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REVIEW ARTICLE

Circulating Advanced Oxidation Protein Products (AOPPs) increases the risk of metabolic syndrome among adults: A systematic review and meta-analysis

Abnoos Mokhtari-Ardekani[1] · Ehsan Fayyazishishavan[2] · Roozbeh Akhavanfar[3] · Mahdieh Abbasalizad-Farhangi[4]

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Abstract

Background Several studies have highlighted the possible role of advanced oxidation protein products (AOPPs) in promotion of metabolic syndrome (MetS). However, due to inconsistencies in this field, we aimed to quantitatively summarize the results of studies that evaluated the association between AOPPs, with MetS indices among adult population.

Methods In a systematic search from PubMed, Embase, and Scopus electronic databases until 15 August 2022 without language restriction, a total of 1225 articles were obtained. Finally, after duplicate removal of 632 articles and removing of 537 articles according to title/abstract, seven article was included in final meta-analysis. These articles all had observational design, were performed in adults aged more than 18 years old, and evaluated the association between circulating AOPPs and MetS.

Results In our meta-analysis, circulating AOPPs was 17.51 μmol/L higher in individuals with MetS versus individuals without MetS (WMD: 17.512; CI: 12.084, 22.939; $p = 0.001$). Gender, age, and sample size were recognized as possible heterogeneity sources in subgrouping and meta-regression. No evidence of publication bias was reported.

Conclusion According to the results of the current meta-analysis, higher circulating AOPPs concentrations might be associated with MetS risk among adults. Further longitudinal studies are needed to better identify the causal associations between these variables.

Keywords Advanced oxidation protein products · Obesity · Adult population · Metabolic syndrome

Introduction

Metabolic syndrome (MetS), being identified also as insulin resistance syndrome or syndrome X [1], is a well-known health problem that is composed of clusters of cardiovascular risk factors including abdominal fat deposition, dyslipidemia, hypertension, insulin resistance, and chronic low grade inflammation [2, 3]. The prevalence estimates vary because of the differences in definitions of this syndrome. The most common definition is the National Cholesterol Education Program (NCEP)-Adult treatment panel (ATP)-III criteria, accordingly, MetS was diagnosed when more than three risk determinants were present [4]: waist circumference (WC) ≥ 88 in women and ≥ 102 cm in men fasting blood sugar (FBS) ≥ 100 mg/dl, high density lipoprotein cholesterol (HDL-C) < 50 mg/dl in women and < 40 mg/dl in men, triglyceride (TG) ≥ 150 mg/dl, and systolic blood pressure (SBP) ≥ 130 mmHg or diastolic blood pressure (DBP) ≥ 85 mmHg. Over the last decade, the prevalence of MetS has augmented in developed countries to about 25% of the adult population [5]. Chronic inflammation and oxidative stress play a crucial role in pathogenesis of MetS. Oxidative stress is a result of an imbalance between net amount of reactive oxygen species (ROS) production and antioxidant defense capacity of the body. Therefore, oxidative stress can occur as a consequence of increased ROS production, depression of the antioxidant system, or both of them [6].

✉ Mahdieh Abbasalizad-Farhangi
abbasalizad_m@yahoo.com; abbasalizadm@tbzmed.ac.ir

[1] Endocrinology and Metabolism Research Center, Institute of Basic and Clinical Physiology Science and Physiology Research Center, Kerman University of Medical Sciences, Kerman, Iran

[2] Department of Biostatistics and Data Science, School of Public Health, The University of Texas Health Science Center at Houston (UTHealth), Houston, TX 77030, USA

[3] School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran

[4] Tabriz Health Services Management Research Center, Tabriz University of Medical Sciences, Attar Nishabouri St., Tabriz 5166614711, 14711, Iran

