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·文献综述·

纤维蛋白原与冠心病的相关性

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[关键词] 纤维蛋白原；　冠心病；　动脉粥样硬化

[摘　要] 纤维蛋白原是在肝脏中合成的一种血浆蛋白凝血因子,与凝血功能和炎症反应相关。冠心病是当今社会中高发病率、高死亡率的疾病。已有研究表明血浆纤维蛋白原浓度升高与冠心病的发病、严重程度及预后呈正相关,纤维蛋白原可作为冠心病的独立预测因子。深入研究纤维蛋白原与冠心病的相关性可指导临床诊断与治疗。本文总结了纤维蛋白原与冠心病的相关性研究。

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Correlation between fibrinogen and coronary heart disease

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[**KEY WORDS**] fibrinogen; coronary heart disease; atherosclerosis

[**ABSTRACT**] Fibrinogen is a plasma protein coagulation factor synthesized in the liver and is associated with coagulation function and inflammation. Coronary heart disease is a disease with high morbidity and mortality in today's society. Previous studies have shown that increased plasma fibrinogen concentration is positively correlated with the morbidity, severity and prognosis of coronary heart disease, which can be used as an independent predictor of coronary heart disease. Further study on the correlation between fibrinogen and coronary heart disease can guide clinical diagnosis and treatment. This article reviews the research progress on the correlation between fibrinogen and coronary heart disease.

纤维蛋白原是由肝细胞合成并分泌的血浆蛋白凝血因子,可以参与机体止血与血栓形成,调节凝血与纤维化,防止感染和炎症扩散[1]。研究发现,纤维蛋白原与癌症[2-3]、神经系统疾病[4]、肺系疾病[5]、炎性疾病[6]及心血管疾病[7]等疾病有一定的相关性,这可能与纤维蛋白原在凝血酶的作用下转化为纤维蛋白时会形成不溶性凝块或凝胶有关。研究表明,高水平的纤维蛋白原与冠心病的严重程度密切相关,可指导冠心病的诊断,判断其预后[8-10]。本文就纤维蛋白原与冠心病的危险致病因素、发病机制、严重程度、预后等方面的相关性研究进展进行综述。

1　纤维蛋白原的结构与功能

纤维蛋白原是一种相对分子质量为 340 kDa 的可溶性大分子糖蛋白,通常存在于人血浆中,质量浓度约为 1.5～4 g/L,总蛋白浓度约为 8.8 mmol/L。纤维蛋白原由 FGA、FGB 和 FGG 三个基因组成,每个基因分别对应 Aα、Bβ 和 γ 三对多肽链,每条肽链分别由 610、461 及 411 个氨基酸残基构成,其相对分子质量分别为 66 500、52 000 和 46 500 Da,肽链与肽链之间由二硫键连接[11]。当血管壁损伤或血细胞活化时,纤维蛋白原在凝血酶的作用下转化为纤维蛋白单体,相互共价结合形成纤维蛋白多聚体,进而形成不溶性凝块或凝胶,这些物质与血小板、

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红细胞及其他细胞共同作用形成血栓[12-13]。生理状态下,血栓的形成对止血、伤口愈合等功能至关重要;病理状态下,纤维蛋白原通过调节细胞黏附和增殖、内皮损伤部位的血管收缩、刺激血小板聚集和血液黏度作用于动脉粥样硬化病变过程,是冠心病、急性心肌梗死等心血管疾病最常见的成因[14-16]。此外,纤维蛋白原可以作为配体与细胞表面受体结合,通过与白细胞、成纤维细胞等相互作用促进炎症发生[17]。研究显示,纤维蛋白原可激活炎性信号通路,刺激巨噬细胞等炎性细胞分泌细胞因子,如肿瘤坏死因子 α(tumor necrosis factor-α,TNF-α)、白细胞介素 10(interleukin-10,IL-10)和核因子 κB(nuclear factor-κB,NF-κB),从而调节炎症反应[18-19]。

2 纤维蛋白原与冠心病发病的相关性

冠心病是冠状动脉发生粥样硬化病变导致血管腔狭窄甚至阻塞,造成心肌缺血、缺氧、坏死而引发的心脏病。冠心病的发生与凝血系统功能紊乱及炎症反应相关[20-22],因而纤维蛋白原与冠心病的发生也可能存在相关性。

