Dermatology Practical & Conceptual

Gasdermin A (GSDMA) Tissue Expression, Serum and Urinary Concentrations with Clinicopathologic Outcome in Psoriasis

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ABSTRACT

Introduction: Psoriasis is a frequent and incurable skin disease that is an important issue in contemporary dermatology, although its pathogenesis is still uncertain. Gasdermin A (GSDMA) is a member of the gasdermin protein family which are able to cause pore formation in cellular membranes leading to cell death called pyroptosis.

Objective: Our aim was to investigate the role of GSDMA in psoriatic patients.

Method: The study enrolled 60 patients with active plaque-type psoriasis and 30 sex- and age-matched volunteers without dermatoses. GSDMA concentration was assessed in serum and urine samples of all participants using ELISA. GSDMA tissue expression was assessed by immunohistochemistry.

Results: GSDMA serum concentration was significantly higher in patients compared to controls, whereas urinary GSDMA/creatinine ratio was insignificantly lower. GSDMA tissue expression was more prominent in psoriatic plaque compared to non-lesional patients' skin and healthy skin of subjects without dermatoses. There was a strong negative correlation between GSDMA serum concentration and ALT activity. GSDMA did not correlate with PASI or psoriasis duration.

Conclusions: Obtained results point to the probable involvement of GSDMA in psoriasis. GSDMA overexpression may probably lead to keratinocytes hyperproliferation and be responsible for triggering inflammation in psoriatic skin. Serum GSDMA could become psoriasis biomarker, whereas urinary GSDMA, not at this point.

Introduction

Psoriasis is a common chronic dermatosis that occurs with an average frequency of 2% worldwide [1]. Although this disease is a constant subject of scientists' investigations, its pathogenesis is still not fully understood. It encompasses genetic predisposition and complex immunological disturbances, additionally exacerbated by external stimuli [2,3]. The microscopic picture of psoriasis consists of the areas of acanthosis (epidermal hyperplasia) and parakeratosis in the stratum corneum with mounds of neutrophils (Munro's microabscesses), inflammatory infiltrates in the dermis, and dilated vessels in dermal papillae [4]. Clinically, such abnormalities translate into erythematous-scaly lesions called psoriatic plaques [4]. Due to the clinical appearance of the lesions and sometimes their significant exacerbation and unfavorable localization, psoriasis may impair the quality of patients' lives and ability to work [5,6]. Nowadays, there is a wide range of antipsoriatic therapies, both topical and systemic agents, including biological agents, yet the disease is not permanently curable [7,8]. That makes it an important problem of contemporary dermatology.

Gasdermins are a group of proteins that are made up of similar two-domain molecular structure, namely globular N- and C-terminal domains separated by a flexible linker region [9]. Their properties and functions are still being discovered, but available data point to their pleiotropic impact [10]. They have been associated with cell proliferation and differentiation. They are engaged in immune response, inflammation, and tumorigenesis [11]. Most importantly, they play a role in cell death via different pathways. Their unique chemical structure allows them to be executors of pyroptosis – the inflammatory cell death type resulting in the formation of pores in cellular membranes and the release of inflammatory cytokines [12]. It has been shown that cells that express gasdermins are determined to die in order to become a part of the cornified layer of the skin or the hardened tube of the inner root sheath or to disintegrate and release lipid compounds [13].

The name of the whole group - 'gasdermins' - originates from gasdermins' expression in the gastrointestinal tract and skin. This is exactly where the first member of this family is mainly observed – gasdermin A (GSDMA) [14]. Its encoding gene is located on chromosome 17q21.1 [15], and it has the ability to participate not only in pyroptosis but also in apoptosis by activating caspase 3 and 7 or via transforming growth factor β (TGF-β) [12]. So far, GSDMA has been implicated in the pathogenesis of asthma, inflammatory bowel diseases, systemic sclerosis, streptococcal infections in humans, and alopecia in mice [16-20]. Surprisingly, it has been suggested that GSDMA is probably not essential for the maintenance of the skin barrier, but its role emerges when pathogens or other stimuli appear, and that is related to the further path of GSDMA activation [14].

Our interest in GSDMA originated from the reports that a mutation in GSDMA gene in mice causes hyperplasia of the epidermis, which is exactly what we see in psoriatic skin [4,20,21]. Therefore, it would be valuable to investigate the role of GSDMA in psoriasis.

Objective

Considering the role of GSDMA in cell proliferation and differentiation and interesting findings regarding the results of its mutation, we wanted to study its potential role in psoriasis, which has been proven to be associated precisely with impaired keratinocytes proliferation and differentiation.