Recently, advanced oxidation protein products (AOPPs), proteins that are damaged by oxidative stress, most notably albumin and its aggregates, have attracted much attention. AOPPs, first identified by Witko-Sarsat et al. [7], are formed during oxidative modification of plasma proteins in the reaction of chlorinated oxidants, such as hypochlorous acid and chloramines [8]. After formation, AOPPs can induce tissue damage as a consequence of imbalance between antioxidant and pro-oxidant levels and ROS accumulation in the body [9]. As a result, increased AOPPs levels is usually a consequence of disturbed balance of the redox homeostasis and because of the difficulties in ROS measurement due to their diverse form and short half-life; circulating AOPPs could be considered as reliable biomarkers of oxidative stress status [10]. Numerous studies have revealed the increased AOPP level as a biomarker of chronic non-communicable disease including atherosclerosis and cardiovascular disease [11–15], kidney disorders [14, 16–18], diabetes mellitus [16, 19–23] and metabolic syndrome [24–26]. The underlying mechanisms of disease-associated actions of AOPPs are increased inflammation via macrophage activation, increased interleukin (IL)-1, IL-6 and tumor necrosis factor (TNF)–α production, and increased production of monocyte chemoattractants protein (MCP)-1 and stromal cell-derived factor (SDF-1) α as inflammatory chemokines, modified lipoproteins, and inhibition of reverse cholesterol transport [27]. No summative study is available to sum up the results of different studies regarding the AOPPs and MetS association. Therefore, in the current work, we summarized the results of studies that evaluated the association between circulating AOPPs and metabolic syndrome among adult population in a systematic review and meta-analysis.

Methods and materials

The protocol of the current meta-analysis is according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Sup. Table1) [28]. The study protocol has also been registered in International Prospective Register of Systematic Reviews system (PROSPERO) (code: CRD42022350224).

Search strategy and study selection

A total of 1225 articles were obtained through a systematic search from PubMed, Embase, and Scopus electronic databases until August 15 2022 without language restriction. Hand-searching from reference lists of all papers retrieved no paper. The search strategy is provided in Sup. Table 2. Since metabolic syndrome is closely related to other metabolic parameters like hypertension, obesity, cardiovascular disease, and in the AOPP-related studies, sometimes it is mentioned as secondary outcome in tables, therefore, we chose our key words from a group of metabolic syndrome–related key word so not miss an article. The retrieved articles were imported into EndNote software. Finally, after removal of 632 duplicate articles and 537 articles according to title/abstract, seven articles were included in final analysis (Fig. 1).

Inclusion and exclusion criteria

Observational studies with case control or cross-sectional design that evaluated the relationship between circulating AOPPs and metabolic syndrome among adults were included. The mean ± standard deviation (SD) of circulating AOPPs in patients with MetS compared with control group were included. In all of the included studies, circulating AOPP concentrations was converted to μmol/L. Interventional case-reports and case-series, experimental and vitro studies, reviews, letter to editors, abstract of congress or seminars, and short communications were excluded. The PICO model (patients, intervention, control-comparator, and outcome) for studies' selection is presented in Table 1.

Data extraction and quality assessment of included studies

The retrieved articles were extracted by three independent researchers using a using a standard Excel extraction datasheet. The general information of included studies including first author name, publication year, journal name, country, age range, design, total number of participants, adjusted confounders, gender, setting, circulating AOPP measurement tools, and main findings of the studies. The methodological quality of included studies were assessed using the Agency for Healthcare Research and Quality (AHRQ) checklist [29] (Table 2). An overall score of 0 to 4 denotes a high risk of bias, scores between 5 and 7 denotes a moderate risk of bias, and 8 to 11 denoted a low risk of bias [30]. All of the included studies had moderate risk of bias.

Statistical analysis

Data analysis was performed by STATA version 13 (STATA Corp, College Station, TX, USA). *p*-values less than 0.05 were considered as statistically significant. The mean and SD of variable were used to calculate the unstandardized effect size calculated by weighted mean difference (WMD) with 95% confidence interval (CI). The

