Journal of Public Health Science (JoPHS)
Volume 3, No 2 – Juni 2026
e-ISSN :3047-3632

THE RELATIONSHIP BETWEEN SERUM SUBSTANCE P LEVELS AND ACNE VULGARIS

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Received:10-05- 2026	Revised:30-05-2023	Approved: 15-06-2026

ABSTRACT

This study aims to analyze the relationship between serum substance P levels and acne vulgaris using the Chi-square test. This is an observational analytical study with a case-control approach. Sampling was conducted at the Cosmetic Division Polyclinic of KSM Dermatology and Venereology. The sample size for this study is 30 acne vulgaris patients and 30 control subjects. Consecutive sampling will be used in this study. The collected data will be analyzed statistically. The study concludes that there is a relationship between serum substance P levels and acne vulgaris. High serum substance P levels associated with of acne vulgaris by 5.4 times. The mean serum substance P level in acne vulgaris is 62.6 ± 32.4 pg/ml. The highest mean serum substance P levels in acne vulgaris are found in the 28-32 year age group. The mean serum substance P levels in acne vulgaris are highest in men by gender.

Keywords: *Acne Vulgaris; Chi square; Level; Serum Substance P*

INTRODUCTION

One of the three most common skin conditions, acne vulgaris is found in 85% of people aged 12 to 25 years (Goh et al., 2019; Bernadette, 2018; Dawson AL and Dellavale, 2013). Approximately ninety percent of adolescents experience acne vulgaris, and more than half of these cases persist into adulthood. Acne vulgaris ranks third in the number of patients consulting dermatology clinics and hospitals, according to the Indonesian Cosmetic Dermatology Study Group (2015). Anggrenni et al. (2014) conducted a study in Medan. The study found that, from January 2010 to December 2012, the proportion of acne vulgaris cases was 1.1% at the H. Adam Malik General Hospital in Medan, and 42 cases at the Polyclinic of the University of North Sumatra Hospital. The majority of acne vulgaris cases occurred at age 21 (Fachry dan Putra, 2015).

Four components are responsible for the cause of acne vulgaris. They are epidermal follicular hyperproliferation, increased sebum production, colonization by Cutibacterium acnes, formerly known as Propionibacterium acnes, and inflammation (Teresa, 2020). Genes, race, stress, diet, cosmetics, medications, pregnancy, the menstrual cycle, alcohol, and smoking are some of the causes of acne vulgaris. One cause of acne vulgaris is stress. The production of hormones, cytokines, and neuropeptides is affected by stress, which contributes to the development and exacerbation of the disease (Rokowska-Waluch et al., 2016). This is due to the fact that there is no evidence to suggest that neurogenic factors in the skin play a role in the development of acne vulgaris.

The amino acid sequence Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH2 forms the undecapeptide substance P. Substance P includes neurokinin A, neurokinin B, neuropeptide K, and neuropeptide γ, which are structurally similar

to "tachykinins" (Almeida et al., 2004). Peripheral nerves release substance P in response to stress. Substance P has the ability to promote the proliferation of sebaceous precursor cells and increase the size of sebocytes. This indicates the ability of substance P to increase lipid synthesis in sebocytes and trigger the proliferation and differentiation of sebaceous glands (Zari and Alrahmani, 2017).

Abdillah et al. (2016) conducted a study in Poland on forty acne vulgaris patients and forty healthy controls. They investigated the relationship between disease severity, stress intensity, and serum substance P concentrations. In this study, acne vulgaris patients had higher serum substance P concentrations compared to controls. An additional study conducted by Toyoda et al. (2002) investigated the possible involvement of neurogenic factors in the cause of acne vulgaris. In this study, immunohistochemical examination was used to compare the distribution of substance P in nerve fibers around the sebaceous glands and the expression of neutral endopeptidase in sebaceous acini in the facial skin of acne vulgaris patients and healthy subjects. Compared with controls, acne vulgaris patients showed neutral endopeptidase expression in sebaceous acini and substance P-immunoreactive nerve fibers closer to the sebaceous glands. Substance P has been associated with acne vulgaris, as shown above. However, research on this issue is still limited.

