index; SD, standard deviation.

significantly decreased in MK-7 group (P: 0.018 and P: 0.012 respectively). Between groups analysis at the end of study showed that FBS was significantly lower in MK-7 group compared to the placebo one (P: 0.024). But, no significant changes were found in anthropometric indices, body fat percentage and dietary intakes between groups at the end of study (P>0.05). More information about the glycemic and anthropometric indices and dietary intakes was reported in our previous study.[30]

Discussion

We verified the impact of 12-weeks MK-7 supplementation on adiponectin, leptin and A/L ratio in overweight/obese T2DM patients. Lower levels of leptin were found in MK-7 group compared to the placebo one, but there was no significant difference among the groups in adiponectin or A/L ratio (Table 2).

This study is the first study that assessed the effects of MK-7 supplementation on adiponectin and leptin levels and A/L ratio in overweight/obese T2DM patients. In the literature review, we found eleven published studies on the effects of vitamin K on adiponectin and leptin levels. Rasekhi *et al.*[26] showed that four weeks phylloquinone supplementation increased adiponectin in prediabetes premenopausal women; but leptin did not change after supplementation. In a rat model of diabetic mellitus, Hussein *et al.*[10] demonstrated that vitamin K2 treatment for eight weeks boosted adiponectin expression. Another

research using colon cancer-induced animals found that supplementing with 50 mg/kg MK-7 raised the level of adiponectin.[23] Kim *et al.*[27] studied the effect of menaquinone on obese mice for three months and observed a significant reduction of leptin level in intervention group. In a study conducted by Gordeladze *et al.*[28] MK-7 led to a significant increase in adiponectin secretion from adipocytes. Knapen *et al.*[25] showed that serum adiponectin increased significantly after 3 years of supplementation with 180 µg/d MK-7 in postmenopausal women with an above-median response in OC carboxylation, but in another study they observed that supplementation with 45 mg/d MK-4 for three years and 10, 20, 45, 90, 180 and 360 µg/d MK-7 for 12 weeks in healthy subjects did not effect on serum adiponectin concentration.[14] Additionally, after giving healthy males 30mg/d of vitamin K2 for four weeks, Choi *et al.*[24] reported no change in adiponectin levels. In postmenopausal women, vitamin K2, as MK-4 supplementation did not result in significant differences between groups for adiponectin and leptin, but leptin levels significantly increased in both groups, according to Koitaya *et al.*[22] In another study by Rønn *et al.*,[29] which had studied postmenopausal women receiving 375 µg/d MK-7, 400mg/d calcium and 19µg/d vitamin D, significant increase in adiponectin level was found after one year of supplementation, whereas leptin and A/L ratio did not change significantly. Contradictory findings were obtained, which may have been caused by differing vitamin K forms and research individuals.

Our study showed significant effects of MK-7 supplementation in serum leptin concentration of overweight/obese T2DM patients (Table 2). Leptin is a pro inflammatory adipokine, so its reduction may have beneficial effects on inflammatory status.[17] At the conclusion of the trial, there were no significant differences between the groups in terms of anthropometric indices, calorie consumption, macronutrient intake, or vitamin K intake;[30] thus, inter-group changes in leptin concentration could not be attributed to these factors. The findings were same when body fat percentage was taken into account as a confounder in the statistical analysis.

As shown in Figure 2, there are several possible mechanisms which could explain the effect of vitamin K on adiponectin and leptin, like: body fat lowering effect,[25] osteocalcin carboxylation[13] and anti-inflammatory effects.[33] Different studies showed that vitamin K intake (dietary or supplementation) is inversely associated with body fat and inhibits adipogenesis and osteoclastogenesis via affecting on differentiation and function of bone marrow cells.[14,34] Leptin, on the other hand, has a direct and strong link with body fat mass and adipocyte size, while adiponectin has an inverse relationship with fat mass.[14,35] Moreover, vitamin K is a cofactor in gamma corboxylation of certain glutamate residues in osteocalcin (a vitamin K dependent protein in bone) and based on previous evidences MK-7 is more effective than vitamin K1 in this context.[13] Vitamin K can increase osteocalcin (OC) expression and level via affecting on osteoblastogenesis.[10] Moreover, OC could mediate energy metabolism in the bone and adipose tissue in animal models and carboxylated form of OC (cOC) has an inverse correlation with fat mass in humans.[36] Leptin level is negatively correlated with cOC and cOC could stimulate adiponectin expression in adipocytes.[37] Therefore, cOC may act as a mediator between the effects of vitamin K supplementation on adiponectin and leptin levels. Another possible mechanism is anti-inflammatory effect of vitamin K via suppressing the expression of some proinflammatory cytokines like TNF-α and inhibiting NF-κB activation.[33] Leptin is a proinflammatory cytokine and mRNA levels of adiponectin have been down-regulated by