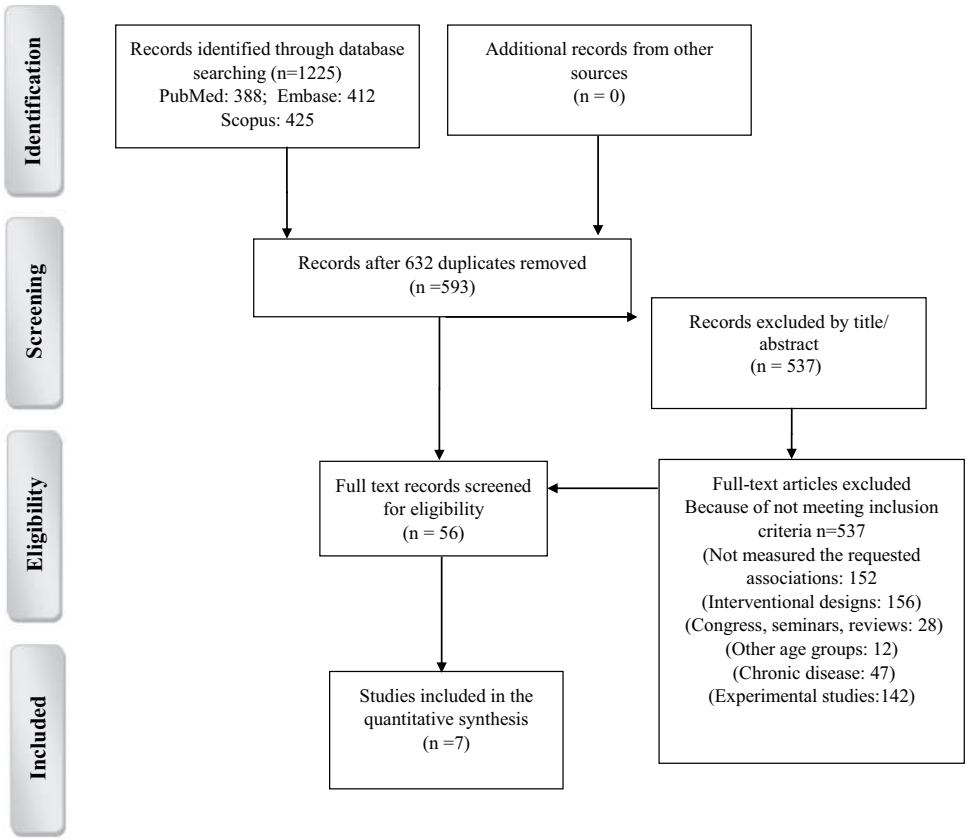

Fig. 1 Study flowchart

DerSimonian and Laird random-effects model was used to estimate the pooled WMD. Cochran's *Q* and *I*-squared tests were used considering for heterogeneity measurements, no heterogeneity for $I^2 < 25\%$, moderate heterogeneity for $I^2 = 25–50\%$, and large heterogeneity for $I^2 > 50\%$ [32]. For significant heterogeneities of either the *Q* statistic with $p < 0.1$ or $I^2 > 50\%$, the random effects model was used [33]. Subgrouping and meta-regression approaches were also performed to identify the source of heterogeneity. Begg's funnel plots followed by Begg's adjusted rank correlation and Egger's regression asymmetry tests were used for assessment of publication bias.

Table 1 The PICO criteria used for the systematic review

PICO criteria	Description
Participants	Adult population
Exposure (interventions)	Patients with MetS
Comparisons	Patients without MetS
Outcome	Circulating AOPPs
Study design	Observational studies with the design of cross-sectional, case control

MetS metabolic syndrome, *AOPPs* advanced oxidation protein products

Results

Study characteristics

A total of seven individual studies [6, 13, 24–26, 31] with the total participants number of 3629 were included in the current study. The characteristics of the included studies are presented in Table 3. The study by Koborová et al. [13] was conducted separately between men and women; therefore, the results were included as two independent studies. Four studies had cross-sectional design [6, 13, 24, 31], while two studies were case–control [25, 26]. The studies were conducted in Turkey [6], Poland [26], Brazil [25], Romania [24], Slovakia [13], and Serbia [31]. Only one study reported no significant difference in circulating AOPPs in patients with MetS compared with patients without MetS [26]. All of the other studies reported significantly higher circulating AOPPs in patients with MetS compared with control group.

Table 2 Agency for Healthcare Research and Quality (AHRQ) checklist to assess quality of the cross-sectional studies

ARHQ methodology checklist items for cross-sectional study	Korkmaz GG [6]	Zurawska-Płaksej E [26]	Venturini D [25]	Gradinaru D [24]	Koborová I [13]	Klisic A [31]
(1) Define the source of information (survey, record review)	⊕	⊕	⊕	⊕	⊕	⊕
(2) List inclusion and exclusion criteria for exposed and unexposed subjects (cases and controls) or refer to previous publications	⊕	⊕	⊕	⊕	⊕	⊕
(3) Indicate time period used for identifying patients	-	-	-	⊕	⊕	⊕
(4) Indicate whether or not subjects were consecutive if not population-based	-	-	-	-	-	-
(5) Indicate if evaluators of subjective components of study were masked to other aspects of the status of the participants	U	U	U	-	-	-
(6) Describe any assessments undertaken for quality assurance purposes (e.g., test/retest of primary outcome measurements)	-	-	-	-	-	-
(7) Explain any patient exclusions from analysis	⊕	⊕	⊕	⊕	⊕	⊕
(8) Describe how confounding was assessed and/or controlled	-	-	⊕	-	-	-
(9) If applicable, explain how missing data were handled in the analysis	-	⊕	⊕	⊕	⊕	⊕
(10) Summarize patient response rates and completeness of data collection	⊕	⊕	⊕	⊕	⊕	⊕
(11) Clarify what follow-up, if any, was expected and the percentage of patients for which incomplete data or follow-up was obtained	⊕	-	-			
Total score	5	5	6	6	6	6

