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ORIGINAL ARTICLE

Levels of TGF-β Serum Positively Correlated with Levels of IgM Anti PGL-1 In Household Contacts of Multibacillary Leprosy Patients

Kadar *Transforming Growth Factor-β* Serum Berkorelasi Positif dengan Kadar *Immunoglobulin M Anti-Phenolic Glycolipid-1* pada Narakontak Serumah Pasien Kusta Multibasiler

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ABSTRACT

Background

Leprosy is a chronic progressive infectious disease. Phenolic glycolipid-1 (PGL-1) is an antigen of *Mycobacterium leprae,* which can trigger the host's antibody response. Transforming growth factor-β (TGF-β) plays an immunosuppressive role when the host is exposed to PGL-1 antigen or other *M. leprae* antigens. This study aims to determine the correlation of TGF-β levels with IgM anti-PGL-1 levels in patients with multibacillary leprosy household contacts.

Methods

Observational analytical study with a cross-sectional approach. The study subjects consisted of 48 household contact subjects and 24 non-household contact subjects aged 15-65 years old who were selected by consecutive sampling based on inclusion and exclusion criteria. 3 mL of venous blood samples were taken and then examined for IgM anti-PGL-1 and TGF-β with the ELISA kit. Data analysis was carried out using SPSS version 23, and a p-value <0.05 was significant.

Results

The mean level of IgM anti-PGL-1 in the household contact group was 685.46 ± 290.79 u/mL, while in the non-household contact group was 345.50 ± 206.58 u/mL. The mean TGF-β level in household contact groups was 256.69 ± 127.41 pg/mL, while in the non-household contact group was 144.85 ± 36.73 pg/mL (p<0.001). This study found a moderate positive relationship (r=0.450, p<0.001) between levels of TGF-β and IgM anti-PGL-1 household contacts and non-household contacts group.

Conclusions

The mean level of IgM anti-PGL-1 and TGF-β in household contacts is higher than in non-household contacts, with a significant difference. There is a moderate positive significant relationship between levels of TGF-β and IgM anti-PGL-1 household contacts and non-household contacts group.

Keywords: contacts, IgM anti-PGL-1, leprosy, TGF-β

ABSTRAK

Latar Belakang

Kusta merupakan penyakit menular kronik progresif. *Phenolic glycolipid-1* (PGL-1) merupakan komponen antigen dari *Mycobacterium leprae* yang memicu respon antibodi dari penjamu. *Transforming growth factor-β* (TGF- β) berperan imunosupresif saat tubuh terpapar antigen PGL-1 maupun antigen *M. leprae* yang lain. Penelitian ini bertujuan untuk mengetahui korelasi kadar TGF-β dengan kadar IgM anti PGL-1 pada narakontak serumah pasien kusta tipe multibasiler.

Metode

Studi analitik observasional dengan pendekatan potong lintang. Sampel pada penelitian ini terdiri dari 48 subjek narakontak dan 24 subjek bukan narakontak berusia 15-65 tahun yang dipilih melalui *consecutive sampling* sesuai kriteria inklusi dan eksklusi. Sampel dilakukan pengambilan 3 mL darah vena yang kemudian diperiksa kadar IgM anti PGL-1 dan TGF-β dengan kit ELISA. Analisis data dengan SPSS versi 23 dan nilai $p<0.05$ bermakna signifikan.

Hasil

Rerata kadar IgM anti PGL-1 kelompok narakontak yaitu 685,46 ± 290,79 u/mL sementara pada kelompok bukan narakontak yaitu 345.50 ± 206.58 u/mL. Rerata kadar TGF-β serum kelompok narakontak yaitu 256.69 ± 127.41 pg/mL sementara pada kelompok bukan narakontak yaitu 144.85 ± 36.73 pg/mL ($p<0.001$). Penelitian ini mendapatkan hubungan positif sedang nilai ($r=0.450$, $p<0.001$) antara kadar TGF-β serum dengan kadar IgM anti PGL-1 pada kelompok narakontak dan bukan narakontak.

Kesimpulan

Kadar IgM anti PGL-1 dan kadar TGF-β serum pada narakontak lebih tinggi dari bukan narakontak dengan perbedaan yang signifikan. Terdapat hubungan positif sedang yang signifikan antara kadar TGF-β serum dan kadar IgM anti PGL-1 pada kelompok narakontak dan bukan narakontak.

