Tumor Necrosis Factor-α Triad: Psoriasis, Cardiovascular Disease, and Depression

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INTRODUCTION

Tumor necrosis factor-α (TNF-α) is a cytokine for which the precursor protein can be synthesized by activated macrophages, T cells, and dendritic cells. This precursor protein is eventually cleaved to release the soluble, mature form of TNF-α. TNF-α, formerly known as “cachexin,” was originally described in 1975 for its ability to lyse tumors in mouse models.1 TNF-α acts by binding to either TNF receptor 1 or TNF receptor 2, which are also known as p55 and p75, respectively.2,3 (Figure 1). It has been shown that these TNF receptors have multiple immune effects, which include the following: (1) stimulation of the release of other inflammatory cytokines (i.e., interleukin-6 and interleukin (IL)-8), (2) upregulation of the expression of endothelial adhesion molecules and chemokines, and (3) coordination of the migration of leukocytes to targeted organs.4 Because of its immune and inflammatory functions, it is not surprising that TNF-α production has been shown to be elevated in chronic inflammatory diseases, such as psoriasis,5 psoriatic arthritis,6 rheumatoid arthritis,7 and inflammatory bowel disease.8

Perhaps the most commonly known skin condition associated with TNF-α is psoriasis, which is a chronic skin condition that affects ≈2.5% of the world population.9 It is believed to be driven by immune cells (specifically T cells) and inflammatory cytokines (i.e., TNF α, IL-6, and interferon (IFN)γ). More recently, psoriasis has been suggested to be a systemic inflammatory disease that is associated with an increased risk of cardiovascular diseases (i.e., MI10,11 or cardiac death12), stroke,10,13 peripheral vascular disease,14 type 2 diabetes mellitus,14,15 and

ABSTRACT

Tumor necrosis factor-α (TNF-α) plays an intricate role in immune defense mechanisms. Over the past decades, studies have demonstrated that inflammatory cytokines, such as TNF-α and interleukin-6, may play an important role in the pathophysiology of psoriasis and depression. More recently, studies suggested an additional association of TNF-α with cardiovascular disease, which has attracted much attention. People with psoriasis, cardiovascular disease (i.e., heart failure or myocardial infarction [MI]), and depression have been found to have higher levels of proinflammatory cytokines, especially TNF-α. This article reviews the roles of TNF-α in psoriasis, cardiovascular disease, and depression.

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metabolic syndrome\textsuperscript{16,17} (associated with obesity, dyslipidemia, hypertension, and impaired fasting glucose). Patients with psoriasis can also experience a negative psychosocial impact in their lives. In fact, a landmark study by Rapp et al\textsuperscript{18} showed that the quality of life in patients with psoriasis is comparable with that of other major chronic medical conditions, such as breast cancer, heart disease, and type 2 diabetes mellitus. Furthermore, studies reported that >30\% of patients with psoriasis have clinical depression.\textsuperscript{19–22} A cohort study using medical electronic data collected from 1987 to 2002 showed that the adjusted hazard ratio for receiving the diagnosis of depression is higher in patients with severe psoriasis compared with mild psoriasis.\textsuperscript{23} For these reasons, patients with psoriasis appear to have an increased risk for cardiovascular diseases and depression. In view of the association among psoriasis, increased risk of cardiovascular disease, and depression, it is reasonable to hypothesize that the connection is related to elevated TNF-\(\alpha\) levels (\textbf{Figure 2}). This article reviews the currently available literature exploring the relationship between TNF-\(\alpha\) and the previously described medical conditions.

\section*{RESULTS}

\subsection*{Roles of TNF-\(\alpha\) in Psoriasis}

Psoriasis is characterized by hyperproliferation of keratinocytes and abnormal cell differentiation, which leads to epidermal hyperplasia.\textsuperscript{24} Psoriasis also has a dense inflammatory infiltrate of immune cells and vascular dilation seen on histology.\textsuperscript{25} TNF-\(\alpha\) has been suggested to play several roles in the pathogenesis of psoriasis, which include the following: (1) stimulation of skin immune responses (inflammatory cell trafficking, antigen presentation, and apoptosis), (2) epidermal growth, and (3) vascular proliferation\textsuperscript{26,27} (\textbf{Figure 3}). It is believed that TNF-\(\alpha\) works synergistically with other cytokines to promote the pathogenesis of psoriasis. In fact, it is suggested that the development of psoriasis depends on the presence of TNF-\(\alpha\).