Results of meta-analysis

The results of the meta-analysis are represented in Fig. 2. As shown in Fig. 2, patients with MetS had 17.51 μmol/L higher circulating AOPPs compared with those without MetS (WMD: 17.512; CI: 12.084, 22.939; $p = 0.001$). Because of high heterogeneity values in these meta-analysis (e.g., 91%), we performed a subgroup analysis (Table 4) and meta-regression (Table 5) to identify heterogeneity source. Gender, age group, and sample size were recognized as possible sources of heterogeneity in subgrouping. However, in meta-regression approach, almost none of variables were able to reduce the Tau^2 values and possibly are not heterogeneity sources. No evidence of publication bias was reported according to visual asymmetry of funnel plots (Fig. 3) and the results of Begg's and Egger's tests (Egger's test ($p = 0.278$) and Begg's test ($p = 0.154$)).

Discussion

In the current meta-analysis, we reported higher circulating AOPPs in those with MetS compared with healthy individuals. Metabolic syndrome exhibits an activation of some of the biochemical pathways that lead to production of reactive oxygen species and oxidative stress; it is clear that ROS production in MetS lead to impaired antioxidant enzymatic defenses, oxidative damage to some of macromolecules (e.g., LDL), and their deposition in tissues, organs, and vascular walls that are responsible for the final MetS consequences [6, 26]. Increased circulating AOPPs in MetS is established via oxidized LDL/β 2-glycoprotein I-dependent pathway [35], and several studies have revealed that metabolic syndrome plays an integral role in the association between AOPPs and other metabolic disorders like CVD or obesity, Morelli et al. [36] reported that increased circulating AOPPs in individuals with obesity is due to metabolic changes and protein oxidation rather than lipid oxidation. This is similar to the report by Venturini et al. [25] that AOPPs were related to fasting glucose and CRP levels and not with BMI among adults with three to five components of MetS. With increased MetS components, circulating AOPPs also increases and subjects with five MetS components had higher circulating AOPPs than those with three or less MetS components [25]. It is even suggested that AOPPs are excellent marker of oxidative stress in patients with MetS, it is because of the integral role of hyperglycemia in origination of AOPPs [37]. It is also suggested that AOPPs are involved in impaired preadipocyte differentiation and the consequence of ectopic lipid accumulation in MetS, this is mainly due to overexpression of TNF-α and interleukin (IL)-6 through activation of nuclear factor κB [38]. Advanced oxidation protein products also induced insulin resistance that is mediated by AOPP-induced inflammatory cytokines (e.g., TNF- α, IL-6, IL-1β) production [6, 38]. Several mechanistic pathways of the effects of AOPPs on MetS development are shown in Fig. 4.

Table 3 Characteristics of studies included in the current systematic review and meta-analysis

Ref	First author/year	Country	Journal	Age	Men/women	Design	Num	Main finding
[6]	Korkmaz GG/2013	Turkey	Metab Clin Exp	30–60	24/51	Cross-sectional	77	Significantly higher circulating AOPPs in patients with MetS versus non-MetS ($p=0.005$)
[34]	Żurawska-Płaksej E/2014	Poland	J Endocrinol Invest	53–55	40/66	Case–control	106	No significant difference in circulating AOPPs in patients with or without MetS ($p=0.18$)
[25]	Venturini D/2015	Brazil	Nutr Res	50	16/80	Case–control	96	Significantly higher circulating AOPPs in patients with MetS versus non-MetS ($p=0.008$)
[24]	Gradinaru D/2017	Romania	Exp Clin Endocrinol Diabetes	60–75	16/64	Cross-sectional	80	Significantly higher circulating AOPPs in patients with MetS versus non-MetS ($p<0.001$)
[13]	Koborová I/2018	Slovakia	Acta Paediatr	18–20	2064/1097	Cross-sectional	2064 + 1097	Significantly higher circulating AOPPs in patients with MetS versus non-MetS ($p<0.001$)
[31]	Klisic A/2019	Serbia	J Med Biochem	40–68	51/83	Cross-sectional	109	Significantly higher circulating AOPPs in patients with MetS versus non-MetS ($p=0.01$)

