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# THE RELATIONSHIP BETWEEN DIABETES MELLITUS AND HYPERTENSION WITH PEMPHIGUS VULGARIS IN PEMPHIGUS VULGARIS PATIENTS

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**ABSTRACT**
Pemphigus vulgaris (PV) is a chronic autoimmune skin disease that manifests as loose vesicles and bullae that affect the mucosa and skin. The first-line therapy for PV is systemic corticosteroids. Although corticosteroid therapy is effective as treatment for pemphigus vulgaris, long-term use of corticosteroids causes various complications such as diabetes mellitus and hypertension. Objectives to examine the relationship of pemphigus vulgaris with diabetes mellitus and hypertension. This study is a retrospective analytic study with a cross sectional approach with a sample size of sixteen people with pemphigus vulgaris. This research was conducted in March – August 2022 at Dr. M. Djamil Hospital in Padang. Relationship analysis is performed using Fisher's exact test by comparing the incidence of diabetes mellitus and hypertension in patients with pemphigus vulgaris with patients with other autoimmune bullous diseases. There is no significant relationship between pemphigus vulgaris and diabetes mellitus ($p = 0.133$) and hypertension ($p = 0.253$). The profile of patients with pemphigus vulgaris is also obtained: the annual incidence of PV is 3.2 cases/year; the majority of PV patients are women, with a female to male ratio of 1:0,78; the majority of PV patients are in the 40-60 year age group; the occupation of the most PV patients is housewives; and the majority of clinical manifestations of patients with PV are found on the skin and mucous membranes. There is no significant relationship between pemphigus vulgaris with diabetes mellitus and hypertension.

Keywords: diabetes mellitus; hypertension; pemphigus vulgaris

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## INTRODUCTION

Pemphigus vulgaris (PV) is a chronic autoimmune skin disease that manifests as loose vesicles and bullae affecting the mucosa and skin. 1,2 This disease is caused by autoantibodies that attack desmoglein (a protein responsible for adhesion between cells) resulting in acantholysis which causes the formation of loose blisters on the mucosa or skin. 3–5The incidence of pemphigus vulgaris (PV) varies depending on the geographical distribution and ethnicity of sufferers. The incidence varies from 0.76 cases/1 million population/year in Finland, to 16.1 cases/1 million population/year in Jerusalem. Prevalence is found to be higher in descendants of Ashkenazi Jewish families. .6,7 Pemphigus vulgaris can affect all ages and genders, but generally cases are found in people aged 40-60 years and female gender. .8 The average age at onset of PV is 50 – 60 years, but this is more common in Europe and North America, whereas in the Middle East the onset of PV tends to be at a younger age (around the 4th decade).

Epidemiological data on pemphigus vulgaris in Indonesia itself is still limited due to the lack of publications on pemphigus vulgaris. There is a study by Wardhana et al. (2013) at Sanglah General Hospital, Denpasar, which used medical record data from January 1995 to December 2002. It was found that the incidence of pemphigus was 4 patients per year with the majority age range being 40–50 years. The female-male ratio found was 2.3:1 with the number of PV patients as many as 26 people. 10First-line pharmacological therapy in PV is systemic corticosteroids, with oral prednisone being the most commonly used drug. Corticosteroid therapy is quite effective as a treatment for pemphigus vulgaris, but long-term use of corticosteroids causes various complications that cause mortality of pemphigus vulgaris to remain high. Pemphigus vulgaris patients can suffer from diabetes mellitus due to complications from corticosteroid use. Research by Derek et al. (2017) stated that of the many comorbid diseases of pemphigus vulgaris studied, type 2 diabetes mellitus is included in the 8 diseases that are closely related to pemphigus vulgaris, along with hypertension. However, unlike other comorbidities that are widely associated with the use of systemic corticosteroids, pemphigus vulgaris patients who do not use systemic corticosteroids are still at much higher risk of developing type 2 DM compared to people in general.

