Section A-Research paper

An Overview about Adiponectin Correlation with Psoriasis

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Abstract

Background: Adiponectin is the most abundant adipokine in human blood with a physiological level of 5–30 μL/mL secreted from adipose tissues. There are two kinds of adipose tissue present in humans: white adipose tissue (WAT) and brown adipose tissue (BAT). Adiponectin (also known as Acrp30, GBP-28, apM1, and AdipoQ) is a protein mainly secreted by WAT adipocytes. Other tissues such as human murine osteoblasts, liver, parenchyma cells, myocytes, epithelial cells, and placental tissue show low levels of adiponectin secretion. The main biological functions of adiponectin include enhanced fatty acid biosynthesis and inhibition of gluconeogenesis in the liver. Patients with psoriasis have lower plasma adiponectin levels, which may worsen the severity of their skin lesions. Previous documents revealed that plasma C-reactive protein (CRP) levels are negatively correlated with plasma adiponectin levels, and a significant negative correlation between CRP and adiponectin mRNA levels was also observed in human adipose tissue. However, in subsequent research, adiponectin serum levels were also positively correlated with the sedimentation rate (SR) and CRP levels, which was somewhat puzzling. Previously, the importance of this relationship in the course of psoriasis was unclear, but now it has been demonstrated that plasma adiponectin decreases and CRP increases as metabolic diseases progress. Therefore, the reduction in adiponectin levels is closely related to the occurrence of psoriasis. As an inflammatory factor, CRP participates with various cytokines in the immune response and may play an important role in promoting the development of psoriasis.

Keywords: Adiponectin, Psoriasis

Introduction

Psoriasis is a common chronic, recurrent, immune mediated disease of the skin and joints. Psoriasis is found worldwide but the prevalence varies among different ethnic groups. It has a strong genetic component but environmental factors such as infections can play an important role in the presentation of disease **(Langley et al., 2005).**

It is characterized by well- demarcated, erythematous plaques covered by silvery- white scales, typically occurring in a symmetrical distribution involving the elbows, knees, trunk and scalp **(Korman, 2020).**

The marked visible appearance of the lesions have a negative impact on body image that leads to decreased self-esteem, hence seriously compromising the patient's quality of life. The clinical picture critically affects the social well-being of the patient since the disease is commonly misunderstood and feared by the social environment as being contagious **(Kouris et al., 2017).**

Epidemiology

The prevalence of psoriasis in Egypt is 0.19-3% **(Omar and Helaly, 2018)**. Approximately 125 million people worldwide have psoriasis **(Armstrong and Read, 2020).**

According to the age of onset, two distinct types of psoriasis are said to exist (i) early onset psoriasis (EOP), beginning before the age of 40 years and (ii) late onset psoriasis (LOP), beginning ≥40 years; with the presence of Human lymphocyte antigen (HLA) Cw6, present in majority of patients with early onset (**Fatema et al., 2021).**

The male-to-female ratio revealed a higher prevalence for male gender. Male patients are diagnosed at a younger age and are more liable to the development of severe psoriasis **(Odorici et al., 2021).**

Approximately 40% of patients with psoriasis have a family history of psoriasis **(Solmaz et al., 2020).** Presence of family history doesn't affect the disease progression or severity **(Tsitsami et al., 2003).**

Pathogenesis

Psoriasis is one of the Immune-Mediated Inflammatory Diseases (IMIDs) which are heterogeneous group of diseases or conditions that share common inflammatory pathways, and for which there is no definitive etiology such as psoriasis, rheumatoid arthritis (RA), Sjőgren's syndrome, systemic lupus erythematosus **(Bellinger and Lorton, 2018).**

The pathogenesis of psoriasis involves antimicrobial peptides (AMPs), dendritic cells (DCs), tumor necrosis factor (TNF)α, interleukin (IL)23, Th17, IL17, IL22, and signal transducer and activator of transcription (STAT) (**Tokuyama and Mabuchi, 2020).**

Genetic factors: Psoriasis has a genetic component that is supported by patterns of familial aggregation. First and second-degree relatives of psoriasis patients have an increased incidence of developing psoriasis, while monozygotic twins have a two to threefold increased risk compared to dizygotic twins **(Rendon and Schäkel, 2019).**

