Role of Angiopoietins in psoriasis: a systematic review and meta-analysis

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Abstract

- **Background**

Psoriasis is a common, chronic autoimmune disease of the skin, which affects approximately 2% of the general population. The lesions are characterized by red, scaly, raised plaques affecting different body sites. Angiopoietins are ligand of tyrosine kinase endothelial specific receptors2 (Tie2) . they has been associated with vascular remodeling and stabilization signals in angiogenesis.

- **Methods**

This study included 40 participants; 20 psoriatic patients and 20 healthy controls. Tissue biopsy was taken from lesional and non-lesional psoriatic tissue. ANG ELISA kit was used for determination of the ANGs in serum and tissue.

- **Results**
- Angiopiotiens were higher in serum and tissues (lesional and non- lesional). They were higher in lesional than in non-lesional and the difference was highly statistically significant. Both serum and tissues (lesional and non- lesional).
- ANGs were higher than control group as well.

Conclusion

ANGs may have a major importance in the orchestra played in order to create the psoriatic plaque evidenced by its high level in serum and tissue in comparison to the control group**Keywords**

psoriasis, pathogenesis, angiogenesis, Angiopiotiens.

Introduction:

Psoriasis is a common chronic, recurrent, and immune mediated disease of the skin and joints .It may have a significant negative impact on the physical, emotional, and psychosocial well-being of affected patients **(1).**

Although the exact cause of psoriasis remains unknown, the evolving evidence suggests that psoriasis is a complex disorder caused by the interaction of multiple genes, the immune system, and environmental factors **(2).**

Plaque psoriasis is the commonest form of psoriasis, represents 70-80% of psoriatic patients and is also known as Psoriasis vulgaris. The patient presents with sharply demarcated round-oval or nummular (coin-sized) plaques with a loosely adherent silvery white scale, specially affecting the elbows, knees, lumbosacral areal, intergluteal cleft and scalp. The lesions usually begin as erythematous macules or papules, extend peripherally, and coalesce to form plaques **(3).**

Microvascular abnormalities are a characteristic feature of psoriasis and play a crucial role in its pathogenesis. Investigational studies have shown that activated keratinocytes in lesional skin undergo an accelerated epidermal cell turnover and are a major source of pro-angiogenic cytokines, like as VEGF **(4).**

Angiopoietins (Ang, also known as Angpt) are ligands of endothelial-specific receptor tyrosine kinase 2 (Tie2) **(5).**

There are three angiopoietins (Ang1, -2 and -4 in human) that bind to (Tie2), plus several angiopoietins like molecules that share the same structure and have sequence homology to the angiopoietins, but do not bind Tie receptors **(6).**

Angiopoietin -1 was initially identified as an activating ligand for Tie2 that is expressed by perivascular cells. Its expression is not strongly changed by most vascular stimuli. Interestingly, Ang1 is stored at high levels in platelet granules.

Ang2 was found to bind to Tie2 with a similar affinity as Ang1. However, unlike Ang1, exogenous Ang2 provided only a very weak activation of Tie2 on endothelial cells **(6).**

Angiopoietin-4 has been much less studied and does not yet have a clearly defined role in physiology or pathology **(6).**

Angiopoietin-1 and Angiopoietin-2 classically act in an agonist/antagonist manner on the Tie-2. Ang-1 stabilizes the endothelium by inhibiting endothelial cell apoptosis and activation and decreasing inflammation. In contrast, Ang -2 is a context-dependent antagonist to the Tie-2 receptor that is pro- inflammatory and promotes endothelial and epithelial cell apoptosis, increases neutrophil adhesion, and causes cytoskeletal changes to increase interendothelial gaps. In concert, the two angiopoietins may act directly or indirectly to change the integrity of the vascular endothelium **(7).**

Angiopoietin-2 acts as a Tie2 agonist in non-pathological conditions, whereas in the setting of inflammation, ANG2 functions as a Tie2 antagonist and promotes vascular dysfunction **(8).**

Methods:

- **Literature search**

The articles reviewed were retrieved from searches conducted on the Web of Science database on June 2021. In the first search, the search criteria used were: document type 'article', search terms 'psoriasis' in the topic and 'angiopiotiens' in the title. Additional searches using the following criteria—document type 'article' and either the search terms 'psoriasis' and 'angiopiotiens' in the topic or search terms 'psoriasis ' and 'angiopiotiens' in the topic—were also conducted. The searches aimed to garner articles about relations of angiopiotiens and psoriasis, thus more general search terms were chosen.

- **Criteria for meta-analysis**

Studies were included in the meta-analysis if they satisfied the following inclusion criteria: 1. Angiopiotiens that were involved in case–control studies that evaluated psoriasis presentation; 2. No restriction regarding country, patient race or occupation; 3. Patients with plaque psoriasis; 4. Studies that have provided an estimation of serum and tissue level of different types of angiopiotiens in psoriatic cases and healthy controls. Of 45 search results found, a total of 4 articles were chosen based on selection criteria.