Hypertension can also occur in patients with pemphigus vulgaris due to the side effects of corticosteroid use, even though they did not previously have hypertension comorbidities. High doses and long periods of corticosteroid use increase the risk of patients suffering from hypertension. The prevalence of hypertension caused by long-term corticosteroid exposure is >30%. Although diabetes mellitus and hypertension can be caused by long-term use of corticosteroids, based on the reasons mentioned above, both diseases can be caused by other factors even in patients with pemphigus vulgaris. Therefore, it is necessary to know the relationship between hypertension and diabetes in cases of pemphigus vulgaris so that the management of related cases can be carried out better and minimize the risk to patients. With the limited research on pemphigus vulgaris that exists, or those related to diabetes mellitus and hypertension in Indonesia, West Sumatra, and also Padang City, the author is interested in studying the relationship between diabetes mellitus and hypertension in patients with pemphigus vulgaris at Dr. M. Djamil General Hospital Padang for the period 2016-2021. Dr. M. Djamil General Hospital was chosen as the location of the study because Dr. M. Djamil General Hospital is the last referral hospital in West Sumatra Province. The selection of the 2016 to 2021 period was chosen because of the limited data available at the Medical Record Installation of Dr. M. Djamil General Hospital. M. Djamil, because medical record data before 2016 has been destroyed according to Minister of Health Regulation 269 of 2008 wh ch states that medical records that are 5 years old since the last visit can be destroyed.

## METHOD

This study is an observational retrospective analytical study with a cross-sectional approach using medical record data of pemphigus vulgaris patients at Dr. M. Djamil General Hospital to examine the relationship between diabetes mellitus and hypertension with pemphigus vulgaris. This study was conducted in March 2022 - August 2022 in the Medical Records Department of Dr. M. Djamil General Hospital Padang. The population of this study were all patients diagnosed with autoimmune bullous disease (PBA) in the medical record data of Dr. M. Djamil General Hospital Padang in the period 2016-2021. The sample used was all patients diagnosed with pemphigus vulgaris in the medical record data of Dr. M. Djamil General Hospital in the period 2016-2021. The sampling technique in this study was total sampling, which means the number of samples is the same as the population.

After data collection, the data will be analyzed using univariate and bivariate analysis. Univariate analysis was conducted to determine the frequency distribution of each variable (pemphigus vulgaris, diabetes mellitus, and hypertension). The data analyzed univariately were the characteristics of pemphigus vulgaris (PV) patients including gender, age,

occupation, lesion location, therapy modality as well as the frequency distribution of PV patients with diabetes mellitus and the frequency distribution of PV patients with hypertension. Bivariate analysis was conducted to determine whether or not there was a relationship between the two dependent variables (diabetes mellitus and hypertension) with one independent variable (pemphigus vulgaris). The research data will be presented in the form of tables and narratives using Fisher's exact test analysis.

## RESULT

In the Medical Record Installation of RSUP. Dr. M. Djamil Padang, samples of 16 people suffering from pemphigus vulgaris were found from 2016 - 2021. The annual incidence obtained was 3.2 cases per year. According to Table 1, we can see that most of the pemphigus vulgaris sufferers in this study were female. Of the 16 samples, 9 people (56.2%) were female, with the remaining 7 men (43.8%). In addition, it can also be seen that the majority of pemphigus vulgaris sufferers are in the 40-60 year age group, with a total of 8 people (50%), followed by the second largest age group, namely <40 years with a total of 7 people (43.8%) and 1 person aged >60 years (6.2%).

