Role of IL-23 gene expression in development of psoriatic arthritis among psoriasis patients

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Abstract---Background: Psoriasis (PS) is an inflammatory skin disorder that lasts for a long time. About 30% of peoples with psoriatic arthritis and characterized as inflammatory arthritis that affects joints or entheses. Although there is growing evidence that interleukin-23 is a kind of interleukin that is produced by (IL-23) Signaling is important in the pathophysiology of both PS and PsA, it is unclear whether IL-23-induced skin inflammation causes joint disease. The goal of this research is to determine the expression of genes (IL-23) in PsA patients in Basrah. Material and Methods: The current study included 88 participants, 59 of whom had Poraisis (Ps), 29 of whom had Psoriatic arthritis, and 40 healthy controls (HC). From August 2020 to February 2022, samples were collected from patients at Al-Sadar Teaching Hospital and Basrah Teaching Hospital's Rheumatology Unite and Biological Therapy Center. Total RNA was collected from peripheral blood and used to evaluate the expression of the genes of interest using qRT-PCR. Results: The binding of the SYBR green dye was unique to the target genes through one peak in the melting curve data and amplification curve for the genes of interest, which included IL-23. Furthermore, qRT-PCR findings revealed that the expression level of IL-23 in PsA groups was 91.4 times higher than in Ps groups, which was 57.45 times lower. Conclusion: Psoriasis patients had

considerably higher blood IL-23 levels, and there was a link between serum IL-23 levels and illness. As a result, IL-23 served as the key triggering mediator for the onset of lesions.

Keywords---psoriatic arthritis, IL-23, real time, PCR, gene expression.

Introduction

In recent years, we've learned a lot more about autoimmune inflammatory diseases pathophysiology like ps, and we've improved our therapy choices as well. Targeted biologic treatments, first with TNF-a inhibitors and subsequently include medicines psoriasis treatments that target interleukin (IL)-12/23 and IL-17 have grown into current therapeutic paradigms. Recent research shows that IL-23 might be an even more effective target for treating psoriasis and other autoimmune inflammatory diseases (Gooderham, Papp, Lynde, & Venereology, 2018). It could be showed that mice with high IL-23 levels in their skin (K23 animals) develop a PS-like illness with inflammatory infiltrates, acanthosis, parakeratosis, hyperkeratosis, and acanthosis in the dermis. PsA was preceded by skin illness such as enthesitis, dactylitis, and bone damage. The advances in enthesitis and dactylitis are not caused by elevated amounts of IL-23 in the blood, since both transgenic and control mice had equivalent circulating system levels of this cytokine The serum of K23 mice had a significant rise in IL-22, a downstream cytokine of IL-23. Although IL-22 loss had no effect on the development of skin disease, it did worsen the PsA-like illness in K23 mice. Our findings show that skin-expressed IL-23 plays a significant role in the beginning PS and pathogenic processes that lead to PsA (Chen et al., 2020). PsA affects both men and women, and most people get it between the ages of 30 and 50 (C. T. Ritchlin, Colbert, & Gladman, 2017). PsA commonly affects the hands, foot, and knees, producing joint swelling and discomfort, as well as widespread digit involvement (dactylitis), inflammatory infiltrates, acanthosis, parakeratosis, hyperkeratosis, and acanthosis in the dermis (Oliveira, Rocha, & Duarte, 2015). A small percentage of people develop axial spondylitis and sacroiliitis (Oliveira, Rocha, & Duarte, 2015). PsA is characterised histologically with synovial hyperplasia and inflammation, as well as cartilage and bone erosive changes, all contribute to the condition. Keratinocytes, dendritic cells, and myeloid cells produce IL-23, a proinflammatory cytokine. It has contained two subunits (which similar to IL-12 is p40, and p19, which is unique to IL-23). It binds to RAR-related orphan receptor gamma-t (RORt) cognate receptors (IL-23R/IL-12R1) in T-helper-17 cells, stabilising RORt, and then releases its cytokine effect of IL-17, IL-21, and IL-22 to induce and worsen local autoimmune reactions and chronic inflammation (Boutet, Nerviani, Gallo Afflitto, & Pitzalis, 2018). Several medicines that target the IL-23/IL-17 axis have been successfully tested in PsO and PsA. (Bridgewood et al., 2020). Inhibitors of IL-12/IL-23p40 and IL-17A, ustekinumab and secukinumab, have been proposed as second-line biological therapies for PsA patients who have failed at least one TNF inhibitor (Coates et al., 2016; Ramiro et al., 2016). While inhibiting these pathways results in a 75 % amelioration in dermatology (PASI75), effectiveness in treating joints is less impressive, with just a 20 percent improvement shown in 35 percent –50 percent of patients (Mease et al., 2015; C. Ritchlin et al., 2014). The novel IL-23p19 selective inhibitors proved demonstrated