LITERATURE REVIEW

Acne Vulgaris

Acne vulgaris is a common disorder of the pilosebaceous unit. It is characterized by non-inflammatory follicular papules and inflammatory lesions such as papules, pustules, nodules, and large cysts, which can cause scarring and discoloration (Layton et al., 2016). Acne vulgaris typically appears on the face, neck, shoulders, upper arms, upper chest, and upper back, but can also appear in other areas with sebaceous glands, such as the thighs and buttocks. Acne vulgaris is a common condition affecting all ages and ethnic groups (Fabbrocini and De Padova, 2013). As the eighth most common disease worldwide, acne vulgaris affects 9.4 percent of people worldwide. Acne vulgaris is the most common skin condition in adolescents aged fifteen to fifteen years. Acne vulgaris is the most common skin condition affecting adolescents aged 15-18. The Global Burden of Disease study showed that nearly 85% of young adults aged 12-25 suffer from acne vulgaris, with a variety of clinical presentations (Lynn et al., 2016).

Four important factors are thought to play a role in the development of acne vulgaris lesions, generally influencing the pathogenesis of acne vulgaris. Acne vulgaris has many complex causative factors. Epidermal hyperproliferation, increased sebum production, colonization by acnes bacteria (formerly known as Propionibacterium acnes), and inflammation are some of these factors (Das and Reynolds, 2014; Maulida & Topik, 2024). Microcomedone formation is caused by follicular epidermal hyperproliferation. Increased keratinocyte cohesion causes the upper hair follicle epithelium, or infundibulum, to become hyperkeratotic. The excess cells and adhesions cause plugging of the follicle ostium. Keratin, sebum, and bacteria then accumulate within the plug. This causes the upper hair follicles to dilate, resulting in the formation of microcomedones, which are precursors to comedones and the inflammatory lesions seen in acne vulgaris.

There is no known cause for keratinocyte hyperproliferation and increased adhesion.

One factor that causes acne vulgaris is stress. Sebaceous glands in the skin have CRH receptors, so when CRH increases during stress, it can cause sebum production, which will block the pilosebaceous gland ducts. Neurogenic inflammation is caused by this neuropeptide. Furthermore, in response to stress, peripheral nerves release substance P. The fact that substance P can induce sebaceous gland proliferation and differentiation and increase lipid synthesis in sebocytes is demonstrated by the fact that substance P can stimulate the proliferation of sebaceous precursor cells and increase sebocyte size. A polymorphic eruption with the primary symptoms of comedones, papules, pustules, nodules, and cysts is the clinical manifestation of acne vulgaris. Acne vulgaris typically occurs on the face, but can also occur on the neck, back, and shoulders with less frequency. Lesions are located near the midline of the body in the trunk area. Lesions can be inflammatory or non-inflammatory. The hallmark of acne vulgaris is comedones, or non-inflammatory acne. This symptom is characterized by miliary papules with sebum plugs in the center.

Supporting examinations, anamnesis, and physical examination can be used to diagnose acne vulgaris (Widaty et al., 2017). During the physical examination of the skin of patients with acne vulgaris, it is recommended to use good and consistent lighting, including headlights and focused lighting. In the physical examination of patients with acne vulgaris, several things that must be considered are the patient's skin type (oily or normal), the location of the lesion, the type of Kapantow lesion, and the clinical diagnosis (Akne, 2018). Acne vulgaris lesions are usually polymorphic, consisting of comedones, papules, pustules, nodules, and cysts in predilection areas with many sebaceous glands such as the face, neck, chest, back, shoulders, and upper arms.

