Original Article

Elevated plasma levels of osteoglycin in cardiovascular patients: a systematic review and meta-analysis

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Background: To evaluate the levels of osteoglycin (OGN) in patients with cardiovascular disease.

Methods: A meta-analysis was conducted on retrospective studies that compared patients with and without cardiovascular disease. Data including the levels of OGN, low density lipoprotein (LDL), and high density lipoprotein (HDL) were analyzed and expressed as mean differences (MD) with a 95% confidence interval (CI).

Results: This meta-analysis included 6 studies with a total of 1,443 patients. The results showed that the concentration of OGN in the blood of patients with cardiovascular disease was significantly elevated compared to that observed in control patients. There were no significant differences in LDL and HDL expression between cardiovascular patients and control patients. Sensitivity analysis and funnel plots showed that this investigation was robust and had low publication bias.

Discussion: This report demonstrated that the blood concentration of OGN in patients with cardiovascular disease is significantly elevated compared to that in control patients. Furthermore, the elevated levels of OGN suggests that OGN may be a biomarker/or therapeutic target for patients with cardiovascular disease. Although the structure of OGN is simple, it is indispensable in many important life processes. It plays a protective role in the occurrence of cardiovascular and cerebrovascular diseases through antioxidant, anti-inflammatory, anti-apoptosis and increasing tolerance to hypoxia.

Keywords: Osteoglycin (OGN); mimecan; cardiovascular disease; meta

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Introduction

The incidence of cardiovascular disease continues to escalate with an aging population, as well as changes in lifestyle and social and economic status. In fact, cardiovascular disease is the leading cause of death worldwide (1,2) and causes significant health and financial burden (3,4). Smoking, hypertension, and hypercholesterolemia are the main risk factors of cardiovascular disease (5-7).

Osteoglycin (OGN) has been noted for its implication in cardiovascular disease in recent studies. OGN is a member of proteoglycans (PGs) and belongs to the family of small leucine-rich proteoglycans (SLRP). The SLRPs share a central structure composed of 6–12 leucine-rich repeats in series and the core protein that is composed of N-terminal and C-terminal-specific cysteine clusters has been shown to play a vital role in cardiovascular function and tumor cell growth, adhesion, and migration (8,9). OGN has vital roles in many biological processes. It exists in the extracellular matrix (ECM) of connective tissues and participates in

matrix synthesis and the regulation of collagen fiber formation (10,11). OGN is thought to be expressed in normal, differentiated, and non-proliferating vascular smooth muscle cells (VSMCs), with increased expression during proliferation, which then decreases at the end of proliferation (12,13). Furthermore, OGN may be involved in the repair and reconstruction of arterial injury and contribute to vascular reconstruction. Studies have shown that OGN is related to cardiovascular function, especially the proliferation of coronary artery smooth muscle cells, which is related with cardiovascular disease (14,15). This is particularly important as the growth of collateral arteries can make up for the impact of central artery stenosis. We present the following article in accordance with the PRISMA reporting checklist (available at https://apm.amegroups.com/article/view/10.21037/apm-22-104/rc).

Methods

Literature search strategy

The whole searching process is based on Population, Intervention, Comparison, Outcomes and Study (PICOS) criteria. A systematic literature search was conducted using the PubMed, Embase, Web of Science, Wangfang and China National Knowledge Infrastructure databases from establishment to July 2019 with no restrictions on year or language of publication. The following keywords were used: osteoglycin; mimecan; OGN; cardiovascular disease; and meta. Boolean operators AND/OR were included in the search strategy for the key terms. To identify additional eligible studies, the reference lists from the literature identified in the database searches were reviewed.

Study selection

The following inclusion criteria were applied to original research articles: (I) the observation group consisted of patients with cardiovascular disease; (II) the control group consisted of healthy patients; and (III) the study related to cardiovascular disease. Literature relating to other diseases or autoimmune diseases, as well as studies with insufficient available data were excluded.

