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Original Article

Effect of *Allium sativum* and *Olea europaea* on serum lipids in patients with diabetes mellitus

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الملخص

أهداف البحث: تم تصميم هذه الدراسة لتقييم آثار مزيج من الثوم والزيتون على مرتسم الدهون في الدم المضطرب بين مرضى السكري من النمط الثاني.

طريقة البحث: شملت الدراسة العشوائية المنضبطة بالشواهد 120 مريضا من كلا الجنسين (تتراوح أعمارهم بين 40-60 عاما) يعانون من داء السكري من النمط الثاني وخلل دهون الدم تم تقسيمهم بالتساوي إلى مجموعتين. تلقى مرضى المجموعة أ عوامل خفض نسبة السكر في الدم والدهون، مثل حبة دواء غليميبيرايد بجرعة 2 مليجرام مع ميتفورمين هيدروكلوريد وحبة من دواء روزفاستاتين بجرعة 10 مليجرام مرة واحدة يوميا عن طريق الفم. تم إعطاء المرضى في المجموعة ب توليفة من الأدوية الإخلافية وزيت الزيتون والثوم على مدار ستة أشهر. تم أخذ عينات الدم في 3 مستويات من الدراسة لتحليل مرتسم الدهون في الدم.

النتائج: أظهرت النتائج أنه بعد المستوى الثاني والثالث من العلاج، انخفض متوسط الكوليسترول في الدم و التريغليسيريد وبروتين الدهون المنخض الكثافة في كلا المجموعتين، ولكن لوحظ انخفاض ذا دلالة إحصائية في مجموعة دراسة الحالة مقارنة بمجموعة التحكم، بينما ارتفع مستوى بروتين الدهون العالي الكثافة في المجموعتين ولكن كان هناك ميل كبير لوحظ في مجموعة دراسة الحالة مقارنة بمجموعة التحكم. الانخفاض المئوي الملاحظ كان الأعلى عند المستوى الثالث في الكوليسترول وبروتين الدهون المنخفض الكثافة والتريغليسيريد وبروتين الدهون العالي الكثافة في مجموعة دراسة الحالة أي 41.5٪ ، 45.9٪ ، 60.4٪ و 58.1٪.

الاستنتاجات: قد يكون النشاط المضاد لفرط دهون الدم المصور ناتجا عن وجود مضادات الأكسدة فيها، ولكن يجب إجراء المزيد من الدراسات بحجم عينة أكبر من أجل تقييم دور مسحوق الثوم وزيت الزيتون في المرضى الذين يعانون من مرضى السكري من النمط الثاني المصابين بخلل دهون الدم.

الكلمات المفتاحية: داء السكري؛ الدهون؛ خلل دهون الدم؛ الثوم؛ زيت الزيتون

Abstract

Objective: This study was designed to assess the effects of a combination of *Allium sativum* and *Olea europaea* oil on disturbed lipid profiles in patients with type 2 diabetes mellitus (T2DM).

Methods: This randomized control trial (RCT) involved 160 patients of either sex (aged 40–60 years) with T2DM and dyslipidemia, and were equally divided into two groups. Group A patients received hypoglycemic and lipid lowering agents (Tab glimepiride 2 mg + metformin HCl 500 mg and Tab rosuvastatin 10 mg once a day orally). Patients in group B were given the same allopathic drugs as group A, in combination with *A. sativum* and *O. europaea* oil over a period of 6 months. Blood samples were taken at three stages of the study to allow the analysis of lipid profiles.

Results: Analysis showed that after 3 and 6 months of treatment, the mean levels of serum cholesterol, triglycerides (TGs) and low-density lipoprotein (LDL) were reduced in both groups and that there was a highly

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significant ($P < 0.001$) decline in group B when compared to group A. High-density lipoprotein (HDL) levels increased in both groups but there was a significant ($P < 0.05$) increase in the group B when compared to group A. The percentage reduction was highest at 6 months of treatment for cholesterol, TGs, LDL and HDL in group B (41.5%, 45.9%, 60.4% and 58.1%, respectively).

Conclusion: The antihyperlipidemic activity observed may be due to the presence of antioxidants in the test substances. Further studies should be conducted with a larger sample size in order to further evaluate the role of *A. sativum* powder and *O. europaea* oil in patients with T2DM with dyslipidemia.