Tabel 1.
Frequency distribution of pemphigus vulgaris patient profile

| Karakteristik | f | % |
|---|---|---|
| Gender | | |
| Male | 7 | 43,8 |
| Female | 9 | 56,2 |
| Age | | |
| < 40 years | 6 | 43,8 |
| 40 – 60 years | 8 | 50 |
| > 60 years | 1 | 6,2 |
| Occupation | | |
| Student | 3 | 18,8 |
| Housewife | 7 | 43,8 |
| Civil Servant | 1 | 6,2 |
| Self-Employed | 4 | 25 |
| Farmer | 1 | 6,2 |
| Lesion Location | | |
| Skin | 3 | 18,8 |
| Mucosa | 0 | 0 |
| Skin and mucosa | 12 | 81,2 |
| Therapeutic Modalities | | |
| Corticosteroids | 15 | 93,8 |
| Adjuvant therapy (immunosuppressants) | 4 | 25 |
| Antibiotics | 10 | 62,5 |
| Antihistamine | 11 | 68,8 |
| Analgesic | 5 | 31,3 |

The occupation of pemphigus vulgaris patients in this study was dominated by housewives with a total of 7 people (43.8%), followed by self-employed with a total of 4 people (25%). There were 3 people (18.8%) as students, and 1 person (6.2%) each for civil servants and farmers. Most samples had lesions that manifested on the skin and mucosa simultaneously, with a total of 13 people (81.2%). The rest of them were patients whose lesions only manifested on the skin, as many as 3 people (18.8%). There are several therapeutic modalities used for pemphigus vulgaris (PV) patients at Dr. M. Djamil Padang General Hospital in this study.

The main therapy used is corticosteroids, among which the most frequently used are methylprednisolone, prednisone, and dexamethasone. Corticosteroids were used in 15 cases (93.8%) of the 16 PV in this study. In addition, there is also adjuvant therapy, where all drugs used as adjuvant therapy are the immunosuppressant azathioprine. This drug was given in 4 cases (25%). In addition to the main therapies mentioned above, there are also other additional therapies such as antibiotics, antihistamines and analgesics. The antibiotics used

include amoxicillin, clindamycin, and ciprofloxacin. In addition, the antihistamines used are ranitidine, loratadine, and cetirizine. While the analgesic given in this study is mefenamic acid. Based on the additional therapy used, 11 people (68.8%) were given antihistamine therapy, 10 people (62.5%) were given antibiotic therapy, and 5 people (31.3%) were given analgesic therapy.

Table 2.
Frequency Distribution of Diabetes Mellitus in Pemphigus Vulgaris Patients

| Diagnosis DM | f | % |
|---|---|---|
| Diabetes | 1 | 6,2 |
| Non-diabetes | 15 | 93,8 |

Frequency distribution of pemphigus vulgaris patients with diabetes mellitus at RSUP. Dr. M. Djamil Padang in 2016-2021 can be observed in Table 2. Table 2 shows that out of 15 samples, only 1 person (6.2%) of them suffered from diabetes mellitus, with the remaining 14 people (93.8%) not suffering from diabetes mellitus.

Table 3.
Frequency Distribution of Hypertension in Pemphigus Vulgaris Patients

| Diagnosis HT | f | % |
|---|---|---|
| Hipertensi | 8 | 50 |
| Non-hipertensi | 8 | 50 |

The frequency distribution of pemphigus vulgaris patients with hypertension at RSUP. Dr. M. Djamil Padang in 2016-2021 can be observed in Table 3. In Table 3 we can see that 8 people (50%) have hypertension from a sample of 16 people, with people without hypertension totaling 8 people (50%).

Table 4.
Analysis of the Relationship between Pemphigus Vulgaris and Diabetes Mellitus in Pemphigus Vulgaris Patients

| | Pemfigus Vulgaris | | | | Total | *p* |
|---|---|---|---|---|---|---|
| | Yes | | No | | | |
| | f | % | f | % | | |
| Diabetes | 1 | 4 | 4 | 14 | 5 | 0,133 |
| Non-diabetes | 15 | 53 | 8 | 29 | 23 | |

Table 4 shows the results of the analysis of the relationship between pemphigus vulgaris and diabetes mellitus. There were 16 samples of pemphigus vulgaris patients and 12 non-pemphigus vulgaris samples, with a total sample of 28 people. In pemphigus vulgaris patients, there was 1 person (4%) with diabetes mellitus and 15 others (53%) did not have diabetes mellitus. Meanwhile, data for non-pemphigus vulgaris patients were taken from data on autoimmune bullous disease (PBA) patients at the same location and period. Among them, there were 4 people (14%) with diabetes mellitus and 8 people (29%) without diabetes mellitus. The results obtained from the analysis using Fisher's exact test were a significance value of $p = 0.133$, which means $p > 0.05$. From these results, we can conclude that there is no significant relationship between diabetes mellitus and pemphigus vulgaris in pemphigus vulgaris patients at Dr. M. Djamil Padang General Hospital.