Psoriasis has a genetic component model with the involvement of a major gene (PSORS1) and a set of minor genes with a variable penetrance depending on the locus **(Ammar et al., 2014).**

Twelve of these (PSORS1-12) have been confirmed by multiple studies in different populations. However, no susceptibility gene has been definitively confirmed within these regions, except for HLA-Cw6 at PSORS1 locus **(Coda et al., 2012).**

Involvement of a host gene polymorphism along with the interaction between infectious agents and killer cell immunoglobulin-like receptors of NK cells have been proposed based on investigations of viral infections such as CMV and HIV which psoriasis cases where aggravated after inquiring (**Huang and Tsai 2021).**

Environmental factors: Many different environmental factors play a role in genetically predisposed patients. This causes epigenetic alternations which may be a linking part in the whole process **(Roszkiewicz et al., 2020).**

Psoriasis patient who exhibits koebnerization (and is said to be "Koebner-positive") will develop new psoriasiform lesions along sites of skin injury, even if trivial. Koebner phenomenon can develop in any anatomic site, including in classic areas of psoriatic involvement and in regions that are usually spared, such as the face. The phenomenon shows dynamic behavior. Patients may be "Koebner-negative" at one point in life but may later become "Koebner-positive **(Sanchez and Sonthalia 2021).**

Working night shifts confers an increased risk of psoriasis based on large epidemiological studies **(Li et al., 2013)**, suggesting the possibility that circadian disruption could contribute to psoriasis development, possibly through an effect on the immune system **(Plikus et al, 2015).**

About 50% of psoriasis patients experience a season-independent disease, however, with a subset of patients who do better in summer. Others again do better in winter, with a few of them having marked worsening in warm periods **(Jensen et al., 2022).**

Streptococcal pharyngitis is a trigger of guttate psoriasis, and exacerbation of psoriasis in the setting of Human Immunodeficiency Virus (HIV) infection is known **(Takeshita et al., 2017).**

The skin inflammation in psoriasis may populate certain gut bacteria, such as *Staphylococcus aureus* and *Streptococcus danieliae,* which worsen the skin inflammation in turn **(Kanda, 2021).**

In HIV-infected patients, psoriasis may have a higher incidence, present atypical and more serious clinical features, and is frequently recalcitrant to treatment. Despite this aggravated severity, treatment options for psoriasis in HIV-infected individuals remain limited due to the risk of fatal immunosuppression associated with both classical immunosuppressants and new biological drugs **(Alpalhão et al., 2019).**

Adiponectin is the most abundant adipokine in human blood with a physiological level of 5–30 μL/mL secreted from adipose tissues **(Obata et al., 2013).** There are two kinds of adipose tissue present in humans: white adipose tissue (WAT) and brown adipose tissue (BAT). Adiponectin (also known as Acrp30, GBP-28, apM1, and AdipoQ) is a protein mainly secreted by WAT adipocytes. Other tissues such as human murine osteoblasts, liver, parenchyma cells, myocytes, epithelial cells, and placental tissue show low levels of adiponectin secretion **(Guerre-Millo, 2002)**.

The main biological functions of adiponectin include enhanced fatty acid biosynthesis and inhibition of gluconeogenesis in the liver **(Cook et al., 2000).** In addition, it enhances glucose uptake in skeletal muscle via signaling pathways. Studies have shown that adiponectin can be used to improve insulin resistance by reducing the amount of intracellular fat through increased oxidation of fatty acid via PPARα activation and enhancement of insulin receptor substrate (IRS) signaling in skeletal muscles and the liver **(Schindler et al., 2017).** Furthermore, adiponectin has been reported to possess antioxidant, anti-inflammatory, and antiatherosclerotic effects **(Thundyil et al., 2012)**.

Adiponectin functions as an insulin sensitizer and exhibits anti-diabetic, anti-inflammatory, and anti-atherogenic effects. Its multifunctional aspects render it a highly favorable target for metabolic disorders. The central role of adiponectin is energy homeostasis with a newly proposed role as a "starvation gene" **(Von-Frankenberg et al., 2017).** The following section explains adiponectin-mediated cellular signaling in different tissues and their associated effects **(Figure 15) (Kadowaki et al., 2008)**.

