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Research Article

Gasdermin C (GSDMC) is Overexpressed in Psoriatic Tissue and Elevated in Psoriatic Serum: A Potential Marker of Cell Proliferation and Local Hypoxia in Psoriasis?

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Psoriasis is an important disease in dermatological practice and, despite many studies, its pathogenesis is still not fully understood. Gasdermin C (GSDMC; melanoma-derived leucine zipper-containing extranuclear factor, MLZE) is a member of the gasdermin protein family. The study enrolled 60 patients with active plaque-type psoriasis and 30 volunteers without dermatoses. GSDMC concentration was assessed in serum and urine samples of all participants using ELISA. GSDMC tissue expression was assessed by immunohistochemistry. The GSDMC concentration was significantly higher in serum of patients than in controls ($p < 0.001$). A urinary GSDMC/creatinine ratio was significantly lower in patients than in controls ($p < 0.05$). Psoriatic lesions exhibited a significantly higher expression of GSDMC than nonlesional patients' skin or controls' skin ($p < 0.001$, $p < 0.01$, respectively). There was a positive correlation between the GSDMC serum concentration and the age of patients ($R = 0.31$, $p = 0.015$) and a negative correlation between GSDMC and RBC ($R = -0.37$; $p = 0.0038$), HGB ($R = -0.26$; $p = 0.047$), and urea concentration ($R = -0.36$; $p = 0.04$). Our study shows the potential involvement of GSDMC in psoriasis. An increased serum GSDMC and a decreased urinary GSDMC/creatinine ratio could be considered noninvasive psoriasis biomarkers, especially of local hypoxia or cell proliferation.

1. Introduction

One of the most common skin diseases is psoriasis. It affects about 125 million people worldwide [1]. It is a genetically determined, chronic, and incurable disorder that is troublesome for both patients and doctors [2]. The hallmark of psoriasis is complex immunological alterations, which lead to the resistance of keratinocytes to apoptosis, epidermal hyperproliferation, and impaired cell differentiation [3, 4]. In psoriasis, the epidermal turnover time is shortened even 6-7 times [5]. From a clinical point of view, the most frequent type of psoriasis—plaque—manifests with erythematous-scaly lesions on the extensor surfaces of the extremities, lumbosacral area, or scalp [6]. Moreover, psoriasis can affect joints or nails, which translates into physical impairment [2, 7]. Considering the big physical and psychological burden of this dermatosis, it became a prominent target of scientific research in order to uncover its pathogenesis and search for biomarkers and new therapeutic options.

In this study, we aimed to investigate psoriasis pathogenesis with a focus on the potential role of a protein from the gasdermin family. This is a relatively recently discovered group of proteins that share some similar structural and functional features and exert wide influence on different biological processes [8].

This time, our study focused on gasdermin C (GSDMC; melanoma-derived leucine zipper-containing extranuclear factor, MLZE) which is the third of the six proteins from the gasdermin family. Its encoding gene is located on chromosome 8q24 [9]. In mice, on which experiments are often performed, there are four GSDMC orthologs (Gsdmc 1–4), unlike humans who possess only one GSDMC [10]. Similar to other gasdermins, GSDMC is made up of the cytotoxic N-terminal domain and the inhibitory C-terminal domain, which are brought together by a polypeptide linker [11]. After the cleavage by caspase 6 or 8, GSDMC leads to pore formation in the cellular membranes and takes part in the inflammatory cell death called pyroptosis [12, 13]. The role of GSDMC in physiology and pathology is still uncertain. Its expression has been observed for instance in the trachea, spleen, stomach, or oesophagus [14]. GSDMC has been studied with regard to tumor development, and its nature seems two-faced in this matter. It has been found to exert a suppressive influence on cancer cells in gastric cancer and to be engaged in tumor progression in breast cancer [15]. Moreover, its overexpression has been found in melanoma, and its expression levels in mice correlated with the metastatic ability of B16 melanoma sublines (hence, its initial name is MLZE) [8, 16].

GSDMC has never been assessed in psoriatic patients' serum, urine, or tissue by immunohistochemistry, so our experiment is the first of this kind.

Besides GSDMC, we have already analyzed other gasdermins in psoriatic patients and obtained interesting results [17, 18]. However, in this particular paper, we present the outcomes of our study concerning GSDMC.