Materials and Methods

The study included 60 patients (21 women and 39 men) with active plaque-type psoriasis, at the mean age of 50±2.34 years and 30 sex- and age-matched volunteers without dermatoses and negative family history of psoriasis. The following exclusion criteria from the study were applied: age under 18 years, pregnancy, types of psoriasis other than plaque psoriasis, dietary restrictions and intake of oral medications at least three months prior to the study, application of topical agents at least one month prior to the study, malignancies, and renal dysfunction. The severity of psoriatic skin lesions was assessed using the Psoriasis Area and Severity Index (PASI) and was always performed by the same dermatologist in all patients. The study group of patients was divided into three subgroups depending on the severity of their disease: PASI I (PASI <10) - mild psoriasis, PASI II (PASI 10-20) - moderate psoriasis, and PASI III (PASI> 20) - severe psoriasis. Body mass index (BMI) was calculated as weight / height^2. Laboratory tests, including C-reactive protein (CRP), complete

blood count, fasting serum glucose, lipid profile, and markers of liver and kidney function, were performed. The study was approved by the Bioethics Committee of the Medical University of Bialystok (number: APK.002.303.2022 and APK.002.19.2020) and was conducted in accordance with the principles of the Helsinki Declaration. Each participant provided written consent before the study commenced.

Serum and Urine

Fasting blood samples were taken using vacuum tubes. They were left to clot for 30 minutes before centrifuging for 15 minutes at 2000g. Urine samples were taken as first morning specimens from a mid-stream; they were centrifugated for 10 minutes at 2000g. The obtained serum and urine were stored at -80 °C until further analysis. Laboratory parameters were measured using routine techniques. GSDMA concentrations were measured with an enzyme-linked immunosorbent assay (ELISA) provided by EIAab® (E11790h) with a minimum detectable dose of 0.156-10 ng/ml. The concentrations were assessed by interpolation from calibration curves prepared with standard samples provided by the manufacturer. All the tests were performed by the same person in standardized laboratory settings.

Tissue

Tissue samples were collected from 33 patients with psoriasis and 20 sex- and age-matched volunteers without skin diseases. All participants did not apply any topical agents on the skin at least a month before the biopsy. Biopsies, obtained from the trunk using a 4 mm punch after local anesthesia, included one each from psoriatic plaque and non-lesional skin in patients and one from non-lesional skin in controls performed during the surgical removal of benign skin lesions. Tissue samples were then fixed in 10% buffered formalin solution. After preservation, they were embedded in the paraffin blocks, and cut into 4 μm sections on silanized slides. The next step was an overnight incubation at 60° C, deparaffinization, and rehydration of tissues. Slides were then incubated with 3% hydrogen peroxide solution to block endogenous peroxidase and with protein block to avoid nonspecific antibody binding. Next, tissues were incubated with rabbit polyclonal anti-human GSDMA antibody (HPA023313, dilution 1:50, Clone OTI1, Sigma-Aldrich®) for 30 minutes at room temperature. Then, Post Primary Block and Novolink Polymer were used (Leica Novolink Polymer Detection System®, United States). Protein expression was visualized with Novolink DAB solution and cell nuclei with hematoxylin (Leica Novolink Polymer Detection System®, United States). Positive control of immunostaining was sebaceous cells in normal skin (Figure 1A).

The presence of GSDMA was presented using a semi-quantitative method. Intensity and localization of immunostaining were analyzed and defined as follow: low expression – weak/medium staining intensity in stratum corneum of epidermis; medium expression – weak/medium staining intensity in stratum corneum, granulosum and spinosum, up to 2/3 of the epidermis; strong expression – strong staining intensity in more than 2/3 of the epidermis or in the whole epidermis. Staining was observed mostly in cytoplasm of epithelial cells, but nuclear staining in cases with strong expression was also noted. Figure 1 (A-L) presents the expression of GSDMA in patients and controls.

Statistical Analysis

All analyses were performed in GraphPad 9.4 Prism. The normally distributed data were analyzed using a one-way analysis of variance (ANOVA) and shown as mean ± SD. The non-Gaussian data were presented as median (full range) and analyzed using non-parametric Mann–Whitney. The chi-square test of independence was used to assess the relationship between two nominal variables. The correlations between the examined parameters were evaluated with Spearman's rank test. The differences were deemed statistically significant when $P < 0.05$.

Results

The basic information on patients and controls is presented in Table 1. We enrolled 60 psoriatic patients (39 men and 21 women) and 30 controls (20 men and 10 women) in total. There was no statistically significant difference between patients and controls in terms of age, sex, or BMI (NS).

Serum and Urine

Serum and urine were assessed in 60 patients and 30 controls. The median GSDMA serum concentration in patients was 0.5437 (0.03–1.407) ng/ml, whereas in the controls it was – 0.3622 (0.031–0.793) ng/ml. The median urinary concentration of GSDMA in patients was 0.138 (0.012–0.779) ng/ml, whereas in the controls it was – 0.1235 (0.027-0.285) ng/ml. The median ratio between urinary GSDMA and urinary creatinine in patients was 0.00295 (0.0005–0.0243), whereas in the controls it was 0.00345 (0.0006–0.0316).

