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Relationship between elevated serum decorin levels and acne vulgaris in women with PCOS

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Abstract. – OBJECTIVE: The primary aim of this study was to investigate the serum levels of decorin, a small leucine-rich proteoglycan, in women diagnosed with polycystic ovary syndrome (PCOS) and concurrently presenting with moderate to severe acne vulgaris.

PATIENTS AND METHODS: Sixty patients with acne vulgaris symptoms, subsequently diagnosed with PCOS according to the revised Rotterdam criteria, were enrolled in the study. Acne severity was assessed using the acne global severity scale (AGSS), with patients fitting AGSS category 4 (moderate) and 5 (severe) grouped into two separate cohorts of 30 individuals each. The moderate acne group comprised patients with few inflammatory lesions and a minor nodule alongside predominantly non-inflammatory lesions, whereas the severe group contained patients with multiple nodules and a mix of non-inflammatory and inflammatory lesions. A control group of twenty healthy women without acne vulgaris or PCOS was also established. The study measured serum testosterone, follicle-stimulating hormone (FSH), Luteinizing Hormone (LH), and insulin levels, and calculated insulin resistance *via* the Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) formula. Quantitative sandwich enzyme immunoassay was employed to determine decorin levels from venous blood samples.

RESULTS: While age, body mass index (BMI), serum FSH, LH, testosterone, and HOMA-IR values demonstrated similarity between the moderate and severe acne cohorts, comparisons between the control and both acne groups (AGSS-4 and AGSS-5) revealed significantly elevated values in the latter, excluding age, BMI, and FSH. Importantly, the serum decorin levels in both acne groups were substantially higher than in controls. A significant positive correlation was observed between serum decorin levels and both HOMA-IR (r=7.88, $p<0.01$) and testosterone (r=0.813, $p<0.01$).

CONCLUSIONS: This study suggests that elevated circulating decorin levels play a pivotal role in the manifestation of acne vulgaris in women with PCOS.

Key Words:
Decorin, Acne vulgaris, PCOS, Androgen, Insulin.

Introduction

Acne vulgaris is one of the most prevalent and complex skin conditions, deeply rooted in the pilosebaceous unit, and presents through various lesions, including comedones, papules, pustules, and nodules. The multifactorial nature of its etiology encompasses a range of elements such as abnormal follicular keratinization, elevated sebum production, proliferation of *Cutibacterium acnes*, and a consequential inflammatory response[1]. A myriad of external and internal factors, including but not limited to diet, genetic makeup, hormonal fluctuations, medications, and stress, intricately interact, often exacerbating the presentation and severity of acne. Of particular note is the hormone-driven onset of acne, especially during pivotal life stages such as puberty. This period witnesses a surge in growth hormone (GH), insulin, Insulin-like growth factor-1 (IGF-1) signaling, and the metabolic processes of adrenal and gonadal androgens, which intricately weave into the tapestry of acne's pathogenesis[2,3].

Polycystic ovary syndrome (PCOS) emerges as a focal point in discussions about acne, especially when its manifestation proves stubborn against conventional treatments. PCOS, marked by an endocrine imbalance, displays a strong linkage with hyperandrogenemia, which in turn accentuates the acne condition, given the correlation between heightened levels of androgens and an increased expression of dihydrotestosterone receptors in sebaceous glands[2,4]. Furthermore, within the PCOS paradigm, the role of insulin cannot be understated. Hyperinsulinemia, stemming from insulin resistance, is a common accompaniment of PCOS and is known to exacerbate both the inflammatory process and sebaceous gland activity integral to acne's emergence[5,6].