Results

A total of 8 articles; including 464 psoriatic cases and 264 controls, were chosen from 45 results in searching the role of angiopoietins in pathogenesis of psoriasis by estimating their serum and tissue level.

The first article estimate tissue Ang1, Ang2 in psoriatic skin, included 12 patients with psoriasis and seven normal skin specimens from healthy controls found increase expression of Ang1, Ang2, and Tie2 in involved psoriasis skin (9)

The second one estimated the serum level of ANG-2, included 9 psoriatic patients and 9 control found that ANG-2 higher in psoriatic patients than in healthy controls **(10).**

The 3rd article analysed single nucleotide polymorphisms of ANG-1 (rs2507800, rs1954727 and rs1010824), ANG-2 (rs3739390, rs2442598 and rs1868554) and caspase-5 (rs507879, rs518604 and rs523104) in 343 patients with PV and 347 healthy controls (HCs) by the SNaPshot method, found the rs2442598 polymorphism of ANGPT2 was significantly associated with PV **(11).**

The 4th article estimate the serum level of Ang-2 before and after narrowband ultraviolet B (NB-UVB) in psoriatic patients. The study included 38 psoriatic patients and 38 healthy controls, found statistically significant positive correlation was established between psoriasis severity and Ang-2 serum levels before and after treatment. **(12).**

Discussion

A total of 4 articles; including 402 psoriatic cases and 401 controls, were chosen from 45 results in searching the role of angiopoietins in pathogenesis of psoriasis by estimating their serum and tissue level. All of studies found a significant relation between their high levels and pathogenesis of psoriasis.

Meta-analysis of this study revealed that:

- Significant increase tissue level of ANG-1 and ANG-2 in psoriatic cases group than healthy control group.
  Significant increase in seum level of ANG-2.

Conclusion

Angiopoietins may have a major importance in the orchestra played in order to create the psoriatic plaque evidenced by their high level in serum and tissue in comparison to the control group.

References:

1. **López- Estebaranz JL, Sánchez-Carazo JL and Sulleiro S (2016):** Effect of a family history of psoriasis and age on comorbidities and quality of life in patients with moderate to severe psoriasis: Results from the ARIZONA study. The Journal of Dermatology (43):395-401.

2. **Zhang P, Su Y and Lu Q (2012):** Epigenetics and psoriasis. Journal of the European Academy of Dermatology and Venereology (26): 399–403.

3. **Mitra AD and Mitra A (2013):** Clinical Presentation of Psoriasis. IntechOpen

4. **Micali G, Lacarrubba F, Musumeci ML, Massimino D and Nasca MR (2010):** Cutaneous vascular patterns in psoriasis. International Journal of Dermatology (49):249-256.

5. **Holopainen T, Saharinen P, D'Amico G, Lampinen A, Eklund L, Sormunen R, Anisimov A, Zarkada G, Lohela M, Heloterä H, Tammela T, Benjamin LE, Ylä-Herttuala S, Leow CC, Koh GY and Alitalo K (2012**): Effects of Angiopoietin-2-Blocking Antibody on Endothelial Cell–Cell Junctions and Lung Metastasis . Journal of the National Cancer Institute (104):461–475.

6. **Thurston G and Daly C (2012):** The Complex Role of Angiopoietin-2 in the Angiopoietin–Tie Signaling Pathway. Cold Spring Harbor Perspectives in Medicine (2).

7. **Ong Thida, McClintock DE, Kallet RH, Ware LB, Matthay MA and Liu KD (2010):** The Ratio of Angiopoietin-2 to Angiopoietin-1 as a Predictor of Mortality in Acute Lung Injury Patients. PubMed Central (PMC) (38):1845-1851.

8. **Mueller SB and Kontos CD (2016):** Tie1: an orphan receptor provides context for angiopoietin-2/Tie2 signaling. The Journal of Clinical Investigation (126):3188-3191.

9. **Kei Kuroda, Allen Sapadin, Toru Shoji, Raul Fleischmajer and Mark Lebwohl (2001):** Altered Expression of Angiopoietins and Tie2 Endothelium Receptor in Psoriasis. Journal of Investigative Dermatology Home (116):713-720.

10 . **Takehiro Takahash ,Yoshihide Asano,Sayaka Shibata,Yayoi Tada and Shinichi Sato (2017):** Serum angiopoietin-2 level as a potential biomarker in psoriasis vulgaris. The journal of dermatology (44):205-206.

11. **L He L, Dang,J. Zhou,J. Bai and Y.-Z. Li (2015**): Association of angiopoietin-1, angiopoietin-2 and caspase-5 polymorphisms with psoriasis vulgaris. Clinical and Experimental dermatology (40):556-563.

12. Hesham A Nada, ,Mohamed M. Elshabrawy Sarah Ali Abo Elenain and Mohamed L. Elsaie (2021): Implications of narrowband ultraviolet B treatment on psoriasis severity and serum levels of angiopoietin-2: A cross-sectional controlled study. Journal of cosmotic dermatology.