



Serum Levels of Interleukin-2 and Interleukin-2 Soluble Receptor in Patients with Vitiligo

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

Background: Vitiligo is a common skin disorder characterized by macular depigmentation of the skin. Although the etiopathogenesis of the disease is still unclear, several studies have shown that within the cascade of pathogenesis of vitiligo, cytokines play an important role.

Objectives: The aim of our study was to evaluate serum concentrations of interleukin- IL-2 (IL-2) and interleukin-2 soluble receptor (IL-2 sR) in patients with vitiligo and healthy subjects and also to assess a possible association between these cytokines and duration of the disease.

Study Design: Case control study.

Place of the Study: The study was carried out in University Clinical Center Sarajevo, Department of Dermatology and Venereology.

Patients and Methods: Twenty one patients (11 female and 10 male; age range 15-53 years) with vitiligo and 20 healthy controls (10 female and 10 male; age range 17-52) were enrolled in the study. The duration of vitiligo ranged from 2 to 252 months. Ten patients (47.62%) had generalized, and eleven patients (52.38%) had localized vitiligo Serum concentrations of cytokines

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were measured using enzyme-linked immunoassay techniques.

Results: Both IL-2 (median 22.600 pg/ml, range 20.900-76.100) and IL-2sR (median 76.100 pg/ml, range 15.700-183.800) in the patient group were significantly higher when compared with that of the normal controls. When the serum cytokine level in vitiligo group were compared to total disease duration (Spearman correlation ρ), serum IL-2 was negatively ($\rho = -0.000573$, $P = 0.9980$) and IL-2 sR was positively ($\rho = 0.241$, $P = 0.2797$) correlated with total disease duration, but it is of borderline significance.

Conclusions: Our results showed high serum levels of IL-2 and IL2 sR among vitiligo patients which may highlight a functional role of these cytokines in the pathogenesis of this disease.

Keywords: Vitiligo; serum cytokines; interleukin-2; soluble interleukin-2 receptor.

1. INTRODUCTION

Vitiligo is one of disorders of melanin pigmentation that affects approximately 0.5-2% of the population [1]. It is characterized by macular depigmentation of varying sizes or shapes with a tendency to progress. Lesions enlarge centrifugally and can appear on any body site, including mucous membranes. Depending on the extent of the lesions, vitiligo can be classified into two main categories: generalized and localized. In both types, the disappearance of functional melanocytes can be detectable.

The cause of disease is unknown, although there is evidence for altered immunological processes in vitiligo, particularly in chronic and progressive condition [2]. In immune processes, a basic role is played by cytokines, secreted by activated cells. They influence other cells via specific membrane receptors, some of which have soluble forms, known as soluble receptors (sR).

Interleukin 2 (IL-2) was discovered in 1976 as a growth factor for T lymphocytes [3]. Since that time it has become an important mediator of immune function though its effects on the growth, development, and activity of T and B lymphocytes. Apart from its most important role to mediate antigen specific T-lymphocyte proliferation, IL-2 modulates the expression of interferon-gamma and major histocompatibility antigens [4,5]. The changes in serum IL-2 levels were found in many diseases, such as systemic lupus erythematosus and psoriasis [6]. In some of these diseases, serum IL-2 concentrations correlated with activity and intensity of the disease, and may be used as a prognostic factor. Because of the central role of IL-2 in immune response, IL-2 turned out to be very important molecule for diagnostic and therapeutic implications.

Interleukin-2 soluble receptor (IL-2 sR) has a potential role in the modulation of immune responses by inhibiting IL-2. Clinically, high levels of IL-2 sR are believed to be associated with a potent activation of the immune system in many diseases such as atopic dermatitis, psoriasis and cutaneous T cell lymphoma [7,8].