Data extraction and quality assessment

The titles and abstracts of all publications identified from the database search using PubMed, Embase, Web of Science, and China National Knowledge Infrastructure were independently screened for inclusion by two reviewers. Relevant data were extracted from the included literature, including first author, publication year, research design, and baseline demographic features. In addition, patient parameters including OGN, low density lipoprotein (LDL), and high density lipoprotein (HDL) levels were collated. The validity of eligible retrospective trials was assessed using the Cochrane risk of bias tool in Review Manager 5.2. Egger's tests and funnel plots were used to evaluate the risk of bias across studies. The quality of each included study was assessed by Cochrane bias risk tool.

Statistical analysis

The Review Manager (Version 5.2, Cochrane Collaboration, 2011) was used to estimate the impact of the results in the selected report. Random-effects meta-analysis was performed to produce unadjusted and adjusted summary effect estimates [odds ratios (OR) with 95% confidence intervals (CI)]. Heterogeneity across studies was measured using I^2 statistic and Cochran's Q test. When $P<0.05$ or $I^2>50\%$, there is a certain degree of heterogeneity in the study, which is analyzed by random effect model. When $P\geq0.05$ and $I^2\leq50\%$, there is no or small heterogeneity between studies, and the fixed effect model is used for analysis. A fixed-effects model was used for calculations without evidence of heterogeneity, otherwise, a random-effects model was applied. Publication bias was represented graphically by funnel plots of the standard difference in means versus the standard error. The asymmetry of the funnel chart was assessed to resolve possible minor effects. A scenario sensitivity analysis was used to evaluate the robustness of the results.

Results

Search process

A total of 1,125 related articles were identified through the main literature search. Among them, 254 were excluded due to duplication, leaving 871 unique articles. After applying the inclusion and exclusion criteria in the title screening process, a further 736 citations were excluded, and 135 eligible articles were selected for full text review. A further 129 articles were excluded due to different research designs or insufficient data. Finally, a total of 6 publications were included for this meta-analysis. *Figure 1* shows a

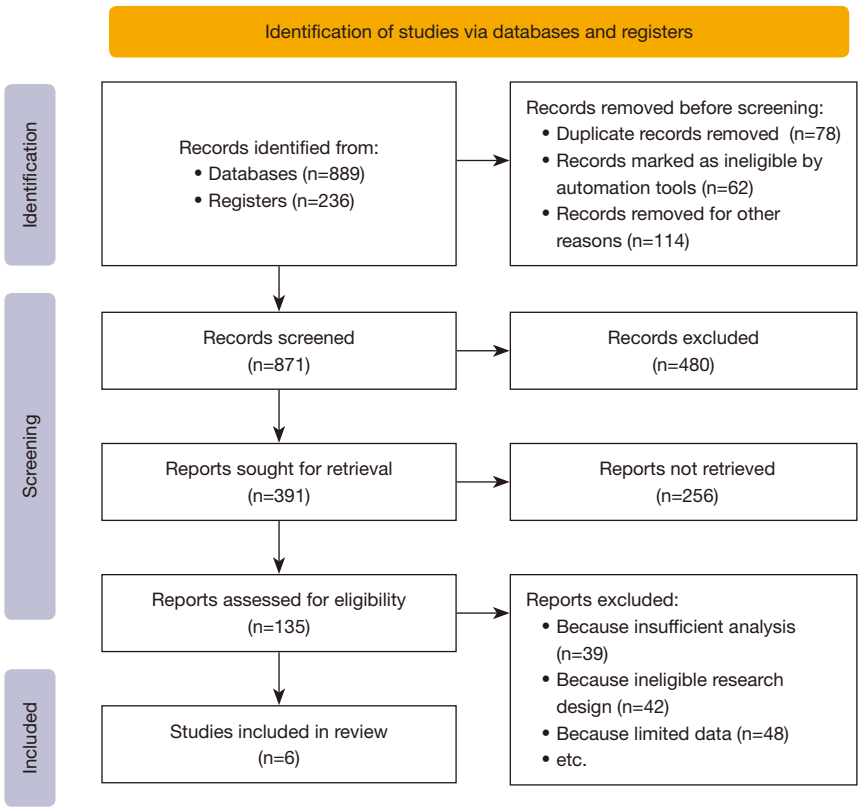

Figure 1 A flowchart of the literature search and study selection process.

flowchart summarizing the literature selection process.