Substance P

The activity of this factor was found in water-soluble extracts of brain and intestinal tissue. It was first referred to as "preparation P" and later as "substance P." Chang et al. discovered the amino acid composition of substance P in the early 1970s (Suvas, 2017; Wasitaatmadja, 2016). Substance P is an undecapeptide with the amino acid sequence Arg-Pro-Lys-Pro-Gln-Gln-Phe-Phe-Gly-Leu-Met-NH2. The family of peptides such as "tachykinins" includes neuropeptide K, neuropeptide γ, and neurokinin A (Koh and Bhatia M. Substance, 2011). The tachykinin-1 (Tac1) gene, also called preprotachykinin-A (PPTA), is responsible for encoding substance P. Substance P is widely distributed in both the peripheral and central nervous systems. However, it has been shown to induce and be expressed in various other cell types, such as monocytes, macrophages, lymphocytes, pancreatic acinar cells, Leydig cells, and various tumors.

According to several studies, human plasma substance P levels can be controlled between 30 pg/ml and 500 pg/ml. The neurokinin-1 receptor (NK1R) is a G-protein-coupled receptor that serves as the endogenous receptor for substance P. Substance P also has the ability to bind and activate neurokinin-2 and neurokinin-3 receptors, although with lower affinity. Neutral endopeptidase

(NEP) and/or angiotensin-converting enzyme (ACE) are also known to be responsible for the mechanisms that reduce substance P and stop its effects.

Substance P is the primary neuropeptide found in cutaneous nerve endings. It is primarily located in primary afferent C-fibers and is released into the skin. This undecapeptide from the tachykinin family performs numerous bioactivities in addition to neurogenic transmission, such as capillary vasodilation, fibroblast and keratinocyte proliferation, and mast cell degranulation. Substance P is also considered a key mediator of neurogenic inflammation and itching. Various skin diseases such as psoriasis, atopic dermatitis, acne vulgaris, and rosacea are caused by cutaneous neuropeptides, particularly substance P (Mijouin et al., 2013).

The Relationship Between Acne Vulgaris and Substances P

Acne vulgaris is a chronic inflammation of the sebaceous follicles that appears during adolescence. Several factors, including psychological and neurogenic factors, influence the development of acne vulgaris. Stress is one predisposing factor thought to cause acne vulgaris. However, to date, only a few studies have examined the relationship between stress and acne vulgaris. This is because there is no significant evidence for the involvement of neurogenic skin factors in the pathogenesis of acne vulgaris (Toyoda and Morohashi, 2003).

Primary afferent sensory nerves, postganglionic cholinergic parasympathetic nerves, and postganglionic adrenergic and cholinergic sympathetic nerves influence the skin. A network of fine C-fibers within the skin forms the cutaneous sensory nervous system, which innervates various cell types and is responsible for inflammation (Meutia & Himayani, 2021). Primary sensory neurons can be activated directly by various stimuli, and impulses can be transmitted centrally via peripheral antidromic axon reflexes. Neurogenic inflammation is a series of changes that occur following the release of proinflammatory neuropeptides from sensory terminals, leading to significant visceromotor and trophic changes in peripheral tissues (Mastuda et al., 2019).

Neuropeptides, which comprise a heterogeneous group of biologically active peptides, are found in neurons in both the central and peripheral nervous systems. Neuropeptides are responsible for signal transmission not only between nerve cells but also within the immune system, where they serve as important mediators for various processes. In addition, it has been reported that immune cells constitutively present in the skin, such as mast cells, or those that enter the skin during inflammatory conditions, produce neuropeptides. Various skin diseases such as atopic dermatitis, psoriasis, and alopecia areata, which are often exacerbated by stress, have clinical evidence supporting a link between neuropeptide secretion and the development of inflammation. A neuropeptide from the tachykinin family known as substance P has been shown to be released by stress, which can induce neurogenic inflammation (Scholzen et al., 1998).

Substance P is associated with a variety of cellular responses. These include vasodilation, increased blood flow, plasma extravasation, mast cell degranulation, axon reflex-induced Whale and Flare reactions, neutrophil and macrophage activation, control of proinflammatory cytokine and chemokine release, and up-regulation of adhesion molecule expression to regulate leukocytes. However,

substance P does not affect sebaceous glands or the acne vulgaris disease process (Toyoda and Morohashi, 2003). Immune reactivity to substance P is rarely found in facial skin specimens without acne vulgaris lesions in healthy subjects. In contrast, specimens taken from acne vulgaris patients show strong immunity to substance P due to the abundance of fine nerve fibers surrounding the sebaceous glands. Beberapa dari substansi P menginvasi ke kelenjar sebasea dan terletak di dekat sebosit.