The serum concentration (Figure 2A) and absolute urinary concentration (Figure 2B) of GSDMA were significantly higher in psoriatic patients than in controls without skin diseases ($P < 0.05$), whereas the urinary GSDMA/creatinine ratio was insignificantly lower (Figure 2C).

After the division of patients into three groups depending on psoriasis severity on PASI, GSDMA serum concentrations were higher in subjects with higher PASI; however, there was no significant difference between the groups (NS) (Figure 3A.). After the division of patients into subgroups depending on the psoriasis duration (Figure 3B) or by sex

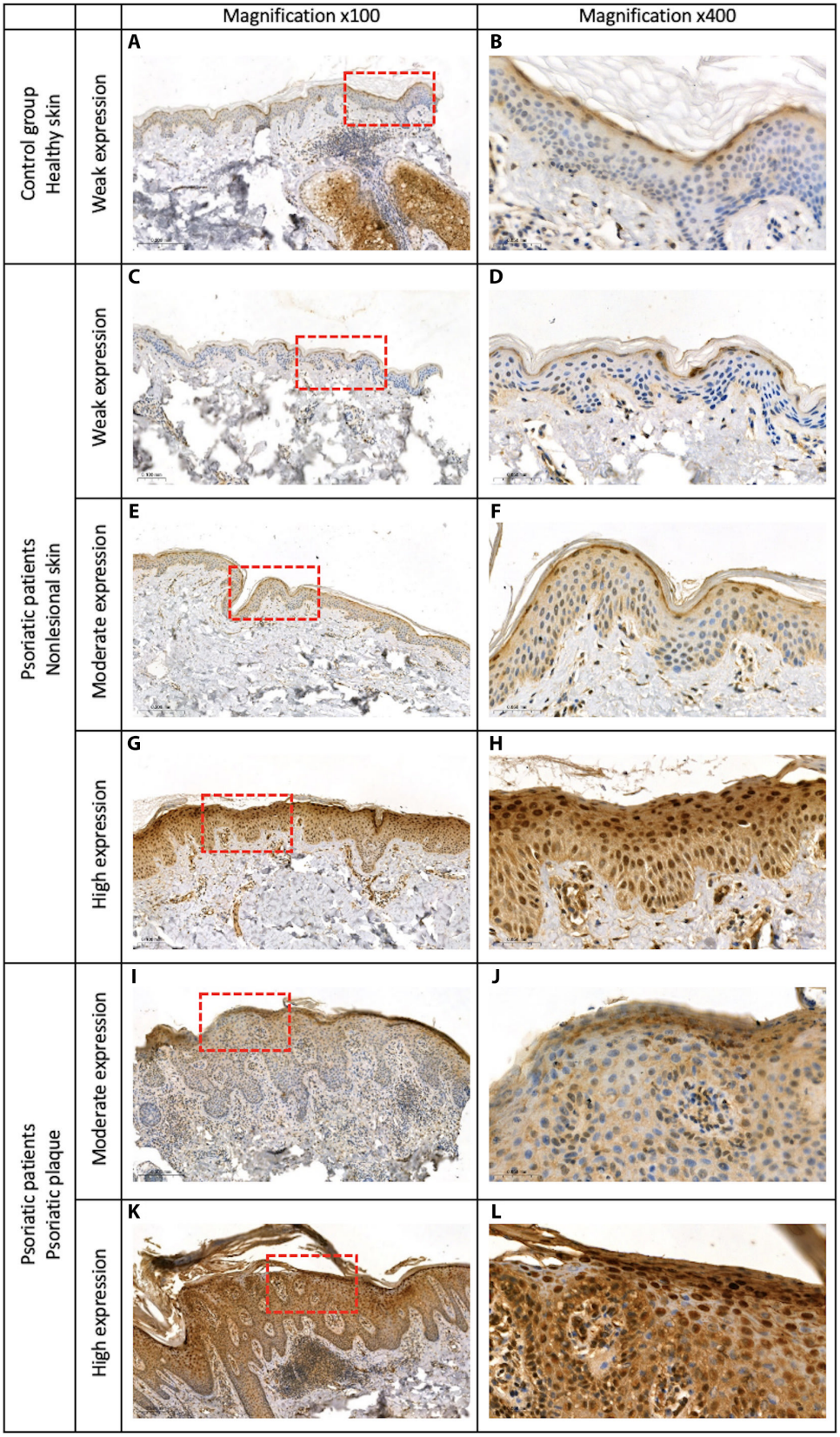

Figure 1. Immunohistochemical expression of GSDMA in healthy group and patients with psoriasis. Healthy skin – GSDMA weak expression in stratum corneum, also positive staining in the sebaceous glands (A,B); Non-lesional skin (patients with psoriasis) – weak expression in stratum corneum (C,D), medium (E,F) and high (G,H) expression in stratum corneum, granulosum, and spinosum, up to 2/3 of the epidermis; Lesional skin (psoriasis) – medium expression in stratum corneum, granulosum and spinosum, up to 2/3 of the epidermis (I,J); Lesional skin (psoriasis) – strong expression in more than 2/3 of the epidermis or in the whole epidermis (K,L). Magnifications x 100 and x 400.