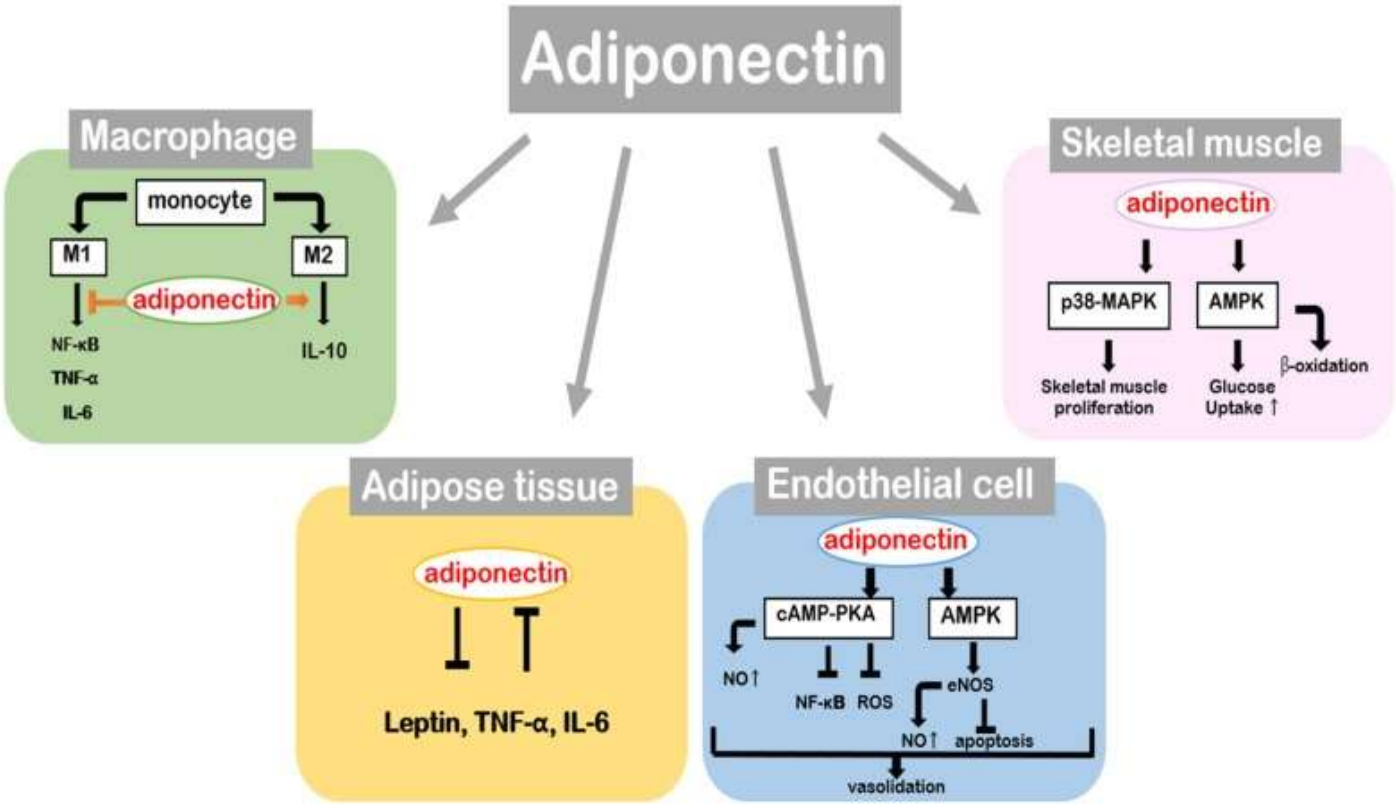

Figure (1): Physiological roles of adiponectin in the main tissues (Kadowaki et al., 2008).

Adiponectin seems to mediate various tissue-specific signaling pathways. On macrophages, adiponectin promotes cellular differentiation of monocytes to M2 macrophages with anti-inflammatory effects and suppresses their differentiation to the M1 macrophages, which shows proinflammatory effects. Adipose tissue releases various adipokines, and adiponectin is mainly involved in controlling the endocrine system of adipose tissue. Adiponectin represses secretion of leptin and proinflammatory cytokines including IL-6 and TNF-α, which lower the expression level of adiponectin **(Choi et al, 2020)**.