\subsection*{Level of TNF-\(\alpha\) in Psoriasis}

Multiple studies have reported a significant TNF-\(\alpha\) elevation in serum\textsuperscript{28–32} and lesional skin\textsuperscript{33–38} in psoriatic patients compared with the healthy controls. Furthermore, research has demonstrated that the removal of the circulating serum TNF-\(\alpha\) resulted in decrease numbers of T cells and a reduction of epidermal hyperplasia in psoriatic
These data support that psoriasis is an immune-mediated inflammatory process.

Benefits of TNF-α Antagonists on Psoriasis
The inflammatory role of TNF-α in psoriasis has made it a potential target for therapeutic blockade. Studies demonstrated significant clinical improvement of psoriasis after treatment with a TNF-α antagonist. Subsequent to these supportive studies, the US Food and Drug Administration approved the use of systemic TNF-α antagonists, such as etanercept (Enbrel), infliximab (Remicade), and adalimumab (Humira) for the treatment of psoriasis.

Caldarola et al. conducted a prospective study on 12 psoriatic patients and evaluated the production and expression of TNF-α and its receptors before and after treatment with etanercept (Enbrel), a fusion protein TNF-α antagonist. After 3 months of etanercept 50-mg weekly treatment, participants showed a marked reduction in the level of TNF-α and its receptors (p55 and p75) in both the lesional and nonlesional skin samples. In this study, Etanercept appeared to act not only on stable lesional plaques but also on the early stage of the disease with effects on nonlesional skin.

Studies have suggested an association between TNF-α level and the severity of psoriasis measured by the Psoriasis Area Severity Index (PASI). For instance, Mussi et al. showed that both PASI scores and the serum TNF-α levels were decreased after effective treatment of the psoriasis. In addition, TNF-α in lesional psoriatic skin has been demonstrated to decrease after effective therapy with infliximab. However, there are a few studies that did not support this observation. Mastroianni et al. showed a decreased serum TNF-α level after 12 weeks of infliximab, but it did not correlate with PASI scores. Similarly, Arican et al. could not demonstrate a correlation between high serum levels of TNF-α with PASI scores in psoriatic patients. Instead, they found that levels of cytokines IFN-γ, IL-12, and IL-18 correlated with the PASI score, and these have been suggested to be used as follow-up markers to monitor psoriatic patients.

Roles of TNF-α in Cardiovascular Disease
There is evidence that inflammatory cytokines (i.e., TNF-α, IL-1β, and IL-6) are involved in the cardiac remodeling process, which includes hypertrophy, fibrosis, and apoptosis. Bozkurt et al. showed that systemic administration of TNF-α promoted progressive cardiac dysfunction, such as dilated cardiomyopathy, in mouse models. Likewise, a study by Kubota et al. showed that cardiac-specific overexpression of TNF-α promotes cardiac hypertrophy, ventricular dilation, and fibrosis in transgenic mice. Thus, elevated TNF-α seems to play a role in heart failure patients.

Level of TNF-α in Cardiovascular Disease
Several studies have shown elevation of TNF-α, as well as IL-1β and IL-6, in both the plasma and circulating leukocytes levels of heart failure patients. Similarly, Cesar et al. showed an elevation of serum IL-6 and TNF-α in patients with clinical cardiac disease (i.e., diagnosis of congestive heart failure, coronary artery disease, peripheral artery disease, or stroke), as well as subclinical cardiac disease (i.e., positive findings on questionnaire for angina or claudication, ankle-brachial index <0.9, or electrocardiogram abnormalities). In this study, only TNF soluble receptor 1 (p55) showed a significant association with clinical cardiovascular disease.

The serum level of inflammatory cytokines, such as TNF-α, appears to have a direct correlation with the function of heart disease, as categorized by the New York Heart Association classification, and

Figure 3. The effects of tumor necrosis factor-α (TNF-α) in psoriasis. TNF-α has an effect on the endothelium, dendritic cells, and keratinocytes in promoting the pathogenesis of psoriasis. IL indicates interleukin.
cardiac performance, as measured by left ventricular ejection fraction (LVEF). A study has also shown an increased TNF-α level within the failing myocardium. Patients experiencing acute-phase MI also demonstrate increased production of TNF-α. This moderate elevation of TNF-α in response to the acute myocardial injury is considered to be essential in wound repair, scar formation, and compensatory hypertrophy. However, it has been suggested that persistent elevation of inflammatory response could contribute to the pathogenesis of heart failure.

