# The prevalence of hyposalivation in type 2 diabetes mellitus patients at Endocrinology Department, Internal Medicine Sub Department of RSUP Dr Hasan Sadikin Bandung

Marini Sundari\*, Tenny Setiani Dewi\*, Nanny Natalia\*\*

\*Department of Oral Medicine Faculty of Dentistry Universitas Padjadjaran
\*\*Department of Internal Medicine Faculty of Medicine Universitas
Padjadjaran

## **ABSTRACT**

Introduction: The salivary flow rate reduces Hyposalivation. Type 2 diabetes mellitus patient with hyposalivation have a high risk of various oral complications if untreated adequately. The aim of this study was to find the prevalence of hyposalivation in type 2 diabetes mellitus patient at RSUP Dr Hasan Sadikin Bandung. Methods: This study was a descriptive observational with a cross-sectional approach and consecutive sampling method to 30 samples. The study was performed with objective assessment through measuring the unstimulated salivary flow of the whole saliva using spitting method for 5 minutes. Results: The result of this study shows that the prevalence of hyposalivation on type 2 diabetes mellitus patient is 10%. The mean of salivary flow rate sample with hyposalivation is 0,07 mL/minute. Conclusion: The conclusion of this study shows a low prevalence of hyposalivation in type 2 diabetes mellitus patients at RSUP Dr Hasan Sadikin Bandung in October 2011.

**Keywords:** Hyposalivation, Type 2 Diabetes Mellitus

# INTRODUCTION

Diabetes mellitus is a chronic metabolic disease characterized by a relative or absolute lack of insulin which has an impact on increasing blood glucose levels and causing impaired metabolism of proteins and fats. 1-2 Insulin deficiency that occurs in diabetes mellitus is made possible by damage to the pancreas gland so that insulin secretion is reduced or the effect of insulin on the tissue is reduced. 3

the American Diabetes Association (ADA) classified in 1997 diabetes mellitus based on aetiology into four types. The four types include

type 1 diabetes mellitus, type 2 diabetes mellitus, other types of diabetes mellitus, and gestational diabetes mellitus. Type 1 diabetes mellitus occurs because of the damage to pancreatic beta cells that produces insulin due to autoimmune or idiopathic. Damage to pancreatic beta cells can cause absolute insulin deficiency. Type 2 diabetes mellitus is characterized by insulin resistance, damage to insulin secreted by pancreatic beta cells and increased glucose production. Pancreatic beta cells produce insulin, but insulin resistance prevents the use of cellular levels. Other types of diabetes mellitus occur due to various specific genetic defects in beta-cell

function and insulin action, pancreatic exocrine disease, endocrinopathy, pancreatic dysfunction due to drugs, chemicals or infections.<sup>6</sup>

Gestational diabetes mellitus includes the development of asymptomatic type 1 diabetes mellitus or asymptomatic type 2 diabetes mellitus. As with type 2 diabetes mellitus, the pathophysiology of gestational diabetes mellitus is accompanied by an increase in insulin resistance.<sup>6</sup> More than 240 million people in the world suffer from diabetes mellitus, and it is estimated that the number will double in the next 10 years.<sup>4</sup> About 90-95% of all cases of diabetes mellitus are type 2 diabetes mellitus.<sup>6</sup>

Diabetes mellitus is a chronic metabolic disease with classic symptoms, namely polyphagia, polydipsia, polyuria, weight loss, xerostomia and dryness of the oral mucosa due to dehydration.<sup>5</sup> Xerostomia is a subjective complaint of dryness of the oral cavity that can be caused by decreased salivary production.<sup>7</sup>

Saliva has a significant role in maintaining oral cavity homeostasis.<sup>8</sup> The main functions of saliva are for hydration, cleansing, digestion, remineralization of teeth, maintaining oral mucosal integration and being antimicrobial.<sup>9</sup> Decreased salivary production from average amounts is called hyposalivation. Lack of saliva in the mouth can cause significant morbidity.<sup>7</sup>

A person with hyposalivation usually complains of difficulty eating dry food, difficulty controlling artificial teeth, difficulty speaking, pain, unpleasant sensations or loss of taste sensation. A dentist plays an essential role in preventing, minimizing, and treating oral complaints that occur due to oral manifestations of systemic disease. Hyposalivation can increase susceptibility to caries, oral ulcers, and infections by bacteria, viruses or fungi.