At the heart of this study lies decorin, a member of the small leucine-rich proteoglycan (SLRP) family, which has recently come into the limelight due to its potential association with skin conditions. As an inherent Transforming growth

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factor beta (TGF-β) inhibitor, decorin demonstrates fluctuating expression within hair follicles, peaking during the anagen (growth) phase and diminishing during the catagen (regression) phase[5-9]. This proteoglycan's profound influence on skin health is evident in its pivotal role in ensuring the structural cohesiveness of human skin – primarily through its facilitation of collagen fibril assembly and its protective action against collagen degradation by matrix metalloproteases[10]. Recent insights into decorin's modulatory effects on follicular cycling, particularly its associations with androgens and its capacity to inhibit TGF-β activation, thereby counteracting diffuse dermal inflammation and fibrosis symptoms, suggest a deep-seated influence in skin homeostasis[11-16]. Such revelations pivot decorin to the forefront of dermatological research, sparking intrigue regarding its potential involvement in the pathogenesis of acne vulgaris. Against this backdrop, our study seeks to illuminate the enigmatic relationship between serum decorin levels and the severity of acne vulgaris in women grappling with a PCOS diagnosis[17].

Patients and Methods

This study received ethics approval from İzmir Tınaztepe University. The assigned approval number is 2023/04, and the date of authorization is the 1st of September, 2023.

Study Participants

A cohort of 60 patients who presented with acne vulgaris symptoms and were subsequently diagnosed with PCOS were enrolled in this study. PCOS diagnosis was established based on the revised Rotterdam criteria, where participants displaying at least two of the following were considered to have PCOS: (i) ovulatory dysfunction or oligomenorrhea, (ii) clinical or biochemical hyperandrogenism, and (iii) polycystic ovarian morphology observed through ultrasonography.

Based on the acne global severity scale (AGSS), participants fitting AGSS categories 4 (moderate) and 5 (severe) were segmented into two distinct groups, each containing 30 patients. Those in the moderate category displayed a few inflammatory lesions, predominantly non-inflammatory lesions, and a minor nodule. In contrast, the severe group was characterized by a blend of non-inflammatory and inflammatory lesions, supplemented by multiple nodules.

A control group was established, comprising 20 healthy women devoid of both acne vulgaris and PCOS symptoms. Exclusion criteria included individuals who had undergone systemic or local acne treatments within the past three months and those who consumed cigarettes or alcohol.

Sample Collection and Analysis

Blood samples were procured from participants on the third day of their menstrual cycle to assess various hormonal and biochemical markers. These samples were collected in the morning following an overnight fast. Parameters such as serum testosterone, follicle-stimulating hormone (FSH), Luteinizing Hormone (LH), and insulin levels were measured. The Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) formula, given by HOMA-IR = fasting insulin concentration (μIU/mL) x fasting glucose concentration (mmol/L) divided by 22.5, was utilized to calculate insulin resistance. Furthermore, body mass index (BMI), values for all participants were determined.

Measurement of Serum Decorin using ELISA

Venous blood samples were subjected to analysis for decorin (DCN) concentrations using the Human Decorin (DCN) ELISA Kit (Sunred Biotechnology Company, Catalog No: 201-12-3612, Shanghai, CHINA), based on the quantitative sandwich enzyme immunoassay technique. Absorbance readings, aligned with the kit's protocol, were obtained *via* the Bio-Tek ELx800 device (BioTek Instruments, VT, USA) at a 450-nanometer wavelength. Concentrations, corresponding to all absorbances, were translated to ng/mL using the formula derived from the standard curve graph. The DCN kit's detection range spanned from 0.2-40 ng/mL, with a minimum detectable concentration of 0.14 ng/mL. The intra-assay CV value stood at less than 10%, and the inter-assay CV was below 12%.

Statistical Analysis

Data normality across groups was verified using the Shapiro-Wilk test. Differences between groups were deduced using the Student's *t*-test for normally distributed data, while the non-parametric Mann-Whitney U test was employed for non-normally distributed data. Associations between decorin and other markers were delineated using Spearman's rank correlation coefficients (r). Statistical significance was acknowledged at *p*-values lower than 0.05.