**Tabel 5** Analysis of the Relationship between Pemphigus Vulgaris and Hypertension in Pemphigus Vulgaris Patients at Dr. M. Djamil Padang General Hospital

| | Pemfigus Vulgaris | | | | Total | *p* |
|---|---|---|---|---|---|---|
| | Ya | | Tidak | | | |
| | f | % | f | % | | |
| Hipertensi | 8 | 28 | 3 | 11 | 11 | |
| Non-hipertensi | 8 | 28 | 9 | 32 | 17 | 0,253 |
| Total | 16 | 56 | 12 | 44 | 28 | |

Table 5 shows the results of the analysis of the relationship between pemphigus vulgaris and hypertension. There were 16 samples of pemphigus vulgaris patients and 12 non-pemphigus vulgaris samples, with a total sample of 28 people. In pemphigus vulgaris patients, there were

8 people (28%) with hypertension and 8 others (28%) did not have hypertension. While for non-pemphigus vulgaris samples, there were 3 people (11%) with hypertension and 9 people (32%) without hypertension. The results obtained from the Fisher's exact test analysis were a significance value of p = 0.253 which means p > 0.05. From these results we can conclude that there is no significant relationship between hypertension and pemphigus vulgaris in pemphigus vulgaris patients at Dr. M. Djamil Padang General Hospital.

## DISCUSSION

In this study, a sample of 16 people suffering from pemphigus vulgaris was found at Dr. M. Djamil General Hospital from 2016 - 2021, with an average incidence of 3.2 cases/year. The average incidence in this study was lower than the study by Surya (2014) at Dr. H. Adam Malik General Hospital, Medan with an average incidence of 4.2 cases/year.23 Likewise, the study by Diana et al. (2021) at Dr. Moewardi General Hospital, Surakarta with an average of 4.17 cases/year. Meanwhile, research by Wardhana et al. (2013) at Sanglah General Hospital, Denpasar found an average incident that was close to this study, namely 3.25 cases/year. 10This study shows that most pemphigus vulgaris sufferers are women. Of the 16 samples, 9 people (56.2%) were women, and 7 men (43.8%). From this data, the ratio of women: men was obtained at 1: 0.78. This is different from the study by Surya (2014) with a ratio of women: men of 1: 1.1, which means that the number of male cases is slightly higher than women. Meanwhile, research by Wardhana et al. (2013) stated that the ratio of women: men in PV (pemphigus vulgaris) sufferers found was 2.3: 1, which means that female cases were more than twice as many as male cases.

Porro et al. (2019) stated that pemphigus vulgaris is indeed dominated by cases in women, such as in Tunisia with a female: male ratio of 4: 120, and in Spain with a female: male ratio of 2: 1. .8 Some of the literature above explains that pemphigus vulgaris sufferers are dominated by women, as is the number of pemphigus vulgaris incidents that can vary in various regions of the world. On the other hand, because pemphigus vulgaris is an autoimmune disease, it is necessary to know that genetically women are more susceptible to autoimmune diseases. Angum et al. (2020) explained this because the X chromosome has a greater number of genes than the Y chromosome, thus creating a much greater possibility for mutations to occur. This puts women at greater risk for autoimmune diseases simply because women have two X chromosomes, while men only have one. This study found that pemphigus vulgaris sufferers at RSUP. Dr. M. Djamil are mostly in the 40-60 year age group, with a total of 8 people (50%), followed by the second largest age group, namely <40 years with a total of 7 people (43.8%) and 1 person aged >60 years (6.2%). From this data we also get the average age of pemphigus vulgaris sufferers, namely 40.8 years. This finding is in line with research by Surya (2014) at RSUP H. Adam Malik Medan which found that the age group with the most cases was the 40-60 year age group with a total of 52.4% of the total sample, followed by the <40 year age group (33.3% of the total sample) and >60 years (14.3%). 17 Research by Wardhana et al. (2013) found that the majority of pemphigus vulgaris sufferers were in the age group >40-50 years (42.3% of the sample), followed by the age group >50 years (30.7%), the age group >30-40 years (19.2%), and finally the age group <30 years (7.7%).

