Psoriasis and Interaction with Simvastatin as Adjuvant Therapy

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Abstract

Psoriasis is a common, chronic inflammatory skin disease, mediated by immune system, with common comorbidities are metabolic syndrome and cardiovascular disease, associated with fat metabolism. One component of fat is cholesterol, an essential lipophilic molecule for humans. The structure of cholesterol is divided into three, hydrophobic, hydrophilic, and rigid structures, allowing cholesterol to regulate various cellular processes in the body. Cholesterol made by cell in the body mostly, and the rest is obtained from food. There is a complex relationship between cholesterol metabolism and psoriasis. Dysregulation of cholesterol metabolism affects keratinocyte function and then worsens psoriasis lesions. Antipsoriasis drugs have varying effects on cholesterol, while statins, cholesterol-lowering drugs, have a good effect on psoriasis patients. Simvastatin has a good effect on psoriasis patients. Using simvastatin as an adjuvant therapy for psoriasis is a good choice to get a better results and long remition time.

***Keywords*:** *psoriasis, cholesterol, simvastatin*

Abstrak

Psoriasis dan Interaksi terhadap Simvastatin sebagai Terapi Tambahan. Psoriasis adalah penyakit inflamasi kronik pada kulit, dimediasi gangguan sistem imun, komorbid paling sering adalah sindrom metabolik dan penyakit kardiovaskular, berhubungan dengan metabolisme lemak. Salah satu komponen lemak adalah kolesterol, molekul lipofilik esensial bagi manusia. Struktur kolesterol terbagi menjadi tiga, struktur hidrofobik, hidrofilik, dan struktur kaku sehingga memungkinkan kolesterol untuk mengatur berbagai proses seluler dalam tubuh. Kolesterol sebagian besar dibuat sendiri oleh tubuh, dan sebagian didapat dari makanan. Terdapat hubungan kompleks antara metabolisme kolesterol dan psoriasis. Disregulasi metabolisme kolesterlol memengaruhi fungsi keratinosit lalu memperburuk lesi psoriasis. Obat antipsoriasis mempunyai efek beragam pada kolesterol, sedangkan statin, obat penurun kolesterol, berdampak baik bagi penderita psoriasis. Simvastatin memberikan efek baik pada pasien psoriasis. Menggunakan simvastatin sebagai terapi tambahan pada psoriasis merupakan pilihan untuk mendapat hasil lebih baik dan memperpanjang waktu remisi.

Kata Kunci: *psoriasis, kolesterol, simvastatin*

Introduction

Psoriasis is a chronic inflammatory skin disease mediated by immune system dysregulation, characterized by cutaneous inflammation, epidermal hyperplasia, and an increased risk of arthritis, cardiovascular disorders, and psychosocial impairment.[1] Psoriasis occurs more frequently in adults than children, particularly in developed countries, with incidence ranging from 30.3 to 321 cases per 100,000 population.[2] The highest prevalence reported is 11.8% in Kazakhstan. In Asia, including Japan, Taiwan, Malaysia, Kuwait, Saudi Arabia, and China, the prevalence ranges between 0.05% and 5.5%.[3] Based on medical records from the outpatient and inpatient clinics at Dr. Mohammad Hoesin Hospital (RSMH) Palembang from 2019–2023, there were 203 psoriasis patients.

The most common comorbidities in psoriasis are metabolic syndrome and cardiovascular disease, associated with lipid metabolism.[4] Lipids play an important role in maintaining homeostasis as components of cell membranes and hormones, storing energy, and acting as cellular signaling mediators.[5] Cellular lipid or cholesterol homeostasis plays a role in adaptive immune system regulation and cytokine production by innate immune cells. Cholesterol can mediate tissue inflammatory responses directly by regulating T helper 17 (Th17) function or assist B cells in producing autoantibodies.[6]

In psoriasis, T cells play a major role in inflammation. Th1 and cytotoxic T (Tc1) cells, along with Th17 and Tc17 cells, secrete pro-inflammatory mediators in response to initial keratinocyte activation. Keratinocyte-activating cytokines subsequently release chemotactic factors, amplifying the inflammatory process.[7]

Simvastatin, a cholesterol-lowering statin, inhibits 3-hydroxy-3-methylglutaryl-CoA reductase (HMG-CoA reductase), an enzyme critical in cholesterol metabolism, stimulating LDL receptors and thereby lowering LDL levels.[4,8] Simvastatin may be considered as adjunctive therapy to reduce inflammatory reactions caused by elevated cholesterol in psoriasis patients.