successful, with ACR20 achieved in roughly 60% of patients, and also a percentage of patients achieved virtually complete PsO clearance (PASI90), only 33 percent–36 percent and 13 percent–20 percent of patients with high-risk joint disease reach ACR50/ACR70 (Deodhar et al., 2020; Mease et al., 2020). The purpose of this research is to determine the expression of genes (IL-23) among people with psoriasis and psoriatic arthritis (PsA) in Basrah. Total RNA was collected from peripheral blood and used to evaluate the expression of the genes of qRT-PCR has piqued the attention

Materials and Methods

For PsA group

The well-established clinical ratings of Disease Activity in Psoriatic Arthritis were used to measure PsA disease activity (DAS 28). The electronic program (Rheuma Helper program) was used for this purpose

Figure 1.

Figure 1. Rheuma Helper program

Molecular study

This study included 88 study volunteers (PsA=29, Ps=29, and HC=40). From August 2020 to February 2022, patients were seen at Al-Sadar Teaching Hospital and Basrah Teaching Hospital's Rheumatology Unite and Biological Therapy Center. Each sample was put in an EDTA tube (5 ml) and then RNA isolation was performed. The study covered two categories of psoriatic patients. WizolTM Reagent was used to extract total RNA, in addition, a Nanodrop spectrophotometer was used to determine the final concentration and quality of eluted RNA. Total RNA quality and quantity varied among samples, with the quality of RNA in a range of 1.32 - 2.4 and the concentrations from 6.6 to 121.7 ng/ml. Until further analysis, all RNA samples were kept at -80°C. WizScriptTM RT FDmix kit (Wizbiosolution, Korea) was used to convert total RNA (400 ng) into cDNA according to the manufacturer's instructions. Macrogen Company (alpha DNA, Canada) provided primers for IL-23 as well as B-actin as a housekeeping gene, and the sequences of primers utilized to detect marker mRNA expression are reported in Table 1.

Table 1. The primers sequence of the genes used in the current study

Primer	Sequence	References
IL-23	F:5'- GTTCCCCATATCCAGTGTGG -3'	(Khodadadi, 2014)
	R:5'- GGATCCTTTGCAAGCAGAAC -3'	
β-actin	F: 5'-CCACACTGTGCCCATCTACG-3'	(Valente, 2012)
	R: 5'-CCGTGGTGGTGAAGCTGTAG-3'	

The reference volumes of a single PCR reaction of (IL-3) and (β-Actin) gene PCR (2-6) µl cDNA, 10 µl master mix GoTaq® qPCR Master Mix (Promega, USA), 1 µl revers primer, 1 µl forward primer, and (2-6)l µl Nuclease-free water were added to final volume 20 µl of the mixture. The expression was measured using the Applied CFX ManagerTM Software (Bio- Rad). The following were the qRT-PCR conditions: Denaturation, 50 cycle at 95°C Tem. for 5 min, GoTaq activation 1 cycle at 95°C Tem. 95℃ Tem. for 30 sec and Annealing/Extension 1 cycle at 72℃ Tem. For 1 min. . The data was analyzed using the ΔΔCT method as follow:

$\Delta CT(PsA) = \Delta CT(Tgene) - \Delta CT(HKgene)$

$\Delta CT(HC) = \Delta CT(Tgene) - \Delta CT(HKgene)$

$\Delta\Delta CT = \Delta CT(PsA) - \Delta CT(HC)$

Gene Exp. $= 2^{-\Delta\Delta CT}$

Fold change (FC) = Gene Exp. PsA / Gene Exp. HC

☐ PsA= Psoriatic Arthritis , HC= Healthy Controls, Tgene= target gene, HKgene= Housekeeping gene, Gene Exp.= gene expression

Results

From the samples, total RNA was extracted. The samples' quality varied from 1.3 to 1.8 A260/A280 and 0.7 to 1.9 A260/A230. The values varied between 14.4 and 244 ng/l.