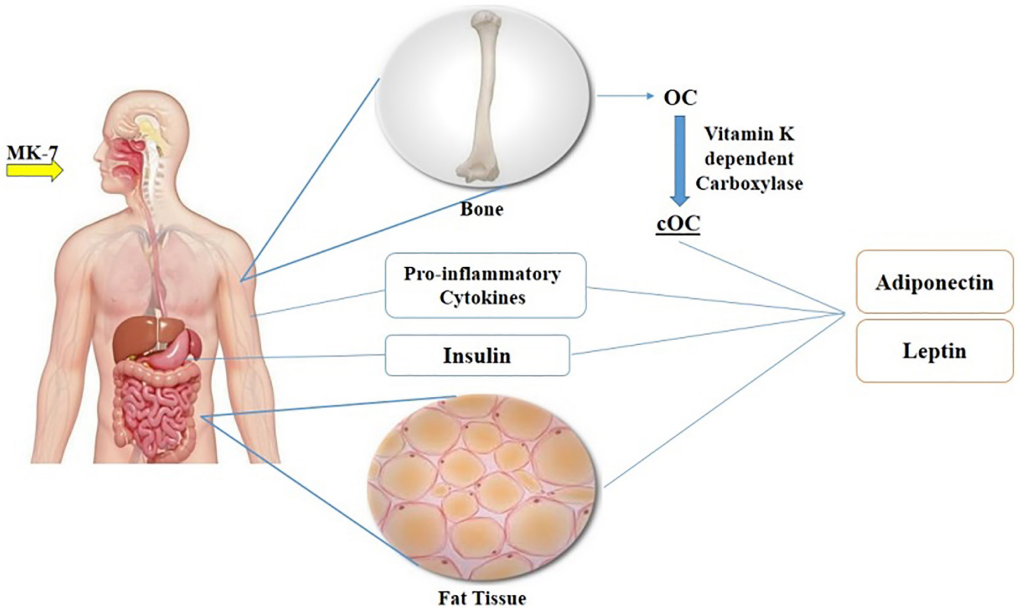

Figure 2. The possible pathways of the effect of vitamin K on adiponectin and leptin. MK-7, menaquinone-7; OC, osteocalcin; cOC, carboxylated form of osteocalcin.

TNF-α,[38,39] so it is possible that suppressing inflammatory mechanisms by vitamin K may have effects on adiponectin and leptin level. Leptin expression was potently increased by insulin and hypoadiponectinemia is closely associated with hyperinsulinemia in T2DM.[40,41] Therefore, insulin-lowering effects of MK-7 could be a possible explanation for leptin and adiponectin changes.[30]

Strengths and limitations

The research is the first to evaluate how vitamin K, as MK-7, affects adiponectin, leptin, and the A/L ratio in individuals with overweight or obesity-related type 2 diabetes. Data on dietary intakes were gathered using a three-day food record and home scales. More exact data may be gathered by using a weighted food record. We could not differentiate the dietary intakes of menaquinone and phylloquinone. Subgroup analysis was not feasible to assess the differences of MK-7 supplementation effects in overweight and obese subgroups of T2DM patients.

Conclusion

MK-7 supplementation significantly improved glycemic status and decreased leptin levels in overweight/obese T2DM patients, while it had not any significant effect on adiponectin and A/L ratio. Future research is required to validate these findings and provide a broad recommendation for vitamin K administration as a means of reducing problems in overweight or obese T2DM patients.