**TNF-α Antagonists on Cardiovascular Disease**

Not surprisingly, researchers have used therapeutic measures to target TNF-α, given its significant role in the pathogenesis of cardiovascular disease. Initially, etanercept seemed to have beneficial effects in heart failure patients. However, subsequently a large study consisting of 1500 patients with symptomatic heart failure and LVEF <30% showed no effect on mortality or hospitalizations after treatment with etanercept. With regard to infliximab, a monoclonal antibody that binds to human TNF-α, Chung et al. showed higher rates of mortality and hospitalization in 150 patients with symptomatic heart failure and LVEF <35% after infliximab treatment. This was especially true in the high-dose infliximab group, 10 mg/kg, which is a dose higher than that used in psoriasis and rheumatoid arthritis. Consequently, the clinical trial on congestive heart failure was stopped prematurely because of this preliminary finding.

Abuabara et al. conducted a cohort study with 25,554 psoriatic patients who received systemic therapy (methotrexate, cyclosporine, alefacept, efalizumab, adalimumab, etanercept, or infliximab) and suggested that there does not seem to be a reduced risk of MI after systemic therapy. These individuals were compared with the control group, who only had phototherapy treatment. The risk ratio was age dependent (i.e., patients aged ≥50 years had higher risk), and the conclusion was based on all of the systemic therapies grouped together in the study. On the other hand, another retrospective cohort study showed that use of a TNF-inhibitor (etanercept, infliximab, or adalimumab) for patients with psoriasis or psoriatic arthritis was associated with a 55% reduction in the incidence of MI compared with patients who only used topical therapy. After adjusting for MI risk factors (i.e., common characteristics and medications that may affect MI risk), the use of TNF inhibitors was associated with 50% lower hazard of incident MI (95% confidence interval, 0.32–0.79) compared with the use of topicals. The median duration of anti–TNF-α therapy was 1.9 years. This study showed that treatment with TNF inhibitors, female sex, treatment with statin, and age <65 years seemed to have a protective effect, whereas patients with type 2 diabetes mellitus, dyslipidemia, hypertension, and psoriatic arthritis seemed to have an increased risk of MI.

A study conducted by Boehncke et al. showed that 25 psoriatic patients who received systemic therapy (fumaric acid esters n = 171, cyclosporine n = 21, methotrexate n = 31, etanercept n = 151, adalimumab n = 41, or ustekinumab n = 11) demonstrated improvement of PASI score with reduction of biomarkers of cardiovascular risk (e.g., high-sensitivity C-reactive protein [hs-CRP], vascular endothelial growth factor, and resistin serum levels) after 24 weeks of systemic therapy mentioned above. For this reason, study authors suggested a potential cardioprotective effect of appropriate continuous anti-inflammatory therapy in psoriatic patients.

**Roles of TNF-α in Depression**

Over the past decades, studies have suggested that TNF-α and other inflammatory cytokines may play a key role in the pathogenesis of depression, a concept known as the “macrophage theory,” formulated by Smith in 1991. There are 3 hypothesized mechanisms to explain how cytokines may lead to depression (Figure 4). The first hypothesis is that cytokines, for example, TNF-α, activate the hypothalamic-pituitary-adrenal system, which would lead to an increase in stress hormone cortisol level that is frequently elevated in depressed patients. The second hypothesis is that cytokines might stimulate serotonin uptake by activating neuronal serotonin transporters, which would lead to serotonin deficiency. This finding operates on the theory that serotonin deficiency is an essential contributor to presentation of depressive symptoms. In this model, selective serotonin reuptake inhibitors (SSRIs) treat depression via antagonism of serotonin transporters. The third hypothesis is that cytokines may stimulate indoleamine 2,3-dioxygenase, which subsequently leads to tryptophan depletion. The amino acid tryptophan is the precursor for serotonin.
Figure 4. Tumor necrosis factor-α (TNF-α) in depression. Potential pathways through which TNF-α may play a part in the pathogenesis of depression. HPA indicates hypothalamic pituitary adrenal; IDO, indoleamine dioxygenase.

synthesis in the brain; therefore, this will eventually lead to serotonin depletion.

