International Journal of Diabetes and Endocrinology
2022; 7(3): 50-53
http://www.sciencepublishinggroup.com/j/ijde
doi: 10.11648/j.ijde.20220703.11
ISSN: 2640-1363 (Print); ISSN: 2640-1371 (Online)

Effect of Genistein on Diabetic Cardiovascular Complications

Na Li[†, *], Guomin Yang[†], Ying Pan, Yu Zhao

Department of General Medicine, Baoan District Central Hospital, The Affiliated Hospital of Guangdong Medical University, Shenzhen, China

Email address:
39909271@qq.com (Na Li)

[*]Corresponding author

† Na Li and Guomin Yang are co-first authors.

To cite this article:
Na Li, Guomin Yang, Ying Pan, Yu Zhao. Effect of Genistein on Diabetic Cardiovascular Complications. *International Journal of Diabetes and Endocrinology*. Vol. 7, No. 3, 2022, pp. 50-53. doi: 10.11648/j.ijde.20220703.11

Received: July 2, 2022; **Accepted**: July 20, 2022; **Published**: July 28, 2022

Abstract: Background: Diabetes mellitus is a chronic disease caused by endocrine metabolic disorders, which has developed into a global public health problem. Currently, the number of people with diabetes has reached approximately 425 million worldwide. It is estimated that the prevalence of diabetes will increase by 48% by 2045. Genistein, a naturally occurring phytoestrogen found mainly in soybeans, is of great importance in the prevention of many diseases, including tumors and cardiovascular disease. Previous studies have shown that dietary supplementation with phytoestrogens can prevent atherosclerosis. Objective: To describe the mechanism and current status of the effect of genistein on diabetic cardiovascular complications, with the aim of improving the prognosis of patients with diabetic combined cardiovascular complications. Methods: To show the specific value of genistein in diabetic cardiovascular complications by elaborating the biochemical properties of genistein and using the interaction of genistein with vascular endothelium, platelet aggregation, lipid deposition, and inflammation as a starting point. Conclusion: The biological properties and mechanism of action of genistein can provide more references for the prevention and treatment of cardiovascular complications in clinical work.

Keywords: Genistein, Diabetes, Cardiovascular, Mechanism

1. Research Status

Diabetes Mellitus (DM) is a common metabolism-related disease and a common chronic disease among middle-aged and elderly people in the community. As of 2019, there were about 116 million adults with diabetes in China, significantly more than before [1]. Among diabetic patients, more than 90% are type 2 diabetes mellitus (T2DM), and the most harmful of its chronic complications is macrovascular complications, such as myocardial infarction, stroke, etc., which is the main cause of disability and death in Chinese patients with type 2 diabetes [2]. With anticipation improvements in quality of life, one of the main goals of scientific research is to combat the development of diseases as well as complications. Genetics Although plays a critical role, lifestyle, dietary habits, and physical activity play a fundamental role in the onset of these diseases as well.

Genistein is a phytoestrogen with a chemical structure of 4 ', 5,7-trihydroxyisoflavone, which is mainly distributed in soybeans and has received much attention in recent years due to its various biological and therapeutic properties [3]. Genistein is present almost exclusively in its glycosylated form in natural sources and only in the biologically active form following food processing. In mammals, it has both estrogen agonist and antagonist properties, as evidenced by synergy with endogenous hormones or induced conformational changes in estrogen, and thus can inhibit tyrosine kinase [4, 5]. And plays an important role in the treatment of hypertension, arteriosclerosis, osteoporosis and the regulation of postmenopausal symptoms [6, 7]. Because of its antioxidant properties, it also plays an important role in reducing deposition in adipose tissue and has also been used as a key molecule involved in the treatment of common diseases [3].