The study by Koborová I et al. [13] was conducted separately between men and women; therefore, the results are included as two independent studies

AOPPs advanced oxidation protein products, *MetS* metabolic syndrome, *NM* not mentioned

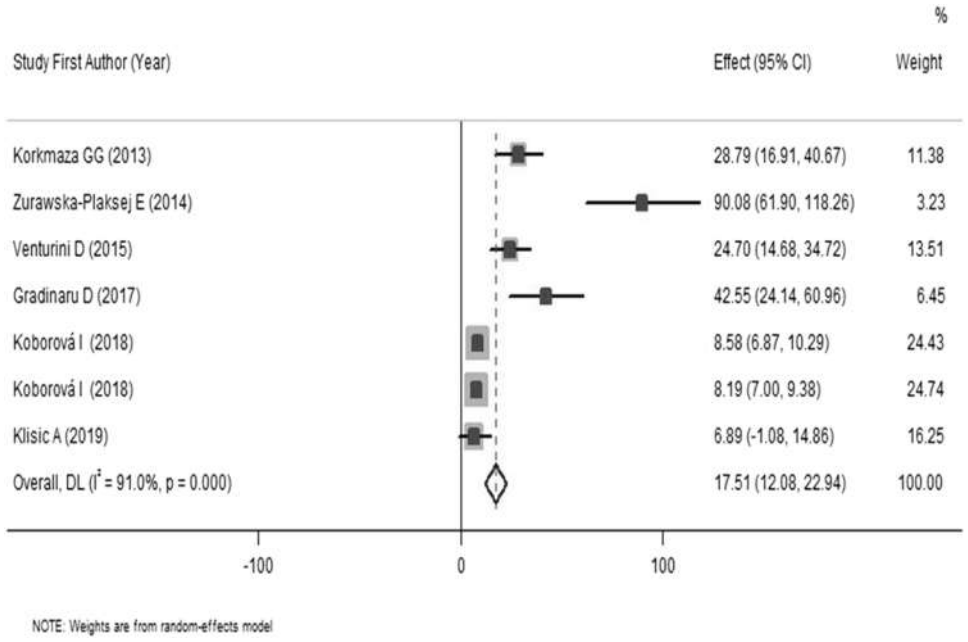

Fig. 2 Weighted mean difference (WMD) with 95% confidence interval (CI) of circulating advanced oxidation protein products (AOPPs) in individuals with metabolic syndrome (MetS) compared with those without MetS. I^2 represents the degree of heterogeneity

Table 4 Subgroup analysis for the comparison of circulating AOPPs between patients with MetS versus control group

Group	No. of studies*	WMD (95% CI)	$P_{\text{within group}}$	$P_{\text{between group}}$ *	$P_{\text{heterogeneity}}$	I^2, %
Total	7	17.512, 12.084, 22.939	< 0.001		< 0.001	91.0
Gender				< 0.001		
Both	5	34.940, 16.314, 53.565	< 0.001		< 0.001	90.6
Male or female	2	8.318. 7.338, 9.297	< 0.001		0.714	0
Design				< 0.001		
Case–control	2	56.009, − 8.005, 120.023	0.086		< 0.001	94.6
Cross-sectional	5	11.340, 7.365, 15.315	< 0.001		< 0.001	83.8
Baseline AOPPs (μmol/L)				< 0.001		
< 100	4	9.290, 6.414, 12.165	< 0.001		0.009	74.1
≥ 100	3	49.979, 17.948, 82.009	0.002		< 0.001	89.7
Age group				< 0.001		
≥ 30	5	34.940, 16.314, 53.565	< 0.001		< 0.001	90.6
< 30	2	8.318, 7.338, 9.297	< 0.001		0.714	0
Sample size				< 0.001		
110>	2	8.318, 7.338, 9.297	< 0.001		0.714	0.0
≥ 110	5	34.940, 16.314, 53.565	< 0.001		< 0.001	90.6