2. Materials and Methods

2.1. Participants. The study was conducted on 60 patients (21 women and 39 men) with present plaque-type psoriasis, at a mean age of 50 ± 2.34 years, and 30 volunteers without skin diseases and a negative family history of psoriasis, matched with the study group considering gender and age (Table 1). The study was approved by the Bioethics Committee of the Medical University of Bialystok (nos. APK.002.303.2022 and APK.002.19.2020) and was conducted in accordance with the principles of the Helsinki Declaration [19]. The exclusion criteria from the study were age under 18 years old, pregnancy, types of psoriasis other than plaque psoriasis, dietary restrictions, and intake of oral medications for least 3 months before the study, malignancies, and kidney impairment.

The severity of skin lesions was evaluated by the Psoriasis Area and Severity Index (PASI) always by the same dermatologist. Patients were additionally divided into three subgroups according to the severity of psoriasis: PASI I (PASI <10)—mild psoriasis; PASI II (PASI 10–20)—moderate psoriasis; and PASI III (PASI >20)—severe psoriasis. Another division was based on the psoriasis duration: more or less than 15 years. Body mass index (BMI) was counted as weight/height2. Laboratory tests, including C-reactive protein (CRP), complete blood count, glucose, lipid parameters, aminotransferases, creatinine (and GFR), urea and uric acid, were performed before the study.

2.2. Serum and Urine Evaluation. Fasting blood samples were taken using vacuum tubes. They were left to clot for 30 minutes before centrifuging for 15 minutes at 2000 g. Urine samples were taken as first morning specimens from a midstream; they were centrifuged for 10 minutes at 2000 g. The obtained serum and urine were stored at −80°C until further analysis. At the same time, laboratory parameters were measured using routine techniques. GSDMC concentrations were measured with an enzyme-linked immunosorbent assay (ELISA) (EIAab®) (Wuhan, China, E1646h) according to the manufacturer's instructions by the same investigator in standardized laboratory settings. In brief, 50 μl of standards and test samples was subjected to a 96-well plate coated with a monoclonal antibody directed against GSDMC and mixed with 50 μl of detection reagent A. After incubation, the plate was rinsed three times using an Elx50-automated microplate washer (BioTEK®). Then, 100 μl of horseradish peroxidase (HRP) was added to each well, incubated, and washed five times. Subsequently, TMB substrate solution was added to each well, and a colorimetric reaction was observed. After incubation, the enzymatic reaction was terminated, and the concentration of GSDMC was measured spectrophotometrically at 450 nm using a Multiskan FC microplate reader (Thermo Fisher Scientific®). The minimum detectable dose of GSDMC concentrations was 0.625–40 ng/ml.

2.3. Tissue Evaluation. Skin biopsy was performed on 33 patients with psoriasis and 20 sex- and age-matched volunteers without skin diseases. All participants were advised not to apply any topical agents to the skin at least a month before the biopsy. Participants were given a local anesthesia with 2% lignocaine, and then, the biopsy was taken from the trunk with a 4 mm punch. From the patients, two samples were taken: one from the lesional skin, psoriatic plaque, and the other one from the nonlesional, clinically healthy skin, approximately 2 cm from the psoriatic plaque. In controls, one skin sample was taken from the nonlesional skin and performed during the surgical removal of benign skin lesions. Tissue samples were then fixed in a 10% buffered formalin solution. After preservation, they were embedded in the paraffin blocks and cut into 4 μm sections on silanized slides. Then, overnight incubation at 60°C was performed, followed by deparaffinization and rehydration of tissues. The slides were then incubated with 3% hydrogen peroxide solution to block endogenous peroxidase and with the protein block to avoid nonspecific antibody binding. The tissues were then incubated with a rabbit polyclonal anti-human GSDMC antibody (dilution 1 : 50, Sigma-Aldrich®, Saint Louis, MI, USA, HPA026317) for 30 minutes at room temperature. Then, Post Primary Block and Novolink Polymer were used (Leica Novolink Polymer Detection System®, Deer Park, IL, USA). Protein expression was

Table 1: Basic demographic data of patients and controls.

Parameters	Controls ($n = 30$)	Psoriatic patients ($n = 60$)
Sex (M/F)	20/10	39/21 NS
Age (years)	48 ± 2.45	50 ± 2.34 NS
BMI	25.85 ± 0.77	27.85 ± 0.64 NS

NS, nonsignificant.

visualized with Novolink DAB solution and cell nuclei with hematoxylin (Leica Novolink Polymer Detection System®, USA).