The results of this study are also in accordance with the explanations by Stanley et al. (2009) and Ingold et al. (2021) who both explained the same thing, namely that the average age of onset of pemphigus vulgaris is 40-60 years. 19,20The exact cause of why pemphigus vulgaris is more common in this age group is not yet known for certain. However, Goronzy et al. (2012) and Zahava et al. (2014) explained that elderly patients are more susceptible to autoimmune diseases due to the presence of T cells that have an affinity for self-antigens and latent viruses. These T cells are known to have a greater ability to become pro-inflammatory and produce excessive cytokines, thereby inducing or strengthening the autoimmune

response. This study found that the most jobs of PV (pemphigus vulgaris) sufferers were housewives with a total of 7 people (43.8%), followed by self-employed people with 4 people (25%), students with 3 people (18.8%), and civil servants and farmers with 1 person each (6.2%). There was a study by Surya (2014) at H. Adam Malik General Hospital Medan which found that from a sample of 21 people, 38.1% of them had self-employed jobs, 23.8% as housewives, 14.3% each for civil servants and farmers, and 9.5% for students. 17 There is also a study by Diana et al. (2021) which is similar to this study, where the most occupations of pemphigus vulgaris sufferers at Dr. Moewardi Surakarta Hospital are housewives (44% of the number of cases) followed by self-employed (16% of the number of cases).

The number of PV sufferers as housewives can be compared with the number of women who are more than men in this study. While for self-employed and farmers can be associated with frequent exposure to sunlight. Excessive exposure to sunlight can cause skin injury that allows blisters and bullae to appear, so UV exposure is known as a risk factor for pemphigus. On the other hand, farming work also has additional risks because exposure to pesticides is known as a risk factor for PV. In this study, 16 samples of pemphigus vulgaris patients were obtained among 28 samples of PBA patients, only 1 person (4%) of PV patients had diabetes mellitus, with 15 people (53%) of PV patients not having diabetes mellitus. Meanwhile, among non-pemphigus vulgaris autoimmune bullae (PBA) patients at the same location and period, there were 4 people (14%) with diabetes mellitus and 8 people (29%) without diabetes mellitus. After the analysis was carried out, a significance value of $p = 0.133$ was obtained, so it can be concluded that there is no significant relationship between diabetes mellitus and pemphigus vulgaris in this study. There is a study by Heelan et al. (2015) which reported that out of 295 pemphigus patients, 18% of them had diabetes mellitus. Similar findings were also found in the study of Darjani et al. (2017) who found that of 36 samples of PV patients, 22.2% of them suffered from steroid-induced diabetes. Darjani et al. also reported that administration of corticosteroids significantly increased the incidence of diabetes.

Research by Hsu et al. (2017) reported on the relationship between pemphigus vulgaris and diabetes mellitus which is different from this study. He explained that in both mild and severe cases of PV (pemphigus vulgaris), type 2 diabetes mellitus is the comorbidity most associated with pemphigus vulgaris. Even without a history of corticosteroid use, PV sufferers have a high risk of developing type 2 diabetes mellitus. While with the use of corticosteroids, PV sufferers have an even higher risk of developing type 2 diabetes mellitus .13In contrast to the results of this study, a meta-analysis study by Phan et al. (2021) on the relationship between pemphigus and diabetes, reported that there was a significant relationship between pemphigus and type 2 diabetes mellitus. Phan et al. stated that this is likely due to immune dysregulation that causes systemic chronic inflammation, which can lead to type 2 diabetes mellitus. Although steroid-induced diabetes is commonly found in pemphigus patients, it should be noted that type 2 diabetes mellitus is still found in pemphigus patients even without the use of systemic corticosteroid therapy, as explained by Hsu et al. above. In addition, Phan et al. (2021) also found no significant relationship between pemphigus and type 1 diabetes mellitus.