All of the included studies were recruited in the combination of both genders and had moderate quality score. Therefore, subgrouping according to these parameters was not performed

AOPPs advanced oxidation protein products, *MetS* metabolic syndrome

Table 5 Meta regression analysis for finding the possible sources of heterogeneity for the association between AOPPs and MetS

AOPPs	Tau^2	*P*	95%CI
Estimate of between-study variance	30.6252		
By design (cross-sectional versus others)	− 130.6207	0.025	− 237.2933, − 23.94798
By baseline AOPPs (≥ 100 versus others)	136.2415	0.004	67.93972, 204.5433
By age (≥ 30 versus others)	104.6848	0.030	14.89838, 194.4712
By sample size (≤ 110 versus others)	104.6848	0.03	14.89838, 194.4712
By gender (both versus others)	104.6848	0.03	14.89838, 194.4712

AOPPs advanced oxidation protein products, *MetS* metabolic syndrome

In our study, all of the included studies had moderate or high study quality and no study had poor quality. In the subgrouping, gender, age group and sample size were considered as possible sources of heterogeneity. Similar to our results, in the study by Komosinska-Vassev et al. [39], increased age was associated with increased circulating AOPPs in both genders, while this association was stronger in men than in women. Also, in another study, post-menopausal women had significantly higher circulating AOPPs than pre-menopausal women [40].

Although, because of the low number of studies in each subgroup, making a reliable conclusion will be limited. In conclusion, in the current systematic review and meta-analysis, for the first time, we summarized the studies that evaluated the association between MetS with circulating AOPPs and we found higher circulating AOPPs in individuals with MetS compared with healthy individuals. Although because of the limited number of studies in this filed, further studies will make more clarified conclusion. Also, because of the observational design of the included studies, the cause-effect relationship will not be inferable and so longitudinal studies are warranted to make this conclusion more reliable.

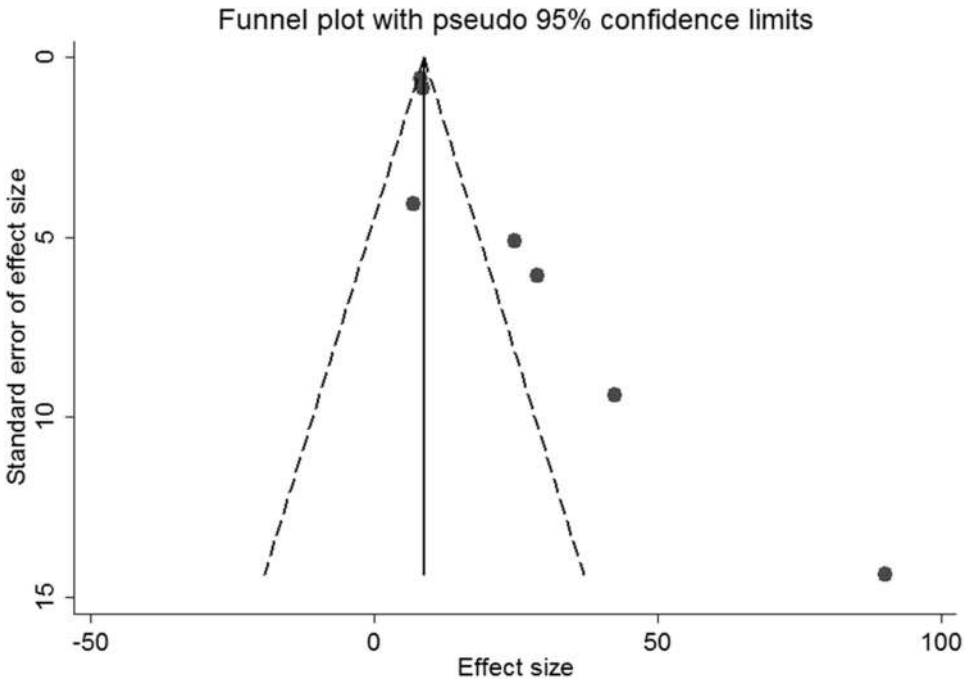

Fig. 3 Begg's funnel plot (with pseudo 95% CIs) of the weighted mean difference (WMD) versus the standard error (se) of (WMD) for the comparison of circulating advanced oxidation protein products (AOPPs) between individuals with metabolic syndrome (MetS) versus individuals without MetS (Egger's test ($p=0.278$) and Begg's test ($p=0.154$))

