ROLE OF INFLAMMATION IN DEVELOPMENT OF DIABETIC COMPLICATIONS AND COMMONLY USED INFLAMMATORY MARKERS WITH RESPECT TO DIABETIC COMPLICATIONS

ARCHANA M. NAVALE, ARCHANA N. PARANJAPE


Email: archanachavan_83@yahoo.co.in

Received: 26 Nov 2012, Revised and Accepted: 05 Jan 2013

ABSTRACT

Diabetes mellitus has been a major health concern since several past decades. Cases of Type 1 as well as types 2 diabetes are increasing day by day. With the immense advancement in pharmaceutical sciences the disease management has become fairly satisfactory. Good new drug therapeutic approaches are available, which makes it possible to keep the patient free from episodes of hyperglycemia or hypoglycemia for many years. With this the concern has shifted to the long term complications of diabetes. The major morbidity caused in the diabetic patients is due to dysfunction of several organ systems after a few years of having diabetes. Research has now clearly proved that these organ dysfunctions have their roots in diabetic pathophysiology. Many components of this pathophysiology have been identified. These components work interdependently with each other. One of the important factors identified is inflammation, which embraces the mechanisms like oxidative stress, neovascularization, apoptosis, cellular proliferation etc. It has been shown that inflammation plays an important role in microvascular as well as macrovascular complications of diabetes. There is a need of experimental work to be done for evaluating drugs for their effectiveness in protecting against inflammatory processes of diabetic complications. However, very less literature is available about methods used for evaluation of inflammation in diabetic complications. In this review we focus on role of inflammation in various diabetic complications followed by common inflammatory markers used by researchers in various studies on diabetic complications.

Keywords: Diabetic complications, Inflammation, Anti inflammatory activity

INTRODUCTION

Diabetes mellitus, especially type-2 diabetes, is a public health problem which has reached epidemic proportions due to the rapidly increasing rates of this disease worldwide. Target organ complications, secondary to diabetes, are one of the most important medical concerns of the present time. Inflammation is a protective mechanism of body. However, in chronic diseases like, diabetes mellitus, hypertension, asthma etc. this protective mechanism becomes an important mechanism for progression of disease. Interleukin (IL)-1β is a pro-inflammatory cytokine involved in autoimmune process of Type 1 diabetes. In Type 2 diabetes mellitus the decreasing β cell mass is also associated with glucose toxicity mediated through IL-1β induced apoptosis. There are many studies emphasizing the presence and importance of inflammatory component in the pathogenesis of Diabetes mellitus. A very important role is played by adipose tissue, which releases various pro-inflammatory cytokines, such as, tumor necrosis factor-alpha (TNF-α), interleukin-1 (IL-1) and interleukin-6 (IL-6) [1]. Recent studies have shown that inflammation, and more specifically pro-inflammatory cytokines, play a determinant role in the development of microvascular diabetic complications. This article takes an overview of importance of inflammation in various diabetic complications followed by a brief account of the commonly used inflammatory markers in various studies on diabetic complications.

INFLAMMATION IN RETINOPATHY

A major pathology of Diabetic retinopathy (DR) is microvascular complications such as non-perfused vessels, microaneurysms, dot/blot hemorrhages, cotton-wool spots, venous beading, vascular loops, vascular leakage and neovascularization. DR is characterized as a microvascular complication of diabetes [2, 3]. Alterations in blood flow, death of retinal pericytes (perivascular contractile cells) and basement membrane thickening accompanied by subtle increases in vascular permeability are the early events of this pathology. In later stages, further alterations in the vascular structure occur, such as, non-perfused vessels, microaneurysms, dot/blot hemorrhages, cotton-wool spots, venous beading, vascular loops and significant vascular leakage [4]. The non-proliferative stage of DR includes increased vascular permeability, macular edema and subsequent visual impairment. The proliferative stage of DR is characterized by neovascularization on the retinal surface because of impaired vascular function by capillary occlusion. In this stage, severe visual impairment or even blindness may be caused by bleusing, hemorrhage and subsequent retinal detachment because of the newly formed fragile vessels [5].