(Figure 3C), there was no significant difference between the groups (NS). After the division of patients according to BMI, there was no significant difference between the subgroups (NS, data not shown).

There was no significant correlation between serum concentration of GSDMA and PASI, BMI, age, sex of patients, or psoriasis duration (NS).

Among the laboratory investigations, there was a strong significant negative correlation between GSDMA serum concentration and ALT activity (R = -0.38; P = 0.0026) (Figure 4).

Tissue

Tissue GSDMA expression was assessed in 33 patients and 20 controls. The presence of GSDMA was presented as low expression (in stratum corneum), moderate expression (in stratum corneum, granulosum, and spinosum, up to 2/3 of the epidermis), or strong expression (in more than 2/3 of the epidermis or in the whole epidermis). Twenty-one samples taken from the psoriatic plaques exhibited strong GSDMA expression, 11 samples had moderate expression, and only one sample had low expression. Among the samples taken from the non-lesional skin of patients, seven samples exhibited strong GSDMA expression, 13 samples had moderate expression, and 13 samples had low expression. Among the control group, all samples exhibited low GSDMA samples, and only 1 with strong GSDMA expression.

The majority of the samples taken from the psoriatic plaque exhibited strong GSDMA expression, whereas the majority of samples from the healthy skin of controls exhibited low GSDMA expression. Strong expression of GSDMA was significantly more prevalent in psoriatic plaques compared to non-lesional patients' skin and healthy skin of controls (P < 0.01 and P < 0.001, respectively). Low expression of GSDMA was significantly more prevalent in the healthy skin of controls than in non-lesional patients' skin and psoriatic plaques (P < 0.001 and P < 0.01, respectively). There was no sample with moderate expression of GSDMA in healthy controls (Figure 5).

After the division of patients according to psoriasis severity on PASI, in subjects with mild psoriasis (PASI I), we observed samples only with low GSMDA expression. The highest number of samples with strong GSDMA expression was found in the subgroup of severe psoriasis (PASI III) (Figure 6).

Table 1. The basic information on patients and controls.

Parameter	Controls (n=30)	Psoriatic patients (n=60)
Sex (M/F)	20/10	39/21 NS
Age [years]	48±2.45	50±2.34 NS
Height [cm]	1.75 (1.5-1.9)	1.71 (1.5-1.9) NS
Weight [kg]	78.40±2.9	85.43±2.5 NS
BMI	25.85±0.77	27.85±0.64 NS

NS, non-significant.

Conclusions

We here report on the possible role of GSDMA in psoriasis. Unfortunately, GSDMA seems to be understudied so far, and the data on its biological role and involvement in other diseases are scarce. That makes our results challenging to interpret at this point. Nevertheless, as for dermatoses, a very recent publication investigated GSDMA in atopic dermatitis (AD). Surprisingly, GSDMA had lower expression in the AD

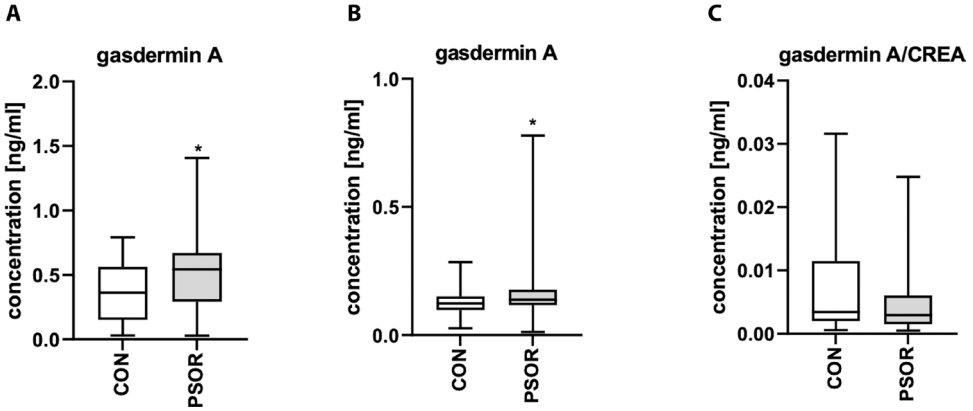

Figure 2. Serum GSDMA concentration (A), absolute urinary GSDMA concentration (B), and urinary GSDMA/creatinine concentration ratio (C) in patients and controls; serum GSDMA concentration after the division of patients depending on PASI, psoriasis duration, and sex compared to controls. *means a statistically significant difference with P < 0.05.

