Review Article

**Vasoprotection by Dietary Supplements and Exercise: Role of TNFα Signaling**

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Vascular dysfunction contributes to the pathogenesis of various cardiovascular diseases. Dietary supplements, including fish oil, dietary fibers, and various natural products, and exercise training exert vasoprotective effects. However, the mechanisms underlying the vasoprotective benefits of dietary supplements and physical activity demand extensive investigation. Accumulating evidence suggests that inflammatory cytokine tumor necrosis factor-alpha (TNFα) plays a pivotal role in the dysregulation of macrovascular and microvascular function. TNFα induces vascular inflammation, monocyte adhesion to endothelial cells, vascular oxidative stress, apoptosis, and atherogenic response and participates in the regulation of thrombosis and coagulation through multiple signaling pathways involving NFκB, Sp1, activator protein 1, JNK, p38, STAT3, and so forth. Dietary supplements and exercise training decrease TNFα production and ameliorate TNFα-mediated pathological changes in vasculature. Thus, the inhibitory effects of dietary supplements and physical exercise on TNFα production and TNFα signaling may contribute to their vasoprotective properties.

1. Introduction

Endothelial dysfunction is an early indicator of cardiovascular diseases, including that seen in type 2 diabetes [1]. Accumulating evidence suggests that mediators of inflammation may be pathogenic by inducing vascular dysfunction [2]. Among the various inflammatory factors, tumor necrosis factor-alpha (TNFα) plays a pivotal role in the regulation of vascular function in various pathological status [3]. TNFα belongs to the TNF superfamily and is produced by many cell types, including macrophages, lymphocytes, and fibroblasts, and so forth [4–6]. TNFα can either exist in a membrane-bound form or be secreted as a soluble cytokine that is able to diffuse from the sites of its initial production [7]. It can bind to, and thus functions through its receptors, TNF receptor type 1 (TNFR1) and TNF receptor type 2 (TNFR2) [8]. Dietary supplements and exercise are emerging as effective adjunctive therapies targeting endothelial dysfunction and vascular wall inflammation [3, 9, 10]. This review summarized the vasoprotective effects of dietary supplements and exercises by inhibiting TNFα production and TNFα-induced signaling (Figures 1 and 2).

2. Dietary Supplements

During the past few decades, there has been renewed interest in dietary components that might favorably reduce risk of vascular dysfunction. Fish oil, dietary fiber, and various natural products have sparked intense interest in epidemiological studies. Extensive exploration of the underlying mechanisms of their healthy benefits became very important to develop new adjunctive therapies from those dietary supplements in order to delay or prevent the development of vascular disorders.

2.1. Fish Oil. Fish and other marine life serve as rich sources of a class of polyunsaturated fatty acids [11]. They are named as omega-3 or n-3 fatty acids because the first of the several...
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Figure 1: Dietary supplements (fish oil, dietary fiber, and various flavonoid and nonflavonoid natural products) exert vasoprotective benefits by inhibiting TNFα production and its downstream signaling pathways. There are dichotomies in the effects of exercise training on TNFα production. Whereas acute exercise has been reported to increase the production of proinflammatory cytokines, chronic exercise reduces TNFα levels.

Figure 2: Multiple mechanisms are involved in the vasoprotective effects of dietary supplements and exercise by inhibiting TNFα signaling.

double bonds occur three carbon atoms away from the terminal end of the carbon chain [11]. The three n-3 polyunsaturated fatty acids (n-3 PUFAs) include alpha linolenic acid (LNA), eicosapentenoic acid (EPA), and docosahexenoic acid (DHA) [12]. The role of fish oil lipids in regulating TNFα expression and TNFα-induced inflammation in vascular cells has been extensively studied in the past decades. Dietary supplementation with n-3 PUFAs improved endothelial function and reduced circulating level of TNFα in offspring of patients with type 2 diabetes [13]. Omega-3 fatty acid markedly suppressed the production of TNFα by monocytes in response to endotoxin. In addition, it also significantly inhibited both monocyte-endothelial adhesion and transendothelial monocyte migration [14]. One of the mechanisms by which fish oil alters the ability of lymphocytes to bind to endothelial cells may be its effects on inhibiting adhesion molecule expression induced by proinflammatory cytokines such as TNFα [15, 16]. Moreover, dietary fish oil resulted in a 50% reduction in concanavalin A (Con A), which enhanced lymphocyte adhesion to TNFα-stimulated endothelial cells [17]. EPA and DHA inhibited TNFα-induced monocyte adhesion to activated endothelial cells in vitro by affecting endothelial platelet-activating factor (PAF) generation [18]. Dietary fish oil supplementation inhibited TNFα production by human peripheral blood mononuclear cells [19]. Acute cod liver oil consumption reduced circulating level of TNFα and intercellular adhesion molecule-1 (ICAM-1) in healthy individuals [20]. These studies suggest that inhibition of inflammatory cell adhesion/migration induced by inflammatory cytokine TNFα may partially explain the protective effects of the fish-oil-rich diet against vascular inflammation.