2.1 纤维蛋白原与冠心病危险致病因素的相关性

2.1.1 *年龄* 血浆纤维蛋白原水平随着年龄的增长呈现增高趋势[23],这可能与纤维蛋白原在肝脏的合成代谢速度随年龄变化而变化相关。Schreiner 等[24]认为纤维蛋白原(尤其是 γ′纤维蛋白原)增加了对年轻人群动脉粥样硬化疾病的预测能力。一项对 35 岁以下的年轻冠心病患者的研究显示,纤维蛋白原是判断极年轻心肌梗死患者冠状动脉狭窄是否存在及严重程度的独立指标,但是这项研究的局限性在于没有女性患者[25]。血浆纤维蛋白原也是老年冠心病患者冠状动脉狭窄的独立危险因素[26],与老年男性冠心病患者死亡率呈显著相关[27],这可能与老年人共同突变的基因 TET2 在动脉壁通过增加巨噬细胞驱动的炎症有关[28]。由此可见,高水平的纤维蛋白原与不同年龄阶段人群冠心病及心血管事件(cardiovascular events,CVE)的发生之间均具有密切的关系。

2.1.2 *性别* 有研究调查 329 例冠心病患者纤维蛋白原在预测非钙化斑块(non-calcified plaques,NCP)或混合斑块(mixed plaques,MP)存在中的作用,分析发现纤维蛋白原是女性 NCP/MP 存在的独立危险因素,且女性预测 NCP/MP 存在的纤维蛋白原最佳截断值为 3.41 g/L,但这种相关性在男性患者中并未发现,此项研究对女性存在 NCP/MP 病变的冠心病患者的诊断及降纤方案治疗提供了依据[15]。另一项研究对 407 例早衰冠心病患者(其 257 例年龄小于 55 岁的女性,150 例年龄小于 45 岁的男性)血浆纤维蛋白原水平分析发现,女性冠心病患者血浆纤维蛋白原水平升高较男性显著,这可能与女性血管紧张素转换酶 DD 基因型相关[29],但是此研究的局限性在于男性样本量较少,且女性和男性的基线特征存在显著差异,可能对结果的准确性有一定的影响。

2.1.3 *其他因素* 血浆纤维蛋白原水平与不良饮食、生活习惯等冠心病相关危险因数有关。研究表明,肥胖儿童的纤维蛋白原水平均有所升高,这会促进动脉粥样硬化斑块形成,增加心血管疾病发生风险[30-31]。巴西的一项研究也发现肥胖青少年纤维蛋白原水平较正常偏高[32],这可能与肥胖患者脂肪组织分泌的促炎细胞因子或是由于铁缺乏引起的相关炎症有关。一项长达 13 年的调查研究结果显示,纤维蛋白原水平随着体质指数、低密度脂蛋白、甘油三酯的增加而增加,随着高密度脂蛋白和体力活动的增加而降低,且戒烟与纤维蛋白原的水平变化也有相关性[33],这项研究可作为引导患者养成低脂饮食、运动等良好生活习惯的依据。Okwuosa 等[34]认为,与从不饮酒的参与者相比,持续饮酒的人纤维蛋白原水平在 13 年间仅有少量升高,相反戒酒的人纤维蛋白原水平显著升高,此结果为了解适度饮酒对冠心病等心血管疾病的保护作用机制提供了新的见解,但是这项研究仅聚焦在美国人群,欧美人群偏爱红酒可能也会对结果造成影响。

此外,纤维蛋白原还与冠心病相关疾病有关。葡萄牙的一项前瞻性研究表明,γ′纤维蛋白原可增加原发性高血压发生风险,这可能与纤维蛋白原能使两个红细胞短暂桥接有关,是冠心病一个重要的危险因素[35]。Yang 等[36]通过对比不同纤维蛋白原水平患者相关指标,发现纤维蛋白原升高的患者糖化血红蛋白和空腹血糖水平较高,这些患者发生心血管事件的风险也随之增加,但此研究并未阐明纤维蛋白原与糖尿病的相关机制。高血压、高血糖等疾病属于冠心病可改变的危险因素,纤维蛋白原与这些疾病的相关性研究对指导临床治疗有重要意义。

2.2 纤维蛋白原与冠心病发病机制的相关性

血管中纤维蛋白原沉积既能引发动脉粥样硬化[37],又能促进斑块生长,这与纤维蛋白溶解活性和纤维蛋白溶酶原浓度的降低有关[38]。流行病学研究表明,高水平的纤维蛋白原可预测缺血性心脏