The expression of GSDMC was presented by a semi-quantitative method, and the reaction was observed in the epidermis as follows: 0: no expression; 1: expression present. Figure 1 presents the negative expression of GSDMC in the control group 1(a), in the nonlesional patients' skin 1(b), and positive expression in the whole epidermis in the area of psoriatic plaque 1(c) (magnification ×100).

This study group was further divided, similar to the subjects who donated serum and urine, into three subgroups depending on the severity of the disease: PASI I: 8 patients, PASI II: 18 patients, and PASI III: 7 patients.

2.4. Statistical Analysis. The normally distributed data were analyzed using the one-way analysis of variance (ANOVA) and shown as mean ± SD. The non-Gaussian data were presented as the median (full range) and analyzed using the nonparametric Kruskal–Wallis test. If the results of ANOVA showed significant differences ($p < 0.05$), Tukey's HSD test was used to verify the level of significance between individual groups. Student's *t*-test or the nonparametric Mann–Whitney test was used to compare differences between the psoriasis group and the control group. The chi-square test of independence was used to test the relationship between two nominal variables. The correlations between the examined parameters were assessed with Spearman's rank test. A p value of less than 0.05 was considered to be a statistically significant difference. All analyses were performed in GraphPad 9.4 Prism.

3. Results

The study included 60 patients with plaque psoriasis (39 men and 21 women) and 30 volunteers without skin diseases and a negative family history of psoriasis as a control group (20 men and 10 women).

There was no statistically significant difference between patients and controls in terms of age, gender, or BMI (NS).

3.1. Serum and Urine. The median serum GSDMC concentration was 0.74 ng/ml (0.032–2.733) in patients and 0.4955 ng/ml (0.124–1.309) in controls. The median urinary concentration of GSDMC was 0.74 ng/ml (0.049–4.238) and 0.77 ng/ml (0.036–4.095) in controls. The median urinary GSDMC/creatinine ratio was 0.0105 (0.001–0.047) in patients and 0.0205 (0.001–0.157) in controls.

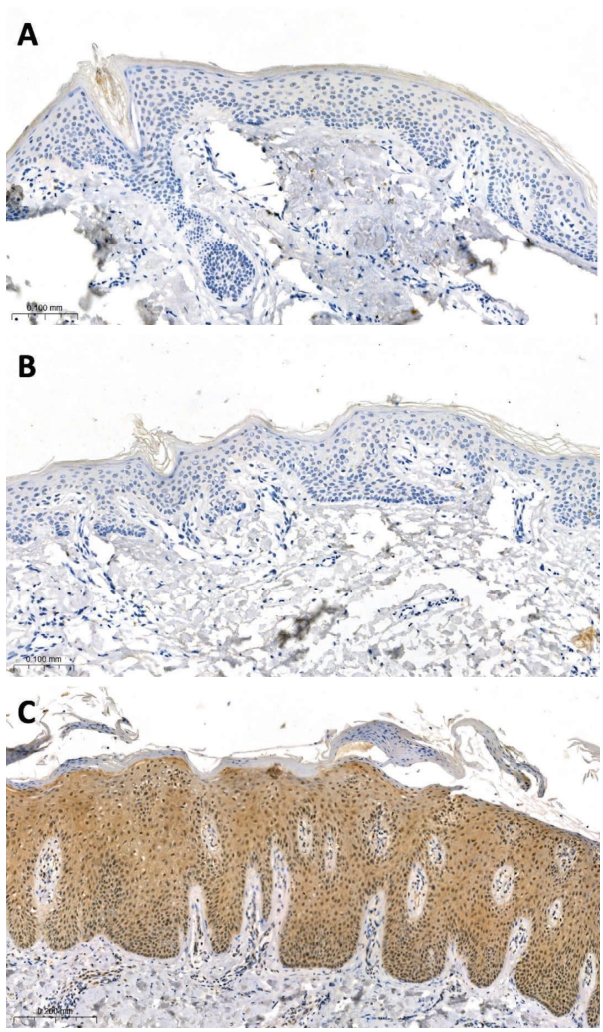

Figure 1: The expression of GSDMC: the negative expression of GSDMC in the control group (A), expression in the nonlesional patients' skin (B), and positive expression in the whole epidermis in the area of psoriatic plaque (C) (magnification ×100).