2. Mechanism of Action of Geinistein on Diabetic Cardiovascular Complications

2.1. Genistein and Vascular Endothelium

Cardiovascular complications are common in chronic macrovascular complications of diabetes mellitus. Atherosclerosis, as a key link in cardiovascular complications, is a vascular disease caused by multiple factors. Endothelial cell apoptosis is thought to be the initial step in atherosclerotic pathology and contributes to the formation and development of atherosclerotic lesions. Normal vascular endothelium maintains vascular homeostasis function by regulating vascular tone, regulating local cell growth and extracellular matrix deposition, and controlling homeostasis and inflammatory responses. Dysregulated endothelial cells recruit distinct inflammatory pathways, culminating in atheromatous plaques forming fat, collagen, and elastin with thin fibrous caps. Abnormal lipid metabolism in diabetic patients can cause fluctuations in blood glucose levels, which activate oxidative stress causing atherosclerosis [8, 9]. In cultured human umbilical vein endothelial cells, Genistein was present over a wide range of concentrations (10 nmol, 100 nmol, 1 μmo l or 10 μmol), Pretreatment with genistein (100 nmol) increased endothelial cell viability [10] compared with oxidized low-density lipoprotein, ox-LDL) treated groups.

2.2. Genistein and Platelet Aggregation

Thrombosis is responsible for high mortality cardiovascular diseases such as myocardial infarction and stroke, and platelets play an important role in the pathogenesis of these diseases. Previous studies have suggested that antiplatelet function may be exerted through cyclic adenosine -phosphate modulation, tyrosine kinase, calcium messenger, and thromboxane A2 (TXA2) pathway inhibition, while inhibition of TxA2- and collagen analogue-induced platelet aggregation [11, 12]. Nitric oxide (NO) plays a role in Genistein -induced inhibition of platelet aggregation, NO is an important endothelium-derived relaxing factor that relaxes blood vessels, and NO can also be released into the vascular lumen to inhibit platelet aggregation and adhesion to the vessel wall, Effective thrombosis prevention [13]. Meanwhile, nitric oxide synthase inhibitors inhibited Genistein platelet anti-aggregation in rat aortic strips [14]. In addition, NO also inhibits the proliferation of vascular smooth muscle cells by inhibiting the release of platelet-derived growth factor [15]. Thus, studies suggest that Genistein has an inhibitory effect on platelet aggregation, but the pathways involved need to be further defined.

2.3. Genistein and Lipid Deposition

Lipid deposition, particularly oxidative modified forms, plays an integral role in the development of cardiovascular complications. Genistein has previously been shown to significantly reduce low-density lipoprotein and total cholesterol [16]. In mice fed a high-fat diet (HFD), treatment with Genistein reduced body and fat pad weights after 6 weeks, and HFD-induced hyperlipidemia was ameliorated [17]. Genistein et al also could inhibit the differentiation of rat preadipocytes and stimulate lipolysis by activating hormone-sensitive lipase [17]. However, a study that included cholesterol from female rabbits fed ovariectomized found no significant effects of estrogen or serum total cholesterol levels [18]. In addition, Genistein also transforms synovial fibroblasts into adipocytes and enhances glucocorticoid-mediated lipogenesis of synovial fibroblasts [19]. Thus, while most experimental evidence suggests that Genistein is beneficial for lipid metabolism, few studies do not support these findings.

2.4. Genistein and Inflammation

Low grade inflammation is associated with atherosclerosis, and Genistein may influence the course of atherosclerosis by inhibiting vascular inflammation. Genistein prevents endothelial dysfunction induced by inflammatory factors and inhibits leukocyte-endothelial interactions [20]. Genistein reduces tumor necrosis factor- α, TNF - α) -induced secretion of monocyte chemoattractant protein-1, a cytokine that recruits leukocytes to sites of inflammation [21]. Genistein pretreatment reduced cytokine-mediated upregulation of leukocyte migration in blood in human brain microvascular endothelial cells [22]. Genistein also decreased mRNA expression levels of E-selectin, cell adhesion factor, and P-selectin triggered by pro-inflammatory bacteria [23]. Genistein also inhibits the activity of secretory phospholipase A2, a key inflammatory enzyme, in mice [24]. Thus, it supports anti-inflammatory effects in Genistein vascular endothelial cells and several other tissues.