Results

Table I provides a detailed overview of the demographic and laboratory characteristics of participants categorized into three distinct groups: AGSS-4 (moderate acne group), AGSS-5 (severe acne group), and a control group. The variables presented include age, BMI, and serum concentrations of FSH, LH, testosterone, HOMA-IR, and decorin. Each entry displays the mean value accompanied by the standard deviation to reflect the data spread. Additionally, *p*-values are provided to signify the statistical differences between groups. A comparison is made between AGSS-4 *vs.* the control group, AGSS-4 *vs.* AGSS-5, and AGSS-5 *vs.* the control group. These *p*-values help determine the statistical significance of the differences. Table I illustrates the demographic and laboratory characteristics of both groups. Upon examination, the age, BMI, serum levels of FSH, LH, testosterone, and HOMA-IR values were found to be analogous between patients in the moderate (AGSS-4) and severe (AGSS-5) acne groups. While the serum decorin levels in the severe acne group displayed a non-significant increase compared to the moderate acne group, significant variations were noted when these groups were individually compared with the control group.

For the AGSS-4 group *vs.* the control group, except for age, BMI, and FSH, all values were observed to be significantly elevated in the acne group. Specifically, serum decorin levels in the AGSS-4 group were substantially higher than in the controls.

The trend was similar for the AGSS-5 group in comparison to the control group, with all values being significantly higher in the AGSS-5 group, except for age, BMI, and FSH. Likewise, serum decorin levels in the AGSS-5 group were notably higher than in the controls. Additionally, there was a notable and significant positive correlation between serum decorin levels with HOMA-IR (r=7.88, $p<0.01$) and testosterone levels (r=0.813, $p<0.01$). No discernible correlation was found between decorin and other measured parameters.

Discussion

Acne vulgaris, prominently recognized as an androgen-dependent dermatosis, stands as a hallmark skin manifestation of PCOS[18-20]. Although frequently associated with adolescents, its reach extends across diverse age groups, testifying to its complex pathogenesis. Hormones, particularly androgens, estrogen, progesterone, and insulin, play a pivotal role in the causation and exacerbation of acne vulgaris[20].

The intricate interplay between the disturbed LH pulse frequency and insulin resistance observed in PCOS precipitates hyperandrogenemia. This, in turn, catalyzes the comedogenesis in sebaceous glands. As these conditions manifest, there is an increased shedding of follicular epithelial cells into the sebum. This amalgamation provides a fertile environment for microbiota colonization. The inherent chronic low-grade inflammation associated with PCOS further complicates this landscape, giving rise to diverse acne lesions, both inflammatory and non-inflammatory, at differing developmental stages[21,22].

The primary aim of this study was to investigate the potential relationship between acne severity, particularly in patients diagnosed with PCOS, and serum decorin levels. Decorin, a small leucine-rich proteoglycan, has gained

Table I. Demographic and laboratory characteristics of the AGSS-4 and AGSS-5 groups.

Parameter	AGSS 4 (n=30) Mean±SD.	AGSS 5 (n=30) Mean±SD.	Control (n=20) Mean±SD.	*p*-values (AGSS-4 *vs.* Control)	*p*-values (AGSS-4 *vs.* AGSS-5)	*p*-values (AGSS-5 *vs.* Control)
Age (years)	25.3±4.22	24.6±3.09	25.2±2.87	0.49	0.34	0.30
BMI (kg/m^2)	23.6±4.76	22.9±3.87	23.1±2.01	0.11	0.59	0.23
FSH (mIU/mL)	5.66±1.32	5.11±1.31	5.09±1.33	0.50	0.69	0.59
LH (mIU/mL)	9.54±1.44	8.99±1.02	5.44±1.06	0.01	0.30	0.02
Testosterone (ng/mL)	0.87±0.11	0.92±0.21	0.43±0.22	0.01	0.81	0.01
HOMA-IR	2.67±0.32	2.54±0.45	1.44±0.29	0.02	0.13	0.03
Decorin (ng/mL)	12.2±2.99	14.1±2.81	9.22±1.03	0.03	0.82	0.01

n: Number, kg: Kilogram, m^2: meter square, IU: International Unit, FHS: Follicle stimulating hormone, BMI: Body Mass Index, LH: Luteinizan Hormone.

interest in recent years due to its role in various pathophysiological conditions, but its link with acne severity in PCOS patients remains under-explored. Our results indicated that while there were no significant differences in age, BMI, serum FSH, LH, testosterone, and HOMA-IR values between the moderate (AGSS-4) and severe (AGSS-5) acne groups, there was a trend toward increased serum decorin levels in the severe acne group. This observation could suggest a potential role of decorin in the progression or severity of acne in PCOS patients.