In one study, researchers used electron microscopy to observe changes in sebaceous glands in organ culture by several types of neuropeptides and nerve growth factors to determine whether skin neurogenic factors affect sebaceous gland morphology. The ultrastructure of intact and medium-only sebaceous glands was similar. Sebaceous cells consisted of a germinative cell layer from the outer to the inner surface; most sebaceous cells contained numerous lipid droplets even in the peripheral area of the gland; these observations suggest that substance P can accelerate lipogenesis.

Of all the agents tested, only substance P significantly increased sebaceous gland area and sebaceous cell size, as well as the number of sebaceous vacuoles per sebaceous cell as distinguished at the electron microscopic level. The increase in the number of sebaceous vacuoles induced by substance P varied depending on the dose.

Anita et al. (2016) conducted a study in Poland to determine how stress intensity, acne vulgaris severity, and serum substance P concentrations in acne vulgaris patients compared to a healthy control group. In this study, 80 patients were divided into two groups: 40 patients with acne vulgaris and 40 controls. To assess the severity of acne vulgaris, the investigator's global evaluation scale (IGA) was used, then stress analysis was carried out using the social improvement scale (SRRS) by Holmes and Rahe. To measure serum substance P concentrations, an enzyme-linked immunosorbent assay (ELISA) was used. The results of this study showed that patients with acne vulgaris had higher serum substance P concentrations than average.

In their study, Lee et al. (2008) investigated the possible involvement of neurogenic factors in the development of acne vulgaris. This study examined the expression of interleukin-1 (IL-1), interleukin-6 (IL-6), tumor necrosis factor-α (TNF-α), and peroxisome proliferator-activated receptors-γ (PPAR-γ) in substance P-stimulated sebocyte cultures through immunohistochemistry and RT-PCR. The results showed that immunity was more sensitive to IL-1, IL-6, TNF-α, and PPAR-γ, as well as that ribonucleic acid (RNA) amplification. This study suggests that substance P contributes to the pathogenesis of acne vulgaris.

RESEARCH METHODS

This study is an observational analytical study using a case-control method. Samples were taken at the Cosmetic Division Polyclinic of KSM Dermatology and Venereology, Universitas Indonesia Hospital, Medan, and blood samples were examined at the Integrated Laboratory of the Faculty of Medicine, Universitas Indonesia. Acne vulgaris patients who were treated at the Cosmetic Division Polyclinic of KSM Dermatology and Venereology, Universitas Sumatera Utara Hospital, Medan, were the target population of the study and met the

inclusion and exclusion criteria. This study will collect 30 acne vulgaris patient samples and 30 control samples. This study will use a consecutive sampling method.

The collected data were analyzed statistically. Univariate analysis was used to evaluate the characteristics of one variable through descriptive tests. Then, bivariate analysis was used to evaluate the relationship between the study variables; in this case, the independent variable, serum substance P, and its dependent variable, acne vulgaris, were identified through a chi-square test. The study status, a ligature device, and a camera for documentation were used. All materials used include aprotinin, test tubes for standard and sample dilutions, as well as substance P controls, one unit of substance P kit, microplate reader, pipettes, pipette tips, deionized or distilled water, spray bottles, dispenser manifold or automatic microplate dryer, 500 milliliter graduated cylinder, horizontal orbital microplate shaker, and removable gloves.

3.1 Ways of working

3.1.1 Basic data recording

Researchers recorded basic data such as research subject identity (age, gender, and address), history taking, physical examination, dermatological examination, and assessment of acne vulgaris severity using the Indonesian Acne Expert Meeting Assessment (Lehmann & Kleber, 2015). Acne vulgaris was assessed by counting the number of lesions in blackheads, pustules, and cysts. There are three levels of acne vulgaris severity: mild, moderate, and severe. Followed by tracking and recording the examination results. Researchers and supervisors at the Dermatology and Venereology Polyclinic of the University of North Sumatra Hospital determined the clinical diagnosis of acne vulgaris.