Characteristics of the included studies

Table 1 lists the main characteristics of the included literature (16-21). There were 6 trials involving 1,443 patients aged in their 60s, including 1,017 (70.5%) males and 426 (29.5%) females. Of the 1,443 patients, 808 patients were healthy controls and the experimental group consisted of 635 cardiovascular disease patients (16-21). All 6 studies were published in English, 4 were from China, and the other 2 were from the United States and the Netherlands.

Quality assessment

A qualitative assessment was performed using the Cochrane tool for risk of bias. A high risk of performance bias and reporting bias was detected in two different studies (*Figure 2*). A summary of the risk of bias assessment for each study is shown in *Figure 3*. In general, 2 trials showed bias risk and 4 trials did not show any risk bias.

Heterogeneity tests

Heterogeneity of OGN levels between normal patients and cardiovascular patients was reported in two studies. Meta-analysis showed that there were significant differences between the two groups (MD =−6.76; 95% CI: −11.69 to −1.83; P<0.00001; random effects model) and the heterogeneity was significant (I^2=100%; *Figure 4*).

A meta-analysis of the heterogeneity of LDL levels between normal patients and cardiovascular patients showed no significant difference between the two groups (MD =−0.10; 95% CI: −0.18 to −0.03; P=0.41; fixed effects model) and the heterogeneity of the included studies was low (I^2=0%; *Figure 5*).

Meta-analysis of the heterogeneity of HDL between normal patients and cardiovascular patients showed no significant difference between the two groups (MD =0.05; 95% CI: 0.01 to 0.09; P=0.17; fixed effects model) and

Table 1 The characteristics of the studies included in this systematic review and meta-analysis

Study	Year	Language	Country	Groups	Gender (male/female)	Age (years)	Numbers	Duration of study
Cheng	2014	English	Netherlands	Healthy participants	136/40	64.5±10.3	176	December 2008 to February 2011
				Cardiovascular disease	68/20	65.8±11.2	88	
Gu	2015	English	China	Healthy participants	30/24	60.3±11.7	54	December 2011 to December 2013
				Cardiovascular disease	60/56	63.6±11.5	116	
Hu	2015	English	China	Healthy participants	42/38	58.75±6.51	80	July 2010 to March 2013
				Cardiovascular disease	40/38	56.38±3.31	78	
Motiwala	2014	English	America	Healthy participants	64/13	59.0±13.8	77	February 2000 to July 2012
				Cardiovascular disease	34/5	71.5±9.6	39	
Shen	2016	English	China	Healthy participants	297/53	63.3±11.0	350	February 2011 and August 2015
				Cardiovascular disease	146/63	69.5±10.0	209	
Yang	2018	English	China	Healthy participants	39/32	59.4±8.6	71	May 2010 to December 2010
				Cardiovascular disease	61/44	64.0±9.5	105	

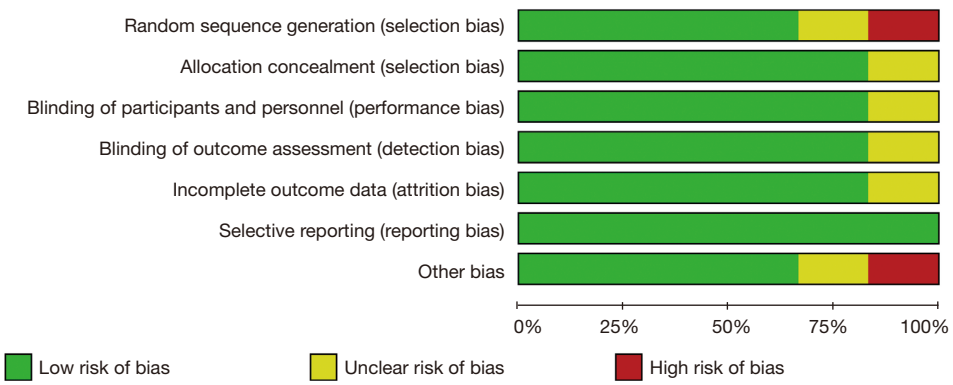

Figure 2 Risk of bias of the included studies. Low bias is represented by green, unclear bias is represented by yellow, and high bias is represented by red.

the heterogeneity of the included study was low (I^2=48%; *Figure 6*).