Ethics Issues

The current research was carried out in accordance with the principles of the Helsinki Declaration, and all study procedures involving human subjects were authorized by the ethical committee of Tabriz University of Medical Sciences in Tabriz, Iran (Ethics code: IR.TBZMED.REC.1399.096). Before the research began, each participant completed a written informed consent form and was given information about how it would be conducted

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Data Sharing

In response to reasonable requests, the data are available from corresponding author.

Author Contributions

Shaghayegh Adeli: Investigation, Formal Analysis, Writing - Original Draft. Bahram Pourghassem Gargari: Conceptualization, Formal Analysis, Writing - Review & Editing. Nahid Karamzad: Investigation, Formal Analysis.

Conflict of Interest

The authors declare that they have no competing interests. All authors have approved the final article.

References

1. Wild S, Roglic G, Green A, Sicree R, King H. Global prevalence of diabetes: Estimates for the year 2000 and projections for 2030. Diabetes Care. 2004;27(5):1047-53. doi:10.2337/diacare.27.5.1047
2. Zheng Y, Ley SH, Hu FB. Global aetiology and epidemiology of type 2 diabetes mellitus and its complications. Nat Rev Endocrinol. 2018;14(2):88. doi:10.1038/nrendo.2017.151
3. Li Y, Chen JP, Duan L, Li S. Effect of vitamin k2 on type 2 diabetes mellitus: A review. Diabetes Res Clin Pract. 2018;136:39-51. doi:10.1016/j.diabres.2017.11.020
4. James SL, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, et al. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: A systematic analysis for the global burden of disease study 2017. Lancet. 2018;392(10159):1789-858. doi:10.1016/S0140-6736(18)32279-7
5. Gray N, Picone G, Sloan F, Yashkin A. The relationship between bmi and onset of diabetes mellitus and its complications. South Med J. 2015;108(1):29. doi:10.14423/SMJ.0000000000000214
6. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, et al. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. N Engl J Med. 2002;346(6):393-403. doi:10.1056/NEJMoa012512
7. Pan X-R, Li G-w, Hu Y-H, Wang J-X, Yang W-Y, An Z-X, et al. E Effects of diet and exercise in preventing NIDDM in people with impaired glucose tolerance. The Da Qing IGT and Diabetes Study. Diabetes Care. 1997;20(4):537-44. doi:10.2337/diacare.20.4.537
8. Martini LA, Catania AS, Ferreira SR. Role of vitamins and minerals in prevention and management of type 2 diabetes mellitus. Nutr Rev. 2010;68(6):341-54. doi:10.1111/j.1753-4887.2010.00296.x
9. Karamzad N, Maleki V, Carson-Chahhoud K, Azizi S, Sahebkar A, Gargari BP. A systematic review on the mechanisms of vitamin k effects on the complications of diabetes and pre-diabetes. Biofactors. 2020;46(1):21-37. doi:10.1002/biof.1569
10. Hussein AG, Mohamed RH, Shalaby SM, Abd El Motteleb DM. Vitamin K2 alleviates type 2 diabetes in rats by induction of osteocalcin gene expression. Nutrition. 2018;47:33-8. doi:10.1016/j.nut.2017.09.016
11. Manna P, Kalita J. Beneficial role of vitamin k supplementation on insulin sensitivity, glucose metabolism, and the reduced risk of type 2 diabetes: A review. Nutrition 2016;32(7-8):732-9. doi:10.1016/j.