Keywords: *Allium sativum*; Diabetes mellitus; Dyslipidemia; Lipid profile; *Olea europaea*

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Introduction

Diabetes mellitus is a metabolic syndrome characterized by hyperglycemia resulting from defects either in insulin secretion or insulin action, or a combination of both. Type 2 diabetes mellitus (T2DM), the most prevalent form of the disease, is often asymptomatic in its early stages and can remain undiagnosed for many years.[1]

T2DM is a disease with a high global burden, affecting approximately 450 million people worldwide. Furthermore, several studies have revealed that patients with T2DM have an increased risk of developing cardiovascular complications in comparison to those without T2DM.[2] The prevalence of this disease is comparatively higher in developing countries including those in South Asia due to increasing urbanization and adaptation to a western style diet. It has been estimated that in Pakistan, 7.6–11% of the adult population suffers from T2DM.[3–5]

It is important to mention that almost all patients with T2DM have lipid abnormalities and that this is associated with high levels of mortality. Dyslipidemia is defined as 'an increase in serum triglycerides (TGs) or in low-density lipoprotein (LDL) levels that may lead to the development of atherosclerosis and microvascular complications involving different organs.[6] Elevated LDL and reduced high-density lipoprotein (HDL) levels are associated with an increased risk of various complications; however, the significance of serum TGs is less clearly understood.[7]

Ischemic heart diseases, such as angina and myocardial infarction, are the main complications of dyslipidemia along with T2DM. Due to the increased prevalence of T2DM, the Asian population is at an increased risk of developing myocardial infarction and diabetic microvascular complications due to the simultaneous presence of dyslipidemia in most patients with T2DM. Considering the high occurrence rate of T2DM and dyslipidemia globally and the fact that dyslipidemia can lead to the development of cardiovascular events in diabetic patients, it is important to explore the dietary modifications that may lead to an improvement of lipoprotein parameters, thus reducing the incidence of sudden deaths that may result from an imbalance in lipid profile parameters. Traditionally, the Mediterranean diet (MD) has long been suggested as being the healthiest diet, predominantly because of its constituents (*Allium sativum* and *Olea europaea* oil), which has been traditionally used for centuries in Asia and is considered to be protective against cardiovascular diseases (CVD).[8]

A. sativum, also known as garlic, belongs to the Amaryllidaceae family of plants and is grown extensively in central Asia where it is still used as flavoring agent and traditional medicine for the mitigation of various disorders. In its powdered form, *A. sativum* contains alliin, alliinase (an enzyme) and allicin whereas fresh *A. sativum* extract, in addition to the above mentioned constituents, also contains antioxidants such as allixin and diallyl sulfide, which lead to increased insulin secretion concurrent with reduced peripheral sensitivity.[9]

O. europaea oil (family Oleaceae), commonly known as olive oil, is obtained from the fruit of *O. europaea* and is produced by pressing whole fruits and extracting the oil. Olive oil is usually utilized as a cooking oil for frying and also as an ingredient in salad dressing. Olive oil is composed of TGs, esters of oleic acid, linoleic acid, palmitic acid and of other fatty acids, along with traces of squalene and sterols. *O. europaea* oil is rich in phenolic compounds, amongst which elenolic acid, alpha-tocopherol, flavonoids, pinoresinol and lignans are the main constituents of its oil.[10]

Dyslipidemia became curable after the development of antihyperlipidemic allopathic medications; however, the high cost and undesirable effects of these medications have significantly impeded their potential impact on the treatment of dyslipidemia, especially in patients residing in middle- and low-income countries. Thus, there is an urgent need to develop cheaper drugs and to make them available to patients in developing countries suffering from dyslipidemias. Hence, this research was conducted to evaluate the effects of *A. sativum* and *O. europaea* oil in maintaining the normal lipid profile of patients with T2DM, thus preventing the hazardous complications that may lead to dyslipidemia in patients with T2DM.

Materials and Methods

Study design

This research was conducted for 6 months (from 16 July 2018 to 15 January 2019) at the Institute of Biochemistry, University of Sindh in collaboration with Department of Medicine, Liaquat University of Medical & Health Sciences (LUMHS), Jamshoro.

This was a randomized controlled study (single-blind). Patients were selected based on their age and sex; the patients were equally distributed into two groups with an equal number of patients in each sex; we did this deliberately to obtain better results and to keep selection bias at a minimum.