Sensitivity analysis and publication bias

A total of 6 studies analyzed the plasma concentration of OGN in patients. The forest plot showed that the concentration of bone glycine in cardiovascular patients is higher than that in the control group. A sensitivity analysis was conducted by removing the study by Hu *et al.* 2015 (17). There was little change in the results (I^2 changed from 100% to 98%; *Figure 7*), suggesting that the results of the included articles are robust.

A funnel chart was used to assess the publication bias of thrombosis. The shape of the funnel chart was symmetrical, indicating no significant publication bias in this meta-

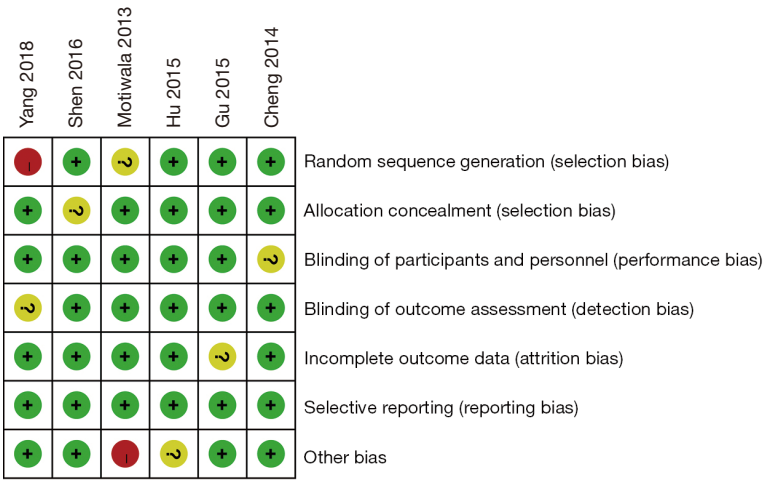

Figure 3 Summary of the risk of bias included in the study. Red shading indicates high risk of deviation, yellow shading indicates some concerns, and green indicates low risk of deviation.

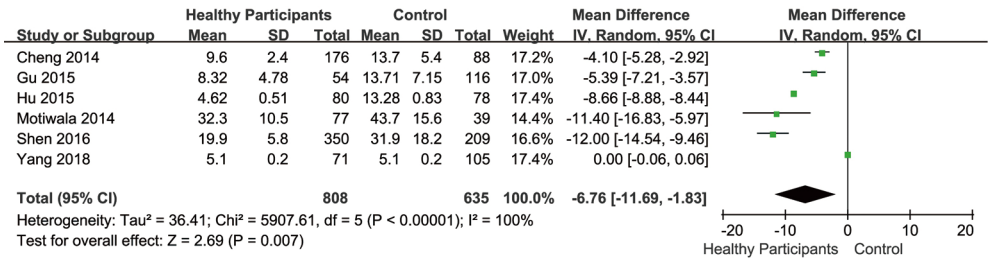

Figure 4 A forest map showing the comparison of osteoglycin concentrations in the blood between normal patients and cardiovascular patients.

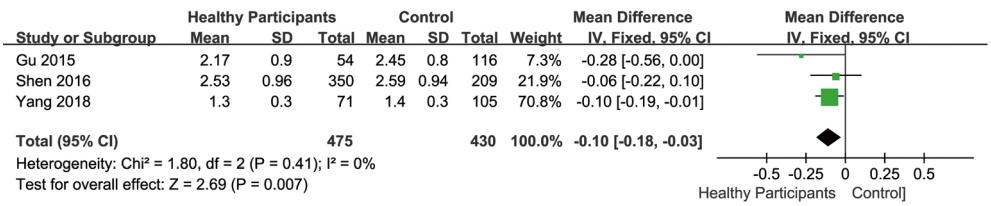

Figure 5 A forest map showing the comparison of low density lipoprotein cholesterol levels in the blood between normal patients and cardiovascular patients.

