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ORIGINAL RESEARCH

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Association between Angiotensin-converting enzyme (ACE) insertion/deletion (I/D) polymorphism on the susceptibility to psoriasis and oxidative stress (OS) in a cohort of pediatric psoriatic patients in Sri Lanka: A cross sectional study

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Abstract

Background: Pediatric psoriasis accounts for nearly one-third of the global psoriasis burden. Multiple lines of evidence have shown the relationship between Angiotensin-converting enzyme (ACE) Insertion (I)/deletion(D) polymorphism with psoriasis susceptibility, and oxidative stress (OS) in psoriatic patients. However, such studies, particularly on pediatric psoriasis, are scarce in the local setting.

Aims: Our study investigated the prevalence of ACE I/D polymorphism and its associations with oxidative stress in pediatric psoriasis patients in Sri Lanka.

Methods: Thirty patients were recruited for this study after obtaining ethical clearance. The polymerase chain reaction was used to explore the ACE I/D polymorphism. Serum Nitric Oxide (NO) levels and the Total Antioxidant Capacity (TAC) were measured using the Griess assay and the FRAP assay. Clinical details were obtained from the clinic reports.

Results: Female predominance (76.67%) in pediatric psoriasis was reported, while Plaque psoriasis (66.67%) was found to be the most prevalent form. I/D was reported as the predominant genotype (66.67%) while I/I and D/D genotypes were recorded in 23.33% and 10% of patients, respectively. Significantly higher NO levels were observed in I/D patients than in I/I patients but not among other groups. No differences in TAC among ACE genotypes were reported.

Conclusion: This pilot study revealed female gender and I/D genotype with increased NO levels as risk factors for pediatric psoriasis in Sri Lanka. However, it is prudent to increase the sample size to further validate the results.

KEYWORDS

ACE I/D polymorphism, oxidative stress, pediatric psoriasis, Sri Lanka

1 | INTRODUCTION

Psoriasis is a chronic inflammatory skin disease with 2%–3% global prevalence and pediatric psoriasis accounts for about one-third of the global burden.[1] Two clinical presentations of psoriasis have been reported: type I (early-onset psoriasis) with a strong genetic background, and type II (late-onset psoriasis) which occurs after the age of 40. Psoriasis can also be classified according to morphologic appearance; plaque, pustular, erythrodermic, and guttate forms where plaque psoriasis/*Psoriasis vulgaris* is the most prevalent form of psoriasis in both adults and pediatric patients.[2,3] Moreover, based on the location of psoriasis lesions, psoriasis can be categorized into nail, scalp, and inverse psoriasis.[2] Erythrodermic can be developed as a progression of plaque psoriasis or other forms.[4]

Psoriasis has been implicated as a disease with multifactorial etiology where geography, ethnicity, genetics, and environment play pivotal roles.[5] Genetics research has provided some important insights into psoriatic etiology, and more than 80 psoriasis susceptibility genes have been identified so far. Angiotensin-Converting Enzyme (ACE) is a carboxypeptidase zinc metalloprotein that is a key regulator of the renin-angiotensin-aldosterone system and among over 160 ACE polymorphisms reported, the insertion/deletion (I/D) polymorphism is a naturally occurring ACE polymorphism characterized by an Insertion/non-insertion (deletion) of 287 base pair Alu retrotransposon in Intron 16. ACE polymorphism determines the plasma and tissue levels of ACE in the human body.[6]

Previous studies have revealed an increased amount of serum ACE in psoriasis patients, particularly in patients with the D/D genotype when compared to I/D or I/I patients.[7] Decreased risk of psoriasis in individuals with I/I and I/D genotypes has also been reported previously.[6,7] The role of oxidative stress (OS) in the pathogenesis of psoriasis and the relationship between ACE polymorphism and OS status is well-established.[8] OS caused by increased production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) and the dysregulated antioxidant system could contribute to psoriasis pathogenesis.[8] Increased OS is implicated in causing endothelial dysfunction (ED) in severe psoriasis patients and carries a risk of subclinical atherosclerosis.[7] Studies on understanding the individual genetic profile and the OS status can help clinicians offer tailor-made treatment options to patients. Due to the scarcity of such studies conducted on psoriasis locally, pediatric psoriasis in particular, ACE polymorphism in pediatric psoriasis patients and their oxidative profiles remain unelucidated currently in Sri Lanka. Therefore, this study was conducted to examine the ACE polymorphism and OS levels in pediatric psoriasis patients with the long-term goal of developing tailor-made treatment strategies for pediatric psoriasis patients.