Collection and storage of blood samples

Blood draws were performed after patients signed an informed consent agreement. Participants were asked to sit or lie down. Patients were asked to clench their fists to view the veins in their upper arms after using the toreiquette. The skin at the puncture site was cleaned with an alcohol swab and allowed to dry. Next, the needle was inserted into the median cubital vein at a 45-degree angle. Once blood had flowed into the needle, it was rotated face down. Patients were asked to unclench their fists to allow blood to flow freely. After the tonic is removed, the syringe is slowly withdrawn until the desired amount of blood is obtained. After the needle is removed, the puncture site is covered with cotton, pressed, and covered with a bandage. Afterward, the venous blood is transferred to a vacutainer tube. Serum samples used with a serum separator tube (SST) are allowed to clot for thirty minutes at room temperature before being centrifuged for fifteen minutes at 1000 rpm. Immediately remove the serum for examination or store below < -20^{o}C.

Blood sample processing

Prepare reagents, samples, and working standards. After removing the excess microplate strip from the plate frame, it is placed back into the foil pouch containing the desiccant pack and reassembled. Next, 100 µL of Calibrator Diluent RD5-45 is added to the non-specifically bound (NSB) well. Then, 50 µL of

Calibrator Diluent RD5-45 is added to the zero standard (B0) well. Next, add 50 µL of sample, standard, or control to the remaining wells. The standards and samples tested are recorded on the layout board. Primary Antibody Solution (50 µL) is added to each well (except the NSB well). After all wells except the NSB well are blue, 50 milliliters of substance P conjugate are added to each well. Now all wells, except the NSB well, are purple. Cover them with adhesive strips. Set a horizontal orbital microplate shaker (0.12" orbit) at 500 rpm (plus or minus 50 rpm) to incubate the samples for three hours at room temperature.

Afterward, the process continues with aspiration and washing of each well, which is repeated three times, for a total of four washes. Fill each well with Wash Buffer (400 µL) using a spray bottle, dispenser manifold, or autowasher to wash the sample. For optimal performance, the liquid should be discarded at each step. After the final wash, remove any remaining desiccant by aspirating or pouring it out. Wipe the plate clean with a clean paper towel. Next, add 200 µL of Substrate Solution to each well. The sample is placed on a benchtop and protected from light for 30 minutes at room temperature. Next, add 50 milliliters of Stop Solution to each well. The color of the well should change from blue to yellow. The color in the well should change from blue to yellow. If the color in the well is green or the color change does not appear uniform, gently tap the plate to ensure thorough mixing.

Within 30 minutes, determine the optical density of each well using a microplate reader set to 450 nm. Adjust to 540 nm or 570 nm if wavelength correction is available. Otherwise, reduce the 540 nm or 570 nm reading to 450 nm. This reduction corrects for optical imperfections in the plate. Readings taken directly at 450 nm without correction may be more accurate and higher.

RESULTS AND DISCUSSION

Demographic Characteristics of Research Subjects

Characteristics based on age

Acne vulgaris is a chronic inflammation of the pilosebaceous unit that is most common in people aged 12 to 25 years (Ghodsi et al., 2009). Acne vulgaris symptoms most often appear during puberty and peak during mid-to-late adolescence. The distribution of study subjects by age is shown below.

Table 1 Distribution of research subjects by age

Age	Acne vulgaris group		Control group	
	n	%	n	%
18-22 year	6	20	6	20
23-27 year	13	43,3	13	43,3
28-32 year	5	16,7	5	16,7
33-37 year	4	13,3	4	13,3
≥ 38 year	2	6,7	2	6,7
Total	30	100	30	100

In both the control and acne vulgaris groups, the majority of study subjects were aged 23-27 years (43.3%), followed by the 18-22 age group (20%), the 28-32 age group (16.7%), the 33-37 age group (13.3%), and the last group aged over 38 years (6.7%).