病(ischemic heart disease,IHD)事件的发生[39],对冠心病的诊断也有重要意义[40]。冠心病的发病风险与纤维蛋白原水平升高呈正相关,与正常人相比,冠心病患者血浆纤维蛋白原水平显著增高。血浆纤维蛋白原水平>3.5 g/L 可作为冠心病的独立预测因素[41],当血浆纤维蛋白原水平增高 1 g/L 时,对冠心病预测的比值比(odds ratio,OR)为 0.94[42]。一项来自 31 项前瞻性研究的 154 211 名没有已知心血管疾病的个体参与者的数据评估了纤维蛋白原水平与心血管疾病之间的关系,结果显示纤维蛋白原水平是冠心病的危险因素,且血浆纤维蛋白原水平每增加 1 g/L,发生冠心病的风险增加 2.42 倍[43]。Haybar 课题组通过冠状动脉造影对慢性稳定型心绞痛患者的研究也发现,这些患者存在明显更高的纤维蛋白原水平,这对提高冠心病患者的识别具有重要意义[44]。在冠心病患者中,高水平的纤维蛋白原与主要不良心血管事件(major adverse cardiovascular events,MACE)的发生显著相关[45],且基线纤维蛋白原水平升高可能是经皮冠状动脉介入治疗(percutaneous coronary intervention,PCI)后 MACE 发生的重要独立预测因素[46]。Yang 等[36]对 1 466 名冠心病患者进行评估发现,与未发生心血管事件的患者相比,发生心血管事件的患者纤维蛋白原水平更高,且血清纤维蛋白原中水平(2.91 ~ 3.51 g/L)和高水平(≥3.51 g/L)患者发生心血管事件概率分别为纤维蛋白原低水平患者的 1.23 倍和 2.20 倍,且 3.515 g/L 可作为纤维蛋白原预测心血管事件的临界值。这些结果在分子生物学研究中也得到证实。此前研究表明,纤维蛋白原链中几种基因多态性可能会影响纤维蛋白原水平,从而影响冠心病的发生。在对纤维蛋白原的 β 基因启动子区的基因多态性进行研究发现,纤维蛋白原单核苷酸多态性(single nucleotide polymorphism,SNP)-455G/A、-148C/T 与血浆纤维蛋白原水平升高及冠心病的发生相关[47],这两个基因多态性可能通过改变启动子与胞嘧啶 IL-6 的相互作用参与冠状动脉事件相关炎症反应。冠心病的发生与凝血系统紊乱相关,人体内的抗凝蛋白组织因子途径抑制物(tissue factor pathway inhibitor,TFPI)升高是血栓形成和心血管疾病风险的主要因素[48]。Naji 等[49]发现 TFPI 的变异与血浆纤维蛋白原水平显著相关,并通过实验证明了 TFPI SNP rs10931292 与冠心病发病风险的相关性,该结果对阐明纤维蛋白原水平和冠心病发展的遗传基础和生物学途径具有重要意义。

虽然大多数研究结果支持纤维蛋白原与冠心病的相关性,但也有少部分研究表明纤维蛋白原水平与冠心病之间没有联系[50-54]。几项动物研究结果也表明,转基因小鼠高水平的纤维蛋白原并未加重动脉粥样硬化病变过程[55-56],而对于心肌缺血再灌注大鼠,补充低浓度和高浓度的纤维蛋白原对心肌梗死面积也没有影响[57]。因为大多数的研究已经很好地评估了纤维蛋白原在冠心病发病机制中的作用,这些矛盾的结果也说明纤维蛋白原在冠心病进展过程中作用的复杂性,究竟纤维蛋白原是冠心病发病的原因还是冠心病形成的标志物还有待探究。