The difference in findings in this study with some of the literature above is likely due to several things, including: West Sumatra, the province where this study was conducted, has a relatively lower prevalence of diabetes mellitus compared to other regions, with a prevalence of 1.6% which is lower than the national average of 2% based on the 2018 Riskesdas. 43 This prevalence is also lower than the average prevalence of diabetes mellitus in Southeast Asia (8.7%) and also the world average prevalence (10.5%) based on data from the International Diabetes Federation (IDF) Atlas, 10th Edition, 2021. 3 These findings also do not take into account Indonesia as one of the countries with the highest prevalence of undiagnosed diabetes mellitus in the world with a proportion of undiagnosed diabetes sufferers of 73.7% based on data from the International Diabetes Federation (IDF) Atlas, 10th Edition, 2021.

Of the 16 samples of pemphigus vulgaris among the 28 samples of PBA patients in this study, 8 people (28%) had hypertension and 8 others (28%) did not have hypertension. Meanwhile, in non-pemphigus vulgaris PBA patients, 3 people (11%) had hypertension and 9 people (32%) did not have hypertension. The data were processed and obtained a significance value of p = 0.253, so we know that there is no significant relationship between hypertension and pemphigus vulgaris in this study. In contrast to this study, there is a study by Hsu et al. (2017) regarding pemphigus comorbidities, it was reported that hypertension is a comorbidity that is closely related to pemphigus, both in moderate to severe PV cases. Hsu et al. also found a significant relationship between pemphigus vulgaris and a history of systemic corticosteroid use as a predictor of hypertension and type 2 diabetes mellitus. However, what is different is that the high risk of pemphigus sufferers having hypertension only exists with a history of corticosteroid use, whereas even without corticosteroid use, pemphigus sufferers still have a high risk of developing type 2 diabetes mellitus. .13Askin et al. (2020) also found something similar where hypertension was the most common comorbidity found in pemphigus vulgaris patients. Askin et al. also reported that hypertension was more common in patients with pemphigus with moderate to severe conditions, so they received higher doses of corticosteroids compared to patients with mild pemphigus with lower doses. With a significance value of p <0.05, Askin et al. concluded that there was a significant relationship between hypertension and corticosteroid use.

For the record, although no relationship was found between hypertension and pemphigus vulgaris in this study, based on medical records, it was found that of the 8 PV patients who had hypertension, 3 people had hypertension before receiving corticosteroids, 4 people had hypertension after receiving corticosteroid therapy and 1 person had received corticosteroids before coming to Dr. M. Djamil Padang General Hospital, so it is not known whether he had hypertension from the beginning or after receiving corticosteroid therapy. This finding is in line with the findings of Pietkiewicz et al. with the percentage of samples who had hypertension when receiving corticosteroids as much as 25% of the total sample. 30

## CONCLUSION

The conclusions that can be drawn from the research that has been carried out are as follows: Pemphigus vulgaris patients have a female to male sex ratio of 1: 0.78, are in the 40-60 year age group, with the most common occupation as housewives, and most have clinical manifestations on the skin and mucous membranes. 2. The incidence of diabetes mellitus in pemphigus vulgaris patients is 6.25% of the total sample. 3. The incidence of hypertension in pemphigus vulgaris patients is 50% of the total sample. 4. No significant relationship was found between diabetes and pemphigus vulgaris in PV patients in this study. 5. No significant relationship was found between hypertension and pemphigus vulgaris in PV patients in this study.

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