2.2. Dietary Fiber. A high intake of fiber-rich carbohydrates might contribute to weight management and is beneficial for reducing the risk of cardiovascular diseases and diabetes. As a mucilaginous material prepared from the seed husk of plants of the Plantago genus, psyllium is an excellent source of mainly soluble fiber. Prolonged feeding of a 3.5% P. ovata husk-supplemented diet prevented endothelial dysfunction and the development of hypertension in obese Zucker rats. The diet also decreased body weight gain, reduced hyperinsulinemia and dyslipidemia, restored plasma adiponectin
concentration, and decreased circulating TNFa concentration [21]. In diabetic women, dietary intake of whole grain, bran, and cereal fibers decreased circulating C-reactive protein (CRP) and TNFR2 concentration [22].

2.3. Natural Products. There is a growing body of literature supporting the beneficial effects of natural products on optimal health and disease prevention. As a group of chemical substances found in plants, polyphenols are characterized by the presence of more than one phenol unit or building block per molecule. The health benefits of several specific polyphenols on vascular dysfunction are well established.

2.3.1. EGCG and other Flavonoid Polyphenolics. Flavonoids are most commonly known for their antioxidative and anti-inflammatory activity. Over 5000 naturally occurring flavonoids have been identified from various plants. Epigallocatechin gallate (EGCG), a green tea catechin, is the major component of green tea flavonoids. EGCG significantly attenuated the elevated TNFa levels and impaired vasodilator response to acetylcholine induced by low density lipoprotein (LDL) in a rat model [23]. EGCG decreases TNFa-induced fractalkine expression by suppressing nuclear factor-kappa B (NFkB) [24] and inhibited TNFa-induced monocyte chemotactant protein-1 (MCP-1) production and the activation of activator protein-1 (AP-1) in vascular endothelial cells via heme oxygenase-1 (HO-1) dependent mechanisms [25, 26]. Apigenin is a flavone that is the aglycone of apiin. Apigenin profoundly reduced monocytes adhesion to human umbilical vein endothelial cells (HUVECs) monolayer by suppressing TNFa-stimulated upregulation of vascular cell adhesion protein-1 (VCAM-1), ICAM-1, and E-selectin mRNA expression [27]. As a flavonol, quercetin downregulated TNFa-induced ICAM-1 and E-selectin expression in human endothelial cells [28-30]. Isoflavone genistein inhibited TNFa-induced apoptosis in human aortic endothelial cells as determined by caspase-3 activation, 7-amin actinomycin D staining, in situ apoptotic cell detection, and DNA laddering [31]. These studies provide a novel mechanism where flavonoids could provide direct vasoprotective benefits in inflammatory cardiovascular diseases by inhibiting TNFa and TNFa-induced inflammation.

2.3.2. Resveratrol and other Nonflavonoid Polyphenolics. For the last few decades, extensive work has been done to establish the biological activities and pharmacological actions of resveratrol and other nonflavonoid polyphenolics in protecting against vascular dysfunction in various disease states.

Resveratrol is a natural phytophenol that can be extracted from grape skins [32]. Epidemiological studies suggest that Mediterranean diet, which is rich in resveratrol, is associated with reduced risk of cardiovascular diseases [33]. Resveratrol ameliorated endothelial apoptosis by inhibiting TNFa-elicted increases in caspase-3/7 activity in endothelial cells and cultured rat aortas [34]. The protective effect of resveratrol was attenuated by the inhibition of glutathione peroxidase and HO-1, suggesting a role for antioxidant systems in the antiapoptotic action of resveratrol [34]. In addition to antiapoptotic effects, resveratrol inhibited TNFa-stimulated monocytes adhesion to endothelial cells [35]. The mechanism might be through inhibiting TNFa-induced NFkB activation and inflammatory gene expression [36]. Matrix metalloproteinases (MMPs) play an important role in extracellular matrix metabolism, which is a critical contributor to arterial pathology. Resveratrol dose-dependently suppressed TNFa-induced proliferation and expression of MMP-9 in vascular smooth muscle cells through the transcription factors NFkB and AP-1 [37]. Upregulated expression of fractalkine is associated with increased atherosclerotic lesion formation in apolipoprotein E−/− (ApoE−/−) mice [38]. Resveratrol strongly suppressed TNFa-induced fractalkine expression in endothelial cells through the suppression of NFkB and Sp1 transcription factor activities [39]. Resveratrol activates eNOS and increases muscle microvascular blood volume and flow via an NO-dependent mechanism, but systemic infusion of TNFa prevented resveratrol-induced muscle microvascular recruitment [40]. Therefore, resveratrol protected against TNFa-induced endothelial apoptosis, monocytes adhesion, cell proliferation, atherogenesis, and dysregulation of vasomotor function through multiple signaling pathways. Resveratrol also suppressed plasma TNFa concentration following inflammatory stimulation by lipopolysaccharide (LPS) [41] and modulates vascular TNFa expression [42]. Aortic TNFa expression was significantly increased in type 2 diabetic mice, accompanied by impaired endothelium-dependent vasorelaxation. Chronic resveratrol treatment improved endothelial function and reduced vascular TNFa expression [42]. Both anti-TNFa treatment and resveratrol markedly inhibited the NFkB pathway through suppressing inhibitor of NFkB (IkB) protein phosphorylation [42, 43], and significantly attenuated vascular oxidative stress and improved NO production. Thus, resveratrol mediated vasculoprotective effects by inhibiting TNFa expression and TNFa-induced signaling pathway.