Kata Kunci: IgM anti PGL-1, kusta, narakontak, TGF-β

INTRODUCTION

Leprosy is a significant progressive chronic infectious disease. Data from the World Health Organization (WHO) in 2020 stated that there were 127,558 new cases of leprosy detected globally. Among these recent cases, 7,198 new cases were detected with level 2 disability. At the end of 2020, there were 129,389 cases of leprosy with treatment, equivalent to 16.7 per one million population.[1] According to the 2019 Indonesia Health Profile, Indonesia is third in world leprosy epidemiology after India and Brazil, discovering 17,017 new leprosy cases.[2] Based on data from the Bali Provincial Health Office in 2017, the prevalence of leprosy in Bali was 1,841 per 100,000 population. Based on medical record data at Prof. Dr. IGNG Ngoerah Central General Hospital from January 2019 to December 2020, there were 76 new cases of leprosy, with 51 cases of multibacillary type (MB).[3]

The immune response and virulence factors of *M. leprae* play an important role in leprosy. The innate immune system is the first immune defense against the *M. leprae*. A low innate immune response will cause macrophages to be unable to kill *M. leprae* so that bacteria will continue to grow in the body and can cause clinical leprosy. Phenolic glycolipid-1 (PGL-1) is an

antigen component of *M. leprae* that can trigger an antibody response from the host. Serological examination of IgM anti-PGL-1 can indicate the number of bacteria in the host.[4-6]

Transforming growth factor-β has many immunoregulatory effects, including proinflammatory, immunosuppressive, cell growth, and differentiation effects. Transforming growth factor-β plays a role in suppressing the response of T cells, inhibits the expression of IFN-ɣ and IL-2, and can hinder the lytic activity of macrophages, which leads to the development of infection. Examination of TGF-β levels can also indicate the number of bacteria in the host. Transforming growth factor-β leprosy plays an immunosuppressive role when the body is exposed to PGL-1 antigen or other *M. leprae* antigens so that TGF-β levels will increase along with increased anti-PGL-1 IgM levels in leprosy and subclinical leprosy patients.[6-9]

Several studies have reported the correlation of levels of various cytokines such as IL-10, IL-17, IL-4, and IL-6 with IgM anti-PGL-1 levels in household contacts of multibacillary leprosy patients. Meanwhile, research on the correlation between TGF-β levels and IgM anti-PGL-1 levels in household contacts of multibacillary leprosy patients has never been reported. This research suggests something new: it aims to prove the role of TGF-β in the pathogenesis of subclinical leprosy, especially in household contacts of patients with multibacillary leprosy.

This research needs to be done because both immunological parameters, TGF-β and IgM anti-PGL-1, can potentially be used to predict the course of disease in subclinical leprosy patients. Therefore, researchers want to investigate further the correlation between serum levels of TGF-β and serum levels of IgM anti-PGL-1 in household contacts of multibacillary leprosy patients at the Dermatology and Venereology Polyclinic, Morbus Hansen subdivision, Prof. Dr. I.G.N.G Ngoerah Central General Hospital Denpasar.

METHODS

This observational analytical study with a cross-sectional design was conducted at Polyclinic Dermatology and Venereology, Morbus Hansen subdivision, Prof. Dr. I.G.N.G Ngoerah Central General Hospital Denpasar. This study was conducted for two months, from February 2023 until March 2023. This research involved the Clinical Pathology Laboratory, Prof. Dr. I.G.N.G Ngoerah Central General Hospital Denpasar for examining levels of TGF-β serum and Leprosy Laboratory, Tropical Diseases Diagnostic Center, Airlangga University, Surabaya, as a reference laboratory for studying levels of IgM anti-PGL-1.

Samples were selected by consecutive sampling based on inclusion and exclusion criteria. The inclusion criteria in this study: (1) all individuals who live in the same house and have had close contact for at least six months with multibacillary leprosy patients who during the study period, visited Polyclinic Dermatology and Venereology at Prof. Dr. I.G.N.G Ngoerah Central General Hospital Denpasar (2) all individuals who were not live in the same house but came from same regency or city with multibacillary leprosy patients, (3) Indonesian citizen, (4) age 15-65 years, (5) good general condition, (6) want to sign informed consent. Meanwhile, the exclusion criteria in this study: (1) subjects who are pregnant/breastfeeding, (2) subject who shows clinical symptoms of leprosy from history taking and physical examination, (3) subject who have history of an autoimmune disease such as psoriasis, rheumatoid arthritis, systemic lupus erythematosus, (4) subject who suffer from infectious diseases such as tuberculosis infection, influenza, hepatitis B,

hepatitis C, human immunodeficiency virus (HIV) and (5) subject who currently receiving systemic corticosteroid in the past four weeks. Because under these conditions, there is an increase in TGF-β levels.