Psoriasis

Psoriasis is an immune-mediated disease often associated with genetic predisposition and manifests in various clinical forms. Plaque psoriasis (psoriasis vulgaris) is the most common form, characterized by erythematous, scaly plaques that may extend according to severity.[9] Psoriasis frequently recurs and currently has no definitive cure, posing a significant psychosocial burden and reducing patients' quality of life.[10]

Environmental factors, including lifestyle and diet, are modifiable risk factors in psoriasis pathogenesis.[11] A 2022 study by Xiao reported an inverse association between high-density lipoprotein (HDL) and psoriasis incidence but a positive association with triglycerides.[12]

Psoriasis pathogenesis involves genetic components (associated with HLA-Cw6 and family history of psoriasis) and immune dysregulation, with triggers such as infection, trauma, medications, and psychological stress (Figure 1). HLA-Cw6 genetic component is also associated with obesity.[1,11]

Comorbidities

Comorbidities may develop after 1–2 years of psoriasis onset and are more common in severe cases.[11] Comorbidities include dyslipidemia, hypertension, type 2 diabetes mellitus, obesity, metabolic syndrome, fatty liver disease, coronary heart disease, malignancy, gastroduodenal disease, osteoarthropathy, infections, depression, and cerebrovascular disease because of psoriasis is a chronic relapse disease.[12-14]

Psoriasis patients typically exhibit a pro-atherogenic lipid profile, with increased serum triglycerides, total cholesterol, especially low-density lipoprotein (LDL) and very-low-density lipoprotein (VLDL), and reduced HDL.[13] Lipid metabolism disorders can affect keratinocyte function, and dietary saturated fatty acids enhance cutaneous inflammation, worsening psoriasis lesions.[15] The anti-inflammatory function of HDL is impaired in dyslipidemia, significantly contributing to psoriasis progression and increasing cardiovascular and infection risk.[12]

A 2021 study by Kafle in Nepal found 95% of psoriasis patients had dyslipidemia, with lipid changes depending on disease duration. HDL levels were lower in severe psoriasis compared to mild-to-moderate disease.[13] Pure hypercholesterolemia (PH), a clinical form of dyslipidemia, is a risk factor for cardiovascular disease. Cholesterol metabolism is linked to autoimmune diseases such as systemic lupus erythematosus and psoriasis. A 2023 Mendelian randomization study by Bai concluded PH has a causal association with psoriasis and psoriatic arthritis.[10]