On endothelial cells, adiponectin induces cAMP-PKA and AMPK to regulate vascular homeostasis. Enhanced COX-2 and eNOS activity and subsequent nitric oxide (NO) production improve endothelial cell function and block secretion of inflammatory factors. On skeletal muscle, adiponectin stimulates AMPK to enhance fatty acid oxidation and glucose uptake. In addition, crosstalk between insulin and adiponectin signaling showed that adiponectin synergistically improves insulin sensitivity and glucose tolerance. The p38-MAPK pathway of adiponectin is known to stimulate the proliferation of skeletal muscle tissue **(Choi et al, 2020)**.

Adipose tissue plays an integral role in regulating energy metabolism and glucose homeostasis. These functions are active at both organ and systemic levels **(Kuryszko et al., 2016).** The adipose tissue is comprised of a variety of cell populations including macrophages, endothelial cells, fibroblasts, and leucocytes. Adipose tissue exerts its endocrine effects by releasing adipokines that act as chemical messengers, which communicate with other organs and control a range of metabolic signals. In addition, adipose tissue plays an indispensable role in lipid mobilization and energy distribution in the body **(Liu and Sweeney, 2014).**

AMPK-endothelial nitric oxide synthase (eNOS) activation promotes NO production, which contributes to vascular protection and endothelium relaxation **(Deng et al., 2010)**. In addition, adiponectin activates protein kinase A (PKA) signaling, which promotes NO production and suppresses ROS generation and NF-κB signaling. Adiponectin knockout mice showed a decreased mRNA level of *NOS* and a production level of PGE2. Treatment with adiponectin reversed the decreased levels of NOS and PGE2 in *adiponectin*-KO mice "Knocked out mice" and also lowered blood pressure **(Ohashi et al., 2006)**.

Circulating serum level of adiponectin is decreased in patients with type 2 diabetes, metabolic syndrome, or cardiovascular disease **(Achari and Jain, 2017).**

Extensive research has shown that adiponectin possesses anti-inflammatory properties **(Ohashi et al., 2012)**. This was the common view, but recent reports have offered contradictory findings that adiponectin also has pro-inflammatory aspects in some diseases. The pro-inflammatory or anti-inflammatory role of adiponectin is reviewed in the context of various inflammatory diseases in this section **(Fantuzzi, 2008)**.

Plasma adiponectin level is inversely associated with BMI; on the other hand, it is positively associated with age, even after adjustment for visceral adiposity **(Obata et al, 2013)**. The decrease in its clearance rate in the kidney may be the cause of high levels of adiponectin in the elderly **(Yaturu et al, 2007).** In extreme thinness, increased production from increased bone marrow adipose tissue combined with increased production from WAT contributes to hyperadiponectinemia **(Cawthorn, 2014).**

Serum levels are low in individuals with obesity as well as in those with type 2 diabetes (T2DM). However, several clinical studies have shown associations between high adiponectin values and major health concerns. These conflicting findings are termed the "adiponectin paradox" **(Tsutamoto, 2007)**. In a

prospective study, increased plasma adiponectin predicted poor outcome in future cardiovascular events in patients presenting with stable angina and preserved systolic function **(Schnabel, 2008)**.

Adiponectin and Psoriasis

Patients with psoriasis have lower plasma adiponectin levels, which may worsen the severity of their skin lesions **(Campanati et al., 2015)**. Previous documents revealed that plasma C-reactive protein (CRP) levels are negatively correlated with plasma adiponectin levels, and a significant negative correlation between CRP and adiponectin mRNA levels was also observed in human adipose tissue **(Fantuzzi, 2008).**

However, in subsequent research, adiponectin serum levels were also positively correlated with the sedimentation rate (SR) and CRP levels, which was somewhat puzzling. Previously, the importance of this relationship in the course of psoriasis was unclear, but now it has been demonstrated that plasma adiponectin decreases and CRP increases as metabolic diseases progress. Therefore, the reduction in adiponectin levels is closely related to the occurrence of psoriasis. As an inflammatory factor, CRP participates with various cytokines in the immune response and may play an important role in promoting the development of psoriasis **(Ghoshal et al., 2021).**