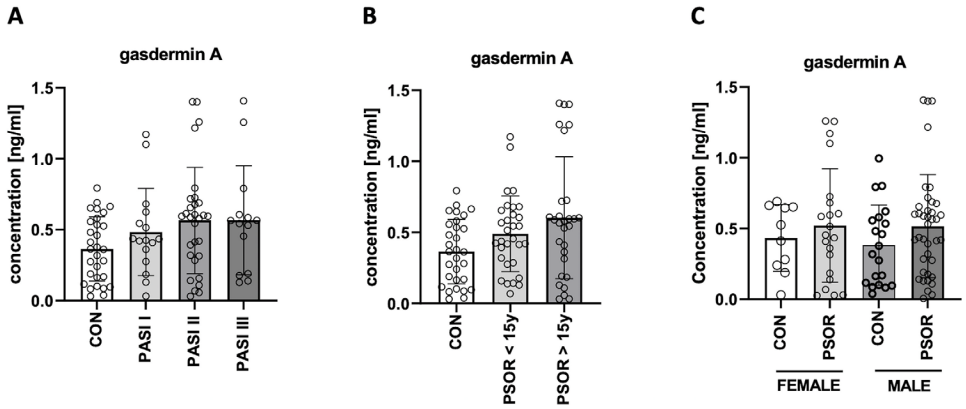

Figure 3. The division of patients depending on (A) PASI, (B) psoriasis duration, and (C) gender compared to controls.

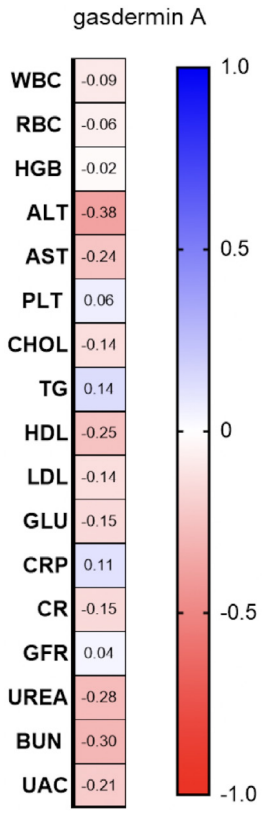

Figure 4. Correlations between serum gasdermin A concentration and basic laboratory parameters. (ALT, alanine transaminase; AST = asparagine transaminase; TG = triglycerides; Chol = total cholesterol; HDL = high-density lipoprotein; LDL = low-density lipoprotein; GLU = fasting glucose; CRP = C-reactive protein; CR = creatinine; GFR = glomerular filtration rate; UAC = uric acid; Urea; WBC = white blood cells; RBC = red blood cells; HGB = hemoglobin; PLT = platelets.**)**.

lesions than in healthy skin, and GSDMA1/A3-deficiency selectively enhanced the Th cells type 2 response. The authors suggested that GSDMA may be involved in AD pathogenesis due to its influence on keratinocytes differentiation and cornification [22].

One of the key yet few studies shedding some light on GSDMA role which could be applied in psoriasis is that by Tanaka et al. In the mice with GSDMA3 mutation, they observed epidermal hyperplasia [21], which is interesting considering histopathological findings in psoriasis. However, in the opposite experiment on GSDMA knock-out mice, there were no changes in their clinical skin condition [21]. The authors suggested that it might be due to other genes taking over the role of GSDMA and that its biological role emerges when stimulated by external factors [21]. Nevertheless, these observations must be approached with caution because they are made on mice, which have three GSDMA orthologs (GSDMA 1-3), whereas humans have only one [21], so results based on GSDMA3 specifically cannot be directly extrapolated on humans, especially GSDMA3, the only gene in which the mutation exhibited epidermal alterations. The authors of the study attempted to explain the mechanism underlying acanthosis since it is not fully clear. They suggested that it is the inflammation in the mice's skin that leads to epidermal hyperplasia [21]. They focused on TGF-β because GSDMA is engaged in TGF-β-mediated apoptosis, and overexpression of TGF-β triggers skin inflammation [21]. TGF-β up-regulates GSDMA and therefore promotes apoptosis [12]. On the other hand, TGF-β has been investigated in psoriasis, and an elevated concentration of TGF-β has been observed in the plasma and scales of psoriatic patients [23]. In addition, this plasma level was associated with skin lesion severity and decreased after antipsoriatic therapy [23,24]. Another study that attempted to discover the role of GSDMA in the skin was that by Lin et al. Their team observed that induction of GSDMA3 expression in mice leads to epidermal hyperplasia and skin inflammation [20]. They concluded that keratinocytes that exhibited GSDMA overexpression suffered from oxidative stress and underwent spontaneous necrosis followed by inflammatory condition