2.5. Genistein and Oxidative Stress

Coronary arteriosclerosis is partly due to increased oxidative stress, reactive oxygen species (ROX) production and lipid peroxidation resulting in decreased bioavailability of nitric oxide. Estrogen alters ROS production and expression of scavenging enzymes and decreases oxidative stress in different cells [25]. In cultured human umbilical vein endothelial cells, Genistein inhibits glucose oxidation the potential of low-density lipoprotein to increase tissue factor synthesis [26]. Bcl-2 protein is essential for regulating cell proliferation and apoptosis under normal and oxidative conditions. Genistein prevented oxidative stress-induced apoptosis through regulation of estrogen beta and Bcl-2/Bax expression and cell survival signaling [27]. Gesintein restores endothelial cell function in men with spontaneous hypertension via estrogen receptor mechanisms independent mechanisms, via increased NO production and protection of NO from oxidative stress driven inactivation [28]. Phytoestrogens also increase levels of the antioxidant glutathione in VSMC [29]. Antioxidant effects of various phytoestrogens may vary in different tissues and cell types. Overall, studies support the antioxidant activity of phytoestrogens, which increases their potential benefits in CVD.

3. Summary

So far, there have been many studies on natural medicine inhibition of cardiovascular lesions, and most of them have reached a certain depth. An increasing number of scholars have focused on the biological properties of Genistein and conducted clinical trials to improve the course of disease activity in diabetic patients with cardiovascular disease. In this paper, we describe the biological characteristics and mechanism of action of Genistein in order to provide more reference for the prevention and treatment of cardiovascular complications in clinical work.

References

[1] Ma, R., Epidemiology of diabetes and diabetic complications in China. Diabetologia, 2018. 61 (6): p. 1249-1260.

[2] Chinese Guidelines for the Prevention and Treatment of Type 2 Diabetes (2013 Edition). Chinese Journal of Diabetes, 2014. 6 (07): 447-498.

[3] Weng L, Zhang F, Wang R, et al. A review on protective role of genistein against oxidative stress in diabetes and related complications [J]. Chem Biol Interact, 2019, 310: 108665.

[4] Ali F, Rahul, Naz F, et al. Protective effect of Genistein against N-nitrosodiethylamine (NDEA) hepatotoxicity in Swiss albino rats [J]. J Pharm Anal, 2015, 5 (1): 51-57.

[5] Zhang L, Gao M, Zhang T, et al. Protective Effects of Genistein against Mono- (2-hexyl) Phthalate-Induced Oxidative Damage in Prepubertal Sertoli Cells [J]. Biomed Res Int, 2017, 2017: 2032697.

[6] Chen C, Zheng H, Qi S. Genistein and Silicon Synergistic Protects Against Ovariectomy-Induced Bone Loss Through Upregulating OPG/RANKL Ratio [J]. Biol Trace Elem Res, 2019, 188 (2): 441-450.

[7] Xi Y D, Yu H L, Ma W W, et al. Genistein inhibits mitochondrial-targeted oxidative damage induced by beta-amyloid peptide 25-35 in PC12 cells [J]. J Bioenerg Biomet, 2011, 43 (4): 399-407.

[8] Lei X W, Li Q, Zhang J Z, et al. The Protective Roles of Folic Acid in Preventing Diabetic Retinopathy Are Potentially Associated with Suppressions on Angiogenesis, Inflammation, and Oxidative Stress [J]. Ophthalmic Res, 2019, 62 (2): 80-92.

[9] Li X, Ke X, Li Z, et al. Vaspin prevents myocardial injury in rats model of diabetic cardiomyopathy by enhancing autophagy and inhibiting inflammation [J]. Biochem Biophys Res Commun, 2019, 514 (1): 1-8.

[10] Zhang H P, Zheng F L, Zhao J H, et al. Genistein inhibits ox-LDL-induced VCAM-1, ICAM-1 and MCP-1 expression of HUVECs through heme oxygenase-1 [J]. Arch Med Res, 2013, 44 (1): 13-20.

[11] Liu M, Wang G, Xu R, et al. Soy Isoflavones Inhibit Both GPIb-IX Signaling and alphaIIbbeta3 Outside-In Signaling via 14-3-3zeta in Platelet [J]. Molecules, 2021, 26 (16).

[12] Kondo K, Suzuki Y, Ikeda Y, et al. Genistein, an isoflavone included in soy, inhibits thrombotic vessel aggregation in the mouse femoral artery and in vitro platelet occlusion [J]. Eur J Pharmacol, 2002, 455 (1): 53-57.