The serum concentration of GSDMC was significantly higher in psoriatic patients than in controls without skin diseases ($p < 0.001$) (Figure 2(a)). The absolute urinary concentration of GSDMC was higher in patients than in controls, but with no significance ($p > 0.05$) (Figure 2(b)). The urinary GSDMC/creatinine ratio was significantly lower in patients than in controls ($p < 0.05$) (Figure 2(c)).

Patients were divided into three groups depending on psoriasis severity in PASI. GSDMC serum concentrations were higher in subjects with higher PASI but not significantly different between the particular PASI subgroups ($p > 0.05$). However, there was a significantly higher concentration in the PASI II subgroup than in controls ($p < 0.001$) (Figure 3(a)). There was no significant difference in the GSDMC concentration between male and female patients ($p > 0.05$) (Figure 3(b)). After the division of patients depending on psoriasis duration (more or less than 15 years), GSDMC serum concentrations were insignificantly higher in patients with a longer duration of psoriasis ($p > 0.05$) (Figure 3(c)).

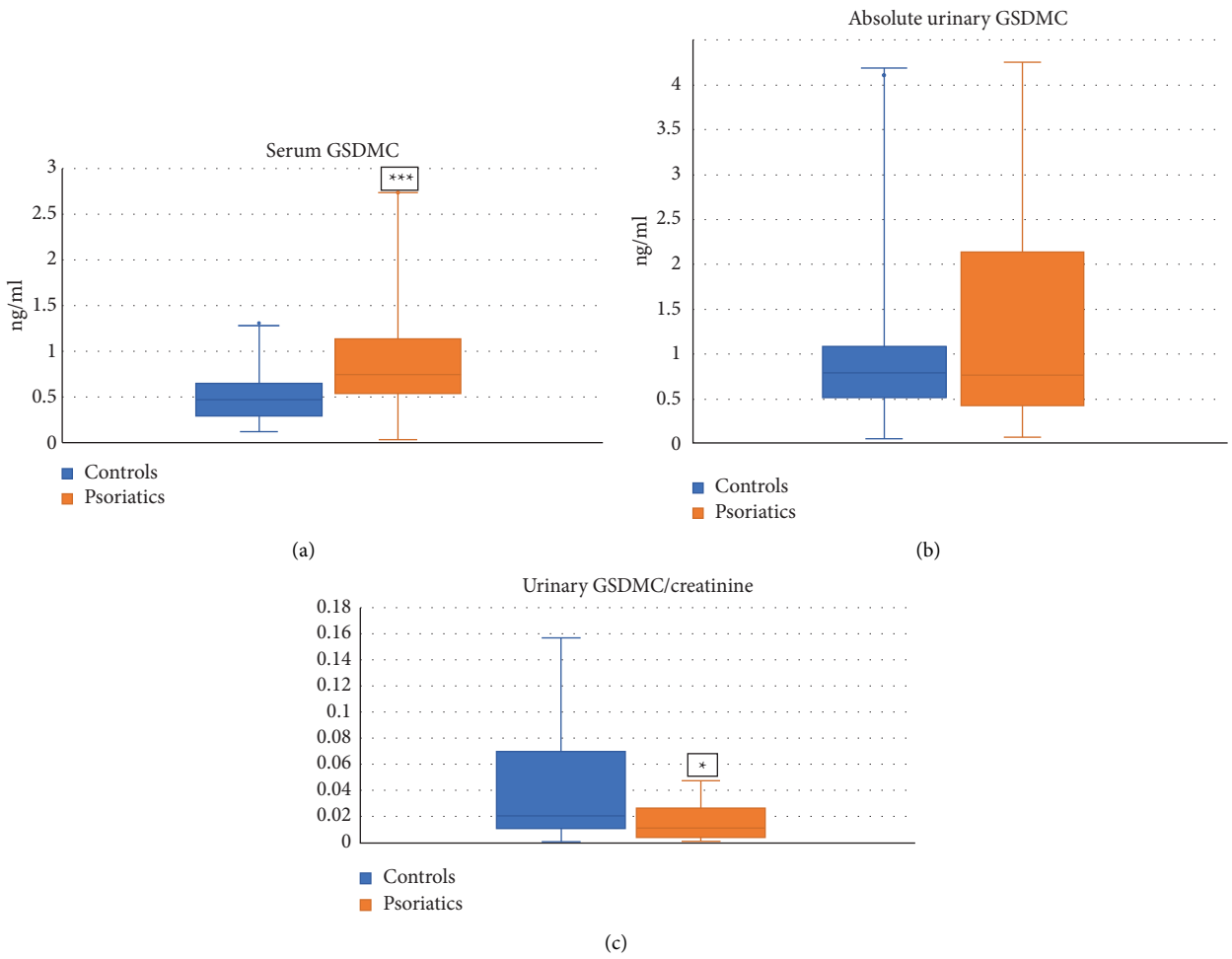

Figure 2: Serum GSDMC concentration (a), absolute urinary GSDMC concentration (b), and urinary GSDMC/creatinine concentration ratio (c) in patients and controls. */*** means statistically significant difference with $p < 0.05/0.001$, respectively.

There was no significant correlation between the serum concentration of GSDMC and PASI, BMI, or psoriasis duration ($p > 0.05$). There was a positive correlation between the GSDMC serum concentration and the age of patients ($R = 0.31$, $p = 0.015$).