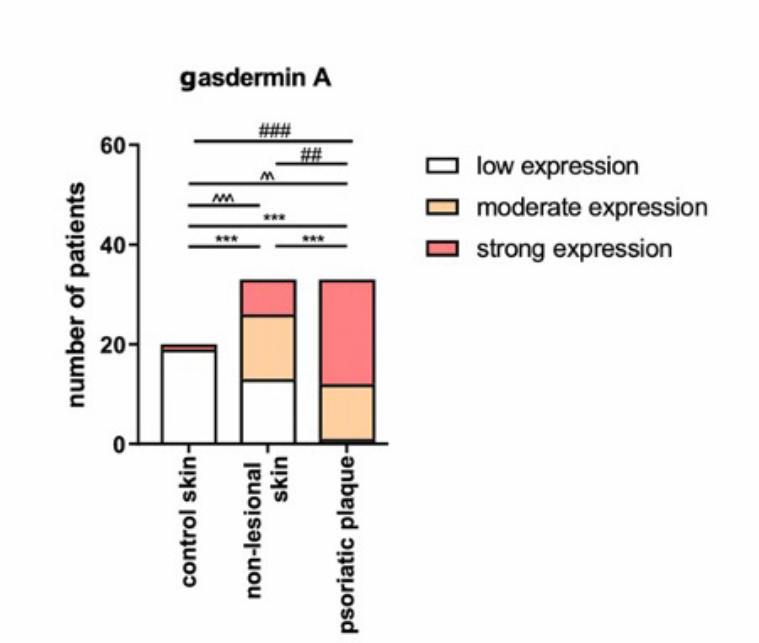

Figure 5. The expression of GSDMA (strong, moderate, low) depending on the site of biopsy (psoriatic plaque, non-lesional patients' skin or healthy skin of controls).

***vs low expression with p<0.001, ^^/^^^ vs moderate expression with p<0.01/0.001 respectively, ##/### vs strong expression with p<0.01/p<0.001, respectively.

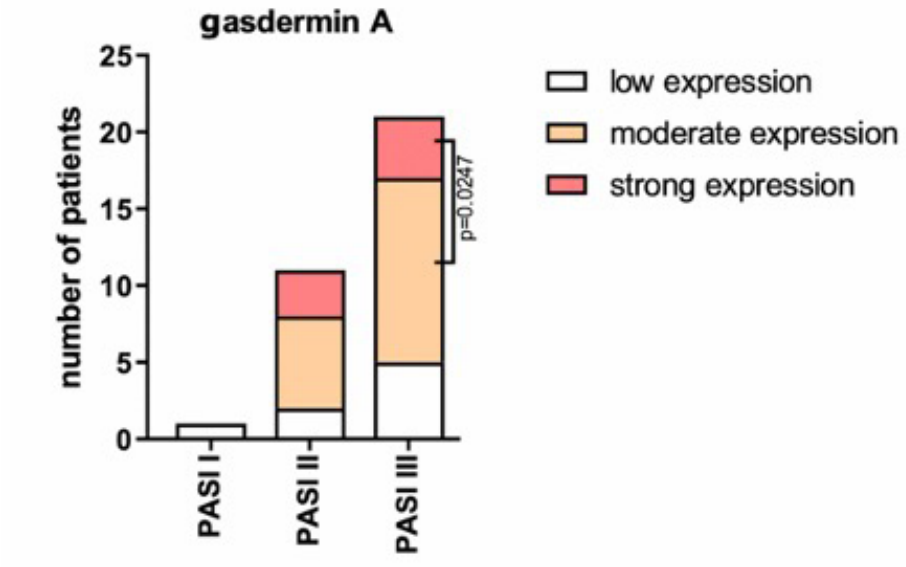

Figure 6. The extent of expression of GSDMA in psoriatic plaque depending on the psoriasis severity in PASI.

in the epidermis [20]. Oxidative stress plays a major role in psoriasis pathology [25].

Although the data on GSDMA are poor, there are more rationales that could support GSDMA's engagement in psoriasis and point to its role in its pathogenesis. Activation of GSDMA leads to stimulation of caspase 3 and further to induction of autophagy [12]. Wang et al. suggested that autophagy is activated in psoriatic epidermis and is probably important in the proliferation and differentiation of keratinocytes in psoriasis [26]. Overexpression of the autophagy-related protein, SQSTM1 has been observed in psoriatic epidermis [27]. Autophagy promotes high-mobility group box 1 (HMGB-1) secretion in psoriasis and leads to chronically sustained inflammatory condition in this dermatosis [26]. Another piece of evidence justifying this hypothesis is that there are polymorphisms in the autophagy gene described which are related to psoriasis [26].

Herein, the data on GSDMA role in the skin are scarce and also sometimes inconsistent. Apparently, GSDMA takes part in cell death in different mechanisms but surely its overexpression exacerbates inflammation. There are also many connections between GSDMA and already recognized links

in the pathogenesis of psoriasis. We must take into consideration, though, that almost all available studies that focused on the role of GSDMA particularly in the skin were performed on mice, not humans. The only experiment on psoriatic skin tissue, albeit on a very small sample size, examined the expression of GSDMA gene, present in all epidermal layers but most prominent in the stratum corneum [28]. We were not able any other study using immunohistochemistry in psoriatic tissue to assess the role of gasdermins.