Estimation of gene expression level in study subjects

The expression of several genes was estimated by qRT- PCR in PsA patients and HC (Ps=29, PsA=59 and HC= 40) using β Actin as a reference gene. The genes of intereste include IL-23 The binding of the SYBR green dye was specific to the target genes through one peak in the melting curve data and amplification curve is shown in Figure 2,3,4
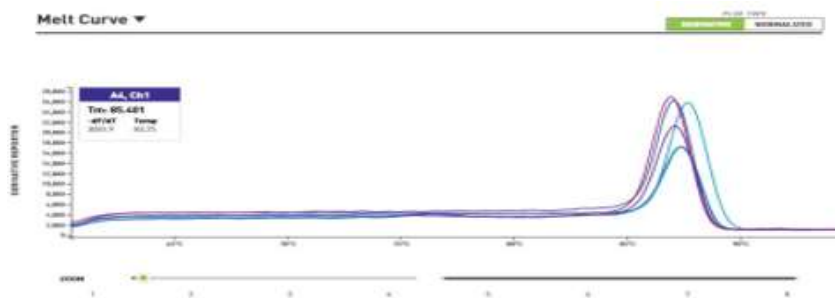

Figure 2. Melting curve for IL-23 gene using SYBR green chemistry qRT-PCR

Note the melt curves for five distinct amplicons are shown in Figure 2. The single peak seen in these samples is usually taken to reflect a single, pure amplicon. he melt curve for an amplicon, on the other hand, exhibits two peaks, which is commonly read as indicating two different amplicons.

How melt curves are produced (principle)

Only when intercalating dyes are attached to double-stranded DNA can they glow in qPCR (dsDNA). In single-stranded DNA (ssDNA) or when the dyes are free in solution, they do not fluoresce. After the amplification cycles are done, the melt curve is frequently created by the thermal cycler used to perform the qPCR. The thermal cycler starts at a preset temperature (typically above the primer Tm; e.g., 65°C) and checks the quantity of fluorescence at the end of the qPCR run. As the device detects fluorescence, the temperature of the sample gradually rises. As the temperature rises, dsDNA denatures, becoming single-stranded, and the dye dissociates, causing the fluorescence to decrease Figure 2.

Curve of amplification (principle)

When the fluorescent signal from each sample is plotted against the cycle number, amplification plots are formed, and they show the accumulation of product throughout the course of the real-time PCR experiment (Figure 2,3). First is known as the initiation phase, and it occurs during the initial PCR cycles when the fluorescence released cannot be separated from the baseline. Fluorescence increases exponentially during the exponential or log phase before reaching the plateau phase. The reagents are depleted at this point, and there is no increase in fluorescence. Quantification is only possible during the exponential phase (Rodríguez-Lázaro & Hernández, 2013)
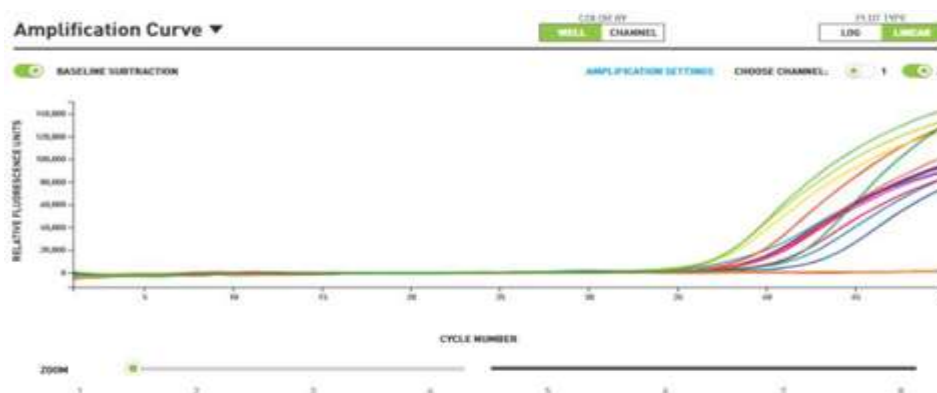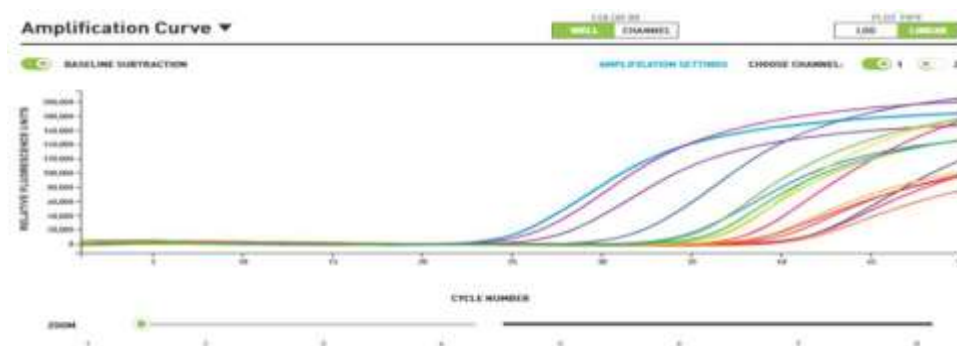