Several hypotheses have been proposed to explain the pathogenesis of vitiligo, and indeed it is likely that more than one mechanism is responsible for the clinical manifestations of the disease [9]. All immune system compartments, including innate and adaptive immunity have been implicated in vitiligo development [10]. Recent progress in the understanding of vitiligo has shown that the regulation of local and systemic cytokines plays an important role in its pathogenesis. Although it is well known that multiple cytokines simultaneously play role in vitiligo, many authors have measured only one particular cytokine. Our study has focused only on IL-2 and IL-2 sR because there are only a few studies that have measured the serum levels of these cytokines with controversial results [11-14]. Therefore, the aim of our study was to evaluate serum concentrations IL-2 and IL-2 sR in patients with vitiligo and healthy subjects and also to assess a possible association between these cytokines and duration of the disease.

2. MATERIALS AND METHODS

The study included 21 patients with vitiligo, 11 female and 10 male, median age 33.96 (± 15.65) years. Of them, there were 10 (47.62%) patients with generalized vitiligo and 11 (52.38%) patients with localized form of disease. A detailed history and examination were taken in all study subjects, including patients age, age at onset and duration of disease. The total disease duration was defined as the period when the first depigmented lesion appeared to the day of sample collection. All patients were examined by the

dermatologist who made the diagnosis of vitiligo based on the history, typical clinical features of depigmented macules and clinical evaluation including Wood's light examination. In doubtful cases, skin biopsy was performed (in four cases). The control group consisted of 20 volunteers, 10 female and 10 male, median age 32.55 (\pm 16.12) years. None of the patients had used any systemic medications for vitiligo treatment for at least 3 months before the study. We excluded the patients with other types of illnesses, such as autoimmune diseases that could affect the outcome of the study. Exclusion criteria consisted of patients who had thyroiditis, psoriasis, collagenoses, alopecia areata, diabetes mellitus and depigmenting disorders other than vitiligo.

All subjects gave their informed consent in accordance with the requirements of the Institutional Ethics Committee. The study was conducted in accordance with the principles of the Declaration of Helsinki.

2.1 Serum Cytokine Determination

Commercially available kits from R&D Systems (Minneapolis, USA) were used for the measurement of serum IL-2 and IL-2 sR levels by enzyme-linked immunosorbent assay (ELISA) carried out in accordance with the manufacturer's instructions.

Briefly, a microplate was coated with a monoclonal antibody that was specific for the cytokines, and standards and samples were pipetted into the wells. After washing, an enzyme-linked polyclonal antibody that was specific for the cytokines was added. The reaction was revealed by addition of the substrate solution. The colour development was stopped and the intensity of the colour was measured at 450 nm with a photometer (Rider Biotek Elx800).

2.2 Statistical Analysis

Statistical analyses were performed using MedCalc Statistical Software version 15.2.2. (MedCalc Software bvba, Ostend, Belgium). Statistical comparisons were performed using T test and Mann Whitney U test for independent samples. The results are expressed as the median and its range. We used Spearman correlation coefficient rho for calculate relationship between duration of disease and

serum levels of cytokines. Data were considered statistically significance at $P < 0.01$.

3. RESULTS

The study group composed of 21 patients with vitiligo (11 female and 10 male; the mean age of the patients was 33.96 years, ranging from 15 to 53 years), and 20 healthy controls (10 female and 10 male; the mean age 32.55 years, ranging from 17 to 52 years). There were no significant difference in age and female/male ratio between the patients and controls. Demographic data of patients and controls are shown in Table 1. The duration of vitiligo ranged from 2 to 252 months. Ten patients (47.62%) had generalized, and eleven patients (52.38%) had localized vitiligo.

Both IL-2 (median 22.600 pg/ml, range 20.900-76.100) and IL-2sR (median 76.100 pg/ml, range 15.700-183.800) in the patient group were significantly higher when compared with that of the normal controls (Table 2).

When the serum cytokine level in vitiligo group were compared to total disease duration (Spearman correlation ρ), serum IL-2 was negatively ($\rho = -0.000573$, $P = .9980$) and IL-2 sR was positively ($\rho = 0.241$, $P = .2797$) correlated with total disease duration, but it is of borderline significance (Table 3).