[13] Cyr A R, Huckaby L V, Shiva S S, et al. Nitric Oxide and Endothelial Dysfunction [J]. Crit Care Clin, 2020, 36 (2): 307-321.

[14] Polini N, Rauschemberger M B, Mendiberri J, et al. Effect of genistein and raloxifene on vascular dependent platelet aggregation [J]. Mol Cell Endocrinol, 2007, 267 (1-2): 55-62.

[15] Luksha L, Agewall S, Kublickiene K. Endothelium-derived hyperpolarizing factor in vascular physiology and cardiovascular disease [J]. Atherosclerosis, 2009, 202 (2): 330-344.

[16] Amerizadeh A, Asgary S, Vaseghi G, et al. Effect of Genistein Intake on Some Cardiovascular Risk Factors: An Updated Systematic Review and Meta-analysis [J]. Curr Probl Cardiol, 2021: 100902.

[17] Guo Y, Wu G, Su X, et al. Antiobesity action of a daidzein derivative on male obese mice induced by a high-fat diet [J]. Nutr Res, 2009, 29 (9): 656-663.

[18] Haines C, James A, Sahota D, et al. Comparison between phytoestrogens and estradiol in the prevention of atheroma in ovariectomized cholesterol-fed rabbits [J]. Climacteric, 2006, 9 (6): 430-436.

[19] Relic B, Zeddou M, Desoroux A, et al. Genistein adipogenesis but leptin induces apoptosis in human synovial fibroblasts [J]. Lab Invest, 2009, 89 (7): 811-822.

[20] Trompezinski S, Denis A, Schmitt D, et al. Comparative effects of polyphenols from green tea (EGCG) and proinflammatory cytokines (genistein) on VEGF and IL-8 release from normal human keratinocytes stimulated with the cytokine TNFalpha [J]. Arch Dermatol Res, 2003, 295 (3): 112-116.

[21] Gottstein N, Ewins B A, Eccleston C, et al. Effect of genistein and daidzein on platelet aggregation and monocyte and endothelial function [J]. Br J Nutr, 2003, 89 (5): 607-616.

[22] Lee Y W, Lee W H. Protective effects of genistein on proinflammatory pathways in human brain microvascular endothelial cells [J]. J Nutr Biochem, 2008, 19 (12): 819-825.

[23] Sandoval M J, Cutini P H, Rauschemberger M B, et al. The soyabean isoflavone genistein modulates endothelial cell behaviour [J]. Br J Nutr, 2010, 104 (2): 171-179.

[24] Dharmappa K K K, Mohamed R, Shivaprasad H V, et al. Genistein, a potent inhibitor of secretory phospholipase A2: a new insight in down regulation of inflammation [J]. Inflammopharmacology, 2010, 18 (1): 25-31.

[25] Wing L Y, Chen Y C, Shih Y Y, et al. Effects of oral estrogen on aortic ROS-generating and -scavenging enzymes and atherosclerosis in apoE-deficient mice [J]. Exp Biol Med (Maywood), 2009, 234 (9): 1037-1046.

[26] Exner M, Hermann M, Hofbauer R, et al. Genistein prevents the glucose autogenic oxidation mediated modification of low density lipoprotein [J]. Free Radic Res, 2001, 34 (1): 101-112.

[27] Xu S Z, Zhong W, Ghavideldarestani M, et al. Multiple mechanisms of soy isoflavones against oxidative stress-induced endothelial injury [J]. Free Radic Biol Med, 2009, 47 (2): 167-175.

[28] Vera R, Galisteo M, Villar I C, et al. Soy isoflavones improve endothelial function in spontaneously hypertensive rats in an estrogen-independent manner: role of nitric-oxide synthase, metabolites, and cyclooxygenase [J]. J Pharmacol Exp Ther, 2005, 314 (3): 1300-1309.

[29] Mizutani K, Ikeda K, Nishikata T, et al. Phytoestrogens attenuate oxidative DNA damage in vascular smooth muscle cells from stroke-prone spontaneously hypertensive rats [J]. J Hypertens, 2000, 18 (12): 1833-1840.