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Plasma levels of PCSK9 and Caspase-1 in patients with psoriasis: biomarker potential and implications for personalized therapeutic strategies

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Abstract

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a central regulator of cholesterol homeostasis through its effect on LDL receptor degradation. Its elevated activity is associated with increased plasma LDL-C levels and may promote atherosclerosis directly and indirectly. The elucidation of proprotein convertase subtilisin/kexin type 9 (PCSK9) as a pivotal regulator of LDL receptor degradation has precipitated a paradigm shift in novel lipid-lowering strategies, with PCSK9 inhibitors now constituting a cornerstone in the therapeutic armamentarium for the management of high-risk hyperlipidemic patients in cardiovascular prevention. A total of 27 patients diagnosed with psoriasis (16 women, 11 men) and 25 healthy controls (13 women, 12 men; age-matched) were included in the study. Patients with psoriasis exhibited significantly elevated plasma levels of PCSK9,

supporting its role in cholesterol metabolism dysregulation and novel biomarker for increased cardiovascular risk. Despite the inflammatory nature of psoriasis, Caspase-1 levels were lower in patients, indicating a possible beneficial effect of anti-inflammatory therapy, as well as decreased programmed cell death known as pyroptosis. Overall, the integration of PCSK9 and Caspase-1 profiling into clinical practice could facilitate personalized management of psoriasis, enabling tailored interventions that address not only skin inflammation but also associated metabolic and cardiovascular comorbidities.

Key words: psoriasis, PCSK9, Caspase-1

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Nivo PCSK9 i Kaspaze-1 u plazmi pacijenata sa psorijazom: potencijalni biomarkeri i značaj u personalizovanoj terapijskoj strategiji

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Proprotein konvertaza subtilizin/keksin tip 9 (PCSK9) je centralni regulator homeostaze holesterola ostvarivanjem efekta na razgradnju LDL receptora. Povišena aktivnost je povezana sa povećanim nivoima LDL-holesterola u plazmi i može direktno i indirektno doprineti razvoju ateroskleroze. Otkrivanje PCSK9 kao ključnog regulatora razgradnje LDL receptora dovelo je do promene paradigme u strategijama za snižavanje lipida, pri čemu su PCSK9 inhibitori sada osnovni deo terapijske strategije u lečenju pacijenata sa visokim rizikom od hiperlipidemije u okviru kardiovaskularne prevencije. U studiju je bilo uključeno ukupno 27 pacijenata sa psorijazom (16 žena, 11 muškaraca) i 25 zdravih ispitanika kao kontrolna grupa (13 žena, 12 muškaraca; starosno usklađeni). Pacijenti sa psorijazom su pokazali značajno povišene nivoe PCSK9 u plazmi, što podržava njegovu ulogu u poremećaju metabolizma holesterola i njegov potencijal kao novog biomarkera za povećani kardiovaskularni rizik. Uprkos inflamatornoj prirodi psorijaze, nivoi kaspaze-1 bili su niži kod pacijenata sa psorijazom, što ukazuje na mogući povoljan efekat antiinflamatorne terapije, kao i

smanjenu programiranu ćelijsku smrt poznatu kao piroptoza.U širem smislu, integracija profilisanja PCSK9 i kaspaze-1 u kliničku praksu mogla bi da doprinese personalizovanom pristupu pacijentima sa psorijazom, jer omogućava ciljane intervencije koje se ne bave samo problemom kožnih manifestacija, već i pratećim metaboličkim i kardiovaskularnim komorbiditetima.

Ključne reči: psorijaza, PCSK9, kaspaza-1

Introduction

Psoriasis is a chronic, immune-mediated, systemic inflammatory skin disorder increasingly recognized for its association with metabolic comorbidities and elevated cardiovascular (CV) risk. Among its numerous systemic manifestations, disruptions in lipid metabolism, particularly involving cholesterol and lipoproteins, represent significant biochemical laboratory findings (1-3). Dyslipidemia is commonly observed in patients with psoriasis, contributing to their elevated risk for CV risk, as it was obtained by a prospective cohort study (4).