Analyzing the laboratory parameters, there was a negative correlation between the GSDMC serum concentration and RBC ($R = -0.37$; $p = 0.0038$), HGB ($R = -0.26$; $p = 0.047$), and urea concentration ($R = -0.36$; $p = 0.04$) (Figure 4).

3.2. Tissue. The expression of GSDMC was observed in patients in the whole epidermis, whereas in controls, it was observed only in the stratum basale, if any. The majority of samples from the psoriatic plaque (23/33 samples) exhibited GSDMC expression, whereas the majority of samples from the nonlesional patients' skin (29/33 samples) or healthy skin of controls (16/20 samples) presented no GSDMC expression. The positive GSDMC expression in psoriatic plaque was significantly more prevalent than in the nonlesional patients' skin ($p < 0.001$) and healthy skin of controls ($p < 0.01$). The number of patients exhibiting a negative expression of GSDMC expression was significantly higher in controls ($p < 0.01$) and nonlesional patients' skin ($p < 0.001$) compared to psoriatic plaque (Figure 5).

After the division of patients according to skin lesion severity in PASI, in all PASI subgroups, the number of skin samples from psoriatic plaques presenting the expression of GSDMC was higher than the ones which did not, and in case of PASI II, it was significantly higher ($p = 0.01$) (Figure 6).

4. Discussion

GSDMC is another protein from the family of gasdermins that has been used in our analysis and brought some