Previous research on adiponectin focused on TNF-α and IL-6, which inhibit anti-inflammatory defences, particularly adiponectin levels **(Fantuzzi, 2008).**

Data from human and rodent in vivo studies have shown that adiponectin levels are negatively correlated with TNF-α and IL-6 **(Bavoso et al., 2019).** Increased levels of pro-inflammatory cytokines, especially IL-6, in patients with psoriasis may be one of the causes of the decline in adiponectin levels in subcutaneous and visceral adipose tissue **(Shibata et al., 2011)**.

Adiponectin can inhibit TNF-α **(Fantuzzi, 2005)**, which can also be negatively regulated by TNF-α in psoriatic patients **(Takahashi, 2008)**. Anti-TNF therapy has also been found to decrease IL-6 levels in patients with psoriasis **(Mehta et al., 2018)**. In addition, upregulation of anti-inflammatory cytokines helps restore the balance between Th (helper T cell) 1, Th17 and Th2 responses in patients with psoriasis **(Campanati et al., 2014)**. In an AMPK-dependent manner, adiponectin inhibits Th0 cell differentiation into Th1 and Th17 cells **(Surendar et al, 2019)**. Among its anti-inflammatory effects is inhibition of IL-17A production **(Shibata et al, 2015)**.

Adiponectin plays a key role in regulating psoriasis by directly inhibiting the secretion of IL-17 by T cells, which suggests new approaches to the study of psoriasis. Similar to adipocytes, sebaceous cells have also been found to differentially express and secrete adipokines. Adiponectin is expressed in human sebaceous glands (SGs), affecting the homeostasis of the dermis and promoting inflammation. Its relationship with systemic inflammation such as psoriasis is an interesting research pathway **(Figure 16) (Ruiyang et al., 2020)** and **(Kovacs et al., 2016)**.