2 | METHODS

2.1 | Study design

Ethical clearance was obtained from the Ethics Review Committee of the Lady Ridgeway Hospital (LRH) (LRH/DA/29/2020). Samples ($n = 30$) were collected from the pediatric dermatology clinic at the LRH, Sri Lanka from February 2022 to October 2022. Sample storage and the bench work were performed at the Combinatorial Research Lab, Department of Zoology and Environment Sciences, Faculty of Science, University of Colombo.

2.2 | Study population

All consenting pediatric psoriasis patients (under the age of 19) belonging to all ethnic groups, socioeconomic statuses, and residential areas, attending Prof. Jayamini Seneviratne's clinic at the LRH upon receiving written informed consent were included in this study. Patients with any other reported illnesses were excluded.

2.3 | Sample and data collection

2.5 mL of blood was collected into a vacutainer tube from each patient, serum was separated and used for the determination of NO and Total antioxidant capacity (TAC). For the DNA extraction, buccal cavity epithelial samples were collected by rubbing a sterile cotton swab on both sides of the buccal mucosa for 15 seconds. The cotton swab was dipped in a tube containing the lysis buffer and proteinase K. DNA was extracted using the phenol-chloroform-Isoamyl alcohol method as previously described.[9] The presence of DNA was confirmed through agarose gel electrophoresis, and the samples were stored at −20°C until further use. Clinical data were collected from the clinic records.

2.4 | ACE I/D gene polymorphism polymerase chain reaction

The ACE I/D gene polymorphism was analyzed as previously described using the polymerase chain reaction.[10] hACE (forward)- 5′-CTGGAGACCACTCCCATCCTTTCT-3′ and hACE (reverse)- 5′-GATGTGGCCATCACATTCGTCAGAT-3' was used as primers. PCR products were separated by 2% agarose gel electrophoresis.

2.5 | Measurement of nitric oxide (NO)

Griess assay for determination of the NO was conducted as previously described.[11] Upon deproteinization, 100 µL of each sample was loaded into a 96-well plate in triplicates. 100 µL VCl_3 was added to each followed by the addition of 100 µL freshly prepared Griess reagent. The absorbance at 540 nm was measured using a microplate reader following 30 min incubation. A Standard graph was used to calculate concentrations of NO in the serum.

2.6 | Measurement of total antioxidant capacity (TAC)

Ferric Reducing Antioxidant Power Assay (FRAP) was performed as described previously.[12] In brief, FRAP solution was prepared by mixing 300 mM Sodium acetate buffer, pH 3.6, 10 mM tris (2-pyridyl)-s-triazine (TPTZ) in 40 mM HCl, and 20 mM iron (III) chloride hexahydrate in a volume ratio of 10:1:1. Serum 5 µL along with 20 µL of H_2O in duplicates were added to microplate wells. 150 µL of warmed (37°C) FRAP Working solution with TPTZ was added to each well, and incubated for 9 min at the 37°C. Optical densities of the reaction mixture were taken at 595 nm, after 9 min of incubation at 37°C. Results were expressed in $FeCl_2$ equivalents.

2.7 | Statistical analysis

All statistical analyses were carried out using the computer program SPSS 25 for Microsoft Windows. Data were reported in terms of median and interquartile range (IQR), and percentages where appropriate. The Shapiro–Wilk test was employed for normality testing. The Kruskal–Walis test was used to compare the means of more than two groups. Correlation analysis was carried out using the Spearman rank correlation test. The significance level was set at $p < 0.05$.