We recruited a sufficient number of patients (initially 400 patients); then, we applied strict inclusion criteria to obtain the final cohort for analysis. This provided a high probability of detecting a clinically important difference between treatments. Sample size was kept constant and selected based on a previous study with significant results. The reason for such group selection was to ensure that all potential confounding factors, such as age and sex, were divided equally among groups and could be compared subsequently (based on structural equivalence). These factors are characteristics that may affect a patient's response to treatment. Hence, the groups were selected in order to reveal any true difference in the treatment group by keeping the influence of other factors to the minimum.[11,12]

A total of 160 patients, aged between 40 and 60 years, were recruited from various medical outpatient departments and diabetic clinics of Sindh, Pakistan. Dyslipidemic and diabetic patients participated in this study voluntarily and provided their consent; the patients were divided equally into two groups. Group A (the control group) included 80 patients with dyslipidemia and T2DM (45 males and 35 females), who were given Tab glimepiride 2 mg + metformin HCl and Tab rosuvastatin 10 mg once a day orally. Group B (the treatment study group), also with 80 patients with dyslipidemia and T2DM (45 males and 35 females), were given Tab glimepiride 2 mg + metformin HCl and Tab rosuvastatin 10 mg once a day orally along with formulated capsules containing 1.1 mg of olive oil and 500 mg of garlic powder for three times a day for up to 6 months. Various parameters were studied, including serum total cholesterol, serum TGs, serum LDL, serum HDL of all subjects at study stage 0 (before the start of treatment) at stage I (after 1 month of treatment), stage II (after 3 months of treatment) and at stage III (after 6 months of treatment).

Sample size

We used a previous study to calculate the sample size using OpenEpi version 2, an open-access computer program. A total of 160 patients (80 in each group) were included.[13]

Inclusion criteria

We performed non-probability sampling for all subjects. We included all participants aged between 40 and 60 years who were diagnosed with T2DM and disrupted lipid profiles.

Exclusion criteria

We excluded patients aged below 40 or above 60 years; those with type 1 diabetes; those who had undergone angioplasty or renal dialysis; patients with liver disorders, cancers, or a history of allergy associated with statins, *A. sativum* powder and *O. europaea* oil.

Preparation of study drugs

Initially, 5 kg of *A. sativum* was purchased from a local supermarket at Hyderabad (HYD), Pakistan, washed with tap water and sliced into small size flakes. The flakes were then dried under shade for 3 days until all moisture had been removed. The flakes were ground to form a fine powder; 5 kg of sliced *A. sativum* produced 1 kg of dry powder. Next, 500 mg of dry *A. sativum* powder was packed into size '0' capsules and packed into air-tight bottles. Fresh *A. sativum* were purchased every time for the preparation of capsules. *A. sativum* (500 mg, three times daily) was administered to patients orally after every meal for 6 months.[14]

Three-liter bottles of *O. europaea* oil (virgin oil) were purchased from the Max Bachat supermarket at Hyderabad, Pakistan. The oil was then packed into gel capsules (1.1 ml in each capsule) and administered orally three times daily to patients after every meal for 6 months.

Getformin 2/500 mg (glimepiride 2 mg + metformin HCl 500 mg) tablets were obtained from Getz Pharma and provided once daily orally.[15] Rovista (rosuvastatin calcium) 10 mg tablets were acquired from Getz Pharma and were given once daily.

Sampling

We obtained 10 ml of venous blood samples under aseptic conditions from all participants at the four stages of follow up (stage 0, before the start of treatment; stages I, II and III after the completion of 1, 3 and 6 months of therapy, respectively). The glucose oxidase method was used for the analysis of fasting blood glucose level. The enzymatic caloric method was carried out on a COBAS autoanalyzer for the estimation of serum cholesterol, TGs, LDLs and HDLs and a microlab was used for the analysis of HbA1c. Body mass index (BMI) and the levels of fetal bovine serum and HbA1c were estimated before the start of study.