Proprotein convertase subtilisin/kexin type 9 (PCSK9) plays a crucial role in lipid metabolism by promoting the lysosomal degradation of low-density lipoprotein (LDL) receptors, thus impairing the clearance of LDL cholesterol. Recently, PCSK9 has emerged as a therapeutic target for hypercholesterolemia and atherosclerosis prevention. The primary physiological function of PCSK9 is to regulate the number of low-density lipoprotein receptors (LDLRs) on the surface of hepatocytes. Under normal circumstances LDLR binds circulating LDL-C and internalizes it via endocytosis, afterwards the LDL particle is degraded in lysosomes, and LDLR is recycled to the cell surface to continue LDL uptake. However, PCSK9 binds to LDLR on the cell surface or in endosomes and directs it toward lysosomal degradation, preventing receptor recycling. This process reduces the number of LDLRs available to clear LDL-C from the bloodstream, thereby increasing plasma LDL-C levels (5-8). PCSK9 is one of 62 proteins that have been found to be substantially associated with the risk of psoriasis in over 50,000 participants (9). A Mendelian randomization (MR) analysis was performed on the medication target for proprotein convertase subtilis kexin 9 (PCSK9) and 3-hydroxy-3-methylglutaryl-assisted enzyme A reductase (HMGCR) inhibitors among the genetic targets of lipid-lowering medications. Psoriasis is one of the common inflammatory skin conditions, and gene-predicted suppression of PCSK9 was causally linked to a lower chance of developing psoriasis (10,11).

Caspase-1, a cysteine protease, is primarily involved in inflammation and pyroptosis—a form of programmed cell death. It activates interleukin (IL)-1β and IL-18, both implicated in psoriasis pathogenesis. Furthermore, Caspase-1 may alter lipid metabolism by inhibiting lipoprotein lipase (LPL) and upregulating Sterol Regulatory Element-Binding Proteins (SREBPs), transcription factors responsible for lipid synthesis in the liver (12,13). Caspase-1 is increasingly recognized as a molecular link between inflammation and metabolic dysregulation. In obesity-associated psoriasis, adipocyte-derived NLRP3 activation and caspase-1 signaling contribute to a chronic inflammatory milieu, further aggravating disease severity (14). This inflammatory-metabolic crosstalk via caspase-

1 may help explain the increased cardiovascular risk in psoriatic patients, independently of traditional lipid parameters (15,16).

This study aimed to investigate plasma levels of PCSK9 and Caspase-1 in psoriasis patients compared to healthy individuals, in order to evaluate their potential roles in lipid metabolism dysregulation and cardiovascular risk.

Patients and Methods

Study Population: A total of 27 patients diagnosed with psoriasis (16 women, 11 men) and 25 healthy controls (13 women, 12 men; age-matched) were included in the study. Inclusion criteria for the patient group included clinical diagnosis of psoriasis. Control subjects were free from any disease or medication. The ages of the patients were 53.8 ± 14.44 years (ranging from 30 to 75) for males, and 56.2 ± 14.22 years (ranging from 23 to 73) for females. All participants gave informed consent, and the study was conducted in accordance with the Declaration of Helsinki, as approved by the Ethics Committee (Decision No. 30976/10).

Exclusion criteria for both groups included the presence of malignancies, other autoimmune diseases, myocardial infarction, or stroke.

*Clinical Assessment:*Psoriasis severity was evaluated using the Psoriasis Area and Severity Index (PASI).

Blood Sampling and Biochemical Analyses: Blood samples were collected in the morning after an 8-hour fasting period. Plasma levels of PCSK9 and Caspase-1 were quantified using enzyme-linked immunosorbent assay (ELISA) kits based on the Sandwich-ELISA principle. Absorbance was measured at 450 nm, and concentrations were calculated using standard curves, for PCSK9 (Human PCSK9 Proprotein convertase subtilisin/kexin type 9 ELISA Kit Fine test EH0251) assay range: 0.625–40 ng/mL; for Caspase-1 detection: based on a biotin-streptavidin HRP system (Elabscience Catalog No : E-EL-H0016; assay range: 78.13-5000 pg/mL)

Statistical Analyses: Data were analyzed using SPSS version 18.0. Results were presented as mean ± standard deviation (SD) and interquartile range. Comparisons between groups were made using the Student's t-test and Mann-Whitney U test for continuous variables. A p value <0.05 was considered statistically significant.