Data collection includes history taking, physical examination, and a sample of 3 mL milliliters of venous blood, which would then be examined for IgM anti-PGL-1 and TGF-β with the ELISA kit. The collected data will be analyzed using statistical tests with the Statistical Package for Social Sciences (SPSS) 23.0 program. A descriptive analysis was presented regarding frequency, percentage, and standard deviation. Then, a correlation analysis was performed using the Spearman rho test by displaying the correlation coefficient value (r). The sensitivity and specificity tests presented are accompanied by showing the AUC value and ROC curve. The p-value is said to be significant if <0.05.

Researchers have received research approval from RSUP. Prof. Dr. IGNG Ngoerah, before the research was carried out with the number LB 02.01/XIV.2.2.2/5563/2023 and a statement of ethical eligibility from the Research Ethics Commission Unit of the Faculty of Medicine, Udayana University with number 38/UN14.2.2.VII.14/LT/2023.

RESULTS

This study involved 48 household contact subjects and 24 non-household contact subjects. The subject's characteristics can be seen in **Table 1**.

Table 1. Characteristics of research subjects

Characteristics	Household Contact Status n (%), mean ± SD		p-value
	Household contact (n= 48)	Non-household contact (n= 24)	
Age (years)	37.48±13.26	34.04±11.63	0.304*
Gender			
Man	23 (47.92)	8 (33.33)	0.239**
Woman	25 (52.08)	16 (66.67)	
BMI (kg/m²)	21.87 ±0.91	21.43 ± 1.18	0.632*
Education			
Elementary School	3 (6.35)	0	
Junior High School	2 (4.17)	0	
Senior High School	32 (66.67)	9 (37.5)	
Diploma	4 (8.33)	14 (58.33)	
Bachelor	7 (14.58)	1 (41.67)	
Occupation			
Private sector employees	23 (47.92)	21 (87.50)	
Doesn't work.	11 (22.91)	2 (8.33)	
Self-employed	8 (16.67)	0	
Trader	2 (4.17)	1 (4.17)	
Student	1 (2.08)	0	
Seamstress	1 (2.08)	0	
Retired	1 (2.08)	0	
Midwife	1 (2.08)	0	
Socioeconomic status	IDR. 2,382,291± IDR. 1,182,653	IDR 2,233,333 ± IDR 699,171	0.890*
a. <IDR 1,500,000	15 (31.25)	5 (20.83)	
b. IDR 1,500,000-2,500,000	19 (39.53)	9 (37.50)	
c. > IDR 2,500,000	14 (29.17)	10 (41.67)	
Length of contact with MB patients, mean ± SD (years)	4.33±6.06	-	
Relationship with patient			

Married couple	21 (43.75)	-	
Child	9 (18.75)		
Parents (father/mother)	2 (4.67)		
Siblings	8 (16.67)		
Grandchild	2 (4.17)		
Parents in law	1 (2.08)		
Son in law	2 (4.17)		
Spouse's brother	1 (2.08)		
Nephew	2 (4.17)		
IgM Anti PGL-1 levels (u/mL)	685.46 ± 290.79	345.50 ± 206.58	<0.001*†
TGF-β levels (pg/mL)	256.69 ± 127.41	144.85 ± 36.73	<0.001*†

SD: standard deviation; * Mann Whitney; ** Chi-Square, † significant

The relationship between variables was analyzed using the Mann-Whitney (non-parametric) test because data were not distributed normally, and data was displayed using the median (minimum-maximum). The median serum TGF-β level in the household contact group was 248.67 pg/mL. This result was significantly higher than the median serum TGF-β level in the non-household contact group, 149.79 pg/mL with p-value <0.001. The median IgM anti-PGL-1 level was significantly higher in the household contact group, 686 u/mL, compared to the non-household contact group, 298 u/mL, with a p-value <0.001.

Correlation analysis between serum TGF-β levels and IgM anti-PGL-1 levels was performed using the Spearman Rho test because the data were not distributed normally. The correlation analysis can be seen in Table 2. Based on the test results, a moderate positive relationship was found between serum TGF-β levels and IgM anti-PGL-1 levels with a correlation coefficient (r) of 0.450 and a p-value <0.001. This indicates that the higher the serum TGF-β level, the higher the IgM anti-PGL-1 level.