Table 1. Demographic characteristics of patients and healthy controls

	Vitiligo group	Control group	P
Men, n (%)	10 (0,47)	10 (50)	
Women, n (%)	11 (0,52)	10 (50)	
Age range, years	18-64	17-68	
Age, mean years (SD)	33.96(15.65)	32.55(16.12)	0.889*

* T test

4. DISCUSSION

Although the etiopathogenesis of the disease is not clear, recent observations support the role of altered cellular immunity, autoimmunity, and a role for cytokines in the pathogenesis of vitiligo.

The involvement of activated peripheral and cutaneous infiltrating T lymphocytes in melanocytotoxicity has been suggested as an important pathomechanism in vitiligo [15]. Immunohistochemical studies of the perilesional skin in generalized vitiligo demonstrate the presence of activated inflammatory T cells,

Table 2. Cytokines levels in patients and controls

Cytokines	Vitiligo (n=21) (pg/ml)	Controls (n=20) (pg/ml)	Mann-Whitney U	Z	P*
IL-2 (med)	22.600	21.300	88.00	3.330	.0009***
Range**	20.900-76.100	10.600-23.800			
IL-2R (med)	76.100	44.900	76.00	3.627	.0003***
Range**	15.700-183.800	28.400-71.300			

* Mann-Whitney U test, ** Range – min-max values, *** Statistical significance ($P < 0.01$)

mainly CD4⁺ and CD8⁺ in the dermal and epidermal infiltrate [16]. These cells express activation molecules such as, mayor histocompatibility complex (MHC) II, CLA antigen IL-2R (CD25) and interferon-gamma (IFN- γ) [17]. In addition, studies showed that the number of citotoxic CD8⁺ T cells was higher in active disease than in stable disease [18].

Table 3. Relationship between duration of vitiligo and serum levels of cytokines (Spearman rank test)

Cytokines	rho	95% CI	P
IL 2	-0.000573	-0.422-0.421	.9980
IL 2R	0.241	-0.201-0.602	.2797

* Statistical significance ($P < 0.01$)

Many of the actions of immune competent T cells are primarily mediated through cytokines, and several reports have shown the presence of these molecules in the peripheral blood circulation [19-21] and cutaneous infiltrates in vitiligo patients [19,22-24].

Cytoknes such as IL-1, IFN- γ or TNF- α are paracrine inhibitors of melanocytes and can initiate apoptosis [22]. An imbalance of keratinocyte –derived cytokines such as IL-6, IL-1 α and TNF- α in the lesional skin has been demonstrated, which could impair the normal life and function of melanocytes [23,24]. Higher levels of the proinflammatory cytokines interleukin-1 α , interleukin-1 β , and interleukin-12 measured in epidermis fluid, were presented in patients whose response to melanocyte transplanted was unsatisfactory [25]. Wang et al. [26] reported elevated tissue mRNA levels of IL-17A in leading edge skin biopsies of vitiligo patients, as well as IL-17A positive T cells by immunohistochemistry and immunofluorescence. *In vitro* studies confirmed an increased production of pro-inflammatory cytokines IL-6 and IL-8 by monocytes of active patients with vitiligo, which will affect effector cell migration, effector target attachment and also cause B cell activation [27].

IL-2 is a cytokine that seems to play an important role in vitiligo patients. Wolkenstein et al. [28] described induction of vitiligo in 4 out of 25 patients treated with IL-2 alone for metastatic melanoma. This study suggested that vitiligo could be caused by an autoimmune response of cytotoxic T lymphocytes against melanocyte antigens. IL-2 is secreted primarily by the T helper lymphocytes, which in turn stimulate the production of IL-2R on the T cell surface. The soluble form of IL-2R (IL-2sR) is then released into the serum during immune response [29]. Serum levels of IL-2 sR can be used to monitor *in vivo* immune activation, and its elevation has been correlated with T-cell mediated immune disease [10].