Inflammation is also a cause of retinal vascular leakage. The microvascular endothelium serves a barrier to control the movement of blood, fluid and proteins across the vessel wall [6] due to its tight junctions and adhesion junctions that join endothelial cells to each other. Various signaling molecules such as, pro-inflammatory cytokines and chemokines induce disorganization/redistribution of junction proteins in the retinal endothelium. This leads to Structural and functional breakdown of this barrier, resulting in an abnormal extravasation of blood components causing retinal edema. TNF-α leads to downregulation of tight junction proteins mediated via PKCζ, resulting in significant retinal endothelial permeability within a few hours [7].

Legend: ICAM-1: intercellular adhesion molecule-1, VCAM-1: vascular cell adhesion molecule-1, iNOS: Inducible form of Nitric oxide synthase, TNF-α: Tumor necrosis factor α, IL-1β: Interleukin 1 β, IL-6: Interleukin 6, NF-κB: Nuclear factor-κB, AGE: advanced glycation end products, ETC: mitochondrial electron transport chain, NADPH oxidase: nicotinamide adenine dinucleotide phosphate oxidase.

Mechanisms leading to capillary degeneration involve endothelial cell death induced by inflammatory cytokines such as, TNF-α and IL-1β. These cytokines increase caspase 3 activity inducing endothelial cell apoptosis [7,8]. Capillary occlusion in DR is mainly due to leukostasis. Leukocytes block blood flow because of their large cell volume and high rigidity. Several studies have shown that transient leukocyte attachment to the vessel wall correlates with capillary non-perfusion, and capillary perfusion may occur when leukocytes detach and move on [9]. In addition to blocking blow flow, leukocytes induce endothelial cell death during leukostasis via Fas ligand (FasL) and Fas-mediated apoptosis [10].

Inflammation also has an important role in pathological neovascularization in DR. Cytokines released in inflamed retinal tissue...
recruits various leukocytes, which release various angiogenic factors and increase the activity of matrix metalloproteinase. This results in formation of new vasculature in inflamed retinal tissue [11]. Figure 1 summarizes the inflammatory process in Diabetic retinopathy (DR).

Fig. 1: It shows the cascade of events that contribute to the inflammatory response in diabetic retinopathy [4].

INFLAMMATION IN DIABETIC NEPHROPATHY (DN)
Several studies have suggested a relationship between pro-inflammatory cytokines and DN mainly, IL-1, IL-6, IL-18, TNF-α and TGF-β1 [12, 13]. Endothelial, mesangial, glomerular and tubular epithelial cells synthesize various pro-inflammatory cytokines, which are implicated in pathologic processes of DR. Interleukin-1 enhances proliferation of mesangial cells and matrix synthesis, increases vascular permeability, leading to the development of intraglomerular microcirculatory abnormalities [14,15]. It also alters the expression of chemoattractant factors and adhesion molecules. It alters intraglomerular hemodynamics by affecting mesangial cell prostaglandin synthesis [16]. Interleukin-6 has strong association with mesangial cell proliferation, increase in fibronectin expression and enhanced endothelial permeability [17, 18]. IL-18 induces the production of other inflammatory cytokines, such as IL-1, interferon γ and tumor necrosis factor, and might be associated with endothelial cell apoptosis [19].