Table 2. Correlation test of serum TGF-β levels with IgM anti PGL-1 levels

Variable		Serum TGF-β levels
IgM Anti PGL-1 levels	r	0.450
	p	<0.001*
	n	72

*Significant if p<0.05; correlation analysis with Spearman rho test

ROC curve analysis was performed in this study to determine the cut-off point of serum TGF-β levels based on IgM anti-PGL-1 levels using a cut-off point of 605 u/mL. The results of the ROC curve analysis showed a sensitivity value of 76.3% and a specificity of 73.5% with a cut-off value of 166.5 pg/mL (Table 3 and Figure 1).

Table 3. Sensitivity, specificity, and cut-off points of serum TGF-β levels

Variable	AUC	Sensitivity	specificity	cut-off point	CI 95%	p-value
Serum TGF-β levels	77.5%	76.3%	73.5%	166.5	0.655 - 0.886	<0.001

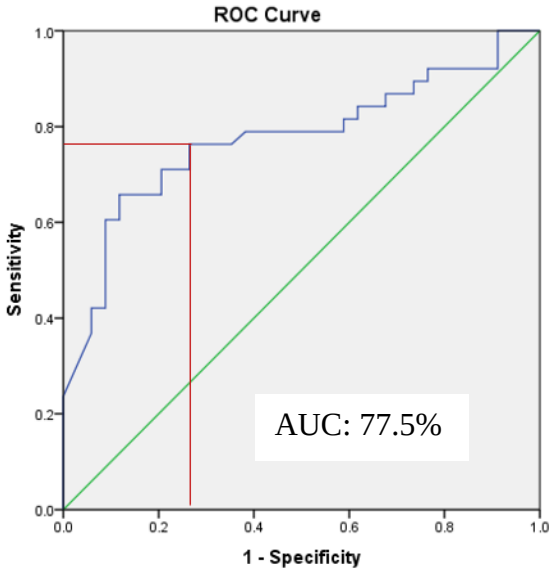

Figure 1. ROC curve of serum TGF-β levels based on the category of IgM anti-PGL-1 levels.

Based on the results of this study, the examination of serum TGF-β levels had a sensitivity of 76.3% and a specificity of 73.5%. This examination is expected to give positive test results in 76.3% of the population with subclinical leprosy and negative test results in 73.5% without subclinical leprosy.

Based on these results, a risk model was developed for levels of IgM anti-PGL-1. In this study, IgM anti-PGL-1 levels > 605 u/mL were categorized as high IgM anti-PGL-1 levels in household contacts of multibacillary leprosy. Seropositive is an IgM anti-PGL-1 level above or equal to 605 U/mL and seronegative if the level is below 605 U/mL; this is the cut-off value for IgM anti-PGL-1 in East Java based on research conducted by Arsyad et al. in 2012.

The risk analysis found a significant association between the serum TGF-β category and the IgM anti-PGL-1 category in contact persons with multibacillary leprosy (p<0.05) (**Table 4**). Based on the risk analysis using the 2x2 table, it was found that an increase in serum TGF-β levels increased the risk 6.8 times of an increase in IgM anti-PGL-1 levels (PR: 6.8; 95% CI: 2.4-19.2, p< 0.001).

Table 4. Risk analysis of increased serum TGF-β levels on increased IgM anti-PGL-1 levels

	IgM anti-PGL-1		PR	CI 95%	p-value
	High >605	Low ≤605			
High TGF-β (>166.5 pg/mL)	27 (75%)	11 (30.5%)	6.8	2.4-19.2	<0.001*
Low TGF-β (≤166.5 pg/mL)	9 (25%)	25 (69.44%)			

*Significant if the value of p<0.05; cross tabulation analysis with Chi-Square test

DISCUSSION

This study found that the average age of contact subjects was 37.48 ± 13.26 years. The age of the subjects in this study matched the age data of contact persons in Bali and Java in previous studies, with an average age range of 30-40 years.[3,10–13]. Leprosy is more common in the productive age group due to higher activity, making it more susceptible to contracting leprosy.

Leprosy is also a chronic disease because of the long incubation period, which can be more than five years.[11] Contact person's risk of subclinical leprosy is 5-10 times greater than non-contacts.[14]

Based on the literature, the levels of various cytokines in the human body change with age. Serum TGF-β in children aged 0-14 years was significantly higher than in adults over 15 years.[9] So, matching the age before evaluating serum TGF-β levels is recommended. IgM anti-PGL-1 levels also increase at a younger age (4-15 years).[15] This study found that age did not affect TGF-β and IgM anti-PGL-1 levels. This is because researchers have limited the age selection of subjects in this study from 15-65 years old.