A study by Skroza et al. (2018) in Italy found similar findings, with the majority of acne vulgaris patients being between the ages of 12 and 25 (58.7%). Another study in Medan by Rahmayani et al. (2019) found the same finding, with the majority of acne vulgaris patients being between the ages of 17 and 25 (96.8%). This is comparable to the study by Sutrisno et al. (2018).

This contrasts with Okoro et al.'s (2016) research in Nigeria, which found 71.7% acne vulgaris in female students aged 15-19 years. Vilar et al.'s (2015) research in Brazil, which found 89.3% acne vulgaris at an average age of 16 years. Fachry et al. (2014) studied USU's Faculty of Medicine students from the 2011 class who suffered from acne vulgaris and found that the most common age was 21 years (53.8%). According to Yutrishia et al.'s (2016) research, the age range of 15 to 21 years is the one that suffers from acne vulgaris.

The majority of study subjects were adolescents to young adults. Acne vulgaris is a major problem for adolescents during puberty, with the highest prevalence occurring in middle and late adolescence. The hormone DHEAS regulates sebaceous gland activity, which increases during puberty. Androgen hormones also increase sebum production, potentially leading to comedones due to hypercornification of the sebaceous ducts (Lucky et al., 1994).

Characteristics based on gender

Acne vulgaris can occur in both men and women, and some studies have shown gender-specific prevalence. The following table shows the distribution of study subjects by gender.

Table 2 Distribution of research subjects by gender

Gender	Acne vulgaris group		Control group	
	n	%	N	%
Man	7	23,3	7	23,3
Woman	23	76,7	23	76,7
Total	30	100	30	100

In this study, the research subjects were more female, namely 23 women (76.7%), compared to 7 men (23.3%) in the control group and the acne vulgaris group. A similar finding was found in a study conducted by Eyuboglu et al. (2018) in Turkey, which also included 164 acne vulgaris sufferers, with 64% being women and 36% being men. A study conducted in Medan by Rahmayani et al. (2019) also reported that the majority of acne vulgaris sufferers were women (60.6%). A study conducted by Sutrisno et al. (2020) in Medan also found a prevalence of acne vulgaris in women of 68%. Contrary to the findings above, a meta-analysis study conducted by Li et al. (2017) in China found that the prevalence of acne vulgaris in men was 39.7% and in women 35.7%. No differences in the prevalence of acne vulgaris were found based on gender.

Researchers believe there are differences in the prevalence of acne vulgaris by gender; this is due to significant differences in the methodology used in each study. Hormonal factors are suspected to be one reason why acne vulgaris is more common in women than in men. This is due to the fact that women begin puberty earlier than men, and they also experience acne vulgaris more frequently (Widiastini et al., 2009). The use of facial cosmetics and women's tendency to seek treatment promptly when experiencing cosmetic

concerns are other factors suspected to influence the incidence of acne vulgaris in women.

Average Serum Substance P Levels in Research Subjects

The following table shows the average levels of substance P in the subjects of this study: the acne vulgaris group and the control group.

Table 3 Mean serum substance P levels in research subjects

Group	Serum substance P level (pg/ml)		
	n	Mean	SD
Acne vulgaris	30	62,6	32,4
Control	30	40,3	17,0

In 30 people with acne vulgaris, the mean serum substance P level was 62.6 ± 32.4 pg/ml, and in 30 people in the control group, the mean serum substance P level was 40.3 ± 17.0 pg/ml. Studies on serum substance P levels in acne vulgaris patients are still very limited. This study was conducted in Poland by Rokowska-Waluch et al. (2016), and the results showed an average serum substance P level of 0.6 ± 0.09 pg/ml in 40 groups of patients diagnosed with acne vulgaris. However, the average value for the control group was 0.49 ± 0.12 pg/ml (Rokowska-Waluch et al., 2016). This is in line with this study because the acne vulgaris group had higher serum substance P levels than the control group.

Salomon et al. (2007) examined plasma substance P levels in 49 atopic dermatitis patients in Poland. During exacerbations, plasma substance P levels were measured, and the average result was 195.25 ± 96.04 pg/ml.