Level of TNF-α in Depressed Individuals
Patients with depression but lacking other inflammatory disorders have been observed to exhibit elevated concentrations of TNF-α and other cytokines (IL-1, IL-6, and CRP) in their blood. This is supported by Dowlati et al.69 who conducted a meta-analysis of 24 studies measuring cytokine concentrations in patients with depression. The study reported significantly higher plasma concentrations of TNF-α and IL-6 in depressed patients as compared with nondepressed patients. Similarly, patients who attempted suicide also have increased levels of TNF-α and IL-6 serum concentrations, as compared with nonsuicidal depressed patients and healthy controls.70 In addition, a cross-sectional analysis conducted by Moorman et al.71 showed a significantly higher level of soluble TNF-α receptor 1 (p55) in heart failure patients with depression compared with nondepressed heart failure patients.

Nevertheless, there are also a few studies that did not show an association between depression and serum TNF-α level. For instance, Brambilla et al.72 reported no alteration in TNF-α level in elderly women with depression. Similarly, Wang et al.73 showed no elevation of TNF-α level in patients with depression and chronic low back pain.

Potential Benefits of TNF-α Antagonists on Depression
Because TNF-α appears to play a role in the pathogenesis of depression, one might question whether a TNF-α antagonist could augment treatment of clinical depression. Multiple studies have investigated this hypothesis, especially in relation to psoriatic patients, because TNF-α antagonists are already US Food and Drug Administration–approved treatments for the management of psoriasis. Tyring et al.74 found that a greater proportion of psoriatic patients receiving etanercept had ≥50% improvement in depression at week 12 compared with those in the placebo group. A study conducted by Feldman et al.75 also documented that patients treated with infliximab had significant improvement, both physically and mentally, after 10 weeks of infliximab therapy using the 36-item Short-Form Health Survey and the Dermatology Life Quality Index. Furthermore, Menter et al.21 showed a significant improvement in the depression score measured by the Zung Depression Scale after 12 weeks of adalimumab therapy in patients with psoriasis. This improvement in depression is positively associated with clinical improvement measured by PASI 75. In fact, psoriatic patients achieving ≥75% improvement from baseline PASI score have a greater reduction in Zung Depression Scale score compared with patients achieving <75% improvement from baseline PASI score. A recent study conducted by Thorslund et al.75 showed a positive correlation (r = 0.53; P < .05) between PASI and the numbers of serotonin transporter protein–positive dendritic cells in the epidermis of involved psoriatic skin. As such, it was suggested that the serotonergic system in the skin may be involved in the chronic inflammation of psoriatic skin.

Association of TNF-α Level and Antidepressive Treatments
Interestingly, studies have also suggested a connection between antidepressive treatments and inflammatory cytokines. To demonstrate this hypothesis, Tuglu et al.76 measured TNF-α in 26 patients with depression before and after 6 weeks of SSRI treatment. During the pretreatment phase, the TNF-α level was higher in patients with depression compared with the control group. After 6 weeks of SSRI treatment, the level of TNF-α in the depression group was comparable with those of the control group. In addition, Hestad et al.77 examined serum levels of TNF-α in 15 healthy control patients compared with 15 depressed patients before, during, and after electric convulsive therapy (ECT). Serum TNF-α level was...
also measured in depressed patients not receiving ECT. Results showed that the TNF-α level was increased in patients with depression compared with the controls. Moreover, clinical improvement with repeated ECT treatments correlated with a significant decline in TNF-α level, which became similar to the healthy controls. This decline was not seen in depressed patients who were not receiving ECT. These studies suggest that SSRIs and ECT may downregulate the inflammatory response system.

DISCUSSION
In psoriasis, TNF-α has been identified as an important cytokine in the inflammatory cascade leading to the pathogenesis. Most studies have shown an elevated level of TNF-α in psoriatic patients. Although there are some conflicting data, there may be an association between TNF-α and the severity of psoriasis. In terms of treatment, the TNF-α antagonist is one of the most efficacious agents in treating psoriasis besides the Goeckerman therapy, which is a combination of ultraviolet B phototherapy and topical application of tar and topical steroids.