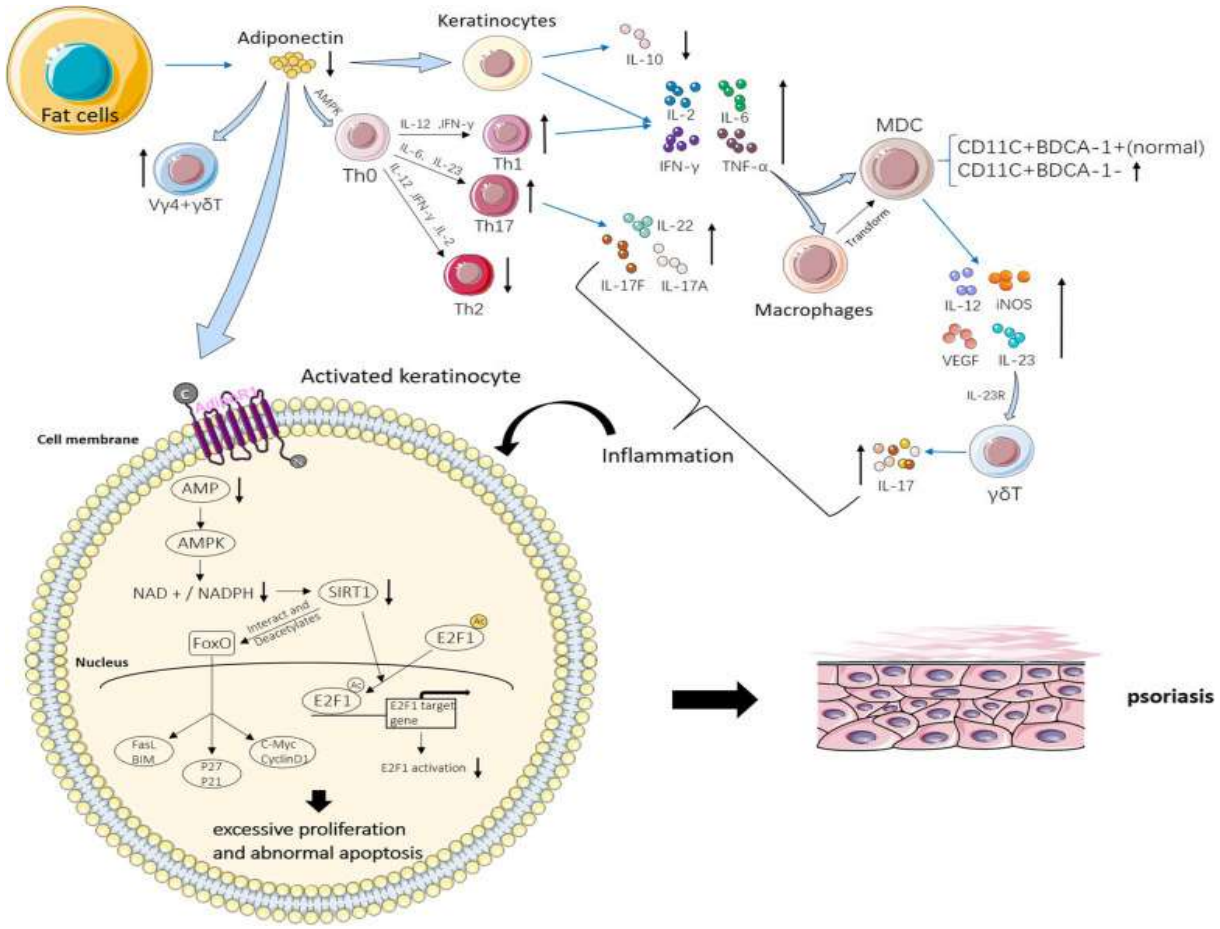

Figure (2): The role of adiponectin in the pathogenesis of psoriasis.

Adiponectin is secreted by fat cells and can act on keratinocytes and naive T cells. Decreased adiponectin content leads to increased pro-inflammatory cytokines and decreased anti-inflammatory cytokines. Among these, TNF-α can further affect macrophages and myeloid dendritic cells, resulting in increased secretion of cytokines **(Kim and Krueger, 2015)**. In addition, adiponectin increases the number of Vγ4γδT cells. In keratinocytes, adiponectin can activate the E2F1 gene through the AMPK pathway, and the decrease in adiponectin levels leads to reduced E2F1 gene activation, thereby promoting the proliferation of keratinocytes **(Chen et al., 2009)**. In addition, SIRT1 protein can interact with the FoxO family. Downregulation of SIRT1 leads to abnormal transcriptional regulation of genes related to cell proliferation, survival, apoptosis, and metabolism, resulting in abnormal cell apoptosis **(Singh and Ubaid, 2020)**. These changes interact with the infiltration of the inflammatory response, which leads to psoriasis **(Ruiyang et al., 2020).**

Subgroup and meta-regression analyses have found no significant correlation in terms of age, sex, psoriasis area and severity index (PASI) or study quality score with the expression level of adiponectin in psoriasis **(Bai et al., 2018)**.

Psoriatic arthritis (PsA) and plasma adiponectin levels are negatively correlated **(Johnson et al., 2019)**. A previous study found that the adiponectin level was significantly higher in PsA patients than in psoriasis patients without arthritis **(Eder et al., 2013)**. However, a study of patients with psoriasis with or without PsA found that adiponectin levels were not significantly different **(Gerdes et al., 2020)**.

In terms of treatment, secukinumab and etanercept have no relevant effect on adiponectin levels and they do not change the adiponectin level. This may highlight that adiponectin levels are not closely related to PASI,

a result consistent with other local and/or systemic treatment studies, except for analyses of secukinumab or other anti-IL-17 inhibitors **(Kyriakou et al., 2018)**.

Patients using anti-inflammatory drugs or phototherapy may also have increased adiponectin levels **(Bavoso et al, 2019)**. After mildly affected patients with no evidence of psoriatic arthritis received systemic methotrexate treatment, the PASI score was significantly reduced, but this treatment did not affect the serum adiponectin level **(Coban et al., 2016)**. During TNF-α treatment, an increase in adiponectin levels can also be observed **(Corrado et al., 2019)**.

Conflicts of Interest: The authors declare no conflict of interest.

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