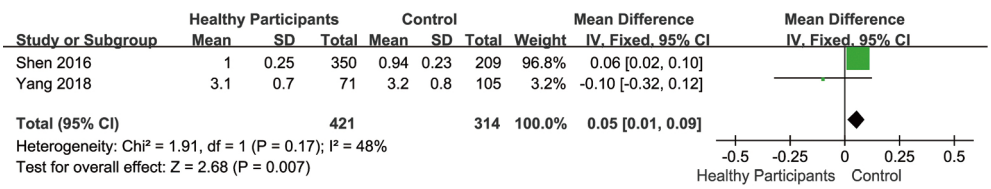

Figure 6 A forest map showing the comparison of high density lipoprotein cholesterol levels in the blood between normal patients and cardiovascular patients.

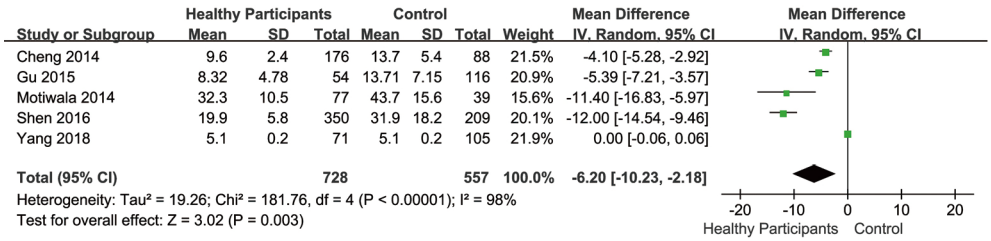

Figure 7 A forest plot showing the pooled sensitivity for the studies.

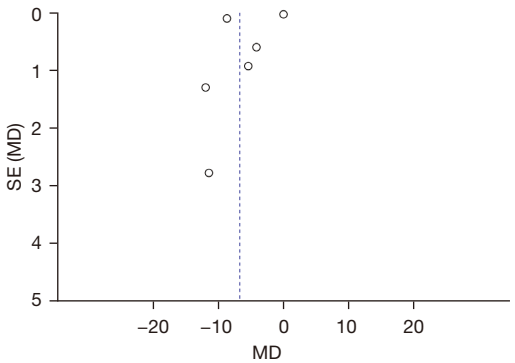

Figure 8 A funnel plot showing publication bias in this meta-analysis. MD, mean difference; SE, standard error.

analysis (*Figure 8*).

Discussion

Cardiovascular and cerebrovascular diseases refer to ischemic or hemorrhagic diseases of the heart, brain, and systemic tissues caused by hyperlipidemia, blood viscosity, atherosclerosis, and hypertension (22,23). It is highly prevalent and is characterized by significant disability, morbidity, and mortality. Despite treatment, more than 50% of survivors of cerebrovascular accidents cannot take care of themselves (24,25). Cardiovascular and cerebrovascular disease is the leading cause of mortality worldwide, contributing to as many as 15 million deaths every year.

OGN, also known as mimecan, is encoded by a single gene located on human chromosome 9q22. It is an ECM protein and belongs to the third family of small leucine rich proteoglycans (SLRPs) (26-28). It has important physiological functions and its main precursor form is secreted in the ECM. Mimecan not only participates in the regulation of collagen fiber formation but also plays an important role in cell migration and proliferation, and tumor growth, adhesion, and migration, as well as the regulation of growth factors.

González-Salvatierra *et al.* (29) demonstrated that bone glycine is closely related to cardiovascular disease and plays a vital role in vascular formation, pathophysiological changes, atherosclerosis, myocardial disease, and heart function. The conclusions in our current report agree with this latter study. Further in-depth investigation relating to the roles and mechanisms of OGN may provide novel insights into the treatment and prevention of cardiovascular diseases (30,31).