In this study, the contact subjects were mostly female. Most household contact leprosy patients who visit the hospital are women. In another study, gender was not associated with increased IgM anti-PGL-1 levels in contact persons.[15] Gender was also not found to be associated with an increase in TGF-β levels.[8] This study found that all subjects had normal nutrition and no association with IgM anti-PGL-1 levels or TGF-β levels. The results of this study are similar to the study conducted in Bali and Java that have been done previously.[3,11,12,16–19]

Low levels of knowledge and poverty are risk factors that increase infection transmission and clinical leprosy.[20] Research in Brazil, Bangladesh, and Egypt showed risk factors for leprosy, including a low level of knowledge and low economic status.[21] This level of education is related to the level of knowledge, the lack of public awareness of leprosy caused by the fact that sufferers do not feel disturbed by the symptoms and their families do not know that these symptoms are early symptoms of leprosy. Hence, leprosy cases become difficult to treat quickly. They are causing the spread to occur more rapidly. Nur's study on the relationship between leprosy counseling and the level of knowledge of leprosy families in Majen District found that most subjects with low education and 90% did not know about leprosy.[22] In Brazil, the country with the most cases of leprosy coming from all over the world, they can conduct early screening of leprosy cases while still in school because teachers in that country have been given education about leprosy and the risk of transmission.[23,24]

The average contact length with MB leprosy patients was 4.33 ± 6.06 years. The results of this study are similar to the results of research conducted by Sittanggang, who obtained contacts, for the most part, having an average of 3-5 years of contact.[25] The results of observations of increased levels of IgManti-PGL-11 occurred mostly after contact ≥3 years.[6] Leprosy transmission occurs through direct contact with bacteria from patients who have not been treated or inhalation of bacteria in the air; continuous contact exposure will make it more susceptible to subclinical leprosy.[6,26,27]

In this study, the most contact persons with MB type leprosy were partners, both husbands and wives, who had no blood related between them, 21 people (43.75%). Factors of transmission of leprosy are influenced by aspects of immunity, nutrition, sanitation, and environmental elements so that even without genetic factors, a person can still be affected by leprosy. [28] Leprosy sufferers with genetic susceptibility have an 8-fold (range 5.9–10.6 times) higher risk of developing clinical leprosy.[8] Genetic factors, namely the human leukocyte antigen (HLA-DR2) gene and non-HLA genes, are thought to play a role in genetic susceptibility to both leprosy in general and types of leprosy. The locus on chromosome 6q25 appears to play a role in controlling

exposure to leprosy. Another study in India showed that the locus on chromosome 10p13 was associated with 2.1 times increased risk of PB-type leprosy.[29]

The mean level of IgM anti-PGL-1 in the household contact group was 685.46 ± 290.79 u/mL, while in the non-household contact group, it was 345.50 ± 206.58 u/mL. The average yield of these contacts exceeded the rate of IgM anti-PGL-1ibodies in leprosy patients with seropositive ranging from 605 u/mL (cut point for East Java population), and the cut point in Bali is 613 u/mL.[18] This shows that most of the contacts have experienced subclinical leprosy.

The mean serum TGF-β level in the household contact group was 256.69 ± 127.41 pg/mL; in the non-household contact group, it was 144.85 ± 36.73 pg/mL. The results of this study in contacts with multibacillary leprosy were lower than the results of serum TGF-β levels in patients with multibacillary type leprosy, 636.42 ± 1027.99 pg/mL.[8] Results are lower compared to leprosy sufferers, but it is enough to prove that TGF-β levels in contacts are higher than in non-contacts. This can happen because the body's immune system in contact is still better than leprosy patients.