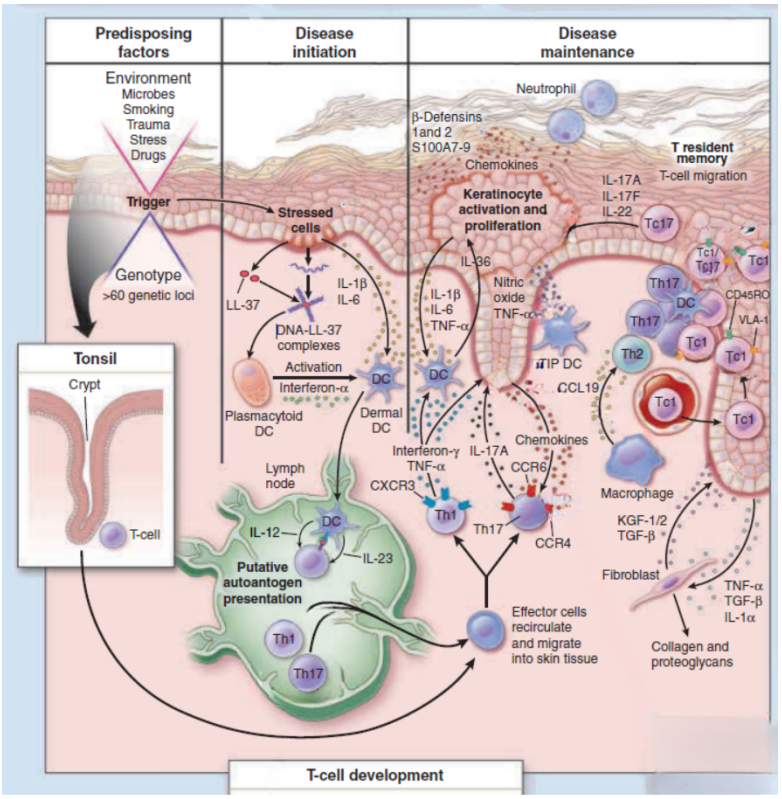

Figure 1. Pathogenesis of psoriasis[1]

Cholesterol

Lipids are broadly divided into fatty acid derivatives and isoprenoids. Cholesterol is an isoprenoid lipid with 27 carbon atoms.[16] It is an essential lipophilic molecule in humans, comprising hydrophobic, hydrophilic, and rigid structural components enabling regulation of various cellular processes.[17] Cholesterol, predominantly located in cell membranes, interacts with surrounding lipids, regulates cell permeability, and binds transmembrane proteins. It is also metabolized into bile acids, steroid hormones, and vitamin D analog.[17,18]

Humans require approximately 1 gram of cholesterol per day, with 600–900 mg produced endogenously and 300–500 mg obtained from diet.[19] Excess cholesterol is excreted through the gastrointestinal tract or stored as lipid droplets.[5] In the skin, cholesterol comprises ~27% of the stratum corneum lipid composition, essential for barrier rigidity and fluidity.[20] Cholesterol homeostasis is regulated through de novo synthesis, intestinal absorption and transport, and conversion and efflux processes.[19]

Altered Cholesterol Metabolism and Psoriasis

Squalene

Squalene, an easily oxidized cholesterol metabolite, lowers serum cholesterol, inflammation, nitric oxide, and TNF-α.[5,21] It promotes production of anti-inflammatory cytokines IL-10, IL-4, and IL-13 and induces M2 macrophage formation. However, oxidized squalene increases IL-6 production and keratinocyte proliferation. Squalene forms from farnesyl pyrophosphate (FPP) via squalene synthase; disruption increases FPP, activating NF-κB and promoting cell proliferation.[5]

Oxidized Low-Density Lipoprotein (Ox-LDL)

Ox-LDL interacts with membrane receptors SR-B1, CD36, and LOX-1, inducing IL-23 production in dendritic cells, worsening psoriasis.[5] Oxidized Low Density Lipoportein also accumulates cholesterol in lysosomes, leading to cell death.[4]

High-Density Lipoprotein (HDL)

HDL mediates reverse cholesterol transport to the liver and possesses anti-inflammatory and antioxidant properties. HDL and apolipoprotein A1 modulate immune cell differentiation and function to exert anti-inflammatory effects.[5] However, HDL anti-inflammatory function is impaired in psoriasis.[22]

Effects of Psoriasis on Cholesterol Metabolism

Psoriasis patients have elevated total lipids, phospholipids, triglycerides, and cholesterol.[20] Cholesterol in tissue plays a role in maintaining cell membrane integrity and altering its fluidity in response of external factors. Cholesterol levels in psoriatic skin increase due to signaling via IL-17A. This results in increased cholesterol in keratinocytes.[4] Cholesterol accumulation in keratinocytes, also promoting inflammatory responses by upregulating IL-17–related genes.[23]