A limited number of studies in the literature have evaluated the serum levels of IL-2 and IL-2 sR in patients with vitiligo, and the results were often contradictory. The results presented in our study demonstrate that the median serum levels of IL-2 and IL-2 sR were significantly elevated in vitiligo patients in comparison with healthy subjects. No significant correlations were found with serum IL-2 and IL-2sR and disease duration. This reason why we did not perform the immunohistochemistry or HE staining here, is that skin biopsy was performed in only four cases, in another words, the biopsy was performed as differential diagnostic procedure. The purpose was to determine vitiligo diagnosis in unclear medical cases.

Recently, increased serum IL-2 [11,30,31] and IL-2 sR concentrations have also been reported in peripheral blood [12,32] and tissue [19] but lower IL-2 sR concentrations [13] were found in active vitiligo patients.

In contrast to our results, in the study of Tembhe et al. [14] serum levels of IL-2 in patients with vitiligo did not differ from the controls. They also found a significant negative correlation with total disease duration for IL-2 in active untreated vitiligo but no correlation was found in untreated stable vitiligo suggesting the involvement of IL-2 in the induction phase of the disease.

In many important skin dermatoses the activation of T lymphocytes is expressed by IL-2 sR and therefore, its increased serum level in patients with vitiligo is usually a reliable marker of acute activation of T cell mediated immunity [19,33]. Yeo et al. [34] showed that IL-2 sR were higher in vitiligo patients compared with normal controls in South Korea, and the IL-2 sR levels in patients with vitiligo of less than 1 year duration was significantly higher than in patients with vitiligo of more than 1 year duration. Additionally, the IL-2 sR levels were not significantly different between active and inactive group, and there was no significant differences in IL-2 sR levels when they were analyzed based on gender of patients, or age of onset. They concluded that the higher IL-2 sR levels in recent onset group would suggest that IL-2 sR level might be an acute immunologic marker in vitiligo patients. Honda *et al.* reported that serum IL-2 sR levels were comparable between localized vitiligo patients and the controls but were significantly elevated in patients with generalized vitiligo compared to controls or to inactive type vitiligo patients in Japan [35]. After that, Shi *et al.* demonstrated the increased serum IL-2 sR levels in vitiligo patients compared to that of healthy controls, and also observed increased serum levels of IL-2 sR in patients with short disease duration, which further suggest that IL-2 sR levels may represent a relative early immunologic marker for vitiligo patients [36].

Also tissue fluids from the margin of hypopigmented macules, especially in active disease, seem to contain higher levels of IL-2 sR than uninvolved skin of the same patients [19]. In addition, Zailaie observed that treatment of vitiligo with single dose of oral aspirin for 12 weeks was able to decrease the levels of IL-2 sR [33]. He concluded that aspirin treatment of patients with active vitiligo can modulate the immunologic factors that cause up-regulation of humoral and cellular immunity involved in melanocyte cytotoxicity. Of these factors, serum vitiligo-IgG and IL-2 sR, which are considered as immunologic markers of vitiligo disease activity.

5. CONCLUSION

Although the initiating event in vitiligo has not yet been defined, a growing body of evidence indicates that cytokines may help the development and the perpetuation of the chronic inflammatory state. The results presented in our study demonstrate that the median levels of IL-2 and IL-2 sR were significantly elevated in vitiligo

patients in comparison with healthy subjects. The imbalance observed in the cytokines examined in the current study suggest their involvement in the pathogenesis of vitiligo.

Further studies with a larger sample size are required to clarify the pathogenic role and clinical significance of IL-2 and its soluble receptor, and these findings may provide important clues to assist in the development of new therapeutic strategies for patients with vitiligo.

CONSENT

All authors declare that written informed consent was obtained from the patients for publication of this research article.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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