Statistical analysis

Statistical analysis was performed using SPSS version 20. The data were analyzed by taking the mean and standard deviation of quantitative variables such as serum cholesterol, TGs, LDL and HDL and the percentage reduction was calculated. The student's t-test was applied to compare between groups and $P < 0.05$ was considered as significant; $P < 0.001$ was considered as highly significant.[16]

Results

The detailed statistical analysis of various lipid parameters and their comparison at four different stages is presented in Table 1. The mean values of serum cholesterol at stage 0 (i.e., at the start of treatment) in groups A and B were almost the same. At stage I, after 1 month of therapy, the serum cholesterol levels were reduced in both groups with no significant difference. After 3 and 6 months of treatment (stages II and III), the mean serum cholesterol levels were reduced in both groups; there was a highly significant ($P < 0.001$) decline observed in group B when compared to group A. The mean serum levels of TGs at stage 0 in both groups were almost the same. At stage I, after 1 month of therapy, the serum levels of TGs were reduced in both groups but with no significant difference. After 3 and 6 months of treatment, at stages II and III, the mean serum levels of TGs were reduced in both groups but there was a significant decline in group B when compared

Table 1: Comparison of serum cholesterol, TGs, LDL and HDL (mg/dl) in groups A and B with and without treatment with *A. sativum* and *O. europaea* oil.

	Group A Getformin + Rovista				Group B Getformin + Rovista + *A. sativum* + *O. europaea*			
Parameters (mg/dl)	Stage 0	Stage I	Stage II	Stage III	Stage 0	Stage I	Stage II	Stage III
Serum cholesterol	283.5 ± 3.8	252 ± 2.9	214.±3.8	182.7 ± 3.5[a]	282 ± 3.9	250 ± 3.5	196.8 ± 4.8[b]	164.8 ± 4.7[b]
TGs	255 ± 2.4	229.4 ± 2.5	197.4 ± 3.1	158.45 ± 5.6[a]	255 ± 2.4	217 ± 4.8	177 ± 3.2[a]	138.10 ± 4.3[b]
LDL	175.5 ± 2.8	151.5 ± 2.9	121.8 ± 2.9	94.03 ± 4.1[a]	175 ± 2.8	131.71 ± 2.7	98.71 ± 3.4[b]	69.52 ± 4.1[b]
HDL	21 ± 1.6	25.8 ± 1.5	35.7 ± 1.5	43.22 ± 1.7[a]	20.8 ± 1.6	28.28 ± 1.6	42.25 ± 2.3[a]	52.88 ± 2.6[a]

Values are mean ± SD. Getformin, glimepiride 2 mg + metformin HCl 500 mg orally once daily; Rovista, rosuvastatin calcium 10 mg orally once daily. Stage 0, before start of treatment; stage I, after 1 month of treatment; stage II, after 3 months of treatment; stage III, after 6 months of treatment.

[a] $P < 0.05$, significant

[b] $P < 0.001$, highly significant.

to group A. Furthermore, after 6 months of therapy, there was a highly significant ($P < 0.001$) reduction of TGs in group B when compared to group A.

The mean serum LDL at stage 0 in both groups was almost the same. At stage I, after 1 month of therapy, the serum LDL levels were reduced in both groups, but a more extensive decline was observed in LDL levels in group B, although this was not significant. After 3 and 6 months of treatment, at stages II and III, the mean serum LDL levels were reduced in both groups but there was a highly significant ($P < 0.001$) reduction in group B when compared to group A. The mean serum levels of HDL at stage 0 in the both groups was almost the same. At stage I, after 1 month of therapy, the serum HDL levels had increased in both groups but with no statistical significance. After 3 and 6 months of treatment, at stages II and III, the mean serum HDL levels had increased in both groups but there was a significant ($P < 0.05$) increase observed in group B when compared with group A.

Figure 1 shows the percentage reduction of serum total cholesterol after the completion of 1 month of therapy (stage I). Serum cholesterol level was reduced in group A by 11.07% compared to 11.37% in group B. After the completion of 3 months of therapy (stage II), the serum cholesterol level was reduced in group A by 24.26% compared to 30.23% in group B. After 6 months of treatment (stage III), the serum cholesterol level was reduced in group A by 35.52% compared to 41.56% in group B.

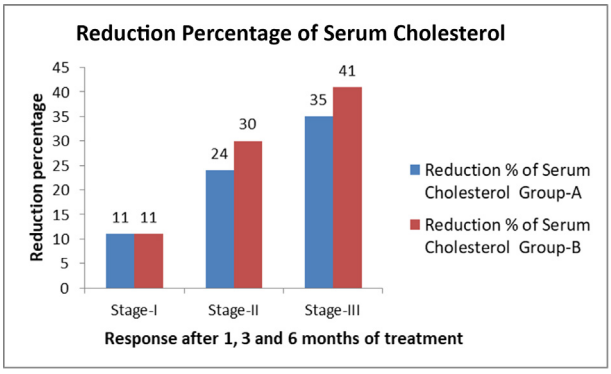

Figure 1: The percentage reduction of cholesterol from stage I to III.