Figure 3. Amplification Curve

Figure 4. The mean threshold cycle (ct) values for the IL-23 gene were determined using a real-time PCR typical amplification plot of qpcr

Gene expression IL-23

The current results from qRT-PCR showed that the expression level of IL-23 in PsA groups was up regulated 91.4-fold than Ps group was down regulated 57.45, as shown in Figure 5.
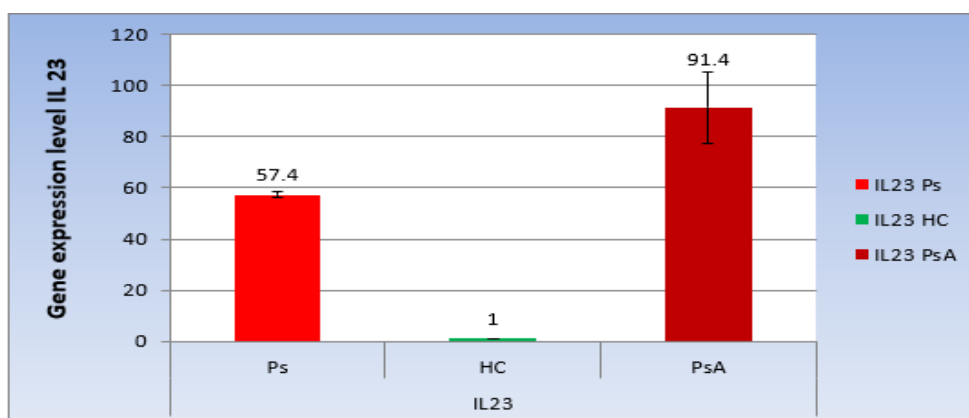

Figure 5. IL-23 mRNA expression in healthy controls and Ps and PsA patients' peripheral blood (Xais). In PsA patients, the relative gene expression (Y axis) of IL-23 was 91.413.77, while in healthy people, it was 57.40.966

Correlation between DAS 28 (hight disease activity) and Up regulation genes (IL-23) in patients of Psoriatic Arthritis (PsA)

The results of Pearson Correlation between DAS 28 and the expression level of IL-23 in pateints of PsA showed no significant negative correlation between two parameters ($R2=-0.27$) Figure 6. From plotting the IL-23 levels with DAS-28 in PsA patients, the results showed a negative correlation between the two factors. The R value was -0.27.
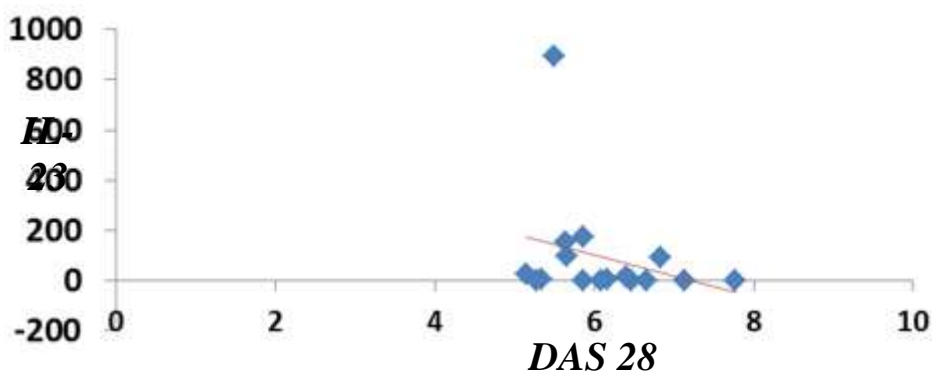
Figure 6. Correlation between DAS 28 (hight disease activity) and IL-23 In Psoriatic Arthritis (PsA)