3 | RESULTS

The study population consisted of 23 females and 7 males under the age of 19 (Median 10.00, IQR: 5.25) exhibiting a female prevalence in pediatric psoriasis cases in the study sample. The study population represented Colombo (43.33%), Gampaha (26.67%), Kalutara (3.33%), Galle (10.00%), Anuradhapura (3.33%), and Rathnapura (6.67%) districts of Sri Lanka. median age (females 7.00, IQR:6.00, males 7.50, IQR:4.00) of diagnosis was 7.25 (IQR: 6.00). The median body weight was 29.50 (IQR 26.38).

In line with the global trends, plaque psoriasis (70%) was the commonest among pediatric patients (Figure 1A). Analysis of the location of psoriasis lesions revealed 36.7% scalp and 3.3% nail involvement (Figure 1B). Among the patients with scalp psoriasis, plaque psoriasis in the scalp (63.64%) showed the highest prevalence, while 9.09% was reported with pustular psoriasis in the scalp. Coexistence of psoriasis types in one individual at a time has been reported previously.[13] In the current population, 3.3%% of the patients exhibited coexistence of plaque and guttate psoriasis. In 3.3%

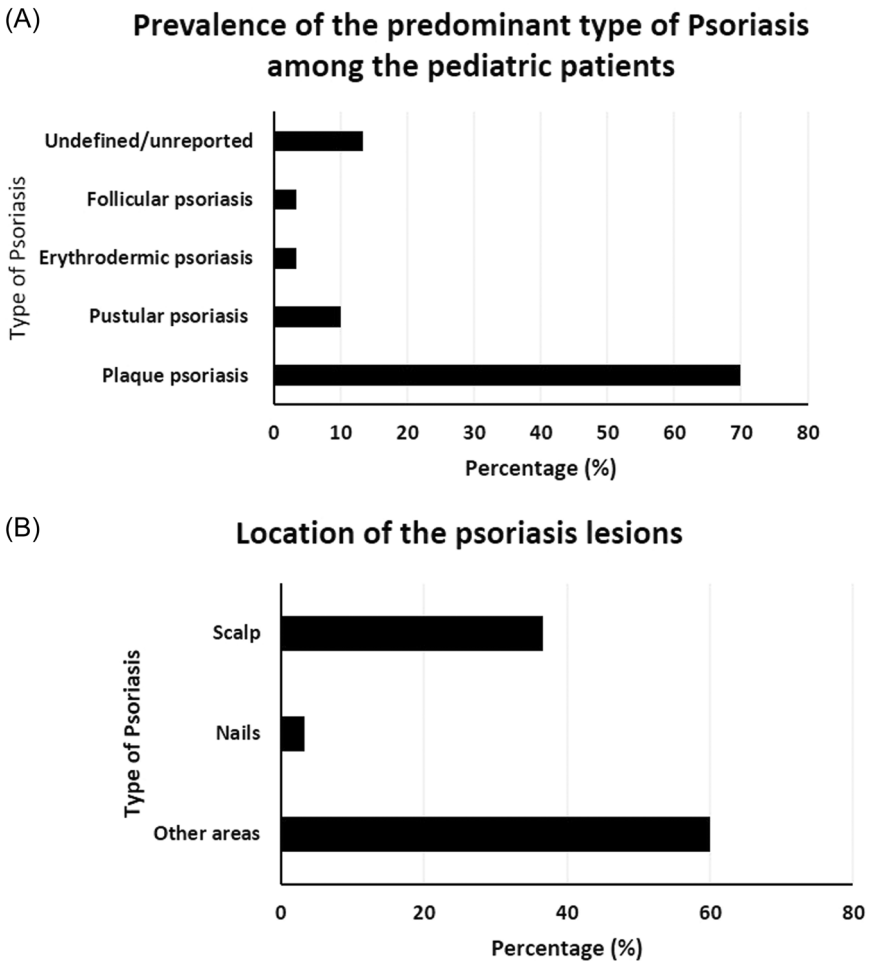

FIGURE 1 The prevalence of psoriasis types (A). Prevalence of predominant types of psoriasis in pediatric patients (B). Locations of the psoriasis lesions.