Results

Plasma PCSK9 level was significantly elevated in patients with psoriasis compared to healthy controls ($p < 0.001$), indicating a highly significant difference between the two groups (Figure 1).

Plasma Caspase-1 level was statistically lower in the psoriasis group (Figure 2). Despite inter-individual variability, the difference between groups was statistically significant ($p < 0.05$).

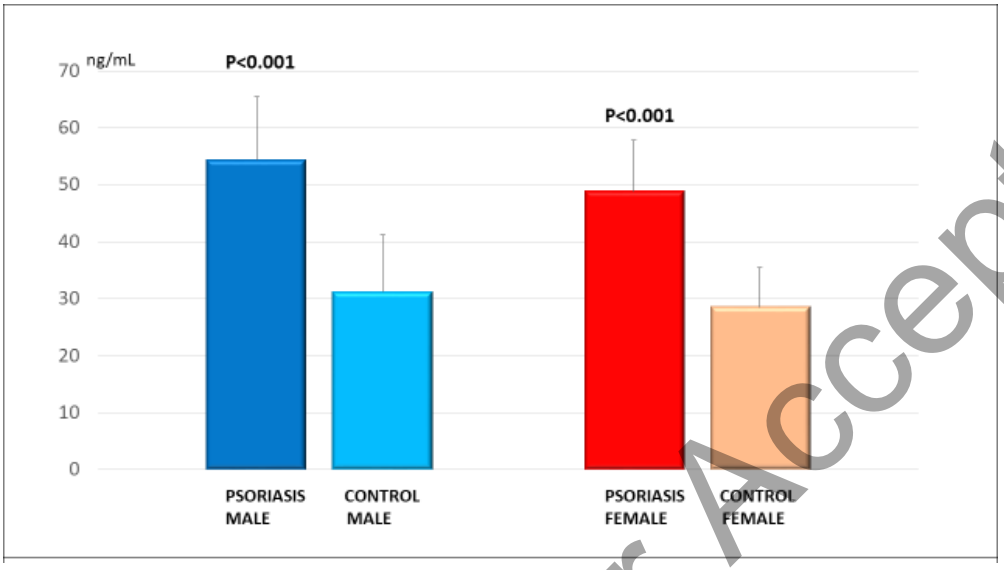

Figure 1. PCSK9 level in patients with psoriasis and control healthy individuals

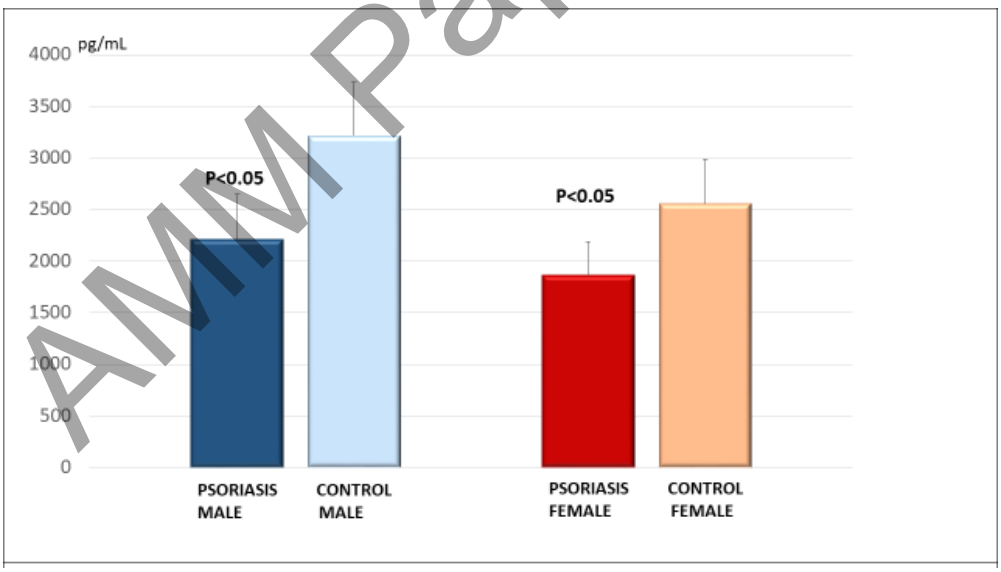

Figure 2. Caspase-1 level in patients with psoriasis and control healthy individuals