Based on the significantly higher GSDMA serum concentration in psoriatic patients and its more prominent expression in plaque psoriasis compared to subjects without psoriasis, we could certainly suspect that it actually plays a role in psoriasis, and its serum concentration could become its biomarker. Overexpression of GSDMA in plaque psoriasis compared to non-lesional skin and healthy skin of controls seems consistent with findings by Lin et al. [20]. Its presence may probably lead to keratinocytes hyperproliferation and be responsible for triggering inflammation in psoriatic skin. However, the exact mechanism in psoriasis remains uncertain. On the other hand, considering the involvement of GSDMA in several types of cell death, it cannot be fully ruled out that GSDMA may be compensatively elevated to lead the cells toward apoptosis – which requires further research.

As for the urine, it is an ideal fluid to collect for screening since it is easy and painless to donate. Considering different kidney functions in patients, we presented our results as absolute urinary concentrations and with creatinine ratio to obtain objective results. Unfortunately, we did not observe significant differences between patients and controls in terms of urinary GSDMA/creatinine ratio, which would be a more objective parameter than absolute urinary concentration, so urine probably cannot be used for biomarker detection in this group of patients. We are not familiar with any other study assessing urinary GSDMA.

Serum GSDMA was not directly correlated with psoriasis severity in PASI, nor is there any significant difference between the PASI subgroups regarding its concentration, although serum GSDMA concentrations were higher in patients with more severe psoriasis and in such subjects, there was higher expression of GSDMA in psoriatic plaque observed. Instead, patients with mild psoriasis had only low expression. Apparently, GSDMA concentration or expression does not directly depend on psoriasis severity and cannot be used as its marker, but its involvement in psoriasis pathogenesis seems more prominent in more severe cases.

As for demographic parameters, namely age and sex, there were no associations with GSDMA serum concentrations, so apparently it would be equally useful regardless of these features. Psoriasis duration does not seem to influence GSDMA concentration either.

In our study, we obtained a negative correlation between GSDMA and ALT, which could serve as an interesting starting point for more in-depth future studies. Therefore, we can hypothesize that GSDMA may exert a protective influence on the liver. Knorr et al. reviewed the role of pyroptosis (thus gasdermins) in different liver diseases, but they did not mention any engagement of GSDMA in this matter [29]. On the other hand, GSDMA gene was included in the set of pyroptosis-related genes that have been found useful to assess the risk score of hepatocellular carcinoma (HCC) [30]. Apart from research on GSDMA in HCC, we were not able to find any information on its role in liver disorders, so we have no data for comparison with our results.

Study limitations include a small, predominantly Caucasian sample and a scarcity of relevant GSDMA studies.

Our study comprehensively examined the role of GSDMA in psoriasis. We report on its increased concentrations in psoriatic patients' sera. Moreover, we found its more prominent expression in plaque psoriasis compared to non-lesional patients' skin and healthy skin of subjects without dermatoses. Our study shows that GSDMA is probably engaged in psoriasis pathogenesis, and its overexpression may probably lead to keratinocytes hyperproliferation and be responsible for triggering inflammation in psoriatic skin. GSDMA serum concentration could be used as its biomarker but not of skin lesion severity. Urinary GSDMA is probably not useful as a biomarker. Considering that the data on GSDMA are sparse and that its role in the skin is unclear, further studies are needed to understand GSDMA function, including in psoriasis. Further research on GSDMA as a potential drug target would be of high value.

References

1. Farley E, Menter A. Psoriasis: Comorbidities and associations. *G. Ital. Dermatol. Veneorol*. 2011;146:9–15.
2. Hirotsu C, Rydlewski M, Araújo MS, et al. Sleep loss and cytokines levels in an experimental model of psoriasis. *PLoS ONE*. 2012; 7:e51183.
3. Lanna C, Mancini M, Gaziano R, et al. Skin immunity and its dysregulation in psoriasis. *Cell Cycle*. 2019;18:2581-2589.
4. Rendon A, Schäkel K. Psoriasis Pathogenesis and Treatment. *Int J Mol Sci*. 2019; 20:1475.
5. Nabieva K, Vender R. Quality of Life and Body Region Affected by Psoriasis: A Systematic Review. *Actas Dermosifiliogr*. 2023; 114:33-38.
6. Saeki H, Kanai Y, Murotani K, et al. Work productivity in real-life employed patients with plaque psoriasis: Results from the ProLOGUE study. *J Dermatol*. 2022;49:970-978.
7. Information about psoriasis, available at: https://www.psoriasis.org/about-psoriasis/ accessed on August 7, 2023.
8. Armstrong AW, Read C. Pathophysiology, Clinical Presentation, and Treatment of Psoriasis: A Review. *JAMA*. 2020; 323: 1945-1960.