This study found a moderate positive correlation between serum TGF-β levels and IgM anti-PGL-1 levels with a correlation coefficient (r) of 0.450 and p-value <0.001. This indicates that the higher the serum TGF-β level, the higher the IgM anti-PGL-1 level. The results of this study are similar to previous research that found a significant difference between the levels of TGF-β and IgM anti-PGL-1 in leprosy patients with recurrent ENL reactions and those without ENL reactions. Increased TGF-β levels and IgM anti-PGL-1 levels in patients with MB-type leprosy can predict recurrent responses. Serum TGF-β levels were also found to have a positive correlation with the bacterial index (BI) in leprosy patients with a regression correlation of IB with serum TGF-β (Spearman Correlation) obtained r=0.266; p=0.008.[8,30]

In leprosy, TGF-β has an immunoregulatory effect. Transforming growth factor-β plays a role in suppressing the response of T cells, inhibits the expression of IFN-ɣ and IL-2, and can hinder the lytic activity of macrophages, which leads to the development of infection. This immunosuppression effect of TGF-β can relate to the PGL-1 antigen so that TGF-β levels will increase along with the increase in IgM anti-PGL-1 levels in leprosy and subclinical leprosy patients.[8]

Increased levels of TGF-β in contact can happen because TGF-β controls the proliferation, survival, activation, and differentiation of B cells, as well as the development and function of innate immune cells, including natural killer (NK) cells, macrophages, dendritic cells, and granulation during infection with *M. lepra*. Transforming growth factor-β also mediates the generation of peripheral T cells (p), Th17, Th9, and Tfh, and tissue-resident T cells that generally play an important role in maintaining peripheral tolerance and driving the immune response to pathogens.[31–34] The increase in systemic proinflammatory mediators due to *M. leprae* infection also causes macrophages to differentiate and produce IL-10 and TGF-β cytokines.[15]

This study has been able to prove that serum TGF-β levels have a moderate positive correlation with IgM anti-PGL-1 levels in household contacts of multibacillary leprosy patients, which means that serum TGF-β can be used as an alternative marker in subclinical leprosy, with a sensitivity of 76.3% and a specificity of 73.5% with a cut-off value of 166.5 pg/mL.

The weakness of this study is that it was limited to the environment in the area where the sample was selected, so to prove that result in various places and conditions, it is necessary to carry out further research and comparative tests with multibacillary leprosy and endemic leprosy. This study has not analyzed vitamin D and zinc consumption, which can affect IgM anti-PGL-1 levels.

The immune response to *M. leprae,* when first exposed in patients with a history of contact with leprosy patients, will start from an innate immune response to an adaptive immune response, which occurs for several years until clinical symptoms develop. One cytokine cannot be used as a reference to determine the severity of a bacterial infection because several cytokines work together continuously.[25]

The leprosy spectrum reflects the balance between Th1 and Th2. In addition, there are also Th17 and T reg cells that play a role in leprosy. TGF-β is one of the many cytokines that play a role in leprosy. It is possible that in contacts who have not yet manifested clinical signs of leprosy, these cytokines work continuously together so that this balancing process occurs.[25]

The samples in this study were primarily husbands or wives of MB leprosy patients who were not related by blood to the patients. If there is a genetic relationship, it will trigger a high marker of leprosy examination. Genetic factors, namely the human leukocyte antigen (HLA-DR2) gene and non-HLA genes, are thought to play a role in genetic susceptibility to leprosy in general and types of leprosy. The locus on chromosome 6q25 plays a role in controlling exposure to leprosy. Another study in India showed that the locus on chromosome 10p13 is associated with an increased risk of PB-type leprosy. [(35)] The risk factor for leprosy from genetic factors can occur eight times with a range of 5.9–10.6 times.[36]

Further research needs to be conducted to assess the correlation of serum TGF-β levels and IgM anti-PGL-1 levels not only in household contacts of multibacillary leprosy patients but to compare various types of leprosy in endemic areas and healthy people using the case-control method, and prognostic observations can be carried out with the cohort method with a larger sample.

CONCLUSION

The mean serum TGF-β and IgM anti-PGL-1 levels in multibacillary leprosy patients' household contacts were higher than in non-household contacts. There is a moderate positive correlation between serum TGF-β levels and IgM anti-PGL-1 levels in household contacts of multibacillary leprosy patients at Prof. Dr. IGNG Ngoerah Central General Hospital Denpasar. This result indicates that the higher the serum TGF-β level, the higher the IgM anti-PGL-1 level.

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AUTHORS CONTRIBUTION

Study conception and design: PYP. Author, LMMR. Author, IGAADK. Author; data collection: PYP. Author; analysis and interpretation of results: PYP. Author, LMMR. Author,

IGAADK. Author; draft manuscript preparation: PYP. Author, KKW. Author, NS. Author, NLPRVK. Author. All authors reviewed the results and approved the final version of the manuscript.

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CONFLICT OF INTEREST

There is no conflict of interest between the authors and no conflict of interest regarding the publication of this research.

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