nut.2016.01.011
12. Ross AC, Caballero B, Cousins RJ, Tucker KL. Modern nutrition in health and disease. 11th ed. Burlington, Massachusetts: Jones & Bartlett Learning; 2020, p. 305-15
13. Schurgers LJ, Teunissen KJF, Hamulyák K, Knapen MHJ, Vik H, Vermeer C. Vitamin K–containing dietary supplements: Comparison of synthetic vitamin k1 and natto-derived menaquinone-7. Blood. 2007;109(8):3279-83. doi:10.1182/blood-2006-08-040709
14. Knapen MHJ, Schurgers LJ, Shearer MJ, Newman P, Theuwissen E, Vermeer C. Association of vitamin k status with adiponectin and body composition in healthy subjects: Uncarboxylated osteocalcin is not associated with fat mass and body weight. Br J Nutr. 2012;108(6):1017-24. doi:10.1017/S000711451100626X
15. Li J, Shen X. Oxidative stress and adipokine levels were significantly correlated in diabetic patients with hyperglycemic crises. Diabetol Metab Syndr. 2019;11(1):13. doi:10.1186/s13098-019-0410-5
16. Tsiotra PC, Halvatsiotis P, Patsouras K, Maratou E, Salamalekis G, Raptis SA, et al. Circulating adipokines and mrna expression in adipose tissue and the placenta in women with gestational diabetes mellitus. Peptides 2018;101:157-66. doi:10.1016/j.peptides.2018.01.005
17. Oh K-J, Lee DS, Kim WK, Han BS, Lee SC, Bae K-H. Metabolic adaptation in obesity and type ii diabetes: Myokines, adipokines and hepatokines. Int J Mol Sci. 2017;18(1):8. doi:10.3390/ijms18010008
18. Juanola-Falgarona M, Salas S. Association between dietary phylloquinone intake and peripheral metabolic risk markers related to insulin resistance and diabetes in elderly subjects at high cardiovascular risk. Cardiovasc Diabetol. 2013;12(1):7. doi:10.1186/1475-2840-12-7
19. Inoue M, Maehata E, Yano M, Taniyama M, Suzuki S. Correlation between the adiponectin-leptin ratio and parameters of insulin resistance in patients with type 2 diabetes. Metabolism. 2005;54(3):281-6. doi:10.1016/j.metabol.2004.09.006
20. Oda N, Imamura S, Fujita T, Uchida Y, Inagaki K, Kakizawa H, et al. The ratio of leptin to adiponectin can be used as an index of insulin resistance. Metabolism. 2008;57(2):268-73. doi:10.1016/j.metabol.2007.09.011
21. Zaletel J, Barlovic DP, Prezelj J. Adiponectin-leptin ratio: A useful estimate of insulin resistance in patients with type 2 diabetes. J Endocrinol Invest. 2010;33(8):514-8. doi:10.3275/6811
22. Koitaya N, Sekiguchi M, Tousen Y, Nishide Y, Morita A, Yamauchi J, et al. Low-dose vitamin K2 (mk-4) supplementation for 12 months improves bone metabolism and prevents forearm bone loss in postmenopausal japanese women. J Bone Miner Metab. 2014;32(2):142-50. doi:10.1007/s00774-013-0472-7
23. Zhang Y, Ma C, Zhao J, Xu H, Hou Q, Zhang H. Lactobacillus casei zhang and vitamin K2 prevent intestinal tumorigenesis in mice via adiponectin-elevated different signaling pathways. Oncotarget. 2017;8(15):24719--27. doi:10.18632/oncotarget.15791
24. Choi HJ, Yu J, Choi H, An JH, Kim SW, Park KS, et al. Vitamin K2 supplementation improves insulin sensitivity via osteocalcin metabolism: A placebo-controlled trial. Diabetes Care. 2011;34(9):2011. doi:10.2337/dc11-0551
25. Knapen M, Jardon K, Vermeer C. Vitamin k-induced effects on body fat and weight: Results from a 3-year vitamin K2 intervention study. Eur J Clin Nutr. 2018;72(1):136-41. doi:10.1038/ejcn.2017.146
26. Rasekhi H, Karandish M, Jalali MT, Mohammadshahi M, Zarei M, Saki A, et al. Phylloquinone supplementation improves glycemic status independent of the effects of adiponectin levels in premonopause women with prediabetes: A double-blind randomized controlled clinical trial. J Diabetes Metab Disord. 2015;14(1):4-9. doi:10.1186/s40200-014-0127-9
27. Kim M, Na W, Sohn C. Menaquinone benefits weight control and improves inflammatory biomarkers in high-fat diet-induced obese rats (815.1). FASEB J. 2014;28:811-5. doi:10.1096/fasebj.28.1_supplement.815.1
28. Gordeladze JO, Reseland JE, Moller M. Vitamin K2 (MK-7) is involved in bone and energy homeostasis: Effects on osteoblast, adipocyte and [beta]-cell regulatory loops. European Calcified Tissue Society Congress 2014; Prague, Czech Republic. Bone Abstracts; 2014;3:PP128. doi:10.1530/boneabs.3.PP128
29. Rønn SH, Harslf T, Pedersen SB, Langdahl BL. Vitamin K2 (menaquinone-7) increases plasma adiponectin but does not affect insulin sensitivity in postmenopausal women: A randomized controlled trial. Eur J Clin Nutr. 2021;75(11):1661-7. doi:10.1038/s41430-021-00884-8
30. Karamzad N, Faraji E, Adeli S, Carson-Chahhoud K, Azizi S, Gargari BP. Effects of mk-7 supplementation on glycemic status, anthropometric indices and lipid profile in patients with type 2 diabetes: A randomized controlled trial. Diabetes Metab Syndr Obes. 2020;13:2239-49. doi:10.2147/DMSO.S253014
31. Seino Y, Ueno S, Yabe D, Suzuki A. Dietary recommendations for type 2 diabetes patients: Lessons from recent clinical and basic research in asia. J Diabetes Investig. 2019;10(6):1405-7. doi:10.1111/jdi.13135
32. BashiriMoosavi F, Farmanbar R, Taghdisi MH, Atrkar RZ. Level of physical activity among girl high school students in tarom county and relevant factors. Iran J Health Educ Health Promot. 2015;3(2):133-40.
33. Ohsaki Y, Shirakawa H, Miura A, Giriwono PE, Sato S, Ohashi A, et al. Vitamin K suppresses the lipopolysaccharide-induced expression of inflammatory cytokines in cultured macrophage-like cells via the inhibition of the activation of nuclear factor kappab through the repression of ikk/alpha/beta phosphorylation. J Nutr Biochem. 2010;21(11):1120-6. doi:10.1016/j.jnutbio.2009.09.011
34. Takeuchi Y, Suzawa M, Fukumoto S, Fujita T. Vitamin