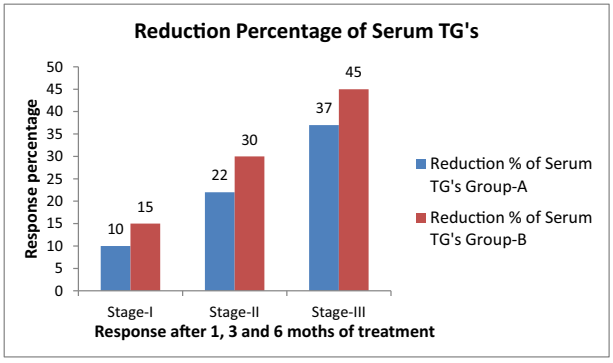

Figure 2: The percentage reduction of TGs from stage I to III.

Figure 2 shows the percentage reduction of serum TGs after 1 month of therapy (stage I). The serum level of TGs was reduced in group A by 10.13% compared to 15.03% in group B. After the completion of 3 months of therapy (stage II), the serum level of TGs was reduced in group A by 22.65% compared to 30.62% in group B. After the completion of 6 months of therapy (stage III), the serum TGs level was reduced in group A by 37.86% compared to 45.99% in group B.

Figure 3 shows the percentage reduction of serum LDL after the completion of 1 month of therapy (stage I). Serum LDL level was reduced in group A by 13.64% compared to 24.93% in group B. After the completion of 3

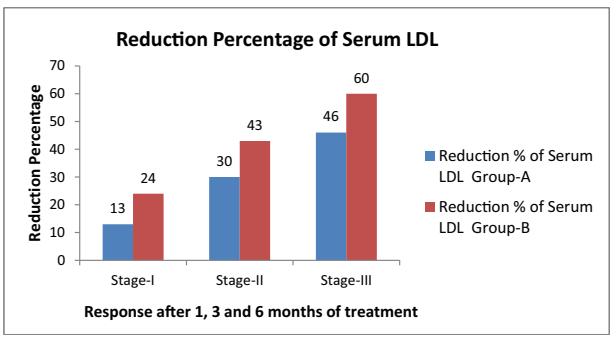

Figure 3: The percentage reduction of LDL from stage I to III.

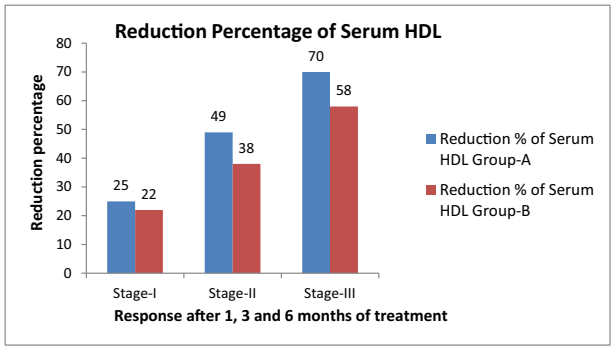

Figure 4: The percentage reduction of HDL from stage I to III.

months of therapy (stage II), serum LDL level was reduced in group A by 30.55% compared to 43.89% in group B. Finally, after the completion of 6 months of therapy (stage III), the serum LDL level was reduced in group A by 46.42% compared to 60.40% in group B.

Figure 4 shows the percentage reduction of serum HDL after the completion of 1 month of therapy. Serum HDL level was reduced in group A by 25.82% compared to 22.01% in group B. After the completion of 3 months of therapy, serum HDL level was reduced in group A by 49.12% compared to 38.71% in group B. After the completion of 6 months of therapy, the serum HDL level was reduced in group A by 70.09% compared to 58.10% in group B.

Discussion

Dyslipidemia combined with T2DM is a serious global health concern that in recent decades has affected an increased number of people in developing countries due to increased urbanization and the consequential changes in dietary habits and lifestyle.[17] The risk of macro- and microvascular complications associated with dyslipidemia and uncontrolled T2DM can be reduced to a greater extent by reducing weight if a patient exceeds a normal BMI, and also by regular physical exercise and the use of allopathic drugs in some cases where glycemic control cannot be achieved with such measures.[18]

In the present study, serum cholesterol, TGs and LDL levels were significantly reduced in group B patients who were given a combination of *A. sativum* and *O. europaea* oil, together with allopathic drugs. These results are in accordance with those of previous studies despite some variations in the study design and the number of patients studied.[19–22] Our results were in agreement with several previously conducted studies.[23,24] It is evident that most of the studies conducted so far support the evidence that *A. sativum* and its modified products have a beneficial effect on lipid parameters and can help to reduce the morbidity and mortality of patients suffering from CVD.