3　纤维蛋白原与冠心病严重程度的相关性

血浆纤维蛋白原可使血液黏度增加,加速血小板和红细胞聚集,促进血栓形成,使平滑肌细胞增殖从而促进斑块生长[58],除了提高冠心病的发病率之外,还可导致冠状动脉病变程度和范围加重。在对 581 名急性冠状动脉综合征(acute coronary syndrome,ACS)或稳定型心绞痛患者进行冠状动脉造影及血浆纤维蛋白原分析后发现,当斑块负荷≥70%时,纤维蛋白原与其存在显著正相关,这说明纤维蛋白原水平可反映冠状动脉粥样硬化程度(尤其对 ACS 患者),但此结果可能与 C 反应蛋白(C-reactive protein,CRP)存在交互作用[59-61]。血浆纤维蛋白原水平与冠状动脉狭窄程度有相关性。用 Syntaxs 评分法评估 752 例 ACS 患者严重程度,发现 Syntaxs 评分高的患者中普遍存在更高水平的纤维蛋白原,当纤维蛋白原水平>4.17 g/L 时,对高 Syntaxs 患者预测准确性达 80.0%[62]。多项研究也采用此评分法评估了冠心病患者冠状动脉狭窄程度,并对冠心病的严重程度进行了分析,结果显示纤维蛋白原水平与冠心病严重程度相关[63-64]。也有研究采用 Gensini 评分评估 2 288 例新发冠状动脉粥样硬化患者冠状动脉狭窄程度,分析后发现高 Gensini 评分患者纤维蛋白原水平显著升高,并发现纤维蛋白原预测冠状动脉狭窄程度的临界值为 3.21 g/L[65]。Gao 等[25]对 418 名 35 岁以下男性急性心肌梗死患者冠状动脉狭窄程度进行评估,发现高水平的血浆纤维蛋白原患者存在更严重的冠状动脉狭窄。纤维蛋白原与 Gensini 评分的正向相关性[66-67]等结果提示血浆纤维蛋白原水平与冠状动脉狭窄及严重程度显著相关,这可能与高动脉粥样硬化性脂质水平的介导有关[68],可作为预测冠心病严重程度的独立预测因子。

4 纤维蛋白原与冠心病预后的相关性

冠心病的死亡率随着纤维蛋白原水平的升高而增加[69-70],且全因死亡率也与纤维蛋白原水平显著相关[71-72]。研究发现,冠心病患者血浆纤维蛋白原水平(>4.65 g/L)显著增高,当血浆纤维蛋白原>4.50 g/L时与死亡率相关[47]。与此研究结果相似,Peng等[73]对3 020例冠心病患者的死亡率的研究发现,纤维蛋白原预测死亡率的最佳截断值为3.17 g/L,无论是对于全因死亡率还是心脏死亡率,纤维蛋白原≥3.17 g/L患者的死亡风险显著高于纤维蛋白原<3.17 g/L的患者,这也证实了纤维蛋白原水平与冠心病患者死亡风险相关。另一项研究结果表明,纤维蛋白原是非ST段抬高型ACS患者PCI术后死亡或非致死性再梗死的独立预测因子,且其准确性与GRACE系统相似[74]。因此,纤维蛋白原水平升高可作为冠心病预后的参考指标,指导临床。

5 小 结

纤维蛋白原作为一种急性期蛋白,通过凝血与炎症刺激反应参与冠心病的发生发展过程中。上述多数研究结果表明高水平的纤维蛋白原与冠心病的发病呈高度相关性,可评估冠状动脉硬化和狭窄的严重程度,是冠心病预后的独立危险因素,可指导临床治疗。但是目前纤维蛋白原与冠心病的相关研究还存在以下几个问题:①二者相关性的研究基本局限于临床病例观察,仅有少数研究涉及冠心病与纤维蛋白原基因层面上的相关性及动物实验研究;②目前还没有具体的实验研究揭示纤维蛋白原与冠心病的关系是单纯的存在相关性还是导致冠心病发生的致病因素;③对于纤维蛋白原升高到底是导致冠心病发生的原因还是冠心病进展过程中的结果仍未有定论;④对于纤维蛋白原与冠心病的发病及冠心病严重程度的浓度参考值还没有统一的共识。因此,今后还需结合基因研究探索纤维蛋白原与冠心病的因果关系,并制定统一的纤维蛋白原预测值,实现纤维蛋白原对冠心病的精准预测与诊断,有针对性地开展治疗,以谋求降低冠心病患者的死亡率,改善预后。

[参考文献]

[1] DAVALOS D, AKASSOGLOU K. Fibrinogen as a key regulator of inflammation in disease[J]. Semin Immunopathol, 2012, 34(1): 43-62.

[2] GRAFETSTÄTTER M, HÜSING A, GONZÁLEZ MALDONADO S, et al. Plasma fibrinogen and sP-selectin are associated with the risk of lung cancer in a prospective study[J]. Cancer Epidemiol Biomarkers Prev, 2019, 28(7): 1221-1227.