In cardiovascular disease, it is becoming more evident that TNF-α plays an important role. However, the exact mechanism of TNF-α affecting cardiovascular disease directly or indirectly is still unclear. Although it is contraindicated to use anti-TNF-α in patients with congestive heart failure classified as grade III to IV by the New York American Heart Association, it is not contraindicated in other heart diseases. In fact, there may be a potential cardioprotective benefit with the use of anti-TNF-α. In support of this view, a recent nationwide Danish cohort study demonstrated that patients with severe psoriasis treated with biological agents and methotrexate were associated with lower rates of death, MI, and stroke, as compared with those treated with other therapies. Studies have demonstrated that the use of anti-TNF-α may lower CRP level, an inflammation biomarker that indicates cardiovascular risk, which is also elevated in psoriasis. This possible cardioprotective effect of anti-TNF-α might be attributed to the lowering of TNF-α, lowering of CRP, or both. It may very well be that decreasing inflammation, in general, could be beneficial in heart disease conditions. In addition, TNF-α may also play an important role in insulin regulation, body weight homeostasis, and lipid metabolism, which are some of the main components of metabolic syndrome. Some studies suggested that patients with rheumatoid arthritis have an improvement in insulin resistance and sensitivity after anti-TNF-α therapy. Therefore, if anti-TNF-α therapy can provide a beneficial effect on metabolic syndrome, then this could be another possible mechanism by which the TNF-α antagonist may lower the risk of cardiovascular diseases.

In depression, TNF-α has been suggested to be one of the key cytokines involved in its pathogenesis. Although there are some conflicting data, a majority of the studies concluded that depressed individuals usually have a higher level of TNF-α. In addition, studies have shown improvement of depression in psoriatic patients after treatment with a TNF-α antagonist. As such, the TNF-α antagonist appears to improve depression through the clinical improvement of psoriasis. However, future research may explore whether the TNF-α antagonist plays a role in the central nervous system. It is quite plausible that the TNF-α antagonist improves depression in both ways, centrally and peripherally.

Based on the current literature review, there are still many unanswered questions. TNF-α seems to be elevated in psoriasis, cardiovascular disease, and depression; however, it is unclear what the significance of the elevated level is. One might hypothesize that the elevated level could be the result of an underlying inflammatory process of each medical condition. If so, could the level of TNF-α correspond with the disease severity of psoriasis, cardiovascular disease, and depression? In addition, the elevated level of TNF-α soluble receptor 1 (p55) demonstrated in patients with cardiovascular disease and depression may suggest that p55 plays a more dominant role compared with p75. It is also unclear whether TNF-α is the main cytokine causing pathogenesis or the mediator among these medical conditions.

Based on the data, anti-TNF-α therapy appears to provide clinical benefits in psoriasis, cardiovascular disease, and depression. Could there be a connection among these conditions in relation to TNF-α? We know that patients with
psoriasis are predisposed to cardiovascular disease, metabolic syndrome, and depression. The importance of finding the connection is that it may lead to a drug, possibly a TNF-α antagonist, that would not only treat clinical symptoms of psoriasis effectively but may also prevent the comorbidities associated with psoriasis (e.g., cardiovascular disease, metabolic syndrome, and depression). As such, this will not only enhance the general overall health (physically and emotionally) of a patient but will also avoid the complications of multiple drug interactions or polypharmacy. It is also important to keep in mind that there may be other players (i.e., CRP, IL-6, or IFN-γ) involved in the pathogenesis process. TNF-α may be only one piece of the puzzle. More studies are needed to further elucidate the mechanism behind the pathogenesis in psoriasis, cardiovascular disease, depression in relation to TNF-α and other cytokines.

CONCLUSIONS

Based on review of the available research findings to date, the inflammatory cytokines, particularly TNF-α, appear to play a role in psoriasis, cardiovascular diseases, and depression. All 3 of these medical conditions have been shown to have an elevated TNF-α level, thus suggesting an underlying inflammatory process for each condition. There could be a shared pathogenesis pathway among psoriasis, depression, and cardiovascular disease. As more studies are conducted to unravel this intricately interwoven mechanism, it is important to keep an open mind regarding the possible additional therapeutic benefits of TNF-α antagonists.

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