A. sativum has long been suggested as being beneficial for the prevention of CVD and stroke associated with dyslipidemia. Various epidemiological studies have shown an inverse relationship between *A. sativum* consumption and the progression of CVD due to dyslipidemia.[25] Previous studies suggested that *A. sativum* exerts strong antihyperlipidemic effects and that this lipid-lowering effect may be due to the presence of allicin and its derivatives.[22] Furthermore, the antioxidants present in *A. sativum* inhibit lipid peroxidation by neutralizing free radicals.[7] Various studies have concluded that the lipid-lowering effect of *A. sativum* could be due to *S*-allyl cysteine and di-allyl-disulfide, which inhibit the enzymes responsible for cholesterol synthesis and its excretion.[7,26,27] Furthermore, *A. sativum* intake leads to a reduction in the activity of lipogenic and cholesterogenic enzymes such as malic enzyme, fatty acid synthase, glucose-6-phosphate dehydrogenase and hydroxy-methylglutaryl coenzyme A reductase together with the reduced absorption of lipids by intestinal epithelial cells. A previous study revealed that *A. sativum* inhibits enzymes involved in lipid synthesis and peroxidation, in addition to preventing platelet aggregation and increasing the antioxidant status of the body.[25] Allicin, an active compound in *A. sativum*, has been shown to prevent the formation of fatty streaks in the aortic sinus.[28] Furthermore, allicin is associated with increased intravascular fibrinolytic activity.[29]

Previous studies have confirmed that the beneficial effects of *O. europaea* oil are due to the presence of oleic acid and polyphenols, which act as antioxidants and therefore prevent oxidative stress.[30–32] Furthermore, oxidative stress and inflammation are interrelated, thus leading to the generation of a vicious cycle that can aggravate many metabolic diseases. An inflammatory condition in an obese patient leads to the release of leptin, adiponectin and cytokines by adipose tissue that can alter many biochemical parameters.[33] In addition, the beneficial effects of *O. europaea* oil in preventing CVD has been highlighted by several studies conducted on the protective effects of MD which contains *O. europaea* oil as one of its main constituents.[30–32]

Although this herbal formulation is an excellent alternative to synthetic medications, which have more side effects and are also costly. However, since the effect of herbal formulations usually takes more time to become noticeable, there is likely to be a certain period of time between testing to explore any desirable reduction in lipid levels.[34] It is for this reason why we acquired samples and analyzed data after the first month of therapy in both groups to assess the response of medications during the early phase of the study for the purpose of strict monitoring of any undesirable effects. Existing literature also suggested that HbA1c levels should be determined in diabetic patients every 3 months to obtain accurate glycemic levels.[35] Hence, in this current study, testing was also performed after 3 and 6 months of therapy in both groups of patients to obtain HbA1c levels as well as lipid levels.

The literature supports the fact that the effects of herbal medications, once achieved, usually last even after the duration of the conducted study; however, the results depend on patient compliance, diet, lifestyle and other factors.[32] There is substantial heterogeneity in the design and conduct of various trials involving herbal medications. Nevertheless, multi-center clinical trials with large sample sizes of different durations, conducted in different regions of the world, with diversity in terms of ethnic origin and age groups, should now be conducted to assess the long-term effects of *A. sativum* and *O. europaea* on serum lipid levels in diabetic patients with dyslipidemia.[36]

Conclusion

Our results concluded that *A. sativum* and *O. europaea* oil exert protective effects against the dyslipidemia associated with T2DM. Further studies with larger population sizes, longer periods of study and different dosages should now be conducted to confirm these findings, while considering epigenetic differences across the globe and the increased burden of T2DM patients worldwide.

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Conflict of interest

The authors have no conflict of interest to declare.

Ethical approval

This randomized interventional clinical study was approved by the ethical committee (#IOB/569/2017, dated 30/10/2017).

Author's contributions

ARM, MAR, and FR conceived and designed this study, conducted the research, provided research materials, and collected, organized, analyzed and interpreted the data. MA, MR and ZI wrote the initial and final draft of the article and provided logistic support. All authors have critically reviewed and approved the final draft and are responsible for the content and similarity index of the manuscript.

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