[3] LIN Y, LIU Z, QIU Y, et al. Clinical significance of plasma D-dimer and fibrinogen in digestive cancer: a systematic review and Meta-analysis[J]. Eur J Surg Oncol, 2018, 44(10): 1494-1503.

[4] JENKINS D R, CRANER M J, ESIRI M M, et al. Contribution of fibrinogen to inflammation and neuronal density in human traumatic brain injury[J]. J Neurotrauma, 2018, 35(19): 2259-2271.

[5] FISK M, CHERIYAN J, MOHAN D, et al. The p38 mitogen activated protein kinase inhibitor losmapimod in chronic obstructive pulmonary disease patients with systemic inflammation, stratified by fibrinogen: a randomised double-blind placebo-controlled trial[J]. PLoS One, 2018, 13(3): e0194197.

[6] KO Y P, FLICK M J. Fibrinogen is at the interface of host defense and pathogen virulence in staphylococcus aureus infection[J]. Semin Thromb Hemost, 2016, 42(4): 408-421.

[7] TOUSOULIS D, PAPAGEORGIOU N, ANDROULAKIS E, et al. Fibrinogen and cardiovascular disease: genetics and biomarkers[J]. Blood Rev, 2011, 25(6): 239-245.

[8] RUSNAK J, FASTNER C, BEHNES M, et al. Biomarkers in stable coronary artery disease[J]. Curr Pharm Biotechnol, 2017, 18(6): 456-471.

[9] MEADE T W. Fibrinogen in ischaemic heart disease[J]. Eur Heart J, 1995, 16(Suppl A): 31-35.

[10] ZHANG J, YANG Y, ZHANG H, et al. Study on the predictive effect of fibrinogen on vascular calcification[J]. Vascular, 2021, 29(6): 952-958.

[11] MOSESSON M W. Fibrinogen and fibrin structure and functions[J]. J Thromb Haemost, 2005, 3(8): 1894-1904.

[12] SILVAIN J, COLLET J P, NAGASWAMI C, et al. Composition of coronary thrombus in acute myocardial infarction[J]. J Am Coll Cardiol, 2011, 57(12): 1359-1367.

[13] SADOWSKI M, ZABCZYK M, UNDAS A. Coronary thrombus composition: links with inflammation, platelet and endothelial markers[J]. Atherosclerosis, 2014, 237(2): 555-561.

[14] UNDAS A, ARIËNS R A. Fibrin clot structure and function: a role in the pathophysiology of arterial and venous thromboembolic diseases[J]. Arterioscler Thromb Vasc Biol, 2011, 31(12): e88-e99.

[15] LI T, WANG F, PENG R, et al. Sex-related differences in the association between plasma fibrinogen and non-calcified or mixed coronary atherosclerotic plaques[J]. Biol Sex Differ, 2018, 9(1): 51.

[16] VAN GAAL L F, MERTENS I L, DE BLOCK C E. Mechanisms linking obesity with cardiovascular disease[J]. Nature, 2006, 444(7121): 875-880.

[17] LUYENDYK J P, SCHOENECKER J G, FLICK M J. The multifaceted role of fibrinogen in tissue injury and inflammation[J]. Blood, 2019, 133(6): 511-520.

[18] JY H, SMITH T D, MELI V S, et al. Differential regulation of macrophage inflammatory activation by fibrin and fibrinogen[J]. Acta Biomater, 2017, 47: 14-24.

[19] LANDERS C T, TUNG H Y, KNIGHT J M, et al. Selective cleavage of fibrinogen by diverse proteinases initiates innate allergic and antifungal immunity through CD11b[J]. J Biol Chem, 2019, 294(22): 8834-8847.

[20] LIBBY P, TABAS I, FREDMAN G, et al. Inflammation and its resolution as determinants of acute coronary syndromes[J]. Circ Res, 2014, 114(12): 1867-1879.

[21] LISOWSKI P, MAŁYSZKO J, LISOWSKA A, et al. Role of the hemostasis in unstable angina pectoris[J]. Pol Merkur Lekarski, 2004, 16(95): 468-471.

[22] ZABCZYK M, NATORSKA J, UNDAS A. Fibrin clot properties in atherosclerotic vascular disease: from pathophysiology to clinical outcomes[J]. J Clin Med, 2021, 10(13): 2999.