9. Rogers C, Alnemri ES. Gasdermins in Apoptosis: New players in an Old Game. *Yale J Biol Med*. 2019;92:603-617.
10. Kovacs SB, Miao EA. Gasdermins: Effectors of Pyroptosis. *Trends Cell Biol*. 2017;27:673-684.
11. Zou J, Zheng Y, Huang Y, Tang D, Kang R, Chen R. The Versatile Gasdermin Family: Their Function and Roles in Diseases. *Front Immunol*. 2021;12:751533.
12. Kuc-Ciepluch D, Ciepluch K, Arabski M. Gasdermin family proteins as a permeabilization factor of cell membrane in pyroptosis process. *Postepy Hig Med Dosw* 2021;75:337-344.
13. Lunny DP, Weed E, Nolan PM, Marquardt A, Augustin M, Porter RM. Mutations in gasdermin 3 cause aberrant differentiation of the hair follicle and sebaceous gland. *J Invest Dermatol*. 2005;124:615-21.
14. Liu X, Xia S, Zhang Z, Wu H, Lieberman J. Channelling inflammation: gasdermins in physiology and disease. *Nat Rev Drug Discov*. 2021;20:384-405.
15. Li L, Kovacs SB, Jørgensen I, Larson HN, Lazear HM, Miao EA. Role of Caspases and Gasdermin A during HSV-1 Infection in Mice. *Viruses*. 2022;14:2034.
16. Deng W, Bai Y, Deng F, et al. Streptococcal pyrogenic exotoxin B cleaves GSDMA and triggers pyroptosis. *Nature*. 2022;602: 496-502.
17. Söderman J, Berglind L, Almer S. Gene Expression-Genotype Analysis Implicates GSDMA, GSDMB, and LRRC3C as Contributors to Inflammatory Bowel Disease Susceptibility. *Biomed Res Int*. 2015;2015:834805.
18. Terao C, Kawaguchi T, Dieude P, et al. Transethnic meta-analysis identifies GSDMA and PRDM1 as susceptibility genes to systemic sclerosis. *Ann Rheum Dis*. 2017;76:1150-1158.
19. Yu J, Kang MJ, Kim BJ, et al. Polymorphisms in GSDMA and GSDMB are associated with asthma susceptibility, atopy and BHR. *Pediatr Pulmonol*. 2011;46:701-8.
20. Lin HY, Lin PH, Wu SH, Yang LT. Inducible expression of gasdermin A3 in the epidermis causes epidermal hyperplasia and skin inflammation. *Exp Dermatol*. 2015;24:897-9.
21. Tanaka S, Mizushina Y, Kato Y, Tamura M, Shiroishi T. Functional conservation of Gsdma cluster genes specifically duplicated in the mouse genome. *G3* (Bethesda). 2013;3:1843-50.
22. Huang LY, Li ST, Lin SC, et al. Gasdermin A Is Required for Epidermal Cornification during Skin Barrier Regeneration and in an Atopic Dermatitis-like Model. *J Invest Dermatol*. 2023;S0022-202X(23)01938-3.
23. Flisiak I, Porebski P, Flisiak R, Chodynicka B. Plasma transforming growth factor beta1 as a biomarker of psoriasis activity and treatment efficacy. *Biomarkers*. 2003;8:437–443.
24. Flisiak I, Chodynicka B, Porebski P, Flisiak R. Association between psoriasis severity and transforming growth factor beta(1) and beta (2) in plasma and scales from psoriatic lesions. *Cytokine*. 2002;19:121–125.
25. Dobrică EC, Cozma MA, Găman MA, Voiculescu VM, Găman AM. The Involvement of Oxidative Stress in Psoriasis: A Systematic Review. Antioxidants (Basel). 2022; 11:282.
26. Wang Z, Zhou H, Zheng H, et al. Autophagy-based unconventional secretion of HMGB1 by keratinocytes plays a pivotal role in psoriatic skin inflammation. *Autophagy*. 2021;17:529-552.
27. Wu DJ, Adamopoulos IE. Autophagy and autoimmunity. *Clin Immunol*. 2017;176:55-62.
28. Zhang, D., Li, Y., Du, C, et al. Evidence of pyroptosis and ferroptosis extensively involved in autoimmune diseases at the single-cell transcriptome level. *J Transl Med* 2022; 20:363.
29. Knorr J, Wree A, Feldstein AE. Pyroptosis in Steatohepatitis and Liver Diseases. *J Mol Biol*. 2022;434:167271.
30. Wang J, Huang Z, Lu H, Zhang R, Feng Q, He A. A Pyroptosis-Related Gene Signature to Predict Patients' Prognosis and Immune Landscape in Liver Hepatocellular Carcinoma. *Comput Math Methods Med*. 2022 Feb 16;2022:1258480.