Distribution of Serum Substance P Levels Based on Age

The following table shows the distribution of serum substance P in the acne vulgaris group based on age.

Table 4 Distribution of substance P levels by age

Age	Serum substance P level (pg/ml)			
	Acne vulgaris group		Control group	
	n	Mean ± SD	n	Mean ± SD
18-22 Year	6	48,5 ± 19,8	6	47,9 ± 18,3
23-27 Year	13	64,9 ± 29,0	13	38,9 ±17,5
28-32 Year	5	87,7 ± 46,6	5	35,5 ± 11,4
33-37 Year	4	57,0 ± 33,4	4	41,3 ± 21,7
≥ 38 Year	2	38,2 ± 25,8	2	36,6 ± 23,5

Based on table 4 above, in the acne vulgaris group, the highest mean serum substance P levels were found in the 28-32 year age group, which was 87.7 ± 46.6 pg/ml, followed by the 23-27 year age group with a mean P substance level of 64.9 ± 29.0 pg/ml, the 33-37 year age group with a mean P substance level of 57.0 ± 33.4 pg/ml, the 18-22 year age group with a mean P substance level of 48.5 ± 19.8 pg/ml, and the ≥ 38 year age group with a mean P substance level of 38.2 ± 25.8 pg/ml. Meanwhile, in the control group, the highest mean serum substance P levels were found in the 18-22 year age group, which was 47.9 ± 18.3 pg/ml, followed by the 33-37 year age group with a mean P substance level of 41.3 ± 21.7 pg/ml, the 23-27 year age group with a mean P substance level of 38.9 ± 17.5 pg/ml, the ≥ 38 year age group with a mean P

substance level of 36.6 ± 23.5 pg/ml, and the 28-32 year age group with a mean P substance level of 35.5 ± 11.4 pg/ml.

To date, researchers have not found any studies examining serum substance P levels based on age in acne vulgaris. However, a study conducted by Siagian et al. (2020) in Japan on 49 healthy individuals aged 17 to 80 years found no significant correlation between serum substance P levels and its metabolites in human tears.

Distribution of Serum Substance P Levels Based on Gender

Acne vulgaris can occur in both men and women. The following table shows the distribution of serum substance P by gender in acne vulgaris patients encountered in this study.

Table 5 Distribution of serum substance P levels by gender

Gender	Serum substance P level (pg/ml)			
	Acne vulgaris group		Control group	
	n	Mean ± SD	n	Mean ± SD
Man	7	63,0 ± 27,5	7	47,8 ± 20,3
Woman	23	62,5 ± 34,3	23	38,0 ± 15,7

In table 5 above, the average value of the serum substance P level of the male acne vulgaris group was 63.0 ± 27.5 pg/ml while the average serum substance P level of the female acne vulgaris group was 62.5 ± 34.3 pg/ml. Meanwhile, the average value of the serum substance P level of the male control group was 47.8 ± 20.3 pg/ml while the average serum substance P level of the female control group was 38.0 ± 15.7 pg/ml.

Researchers have not found any studies that examine the correlation between gender and human serum substance P levels. To date, the only study researchers have found is a study conducted by Siagian et al. (2020) in Japan, which examined the levels of substance P and its metabolites in human tears. This study found no significant differences in substance P levels based on gender, but the mean substance P level was 306 ± 96.5 pg/ml. However, the mean substance P level in women was higher than in men.

Relationship between Serum Substance P Levels and Acne Vulgaris

The relationship between substance P levels and acne vulgaris can be seen in table 6 below:

Table 6 The relationship between serum substance P levels and acne vulgaris

Serum substance P levels	Group		Total	p
	Acne vulgaris	Control		
	n (%)	n (%)		
High	21 (70)	9 (30)	30 (50)	0,005
Low	9 (30)	21 (70)	30 (50)	
Total	30 (100)	30 (100)	60 (100)	

In table 6 above, the results of the relationship between serum substance P levels and acne vulgaris are presented in a 2x2 table. The serum substance P category is divided into two, namely, high at ≥44.65 pg/ml and low at <44.64 pg/ml. The subject groups in the study consisted of the acne vulgaris group and the control group. The statistical analysis used in this study was the Chi-square test. Based on the Chi-square test, it can be seen that the p-value is 0.005, so it is concluded that there is a statistically significant relationship between serum substance P levels and acne vulgaris. Furthermore, to assess the effect of serum substance P levels on the incidence of acne vulgaris, the Odds Ratio (OR) value was calculated, namely 5.4 (95% CI 1.8-16.4). This shows that high serum substance P levels cause a 5.4-fold risk of acne vulgaris.