[23] YARNELL J W, SWEETNAM P M, ELWOOD P C, et al. Haemostatic factors and ischaemic heart disease[J]. Br Heart J, 1985, 53(5): 483-487.

[24] SCHREINER P J, APPIAH D, FOLSOM A R. Gamma prime γ′ fibrinogen and carotid intima-media thickness: the atherosclerosis risk in communities study[J]. Blood Coagul Fibrinolysis, 2017, 28(8): 665-669.

[25] GAO X Y, ZHOU B Y, ZHANG M Z, et al. Association between fibrinogen level and the severity of coronary stenosis in 418 male patients with myocardial infarction younger than 35 years old[J]. Oncotarget, 2017, 8(46): 81361-81368.

[26] HAN K, LU Q, ZHU W J, et al. Correlations of degree of coronary artery stenosis with blood lipid, CRP, Hcy, GGT, SCD36 and fibrinogen levels in elderly patients with coronary heart disease[J]. Eur Rev Med Pharmacol Sci, 2019, 23(21): 9582-9589.

[27] YANO K, GROVE J S, CHEN R, et al. Plasma fibrinogen as a predictor of total and cause-specific mortality in elderly Japanese-American men[J]. Arterioscler Thromb Vasc Biol, 2001, 21(6): 1065-1070.

[28] FUSTER J J, MACLAUCHLAN S, ZURIAGA M A, et al. Clonal hematopoiesis associated with TET2 deficiency accelerates atherosclerosis development in mice[J]. Science, 2017, 355(6327): 842-847.

[29] KRYCZKA K E, PŁOSKI R, KSIEŻYCKA E, et al. The association between the insertion/deletion polymorphism of the angiotensin-converting enzyme gene and the plasma fibrinogen level in women and men with premature coronary artery atherosclerosis[J]. Pol Arch Intern Med, 2020, 130(9): 748-756.

[30] YILDIRIM Ö, DEMIRCAN T, TÜFEKÇI Ö, et al. Anemia and its effect on cardiovascular findings in obese adolescents[J]. Turk J Haematol, 2018, 35(3): 192-196.

[31] 陈 焱, 赵 昕, 艾冠男, 等. 高血压前期患者残余胆固醇与冠状动脉狭窄严重程度的相关性[J]. 中国动脉硬化杂志, 2021, 29(12): 1047-1052.

[32] AZEVEDO W F, CANTALICE A S, GONZAGA N C, et al. Fibrinogen: cardiometabolic risk marker in obese or overweight children and adolescents[J]. J Pediatr (Rio J), 2015, 91(5): 464-470.

[33] OKWUOSA T M, KLEIN O, CHAN C, et al. 13-year long-term associations between changes in traditional cardiovascular risk factors and changes in fibrinogen levels: the coronary artery risk development in young adults (CARDIA) study[J]. Atherosclerosis, 2013, 226(1): 214-219.

[34] OKWUOSA T M, KLEIN O, CHAN C, et al. Long-term change in alcohol-consumption status and variations in fibrinogen levels: the coronary artery risk development in young adults (CARDIA) study[J]. BMJ Open, 2013, 3(7): e002944.

[35] GUEDES A F, CARVALHO F, MOREIRA C, et al. Essential arterial hypertension patients present higher cell adhesion forces, contributing to fibrinogen-dependent cardiovascular risk[J]. Nanoscale, 2017, 9(39): 14897-14906.

[36] YANG S H, DU Y, ZHANG Y, et al. Serum fibrinogen and cardiovascular events in Chinese patients with type 2 diabetes and stable coronary artery disease: a prospective observational study[J]. BMJ Open, 2017, 7(6): e015041.

[37] ZEB I, JORGENSEN N W, BLUMENTHAL R S, et al. Association of inflammatory markers and lipoprotein particle subclasses with progression of coronary artery calcium: the multi-ethnic study of atherosclerosis[J]. Atherosclerosis, 2021, 339: 27-34.

[38] SMITH E B. Fibrinogen, fibrin and fibrin degradation products in relation to atherosclerosis[J]. Clin Haematol, 1986, 15(2): 355-370.

[39] YARNELL J W, PATTERSON C C, SWEETNAM P M, et al. Haemostatic/inflammatory markers predict 10-year risk of IHD at least as well as lipids: the Caerphilly collaborative studies[J]. Eur Heart J, 2004, 25(12): 1049-1056.