This meta-analysis revealed that the blood concentration of OGN in patients with cardiovascular disease is significantly elevated compared to that in control patients, suggesting that OGN may be a novel therapeutic target for the treatment and prevention of cardiovascular disease (32,33). However, there were some limitations to this study. First, this study did not document the medications used by the patients nor the details of any co-existing morbidities (34,35). Second, the report is limited by the number and quality of included studies. The conclusion should be further verified by using a larger cohort in multicenter follow-up controlled trials.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://apm.amegroups.com/article/view/10.21037/apm-22-104/rc

Conflicts of Interest: All authors have completed the

ICMJE uniform disclosure form (available at https://apm.amegroups.com/article/view/10.21037/apm-22-104/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

References

1. Yusuf S, Islam S, Chow CK, et al. Use of secondary prevention drugs for cardiovascular disease in the community in high-income, middle-income, and low-income countries (the PURE Study): a prospective epidemiological survey. Lancet 2011;378:1231-43.
2. Kampmann A, Fernández B, Deindl E, et al. The proteoglycan osteoglycin/mimecan is correlated with arteriogenesis. Mol Cell Biochem 2009;322:15-23.
3. Ceriello A. The post-prandial state and cardiovascular disease: relevance to diabetes mellitus. Diabetes Metab Res Rev 2000;16:125-32.
4. Gao W, Chen H, Meng T, et al. Study on the expressions and correlation of mimecan gene, nuclear factor-κB and interleukin-24 in preeclampsia. Medical Journal of West China 2015.
5. Anker SD, von Haehling S, Germany R. Sleep-disordered breathing and cardiovascular disease. Indian Heart J 2016;68 Suppl 1:S69-76.
6. Tanaka K, Matsumoto E, Higashimaki Y, et al. Role of osteoglycin in the linkage between muscle and bone. J Biol Chem 2012;287:11616-28.
7. Williams MA, Haskell WL, Ades PA, et al. Resistance exercise in individuals with and without cardiovascular disease: 2007 update: a scientific statement from the American Heart Association Council on Clinical Cardiology and Council on Nutrition, Physical Activity, and Metabolism. Circulation 2007;116:572-84.
8. Hooper L, Summerbell CD, Thompson R, et al. Reduced or modified dietary fat for preventing cardiovascular disease. Sao Paulo Med J 2016;134:182-3.
9. Martínez-González MA, Ros E, Estruch R. Primary Prevention of Cardiovascular Disease with a Mediterranean Diet Supplemented with Extra-Virgin Olive Oil or Nuts. N Engl J Med 2018;379:1388-9.
10. Wood DA, Kotseva K, Connolly S, et al. Nurse-coordinated multidisciplinary, family-based cardiovascular disease prevention programme (EUROACTION) for patients with coronary heart disease and asymptomatic individuals at high risk of cardiovascular disease: a paired, cluster-randomised controlled trial. Lancet 2008;371:1999-2012.
11. Mantovani A, Mingolla L, Rigolon R, et al. Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular disease in adult patients with type 1 diabetes. Int J Cardiol 2016;225:387-91.
12. Ujita M, Shinomura T, Kimata K. Molecular cloning of the mouse osteoglycin-encoding gene. Gene 1995;158:237-40.
13. Tasheva ES, Koester A, Paulsen AQ, et al. Mimecan/osteoglycin-deficient mice have collagen fibril abnormalities. Mol Vis 2002;8:407-15.
14. Heikens J, Ubbink MC, van der Pal HP, et al. Long term survivors of childhood brain cancer have an increased risk for cardiovascular disease. Cancer 2000;88:2116-21.
15. Meier-Kriesche HU, Schold JD, Srinivas TR, et al. Kidney transplantation halts cardiovascular disease progression in patients with end-stage renal disease. Am J Transplant 2004;4:1662-8.
16. Gu X, Zhao L, Zhu J, et al. Serum Mimecan Is Associated With Arterial Stiffness in Hypertensive Patients. J Am Heart Assoc 2015;4:002010.
17. Hu Y, Liu J, Zhao Q, et al. Correlation between mimecan expression and coronary artery stenosis in patients with coronary heart disease. Int J Clin Exp Med 2015;8:21641-6.
18. Motiwala SR, Szymonifka J, Belcher A, et al. Measurement of novel biomarkers to predict chronic heart failure outcomes and left ventricular remodeling. J Cardiovasc Transl Res 2014;7:250-61.
19. Cheng JM, Akkerhuis KM, Meilhac O, et al. Circulating osteoglycin and NGAL/MMP9 complex concentrations predict 1-year major adverse cardiovascular events after coronary angiography. Arterioscler Thromb Vasc Biol 2014;34:1078-84.
20. Yang Y, Wu QH, Li Y, et al. Association of SLRPs with carotid artery atherosclerosis in essential hypertensive