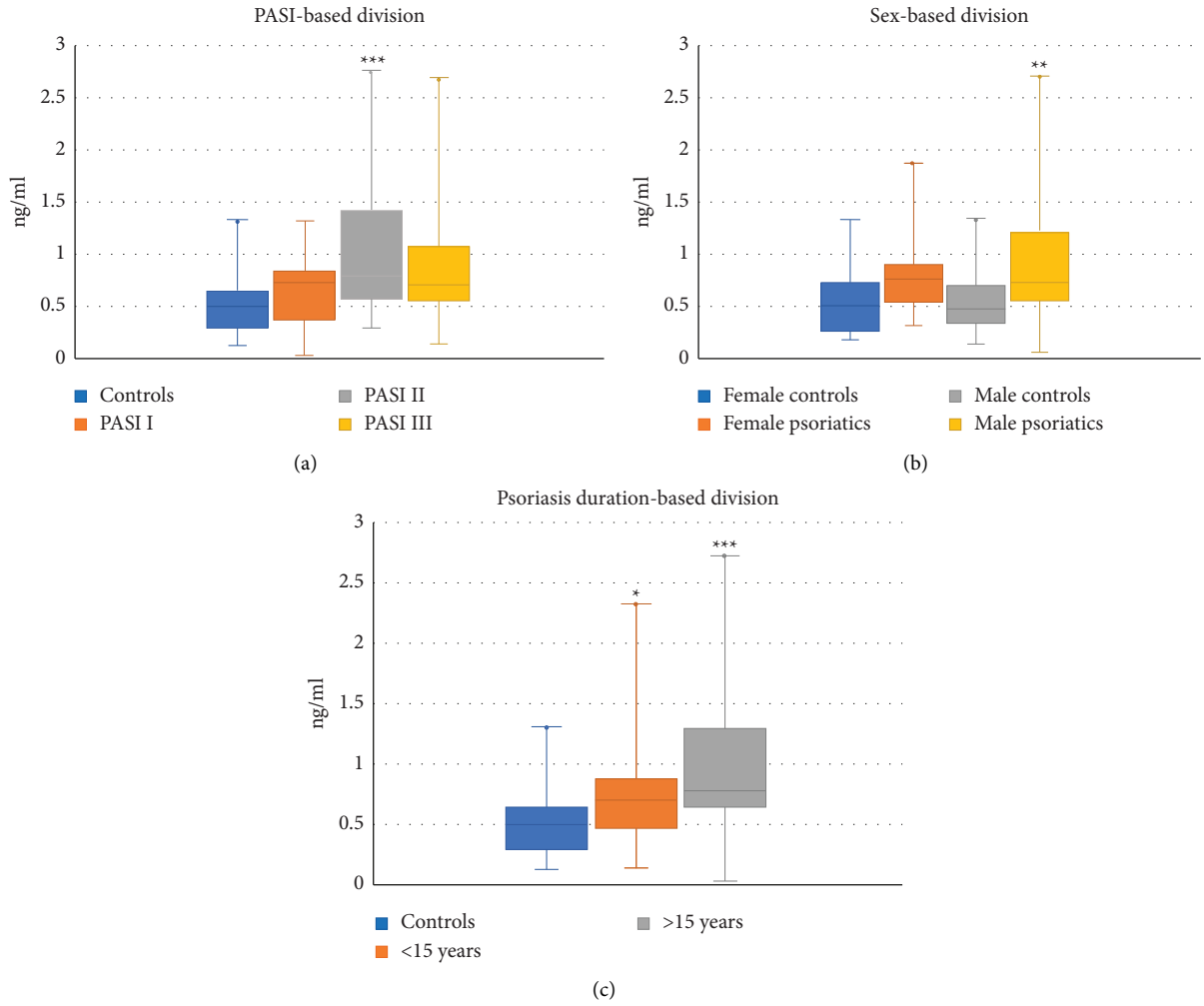

FIGURE 3: Serum concentration of GSDMC based on the division of patients depending on PASI (a), gender (b), and duration of psoriasis (c) compared to controls. */**/*** means statistically significant difference with $p < 0.05/0.01/0.001$, respectively.

meaningful results. Compared to other gasdermins, especially GSDMD or GSDME, it seems to be the least explored. The GSDMC biological role is not fully elucidated, but it has been shown that it has the property of influencing the proliferation, growth, and migration of cells [20]. For instance, it has been reported that in case of GSDMC silencing in pancreatic adenocarcinoma cells, their proliferation and migration were indeed suppressed [20]. Considering that the hallmark of psoriasis is the dysregulation in the proliferation and differentiation of keratinocytes, the abovementioned observation is worth attention. So far, GSDMC has never been evaluated in psoriatic tissue by immunohistochemistry, but its gene expression was studied by Zhang et al. on a few samples from psoriatic plaques [21]. GSDMC was mainly expressed in the stratum corneum and less in the deeper epidermal layers [21].

In our study, we found a highly significantly increased serum concentration of GSMDC in psoriatics compared to subjects without psoriasis, as well as more significant GSDMC expression in psoriatic plaque than in the nonlesional skin of patients and the healthy skin of controls. All of that indicates GSDMC potential engagement in psoriasis pathogenesis. Besides serum and tissue, the urinary GSDMC concentration/creatine ratio was significantly lower in patients than in controls, suggesting that both serum and urinary concentrations of GSDMC could become psoriasis biomarkers. Serum and urine are body fluids that are easy to collect in daily clinical practice and could be used for the purposes of psoriatic patients' management.

We did not observe any direct association between the GSDMC serum or urinary concentration and PASI or psoriasis duration. Apparently, neither skin lesion severity nor disease duration affects GSDMC. It cannot be used as a predictor of psoriasis severity.

Noteworthy, we observed a negative correlation between the GSDMC serum concentration and red blood cells (RBCs) and hemoglobin (HGB). RBCs, and HGB that they contain, obviously take part in oxygen transportation [22]. In case of their deficiency (anaemia), hypoxia may occur. Hypoxia, on the other hand, has been proven to induce hypoxia-inducible factor 1α (HIF-1α) and GSDMC [23, 24]. As it happens, HIF-1α levels are documented to be significantly higher in both