[40] XIONG W X, SHEN Y, DAI D P, et al. Clinical utility of the ratio between circulating fibrinogen and fibrin (ogen) degradation products for evaluating coronary artery disease in type 2 diabetic patients[J]. Chin Med J (Engl), 2015, 128(6): 727-732.

[41] DEVECI B, GAZI E. Relation between globulin, fibrinogen, and albumin with the presence and severity of coronary artery disease[J]. Angiology, 2021, 72(2): 174-180.

[42] SONG B, SHU Y, XU Y N, et al. Plasma fibrinogen lever and risk of coronary heart disease among Chinese population: a systematic review and meta-analysis[J]. Int J Clin Exp Med, 2015, 8(8): 13195-13202.

[43] FIBRINOGEN STUDIES COLLABORATION, DANESH J, LEWINGTON S, et al. Plasma fibrinogen level and the risk of major cardiovascular diseases and nonvascular mortality: an individual participant meta-analysis[J]. JAMA, 2005, 294(14): 1799-1809.

[44] HAYBAR H, AHMADZADEH A, ASSAREH A, et al. Intermediate-risk chronic stable angina: neutrophil-lymphocyte ratio and fibrinogen levels improved predicting angiographically-detected coronary artery disease[J]. Iran Red Crescent Med J, 2016, 18(9): e18570.

[45] LIU S L, WU N Q, SHI H W, et al. Fibrinogen is associated with glucose metabolism and cardiovascular outcomes in patients with coronary artery disease[J]. Cardiovasc Diabetol, 2020, 19(1): 36.

[46] ZHANG L, XU C, LIU J, et al. Baseline plasma fibrinogen is associated with haemoglobin A1c and 2-year major adverse cardiovascular events following percutaneous coronary intervention in patients

with acute coronary syndrome: a single-centre, prospective cohort study[J]. Cardiovasc Diabetol, 2019, 18(1): 52.

[47] CANSECO-AVILA L M, LOPEZ-ROBLERO A, SERRANO-GUZMAN E, et al. Polymorphisms −455G/A and −148C/T and fibrinogen plasmatic level as risk markers of coronary disease and major adverse cardiovascular events[J]. Dis Markers, 2019. DOI: 10.1155/2019/5769514.

[48] MAST A E. Tissue factor pathway inhibitor: multiple anticoagulant activities for a single protein[J]. Arterioscler Thromb Vasc Biol, 2016, 36(1): 9-14.

[49] NAJI D H, TAN C, HAN F, et al. Significant genetic association of a functional TFPI variant with circulating fibrinogen levels and coronary artery disease[J]. Mol Genet Genomics, 2018, 293(1): 119-128.

[50] WANG J, JIA L, LI X, et al. New insights into the association between fibrinogen and coronary atherosclerotic plaque vulnerability: an intravascular optical coherence tomography study[J]. Cardiovasc Ther, 2019: 8563717.

[51] APPIAH D, SCHREINER P J, MACLEHOSE R F, et al. Association of plasma γ′fibrinogen with incident cardiovascular disease: the atherosclerosis risk in communities (ARIC) study[J]. Arterioscler Thromb Vasc Biol, 2015, 35(12): 2700-2706.

[52] KARIM M, KARTSONAKI C, BENNETT D A, et al. Systemic inflammation is associated with incident stroke and heart disease in East Asians[J]. Sci Rep, 2020, 10(1): 5605.

[53] KEAVNEY B, DANESH J, PARISH S, et al. Fibrinogen and coronary heart disease: test of causality by Mendelian randomization[J]. Int J Epidemiol, 2006, 35(4): 935-943.

[54] WARD-CAVINESS C K, DE VRIES P S, WIGGINS K L, et al. Mendelian randomization evaluation of causal effects of fibrinogen on incident coronary heart disease[J]. PLoS One, 2019, 14(5): e0216222.

[55] GULLEDGE A A, MCSHEA C, SCHWARTZ T, et al. Effects of hyperfibrinogenemia on vasculature of C57BL/6 mice with and without atherogenic diet[J]. Arterioscler Thromb Vasc Biol, 2003, 23(1): 130-135.

[56] REZAEE F, GIJBELS M J, OFFERMAN E H, et al. Overexpression of fibrinogen in ApoE * 3-Leiden transgenic mice does not influence the progression of diet-induced atherosclerosis[J]. Thromb Haemost, 2002, 88(2): 329-334.