Discussion

Each from Ps and PsA are multifactorial chronic illnesses reasoned by a complicated interaction of hereditary factors, environmental variables, and immunological dysfunction. Due to its great sensitivity, specificity, reproducibility, and lowering of post-PCR procedures, the qPCR technology is commonly employed in clinical virology diagnostic laboratories (Josko, 2010). SYBR-Green-based qPCR is less expensive, but TaqMan-based qPCR is more costly. Furthermore, although TaqMan probes improve specificity by evaluating only sequence-specific fluorescence signals, qPCR specificity is mostly determined through the utilization of particular primers (Tajadini, Panjehpour, & Javanmard, 2014). Furthermore, when the assay is appropriately constructed, qPCR provides for high throughput testing and consistent target quantification across a wide dynamic range with a detection limit of single-copy numbers (Valasek & Repa, 2005). In addition, keeping track of a patient's viral load could be crucial for disease progression and clinical outcomes (Pujadas et al., 2020). The fact that a large number of people with skin psoriasis acquire PsA suggests that Ps and PsA have a partially overlapping genetic vulnerability. Even people with only first-degree experience with Ps but no history of personal skin disease might develop PsA-like clinical symptoms (Olivieri, Padula, D'ANGELO, & Cutro, 2009). Furthermore, according to several research, monozygotic twins have a conformity ratio for Ps between from 20% to 64%; altogether, genetic variables appear to account for roughly 70% of the diversity in Ps susceptibility (Generali, Ceribelli, Stazi, & Selmi, 2017). Psoriatic arthritis (PsA) is a spondyloarthritis (SpA)-related chronic systemic immune-mediated inflammatory illness. PsA is found in 6 percent to 42 percent of people with cutaneous psoriasis (Scher, Ogdie, Merola, & Ritchlin, 2019; Zabotti, Tinazzi, Aydin, & McGonagle, 2020) . RT-qPCR was created and is now often used to assess messenger RNA expression levels in a variety of scientific operations (Fleige & Pfaffl, 2006). In many research, several types of reference genes are utilised as internal controls to standardise the expression of target genes across samples (Chervoneva et al., 2010). (Hawkes, Yan, Chan, & Krueger, 2018) found that T cells that produce a lot of interleukin-17 (IL-17) cause keratinocytes to have a self-amplifying, feed-forward inflammatory response, which leads to the production of thicker skin lesions infiltrated with a variety of inflammatory cell populations. Multiple extremely

successful psoriasis medicines that disrupt interleukin-17 (IL-17) and interleukin-23 (IL-23) signaling the skin recently authorised by the FDA, signifying a dramatic shift in how psoriatic disease is controlled. In the current study, psoriatic arthritis (PsA) illness patients had considerably higher serum IL-23 levels than healthy controls. (Bilgiç, Sivrikaya, Toker, Ünlü, & Altınyazar, 2016) discovered that IL-23 levels in the serum and skin psoriasis patients were considerable grater, indicating that IL-23 plays a role in disease aetiology. (Bai et al., 2018) found no significant difference in serum IL- 23 levels among psoriasis patients and the control group in a meta-analysis. Psoriasis patients had lower blood IL-23 levels than the control group, according to (Michalak-Stoma et al., 2013) albeit the variation was not statistically considerable. The current study found that serum IL- 23 levels were considerably greater in psoriasis patients compared with the control group, supporting findings (Michalak-Stoma et al., 2013). The length of psoriatic arthritis (PsA) illness linked with serum IL-23 levels. Increased IL-23 levels in early psoriasis lesions were identified by (Alobaidi, Mothana, Najem, Alsamarai, & Venereology, 2012) .who discovered a substantial link between blood IL-23 levels and the length of sickness they theorized that IL-23 was an early mediator involved in the development of psoriatic lesions. Because serum IL-23 levels were considerably greater in psoriasis patients, and a link was discovered among IL-23 levels and disease duration, it's possible that IL-23 was the primary triggering mediator for the onset of lesions, and that other cytokines took its place in the later stages of the disease. The results showed that there was a negative connection between DAS28 (high disease activity) and Up regulation genes (IL-23) in individuals with Psoriatic Arthritis (PsA). This led to the idea that patients with higher histology synovitis but not necessarily higher disease activity preferentially expressed the IL-23-axis, resulting in variable joint response rates in PsA that often diverged from skin response. According to (Nerviani et al., 2021) IL-23 transcriptomic/protein expression was substantially associated with persons with high-grade synovitis who could not be distinguished by known clinimetric criteria (2020). The IL-23 axis profile of PsA synovial tissue differs from that of comparable skin. Clinically indistinguishable people who are more likely to respond to IL-23 inhibitors can be identified using synovial molecular pathology.

Conclusion

To summarize, the current research shows that psoriatic arthritis (PsA) is a chronic inflammatory arthritis with an unclear origin, the cellular and molecular connections that govern its pathogenesis are still unknown. It is widely known that interleukin-23 (IL-23) has a role in the development of psoriasis and PsA. Because IL-23 controls the development and activation of innate and adaptive immunity, it is linked to a complicated pathophysiology involving several effectors and transducers.

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