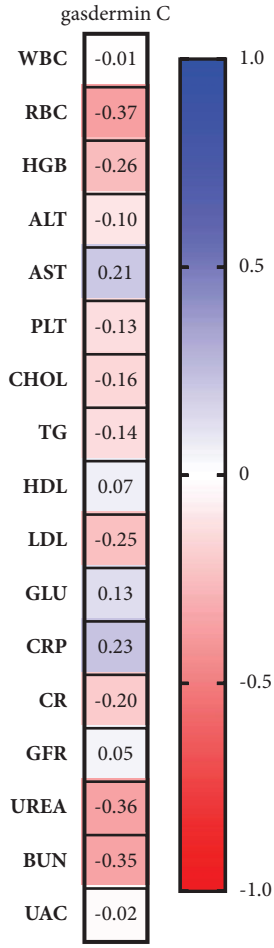

Figure 4: Correlations between serum gasdermin C concentration and basic laboratory parameters. TGs, triglycerides; ALT, alanine transaminase; AST, asparagine transaminase; GLU, fasting glucose; Chol, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; RBC, red blood cells;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

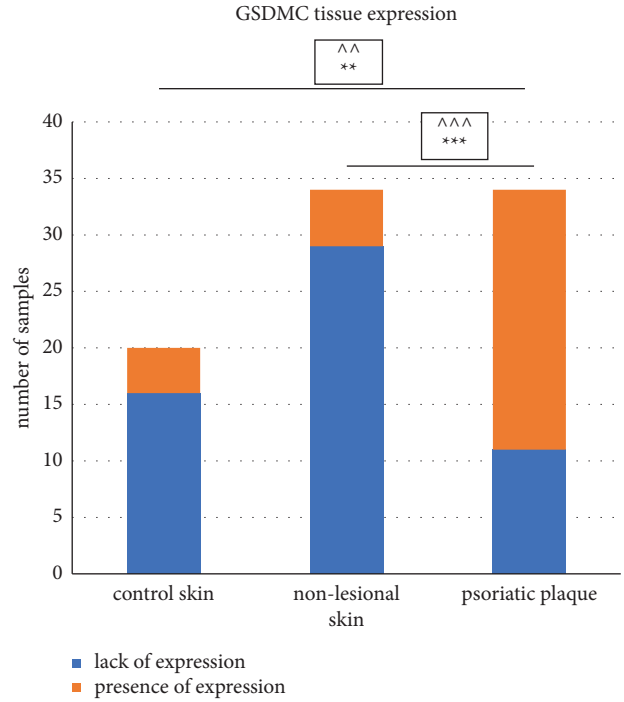

Figure 5: The expression of GSDMC in the psoriatic plaque, nonlesional patients' skin, and healthy skin of controls. **/*** vs. lack of expression with $p < 0.01/0.001$, respectively; ^^/^^^ vs. presence of expression with $p < 0.01/0.001$, respectively.

serum and tissues of psoriatic patients than in healthy people [23, 25]. Increased HIF-1α in keratinocytes, due to local hypoxia, leads to the induction of angiogenesis and inflammation. HIF-1α has the ability to inhibit cell differentiation and promote proliferation which is convergent with what we observe in psoriatic epidermis [23]. Considering our results, perhaps GSDMC could be considered a marker of local tissue hypoxia in psoriasis and a new link in its pathogenesis.

Another interesting observation that binds together GSDMC and psoriasis is that GSDMC expression is increased by ultraviolet radiation in human keratinocytes [26]. Moreover, in turn, overexpression of GSDMC promotes the expression of matrix metalloproteinase 1 (MMP-1) [26]. At the same time, metalloproteinases, including MMP-1, have already been proven to be involved in psoriasis and exert significant mutual influence on several cytokines [27]. MMP-1 has been demonstrated to regulate the migration of keratinocytes within the epidermis [27] and found to be elevated in psoriatic skin [28] and in psoriatic plasma, additionally decreasing after topical antipsoriatic treatment [29]. Perhaps GSDMC may be a part of a complex metalloproteinase network in psoriatic skin which requires more in-depth research. Serum MMP-1 has also been demonstrated to be positively correlated with age [30], which could indirectly explain similar observations about GSDMC in our study.