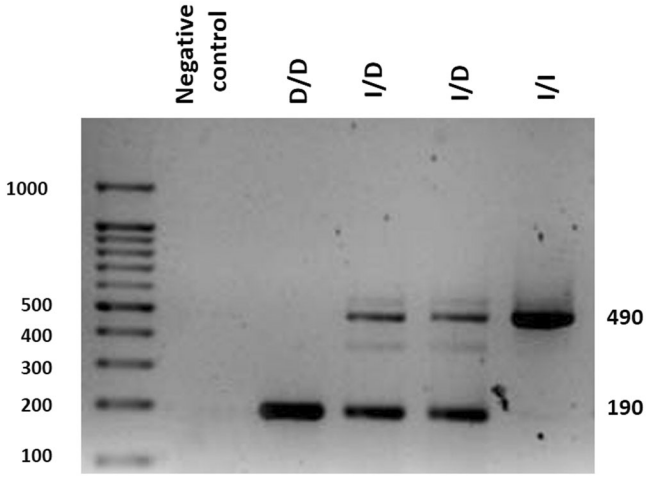

FIGURE 2 ACE insertion/deletion polymorphism PCR. D/D, Deletion/Deletion genotype; I/D, Insertion/Deletion genotype; I/I, Insertion/Insertion genotype.

TABLE 1 NO levels and TAC in severity groups.

		NO levels	FRAP
Severe psoriasis	Mean ± SD	26.160 ± 7.086	386.619 ± 190.126
	Median	26.73	428.94
	IQR	14.63	352.80
Moderate psoriasis	Mean ± SD	28.685 ± 7.541	394.758 ± 85.463
	Median	30.07	394.36
	IQR	11.47	66.55
Mild psoriasis	Mean ± SD	25.097 ± 6.173	433.362 ± 100.888
	Median	22.80	418.17
	IQR	11.53	113.81

Note: NO production and TAC among severity groups (Kruskal-Wallis test: $p > 0.05$)

Abbreviations: FRAP, Ferric Reducing Antioxidant Power Assay; IQR, interquartile range; NO, Nitric Oxide; TAC, total antioxidant capacity.

of cases each, plaque psoriasis has progressed to erythrodermic psoriasis, and pustular psoriasis has advanced to erythrodermic psoriasis.

Analysis of the clinical data based on the Body Surface Area (BSA) score (Mild <3% of the BSA, Moderate >3% BSA < 10%, Severe > 10% BSA) provided by the clinician revealed that 45%, 35% and 20% of the patients with moderate mild, and severe disease, respectively. Even though type I (early-onset psoriasis) is reported to have a strong genetic/family background to our surprise, in this study, only 6.67% of patients had a family history of psoriasis.

PCR amplification of patient DNA categorized the patients into 3 genotypes; I/I (190 bp band), I/D (190 bp and 490 bp band), and D/D (490 bp band) (Figure 2). The comparison of the ACE genotypes based on PCR results revealed I/D as the most prevalent genotype in Sri Lankan pediatric patients (66.67%) followed by I/I (23.33%) and D/D (10.00%). Comparison of the ACE genotypes in different severity groups also revealed I/D as the most prevalent genotype among severe, moderate, and mild psoriatic patients. There was no significant difference between ACE genotypes and the age of the first diagnosis ($p = 0.816$: Kruskal Wallis test).

The comparison of NO production and the TAC between the different severity groups revealed no significant difference between the groups (Table 1). Comparison of the NO levels between I/I, I/D, and D/D genotypes revealed a significant difference between the groups ($p = 0.021$: Kruskal Wallis test) and the pairwise analysis revealed a significant difference between the I/I and the ID groups ($p = 0.020$: Mann–Whitney U test) but not within I/D and D/D ($p = 0.059$: Mann-Whitney U test) or I/I and D/D genotypes ($p = 0.77$: Mann-Whitney U test) (Figure 3A). However, the comparison of the TAC between I/I, I/D, and D/D genotypes did not reveal a significant difference between the genotypes ($p = 0.155$: Kruskal Wallis test) (Figure 3B).