Discussion

Elevated plasma PCSK9 levels in patients suggest impaired LDL cholesterol clearance, consistent with previous findings linking PCSK9 with potential development of hypercholesterolemia and increased cardiovascular risk. Given the high prevalence of dyslipidemia among psoriasis patients, elevated PCSK9 may serve as a potential biomarker for CV risk stratification in this population. The relevance of PCSK9 in cardiovascular health is supported by both genetic studies and clinical evidence, since mutations in the PCSK9 gene lead to familial hypercholesterolemia, characterized by markedly elevated LDL-C levels and increased risk of premature atherosclerotic cardiovascular disease (ASCVD). From the other side, the loss-of-function mutations result in reduced LDL-C levels and significantly lower risk of coronary artery disease (CAD), independent of other traditional risk factors (17). The pro-atherogenic role of PCSK9 extends beyond lipid metabolism, observed in endothelial dysfunction, where PCSK9 promotes inflammation and oxidative stress in endothelial cells, leading to endothelial injury, an early step in atherogenesis. PCSK9 enhances foam cell formation by promoting LDL uptake and suppressing cholesterol efflux, contributing to plaque development. It may increase matrix metalloproteinase activity and vascular smooth muscle cell apoptosis, factors involved in plaque rupture and thrombosis (18-20).

Unexpectedly, Caspase-1 levels were lower in psoriasis patients compared to controls, despite the inflammatory nature of psoriasis. This finding may reflect a complex interplay of immune regulation and compensatory mechanisms, but it can also induce a form of programmed cell death known as pyroptosis, distinct from classical apoptosis. However, under certain conditions, caspase-1 may contribute to apoptosis by activating downstream effector caspases or through mitochondrial pathways. Alternatively, increased Caspase-1 activation at the tissue level may not translate into elevated circulating levels, possibly due to its consumption or compartmentalization. The inflammasome is a multiprotein cytosolic complex that senses pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs). In psoriasis, several DAMPs such as ATP, uric acid crystals, nucleic acids, and lipid derivatives are released from stressed or dying keratinocytes and immune cells, thereby triggering inflammasome activation, particularly the NLRP3 inflammasome. Upon assembly, the inflammasome recruits and activates pro-Caspase-1 via the adaptor protein ASC (apoptosis-associated speck-like protein containing a CARD). Activated Caspase-1 cleaves the inactive pro-forms of interleukin-1β (pro-IL-1β) and interleukin-18 (pro-IL-18) into their biologically active forms, IL-1β and IL-18, which are then secreted into the extracellular

environment (21,22). Studies have shown elevated expression of NLRP3, ASC, and caspase-1 in both lesional and non-lesional psoriatic skin, indicating a pre-activated innate immune state. In psoriasis, pyroptosis contributes to keratinocyte damage, immune cell activation, and amplification of the inflammatory loop, exacerbating both local and systemic inflammation. This non-apoptotic cell death mechanism may also disrupt skin barrier function, facilitating secondary inflammation and microbial colonization (23-25). Given that our patients are now receiving anti-inflammatory treatment, the therapy effect can account for our findings. As PCSK9 is most likely a genetically determined patient characteristic, the medication appears to have effects on caspase-1 but not on PCSK9.

Conclusion

This study demonstrates a significant elevation of plasma PCSK9 levels in patients with psoriasis, supporting its role in genetically associated dysregulated lipid metabolism associated with psoriasis. Conversely, Caspase-1 levels were unexpectedly lower in psoriasis patients compared to healthy controls, despite its well-established role in inflammasome activation and pro-inflammatory cytokine maturation. This discrepancy may reflect complex regulatory mechanisms, and differential local, therapy-induced versus genetic-systemic expression in psoriasis. The identification of elevated PCSK9 levels in psoriasis not only reinforces the systemic nature of the disease but also highlights a potential biomarker for cardiovascular risk stratification. Moreover, it supports the consideration of PCSK9 inhibitors as part of a personalized therapeutic strategy in psoriatic patients. The role of Caspase-1 contribution to local inflammation and metabolic dysregulation suggests that therapeutic targeting of inflammasome pathways and immune activation, may be beneficial in select patient subsets, particularly those with severe or treatment-resistant disease.

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