There is evidence of caspase 8-induced activation of GSDMC; at the same time, TNFα—an important cytokine from the point of view of psoriasis pathology—is able to induce apoptosis mediated precisely by caspase 8 [14, 31]. It has been reported that depending on the oxygen status—with regards to what has been stated earlier in the discussion—different types of cell death can occur. Namely, in case of normoxia, TNFα induces apoptosis, but in case of hypoxia, GSDMC, activated by caspase 8, has the ability to switch from apoptosis to pyroptosis [31]. Such a mechanism has been observed in malignant tumors [31], but in case of psoriasis, it could be potentially a path of chronic inflammation sustain. Another molecule that has been found to activate caspase 8, so indirectly also GSDMC, is α-ketoglutarate [32]. At the same time, an increased concentration of α-ketoglutarate in psoriatic patients has been observed [33]. First, it has been associated with increased keratinocyte proliferation, and moreover, it is involved in the immune dysregulation characteristic of psoriasis [33]. It has been demonstrated in cell cultures that α-ketoglutarate promotes cytotoxicity of macrophages due to elevated secretion of TNFα and nitric oxide and subsequently can induce collagen synthesis in the dermis [33]. Last, continuing the issue of the caspase 8 role in GSDMC activation,

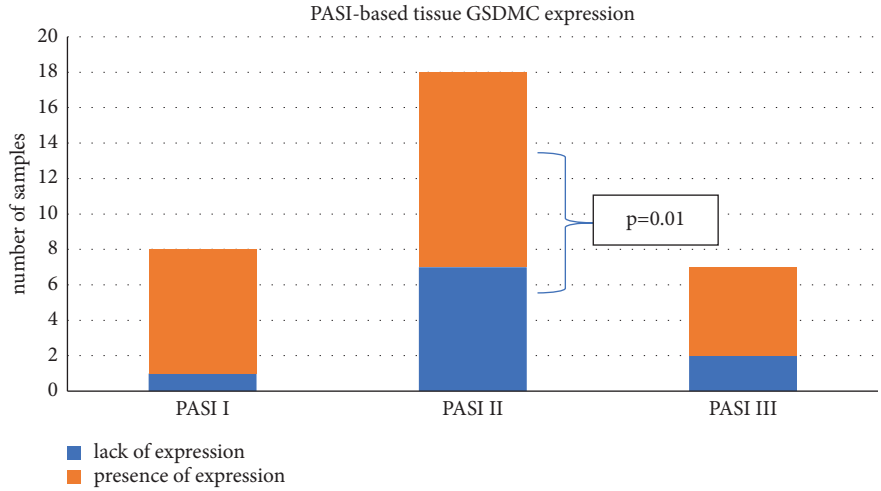

Figure 6: The expression of GSDMC in psoriatic plaques depending on the severity of PASI.

it should be mentioned that oxidative stress is an established phenomenon in psoriasis pathogenesis [34]. As it happens, it is also important for the activation of GSDMC. Reactive oxygen species can induce the oxidation of the death receptor 6 (DR6) which is further internalized into the cytosol and is subsequently responsible for recruitment of GSDMC and procaspase 8 to the DR6 receptosome. There, active caspase 8 can cleave GSDMC which can further release pyroptotic cascade [35].

Taken altogether, however, the data on GSDMC are sparse, and there are several links between this gasdermin and psoriasis that make it an interesting potential link in its pathogenesis, especially associated with cell proliferation and topical hypoxia.

The limitation of our study is a relatively small group of participants, of exclusively Caucasian ethnicity, originating from one city only. Another inconvenience is the paucity of data on the GSDMC role at this point which slightly restricts us from drawing more definite conclusions.

5. Conclusions

Hereby, we present the first comprehensive study on the role of GSDMC in psoriasis, in which we examined this protein in serum, urine, and tissue. We observed a significantly higher serum concentration of GSDMC and a decreased urinary GSDMC/creatinine ratio in psoriatic patients, as well as significantly more prevalent positive GSDMC expression in psoriatic plaque than in the nonlesional patients' skin and healthy skin of controls. Based on our results, GSDMC might play a role in psoriasis pathogenesis. First, based on several mechanisms, it may be involved in keratinocyte proliferation and migration. Second, GSDMC could perhaps be also considered a factor contributing to local tissue hypoxia in psoriasis. As for potential clinical application, we conclude that an elevated serum GSDMC and a decreased urinary GSDMC/creatinine ratio could become psoriasis biomarkers. GSDMC expression or serum concentration is probably not associated with psoriasis severity. GSDMC could be further investigated as a possible point of action for antipsoriatic drugs.

Data Availability

The data that support the findings of this study are available upon request to the authors.

Conflicts of Interest

The authors declare that there are no conflicts of interest regarding the publication of this paper.

Acknowledgments

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