Studies measuring substance P in the serum of acne vulgaris patients are still very limited. Research conducted by Rokowska-Waluch et al. (2016) was conducted in Poland on 40 acne vulgaris patients and 40 controls aged between 18 and 34 years. The aim of this study was to find the relationship between the severity of acne vulgaris, the intensity of emotional stress, and serum concentrations of substance P. The results showed that acne vulgaris patients had higher serum levels of substance P than controls, but this result was not statistically significant. This is in accordance with the findings of this study.

Substance P is known to be involved in the pathogenesis of acne vulgaris because it can cause adipogenesis by increasing PPAR-γ. Based on research by Lee et al. (2008), it was found that the addition of substance P to sebocyte cultures caused immunoreactivity and increased RNA amplification of IL-1, IL-6, TNF-α and PPAR-γ. This further supports that substance P is involved in the pathogenesis of acne vulgaris. In addition, Toyoda et al. (2002) in Japan found that nerve fibers closer to the sebaceous glands in acne vulgaris patients were more immunoreactive to substance P than in controls.

Substance P has also been linked to other skin conditions in several additional studies. Salomon et al. (2007) studied 49 individuals in Poland with atopic dermatitis aged between 17 and 56 years. In this study, plasma levels of substance P were evaluated in patients with atopic dermatitis during exacerbations, remissions, and control periods. The results showed that plasma levels of substance P in patients with atopic dermatitis during exacerbations and remissions were significantly higher than in the control group.

One advantage of this study is that the patient and control groups had similar or nearly identical characteristics, thus reducing bias in the results. Diseases that could affect serum substance P levels were also excluded. Substance P is a major mediator of inflammation and neurogenic itching. Various skin diseases such as psoriasis, atopic dermatitis, acne vulgaris, and rosacea are influenced by skin neuropeptides, particularly substance P (Mijouin et al., 2013).

One factor that causes acne vulgaris is stress. This is consistent with research by Sutrisno et al. (2020) conducted in Medan. This observational analytical study examined one hundred individuals with acne vulgaris. Based on the Lehmann criteria, the Acne Grading of the 2015 Indonesian Acne Expert Meeting was used to evaluate the severity of acne vulgaris in each patient. Furthermore, stress was measured using the Holmes-Rahe stress scale

questionnaire. The results showed a relationship between stress levels and acne vulgaris severity.

In addition, Rokowska-Waluch et al. (2016) examined the relationship between stress scales and serum substance P levels. Both control and acne vulgaris groups were tested. The Holmes-Rahe stress scale questionnaire was used to assess stress levels. This study showed a statistically significant difference between the control and acne vulgaris groups. The results showed that serum substance P levels in the acne vulgaris group were higher than in the control group. Substance P is released by peripheral nerves in response to stress. This suggests that substance P has the ability to trigger the proliferation of sebaceous precursor cells and increase sebocyte size. This suggests that substance P has the ability to trigger the differentiation and proliferation of sebaceous glands and increase lipid synthesis in sebocytes (Suvas S. 2017; Layton et al., 2016).

CONCLUSION

Based on the results of research on the relationship between serum substance P and acne vulgaris, it was found that there is a relationship between serum substance P levels and acne vulgaris. The average serum substance P level in acne vulgaris was 62.6 ± 32.4 pg/ml, and the highest serum substance P levels were found in the 28 to 32 year age group. In addition, the average serum substance P level in acne vulgaris was 62.6 ± 32.4 pg/ml.

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