TNF-α has important implications in inflammatory processes of DN. Studies have demonstrated enhanced expression of TNF-α mRNA in kidneys of diabetic rats [20, 21]. Due to its cytotoxic action towards glomerular, mesangial and epithelial cells, TNF-α may induce significant renal damage [22]. The harmful effect of TNF-α on the protein permeability barrier of the glomerulus is independent from alterations in haemodynamic factors or effects on recruited inflammatory cells [23]. TNF-α has been suggested as a critical factor for important renal alterations that occur during the initial stage of DN e.g. sodium retention and renal hypertrophy [24]. It has also been demonstrated that increased urinary and renal interstitial concentrations of TNF-α precede the occurrence of albuminuria [25]. A significant relationship has been observed between serum levels of TNF-α and urinary protein excretion in diabetic patients with normal renal function as well as in subjects with overt nephropathy and renal failure [12, 13]. This indicates that the deleterious effects of TNF-α begin very early in the process of diabetic nephropathy. Thus, it may serve as trigger for many inflammatory mechanisms. Apart from this it may also have a perpetuating role in the progression of pathology as it has been shown that there is a significant rise of urinary TNF-α excretion as DN progresses.

There is an increased expression of TGF β1 in glomeruli of streptozotocin induced diabetic animal [26]. There is clear evidence indicating the contribution of TGF β1 to cellular hypertrophy and increased synthesis of collagen, which have fibrogenic effects in kidneys leading to thickening of glomerular basement membrane observed in diabetic nephropathy [26-29]. The important role of TGF β1 is indicated by amelioration of DN in mice by administration of hepatocyte growth factor which specifically blocks profibrotic action of TGF β1[30].

INFLAMMATION AND DIABETIC NEUROPATHY
Diabetic neuropathy develops as a result of local metabolic, enzymatic and microvascular changes induced by hyperglycaemia.
INFLAMMATION AND MACROVASCULAR COMPLICATIONS

Several studies have shown an association between inflammatory markers and increased incidence of cardiovascular disease in diabetic patients. Extravascular or intravascular proinflammatory conditions such as oxidized LDL, advanced glycosylation end-products (AGE), or chronic infection lead to increased production of proinflammatory cytokines such as interleukin-1 (IL-1), TNF, and IL-6. These in turn influence all processes of atherogenesis with no induced diabetes show increased inflammatory response as markers of endothelial dysfunction and preservation of the nerve

INFLAMMATORY ACTIVITY WITH RESPECT TO DIABETIC COMPLICATIONS

Determination of inflammatory markers is an important parameter used by various preclinical and even clinical studies. Estimation of various cytokine levels or their upstream or downstream mediators is the mostly widely used approach.

PKC-β1 and 2 are chiefly responsible for the deleterious effects on retinal, neural, and renal tissues. These isoforms impair retinal and renal blood flow and increase capillary leakage. PKC-induced increased extracellular matrix production and upregulation of various inflammatory cytokines further damage the macro and microvascular systems [39]. Tsai et al determined glnomerular PKC activity in inflammatory nephropathy, and the data demonstrated an increased expression of NFκB and an increased secretion of TNF-α, IL-1, and IL-6. These in turn influence all processes of atherogenesis.

It has been clearly indicated that chronic subclinical inflammation is a part of insulin resistance syndrome [45]. Drugs which are effective in dampening such subclinical inflammation may provide protection against development of diabetic complications, which may be reflected partly as a protection provided by drug in experimental models of inflammation. Fateh et al, has studied effects of Genistein, a tyrosine kinase Inhibitor on acute and chronic inflammation in STZ-induced diabetic mice. Carrageenan-induced paw edema in mice is used as model of acute inflammation, while chronic inflammation is produced by cotton pellet induced granuloma in mouse [46]. Mice with no induced diabetes show increased inflammatory response as compared to normal mice because of ongoing inflammation in the tissues. Chronic treatment with drug hampers the process of inflammation, which may be reflected as effectiveness in these experimantal models.

CONCLUSION

Diabetic complications are the concern for health system in today’s scenario. Different diabetic complications have significantly higher prevalence in developing countries like India. As a need for developing antidiabetic drugs which may also protect against diabetic complications is necessary. It is important to understand the pathophysiological mechanisms involved in them. Many factors have been identified, and studied, of which inflammation is the major one. However, methods available for study of anti inflammatory activity with respect to diabetic complications are very few. There is a need to develop simple model which represents inflammation of diabetic complications to gear up drug discovery in this area.
REFERENCES