K2 inhibits adipogenesis, osteoclastogenesis, and odf/rank ligand expression in murine bone marrow cell cultures. Bone. 2000;27(6):769-76. doi:10.1016/S8756-3282(00)00396-3
35. Zurowski D, Koprowska B, Thor PJ. The role of leptin in metabolic regulation. Folia Med Cracov. 2001;42(1-2):83-93.
36. Jamka M, Walach H, Houbiec M, Wasiewicz M, Walkowiak J. Effect of vitamin K supplementation on anthropometric parameters and adipokine levels--a systematic review. J Health Sci. 2019;88(4):244-55. doi:10.20883/medical.402
37. Ferron M, Hinoi E, Karsenty G, Ducy P. Osteocalcin differentially regulates beta cell and adipocyte gene expression and affects the development of metabolic diseases in wild-type mice. Proc Natl Acad Sci U S A. 2008;105(13):5266-70. doi:10.1073/pnas.0711119105
38. Goldberg RB. Cytokine and cytokine-like inflammation markers, endothelial dysfunction, and imbalanced coagulation in development of diabetes and its complications. J Clin Endocrinol Metab. 2009;94(9):3171-82. doi:10.1210/jc.2008-2534
39. Fasshauer M, Neumann S, Eszlinger M, Paschke R, Klein J. Hormonal regulation of adiponectin gene expression in 3T3-L1 adipocytes. Biochem Biophys Res Commun. 2002;290(3):1084-9. doi:10.1006/bbrc.2001.6307
40. Weyer C, Funahashi T, Tanaka S, Hotta K, Matsuzawa Y, Pratley RE, et al. Hypoadiponectinemia in obesity and type 2 diabetes: Close association with insulin resistance and hyperinsulinemia. J Clin Endocrinol Metab. 2001;86(5):1930-5. doi:10.1210/jcem.86.5.7463
41. Jaganathan R, Ravindran R, Dhanasekaran S. Emerging role of adipocytokines in type 2 diabetes as mediators of insulin resistance and cardiovascular disease. Can J Diabetes. 2018;42(4):446-56. doi:10.1016/j.jcjd.2017.10.040