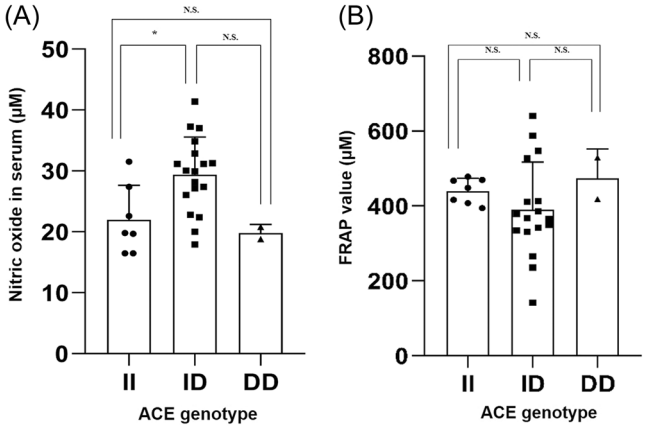

FIGURE 3 Nitric oxide (NO) concentration and total antioxidant capacity (TAC) in serum (A) NO concentration in pediatric patients according to genotypes (B) TAC determined by the Ferric Reducing Antioxidant Power (FRAP) value in pediatric patients according to the genotypes.

4 | DISCUSSION

According to our knowledge, this is the first study to collectively report the prevalence of psoriasis types in pediatric patients, ACE I/D polymorphism, and its relationship with the oxidative stress status both locally and globally.

Several studies have reported female predominance in the susceptibility to psoriasis, while some groups have reported no gender bias in pediatric psoriasis prevalence.[14] However, previous studies in Sri Lanka have revealed a higher psoriasis prevalence in adult males (53.2%) than the females.[15] Even though an early onset of psoriasis in females was reported by local and global research groups, this study group reported no significant difference between males and females in the age of onset.[16]

During this study, the majority of pediatric patients showed moderate severity (45%). However, a recent study conducted among the patients attending the Tertiary Care Dermatology Unit, Sri Lanka, has reported 52% mild, 31% moderate, and 17% severe chronic Plaque psoriasis cases.[17] ACE I/D polymorphism has been identified as the predominant genotype in most psoriatic cases globally.[14] Correspondingly, in this study, 66.67% I/D, 23.33% I/I, and 10% D/D ACE genotypes were reported among Sri Lankan pediatric patients. Similarly, a study conducted in Pakistan has also reported 31%, 37%, and 32% for I/I, I/D, and D/D genotypes respectively among all psoriasis cases, while another study has reported 24% for I/I, 49% for I/D, and 27% for D/D genotypes across all ages, further confirming the I/D predominance in Asia and Globally.[18,19]

However, a case-control study recruiting a larger number of study participants is crucial to evaluate whether I/D individuals have an increased risk of developing psoriasis locally. Currently, studies on the prevalence of ACE genotypes in the general (healthy) population are limited locally, making it challenging to draw definitive conclusions about the significance of the I/D genotype in our patient population. While global data on ACE genotype frequencies reports I/D polymorphism to be the commonest in many populations, the applicability of these findings to our local population remains uncertain due to ethnic variations in ACE gene polymorphism allele frequencies.[20–22] Thus, to better understand the potential role of the I/D genotype as a risk factor for psoriasis, future research should focus on conducting local studies that include a control population. These studies will help determine the specific prevalence and impact of ACE genotypes in our region, thereby providing more accurate insights into their association with disease risk.

The association between oxidative stress and the pathophysiological conditions of the skin is well established. According to previous studies, an increase in the production of ROS/RNS and the malfunction of the antioxidant system could trigger the onset of psoriasis.[23,24] This study showed no significant difference between the severity groups for NO production and the TAC. The lack of statistically significant differenceamong severity groups in our data may be due to the lower sample size in each severity group. Thus, future studies should be focused on increasing the sample size of each psoriasis group.