Furthermore, when compared to the control group, both AGSS-4 and AGSS-5 acne groups had significantly higher values for most parameters, except for age, BMI, and FSH. Most notably, serum decorin levels in both acne groups were significantly elevated in comparison to controls. This further strengthens the association between elevated decorin levels and the presence of acne in this cohort.

The significant positive correlation between serum decorin levels and both HOMA-IR and testosterone levels offers intriguing possibilities. Insulin resistance (as indicated by HOMA-IR) and elevated testosterone levels are both characteristic features of PCOS and have been implicated in the pathogenesis of acne. Our findings hint that decorin could be a mediating or exacerbating factor in this pathway.

Intriguingly, nearly all predisposing factors for acne vulgaris are omnipresent in patients diagnosed with PCOS. The triumvirate of androgen elevation, insulin resistance, and low-grade inflammation, either individually or in concert, serve as formidable triggers for acne development. However, the presence of lesions at varying developmental stages in patients might be intricately woven with other variables such as genetic susceptibilities, dietary predilections, and specific medications[23-25].

Data derived from our study underscores the pertinence of hyperandrogenemia and insulin resistance in the genesis of acne. Elevated LH, testosterone, and HOMA-IR levels in patients at the AGSS-4 and AGSS-5 stages bolster this connection[26]. Meanwhile, the comparative analysis between AGSS-4 and AGSS-5 groups and the control group revealed discernible differences in serum decorin levels.

The multifaceted role of decorin, predominantly as a leucine-rich proteoglycan in the dermal ECM, cannot be overstated[27-29]. Its inherent ability to thwart the electrostatic interaction between glycosaminoglycans and collagen fibrils substantiates its critical position in skin health dynamics[11]. Further, decorin's augmented expression during the hair follicles' anagen phase – owing to its inhibitory influence on TGF-β – may hint at its potential to instigate collagen fibril destruction. This destructive cascade might culminate in the amplification of sebum production and comedogenesis[5-7]. This observation gains more traction when one considers the progressive decline in decorin's molecular size and volume with aging, potentially offering a clue to the fluctuating prevalence of acne vulgaris across age strata[30-32].

Conclusions

This study sheds light on the potential involvement of serum decorin levels in the severity and pathogenesis of acne in patients with PCOS. Elevated decorin levels in both moderate and severe acne groups compared to controls highlight its potential role in acne development or progression. The association between decorin and both HOMA-IR and testosterone levels further suggests its importance in the PCOS-acne pathway.

While these findings are significant, further research with larger cohorts and mechanistic studies is essential to understand the precise role of decorin in acne and PCOS. It would also be valuable to investigate if therapeutic interventions targeting decorin could offer a novel avenue for acne treatment in PCOS patients.

Our investigation offers pioneering clinical insights, shedding light on decorin's probable involvement in the manifestation of acne vulgaris, especially in the backdrop of PCOS. Elevated serum decorin levels across both moderate and severe acne cohorts, as juxtaposed against healthy controls, hint at decorin's contributory role in acne onset. Yet, its constant levels between the two acne severity groups also suggest that it might not drive the progression continuum directly.

The observed positive correlations between serum decorin levels with both HOMA-IR and testosterone levels provide compelling evidence of the potential interconnections between insulin resistance, hyperandrogenemia, and decorin[5]. Yet, the mechanisms underpinning this triadic relationship remain elusive. Future research, especially focused on elucidating decorin's distribution across the skin and its appendages using advanced antibody-based techniques, may bring clarity to this intricate web of interactions.

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Ethics Approval
All subjects in this study were among the participants in a prior study. All participants provided written informed consent prior to voluntary participation in the study, and the study protocol was approved by the Ethics Committee of the Izmir Tınaztepe University.

Informed Consent
Written consent was obtained from the participants.

Conflict of Interest
The author declared no competing interest.

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Availability of Data and Materials
The datasets generated during and/or analyzed during the current study are available from the corresponding author upon reasonable request. The authors assure that this paper has not been published before, nor has it been submitted for publication to another scientific journal.

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