Psoriasis is associated with reduced lipocalin, which normally converts triglycerides into HDL; thus, psoriasis patients with hyperlipidemia often have low HDL. Low lipocalin correlates with increased TNF-α and IL-6.[24] Prolonged TNF-α elevation stimulates LDL and Ox-LDL production and inhibits HDL production.[4,22,25] High serum IL-6 also disturbs lipid metabolism by increasing free fatty acids, cholesterol, and triglycerides from adipose tissue, resulting dyslipidemia in psoriasis patient.[4,26] Cross-sectional research by Sahoo reported a positive correlation between total cholesterol and IL-6 with psoriasis severity.[27] Pietrzak reported IL-6 as a potential marker of lipid abnormalities in psoriasis.[26]

Cyclosporine is a systemic antipsoriatic drug with hyperlipidemia as a side effect.[4] Conversely, methotrexate reduces PCSK9 concentration, leading to decreased cholesterol levels.[28] Anti-TNF-α agents lower cholesterol levels. Secukinumab (anti-IL-17A) does not affect cholesterol.[4,29,30]

Statins

Statins inhibit HMG-CoA reductase, metabolized in the liver, stimulate LDL receptors, and decrease LDL concentration. In psoriasis patients, statins reduce disease severity. Statin are reversible competitive inhibitors of HMG-Coa reductase. By reducing the intracellular pool of cholesterol in the lover, statins increase the number of LDLR on cell surfaces, which enhances catabolism and clearance of circulating plasma LDL.[4,31] Simvastatin, semisynthetic derivate of lovastatin, is a member of the class of hexahydronaphthalenes that is lovastatin in which the 2-methylbutyrate ester moiety has been replaced by a 2,2-dimethylbutyrate ester group chemically modified forms of the natural statin compounds (Figure 2). Maximal simvastatin dose is 40 mg each day. It can reduced LDL concentration 41% in daily using 40 mg each day. It also reduced triglyceride

10-20% and increase HDL serum 6-8%. Rhabdomyolysis, with acute renal failure secondary to myoglobinuria, has been caused by therapy with statin drug. The risk of statin-induced is dependent on the drug combination used.[31]

Han et al in 2024 in their cohort study shows that statin may reduce the incidence of psoriasis. They use hydrophilic statins which is pravastatin and rosuvastatin, and lipophilic statins which is atorvastatin, fluvastatin, lovastatin, pitavastatin, and simvastatin. The result show that hydrophilic and lopophilic has similar impact in cholesterol.[32] A case control study by Trong in 2019 show that oral simvastatin can decrease psoriasis area and severity index (PASI) score in psoriatic patients.[33] A 2024 meta-analysis by Aleid concluded statins improve psoriasis severity and quality of life by suppressing IL-1, IL-6, TNF-α, and C-reactive protein.[8]

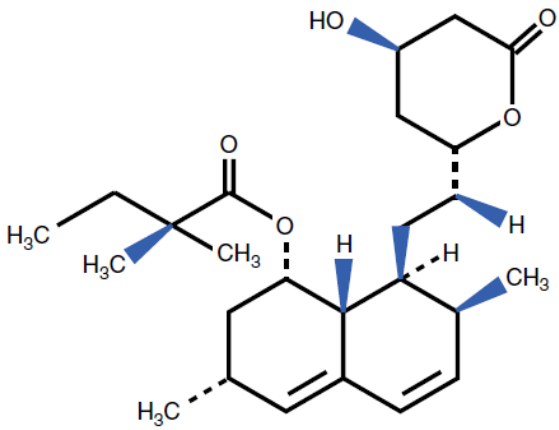

Figure 2. Simvastatin structure[31]

Conclusion

Psoriasis and cholesterol metabolism are interrelated. Cholesterol influences immune mechanisms in psoriasis, and psoriasis disrupts cholesterol metabolism. Antipsoriatic therapies exert variable effects on lipid profiles, whereas statins, especially simvastatin may improve both lipid abnormalities and psoriasis severity.

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