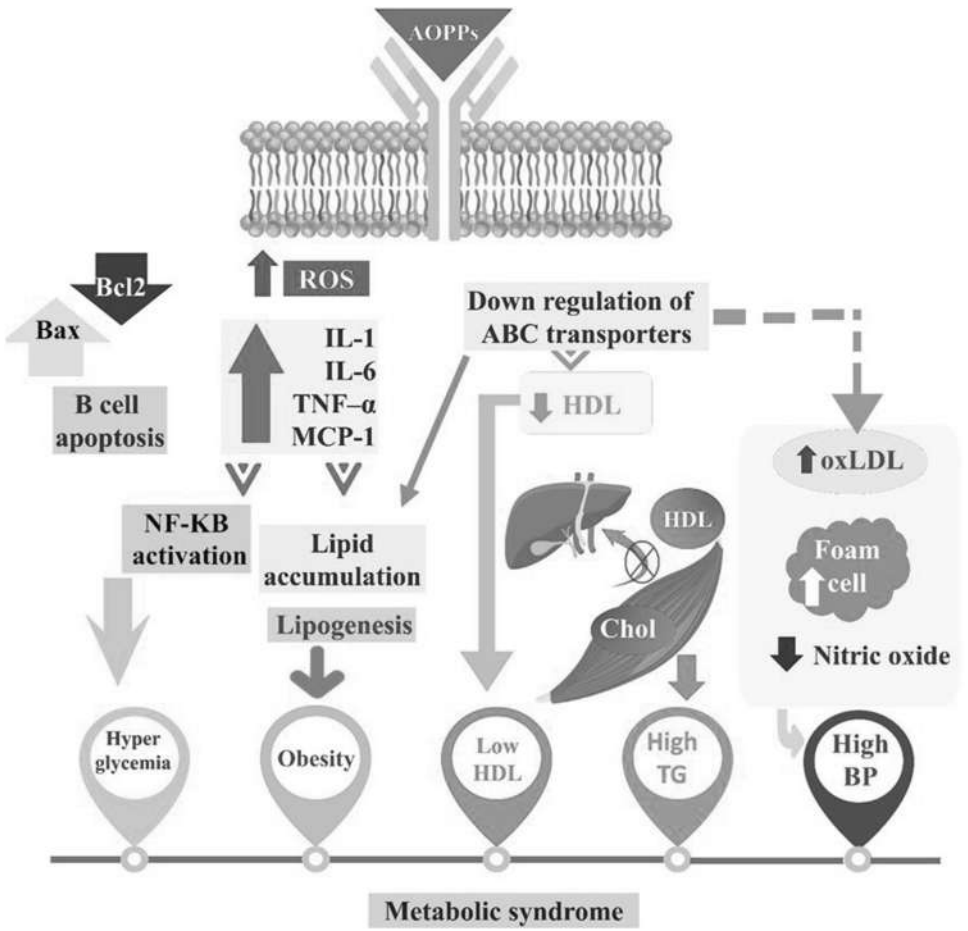

Fig. 4 The underlying mechanisms of metabolic syndrome associated actions of AOPPs. AOPPs, advanced oxidation protein products; Chol, cholesterol; TG, triglycerides; BP, blood pressure; ROS, reactive oxygen species; IL, interleukin; TNF–α, tumor necrosis factor alpha; MCP-1, monocyte chemoattractant protein-1; OxLDL, oxidized LDL; HDL, high-density lipoprotein; ABC, ATP-binding cassette; PKC, protein kinase-C; Cyt-C, cytochrome c; BCL2, B cell leukemia/lymphoma 2; Bax, BCL2-associated X protein

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s13410-023-01178-4.

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Author contribution All authors approved the final version of the article. MAF designed the project and supervised it. MAF and EF also contributed in statistical analysis and manuscript writing. AMA and MAF were involved in hypothesis generation and statistical approach. AMA and RA were also involved in extraction and search. EF was also involved in quality assesement of the included studies.

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Data availability The datasets of the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate The study protocol has also been registered in International Prospective Register of Systematic Reviews system (PROSPERO) (code: CRD42022350224).

Consent for publication Not applicable.

Competing interests The authors declare no competing interests.

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