Curcumin is another important natural polyphenol. It inhibited TNFa-mediated adhesion of monocytes to endothelial cells by suppression of cell surface expression of adhesion molecules and of NFkB activation [44, 45]. The mechanism was through inhibiting TNFa-induced IkBα degradation and the nuclear import of NFkB. In contrast, curcumin inhibited AP-1 by direct interaction of curcumin with AP-1 binding to its DNA binding motif, therefore, reduced the expression of endothelial tissue factor (TF), the central mediator of coagulation [46]. Thrombomodulin (TM) functions as a cofactor in the thrombin-induced activation of protein C in the antithrombotic pathway. Curcumin effectively blocked TNFa-induced downregulation of TM and endothelial protein C receptor (EPCR) at both mRNA and protein levels in several human endothelial cells [47]. Curcumin also reduced the intracellular reactive oxygen species (ROS) levels, phosphorylation of c-Jun N-terminal kinases (JNK), p38 mitogen-activated protein kinases (p38), and signal transducer and activator of transcription-3 (STAT3), and the expression of ICAM-1, MCP-1, interleukin-8 (IL-8), and lectin-like oxidised LDL receptor-1 (LOX-1) in TNFa-stimulated HUVECs [48, 49].
In summary, the anti-inflammatory, antithrombotic, anti-apoptotic, and antioxidative effects contribute to the health benefits of those nutritional supplements, which protect against vascular damage at least partially by decreasing TNF-α production and inhibiting TNF-α-mediated pathological changes through multiple signaling pathways.

3. Exercise

There are dichotomies in the effects of exercise on the production of inflammatory cytokines. A cross-sectional study suggested that inflammatory markers, such as CRP, IL-6, and TNF-α, were lower in older adults with higher levels of exercise and nonexercise activity and in antioxidant supplement users regardless of exercise level [50]. However, a study using treadmill running mice showed that exercise could increase plasma IL-6 concentrations and lung TNF-α mRNA expression [51]. This dichotomy may be attributed to the intensity of exercise. Chronic heart failure is associated with increased levels of TNF-α and markers of endothelial damage, including soluble ICAM-1 (sICAM-1) and E-selectin. Whereas acute bouts of exercise lead to an increase in proinflammatory cytokines and markers of endothelial damage; these effects were not seen when exercise was performed chronically in chronic heart failure patients [52]. A 10-week moderate intensity exercise training improved coronary arteriolar endothelial function and reduced TNF-α level in the myocardial tissue homogenate of type 2 diabetic mice [53]. Interestingly, diet plus exercise training may exert remarkable benefits when either diet or exercise alone could not demonstrate evident benefits. In obese postmenopausal women, diet plus exercise, but not diet alone, decreased plasma levels of CRP, IL-6, sIL-6R, and sTNFR1 and increased basal and postreceptor stimulated lipolysis in both abdominal and gluteal regions [54]. After eccentric exercise in untrained men, Omega-3 fatty acids supplementation attenuates plasma TNF-α level [55]. These results suggest that diet supplementation in exercise training is effective in reducing chronic inflammation.

4. Perspectives

It is of interest to notice that nutrition and exercise have almost always been studied separately although they are closely related and may amplify each other to maximize their beneficial effects. Studies of diet/dietary supplements plus exercise training in animals and human beings would be meaningful to explore the mechanisms of dietary supplements and exercise in protecting against vascular dysfunction and the involvement of TNF-α signaling.

5. Concluding Remarks

In conclusion, TNF-α is known to amplify several signaling pathways leading to vascular inflammation, apoptosis, oxidative stress, and thrombosis, which are key mediators in the pathogenesis of vascular dysfunction. Dietary supplements and/or exercise decrease TNF-α level and inhibit TNF-α-mediated pathological changes through multiple signaling pathways, whereby exerting vasoprotective benefits. We believe that further investigations in this exciting field would facilitate the development of dietary supplements and exercise as adjunctive therapies in the management of cardiovascular diseases.

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