[57] HEINEN A, WELKE V, BEHMENBURG F, et al. Haemotherapy with fibrinogen for perioperative bleeding prevention: a view on arterial thrombogenesis and myocardial infarction in the rat in vivo[J]. J Clin Med, 2019, 8(6): 880.

[58] DE MOERLOOSE P, BOEHLEN F, NEERMAN-ARBEZ M. Fibrinogen and the risk of thrombosis[J]. Semin Thromb Hemost, 2010, 36(1): 7-17.

[59] BULJUBASIC N, AKKERHUIS K M, CHENG J M, et al. Fibrinogen in relation to degree and composition of coronary plaque on intravascular ultrasound in patients undergoing coronary angiography[J]. Coron Artery Dis, 2017, 28(1): 23-32.

[60] 吴 坤, 梁晓娜, 王玲玲, 等. 冠心病心肌缺血患者心功能与血清生化指标的相关性[J]. 中国动脉硬化杂志, 2021, 29(5): 428-432.

[61] 柳 强, 胡有志, 薛 雪. 冠心病患者单核细胞/淋巴细胞比率与冠状动脉病变严重程度的相关性分析[J]. 中国动脉硬化杂志, 2019, 27(10): 868-873.

[62] KURTUL A, YARLIOGLUES M, MURAT S N, et al. The association of plasma fibrinogen with the extent and complexity of coronary lesions in patients with acute coronary syndrome[J]. Kardiol Pol, 2016, 74(4): 338-345.

[63] KARAHAN O, ACET H, ERTAŞ F, et al. The relationship between fibrinogen to albumin ratio and severity of coronary artery disease in patients with STEMI[J]. Am J Emerg Med, 2016, 34(6): 1037-1042.

[64] TABAKCI M M, GERIN F, SUNBUL M, et al. Relation of plasma fibrinogen level with the presence, severity, and complexity of coronary artery disease[J]. Clin Appl Thromb Hemost, 2017, 23(6): 638-644.

[65] ZHANG Y, ZHU C G, GUO Y L, et al. Higher fibrinogen level is independently linked with the presence and severity of new-onset coronary atherosclerosis among Han Chinese population[J]. PLoS One, 2014, 9(11): e113460.

[66] HONG L F, LI X L, LUO S H, et al. Association of fibrinogen with severity of stable coronary artery disease in patients with type 2 diabetic mellitus[J]. Dis Markers, 2014: 485687.

[67] LI M, TANG C, LUO E, et al. Relation of fibrinogen-to-albumin ratio to severity of coronary artery disease and long-term prognosis in patients with non-ST elevation acute coronary syndrome[J]. Biomed Res Int, 2020: 1860268.

[68] ZHANG Y, ZHU C G, GUO Y L, et al. Fibrinogen and the severity of coronary atherosclerosis among adults with and without statin treatment: lipid as a mediator[J]. Heart Lung Circ, 2016, 25(6): 558-567.

[69] BENDERLY M, GRAFF E, REICHER-REISS H, et al. Fibrinogen is a predictor of mortality in coronary heart disease patients[J]. Arterioscler Thromb Vasc Biol, 1996, 16(3): 351-356.

[70] 苏 文, 李虹伟, 李卫萍, 等. 纤维蛋白原水平对急性心肌梗死患者远期预后的影响[J]. 中国循环杂志, 2021, 36(9): 858-862.

[71] JIANG P, GAO Z, ZHAO W, et al. Relationship between fibrinogen levels and cardiovascular events in patients receiving percutaneous coronary intervention: a large single-center study[J]. Chin Med J (Engl), 2019, 132(8): 914-921.

[72] MJELVA Ø R, SVINGEN G F, PEDERSEN E K, et al. Fibrinogen and neopterin is associated with future myocardial infarction and total mortality in patients with stable coronary artery disease[J]. Thromb Haemost, 2018, 118(4): 778-790.

[73] PENG Y, WANG H, LI Y M, et al. Relation between admission plasma fibrinogen levels and mortality in Chinese patients with coronary artery disease[J]. Sci Rep, 2016, 6: 30506.

[74] SONG J, YU T, SUN Z, et al. Comparison of prognostic significance between serum fibrinogen and global registry of acute coronary events score for prognosis of patients with non-ST-elevation acute coronary syndromes undergoing percutaneous coronary intervention[J]. Coron Artery Dis, 2020, 31(2): 124-129.

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