Active angiotensin II increases the production of oxidants and the synthesis of pro-inflammatory cytokines while bradykinin is involved in stimulating NO and pro-inflammatory cytokine production.[25] ACE also plays an important role in the kinin–kallikrein cascade, metabolizing bradykinin, and neurokinin degeneration. Studies have shown that the effect of ACE I/D polymorphism on the kallikrein–kinin system can lead to oxidative stress.[26] This could probably explain the relationship between Ace gene polymorphism and NO levels as the serum ACE level is regulated by ACE polymorphism. However, further studies are needed to reveal and confirm the relevant mechanisms. In this study, no significant differences were observed in nitric oxide (NO) production among different severity groups or in total antioxidant capacity (TAC) across ACE I/D genotypes. However, significant variations in NO levels were noted between the I/I and I/D genotypes, but not between other genotype comparisons. A study conducted on Vitiligo patients showed significantly higher serum nitrite levels in patients with the D/D genotype when compared with the I/I genotype.[27] Another study conducted on exercise intensity and blood parameters has shown significantly higher NO_2-release in participants with I/I, and I/D genotypes compared to D/D genotypes after exercising.[28] Moreover, a study done on infertile men has shown that Total antioxidant capacity in seminal fluids was significantly higher in the I/I genotype than in I/D or D/D.[29] Furthermore, a study conducted on Chronic Obstructive Pulmonary Disease (COPD) and Hypertension has suggested that lower risk of ROS production with the I/I genotype.[30] Collectively, the results have been divergent depending on the study groups and the diseases associated with oxidative stress and ACE I/D polymorphism.

This study was limited to determining NO levels in patient serum due to restrictions on getting down the chemicals related to lipid peroxidation assay for ROS determination. Examining both RNS and ROS arms would have given a complete understanding of the oxidative stress status in pediatric psoriasis patients. Since the pediatric patients were being evaluated this was conducted as a cross-sectional study without the participation of a control group due to ethical considerations.

Moreover, the generalizability of this data might be a limitation since the study was carried out with only patients in one geographic area of the country.

There was no significant difference or significant correlation observed between ACE genotypes and the age of first diagnosis and no correlation was observed between the age of first diagnosis and the I/I, I/D, and D/D genotypes ($p = 0.816$: Kruskal Wallis test and $p = 0.543$: Spearman's correlation). In contrast, a study conducted in Kuwait across all ages reported a significantly higher frequency of the I/I genotype in late-onset psoriasis (>40 years).[10] Another study conducted in Taiwan has reported no significant difference in the onset age between the three genotypes.[31] The contradictory nature of these results has led to difficulties in interpreting global psoriasis demography. Therefore, more studies are needed to understand the relationship between the ACE genotype and the onset age in pediatric psoriasis.

In summary, the prevalence data obtained through this study provide interesting demographical information on pediatric psoriasis in Sri Lanka. An association between ACE I/D polymorphism and NO level in serum was observed although other parameters analyzed to find associations didn't provide any significant results. This may have been caused due to the low sample number collected due to the difficulties faced by investigators and patients with the current situation in the country. This study needs to be extended with more sample numbers and tests for ROS level detection to increase the validity of the results.

AUTHOR CONTRIBUTIONS

S. A. K. Udayanga: Sample collection; performing lab work; data analysis and drafting the manuscript and revising it. **J. Seneviratne**:

Sample provision and provision of necessary clinical data; project co-supervision. **M. G. A. Saumyamala**: Statistical analysis of data and interpretation of the results. **A. D. D. S. Amarasekara**: Concept design; overall project supervision and finalizing the manuscript. All authors have read and approved the final version of the manuscript.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request. Amarasekara A.D.D.S had full access to all of the data in this study and takes complete responsibility for the integrity of the data and the accuracy of the data analysis.

ETHICAL APPROVAL AND INFORMED CONSENT

Ethical clearance was obtained from the Ethics Review Committee of the Lady Ridgeway Hospital (LRH/DA/29/2020). An information sheet and a consent form were given to the guardians. The purpose of the study, procedure, risks, and the role expected from a participant was clearly explained. Once the guardian was well informed, written informed consent was obtained voluntarily from the guardians of the subject. All authors consent to the publishing of this research work.

TRANSPARENCY STATEMENT

The lead author A. D. D. S. Amarasekara affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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