patients. J Hum Hypertens 2018;32:564-71.
21. Shen Y, Ding FH, Zhang RY, et al. Association of serum mimecan with angiographic coronary collateralization in patients with stable coronary artery disease and chronic total occlusion. Atherosclerosis 2016;252:75-81.
22. Petretto E, Sarwar R, Grieve I, et al. Integrated genomic approaches implicate osteoglycin (Ogn) in the regulation of left ventricular mass. Nat Genet 2008;40:546-52.
23. Pollin TI, Ordovas JM, Guevara-Cruz M. Genetic Influences on Blood Lipids and Cardiovascular Disease Risk - ScienceDirect. Nutrition in the Prevention and Treatment of Disease (Fourth Edition) 2017;89:571-93.
24. Wald DS, Wald NJ, Morris JK, et al. Folic acid, homocysteine, and cardiovascular disease: judging causality in the face of inconclusive trial evidence. BMJ 2006;333:1114-7.
25. Hadjiphilippou S, Ray KK. Evolocumab and clinical outcomes in patients with cardiovascular disease. J R Coll Physicians Edinb 2017;47:153-5.
26. Mosca L, Appel LJ, Benjamin EJ, et al. Summary of the American Heart Association's evidence-based guidelines for cardiovascular disease prevention in women. Arterioscler Thromb Vasc Biol 2004;24:394-6.
27. Wang Y, Ma Y, Lü B, et al. Differential expression of mimecan and thioredoxin domain-containing protein 5 in colorectal adenoma and cancer: a proteomic study. Exp Biol Med (Maywood) 2007;232:1152-9.
28. Tracy RP. C-Reactive Protein and Other Markers of Inflammation in the Prediction of Cardiovascular Disease in Women-NEJM 2015.
29. González-Salvatierra S, García-Fontana C, Andújar-Vera F, et al. Osteoglycin as a Potential Biomarker of Mild Kidney Function Impairment in Type 2 Diabetes Patients. J Clin Med 2021;10:2209.
30. Townsend N, Nichols M, Scarborough P, et al. Cardiovascular disease in Europe--epidemiological update 2015. Eur Heart J 2015;36:2696-705.
31. Ge G, Seo NS, Liang X, et al. Bone morphogenetic protein-1/tolloid-related metalloproteinases process osteoglycin and enhance its ability to regulate collagen fibrillogenesis. J Biol Chem 2004;279:41626-33.
32. Ettehad D, Emdin CA, Kiran A, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957-67.
33. Marconi VC, Duncan MS, So-Armah K, et al. Bilirubin Is Inversely Associated With Cardiovascular Disease Among HIV-Positive and HIV-Negative Individuals in VACS (Veterans Aging Cohort Study). J Am Heart Assoc 2018;7:007792.
34. Tasheva ES, Pettenati M, Von Kap-Her C, et al. Assignment of mimecan gene (OGN) to human chromosome band 9q22 by in situ hybridization. Cytogenet Cell Genet 2000;88:326-7.
35. Tasheva ES. Analysis of the promoter region of human mimecan gene. Biochim Biophys Acta 2002;1575:123-9.

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