Infection of the teeth and surrounding connective tissue can form a focus of infection. The focus of infection is a bacterial infection that is localized to certain parts of the body which if not getting adequate treatment, the centre of the infection can spread to other parts of the body and cause secondary infections such as rheumatic fever, endocarditis, certain diseases of the gastrointestinal tract, eyes and kidneys. Central General Hospital (RSUP) Dr Hasan Sadikin Bandung is a hospital that has complete facilities,

including the installation of endocrinology in the internal medicine department. Endocrinology is a particular installation to treat patients with hormone disorders such as diabetes mellitus. Based on these descriptions, the authors aim to identify the prevalence of hyposalivation in patients with type 2 diabetes mellitus in the Endocrinology Installation of Internal Medicine Department Dr Hasan Sadikin Bandung.

### **METHODS**

This type of research is observational descriptive with a cross-sectional approach. In this study, observations were made while aiming to describe the phenomena found without any treatment and follow-up on the research subjects. <sup>11</sup> The population in this study was outpatients in the Endocrinology Installation of Internal Medicine Department Dr Hasan Sadikin Bandung.

Samples were taken using the consecutive sampling method, where samples that obey the selection criteria were included in the study until the required number of samples were met.<sup>11</sup> The number of samples taken in this study was 30 people as a standard minimum limit needed.<sup>12</sup> Inclusion criteria included are (1) research subjects were men or women aged less than 60 years, (2) research subjects had been diagnosed with type 2 diabetes mellitus and had used antidiabetic drugs (3) research subjects were willing to participate by signing informed consent.

The study exclusion criteria included (1) non-cooperative research subjects, (2) research subjects had other systemic conditions that could cause hyposalivation such as Sjogren's syndrome, lupus erythematosus, vasculitis, chronic hepatitis, HIV, AIDS, primary biliary cirrhosis, currently in the treatment of regional radiotherapy head and neck, now in chemotherapy, and fasting, (3) research subjects are taking drugs that can cause xerostomia, such as anti-cholirgenics, antidepressants and antipsychotics, muscle relaxants, diuretics, antihypertensives, sedatives, analgesics and antihistamines. The tools and materials used in this study consisted of (1) informed consent sheets, (2) questionnaire sheets and research sheets, (3) tools commonly used in dentistry in the form of mouth glass, sonde, tweezers, trays, laboratory coats, masks,

gloves, slabbers, gargles, flashlights, tissues, (4) measuring cups (5) glass funnels, (6) stopwatches, (7) stationery.

### **RESULTS**



Figure 1. Research Tools and Materials

The total research subjects were 30 patients with type 2 diabetes mellitus who went to the Endocrinology Installation of Dr.Hasan Sadikin Hospital Bandung in the period from October 11, 2011, to October 31, 2011, and met the inclusion and exclusion criteria. Thirty people consisted of 15 men and 15 women with an average age of 51.7 years (age range 38-59 years).

The results of measuring the total unstimulated salivary flow rate with a spitting method for 5 minutes can be seen from the table attached in appendix 6. Someone who is declared as hyposalivating, if the salivary flow rate is <0.1 mL/min while under normal conditions the total salivary flow rate> 0.3 mL/minute.<sup>6,13</sup> The prevalence of hyposalivation assessment by sex can be seen in Table 1. below:

Table 1. shows that 3 people (10%) of the subjects experienced hyposalivation, while 27 other people (90%) did not experience hyposalivation.

Table 1. Prevalence of Hyposalivation Assessment by Gender

Assessment	Hyposalivation		Female		Male	
	f	%	f	%	f	%
Yes	3	10	2	6,7	1	3,3
No	27	90	13	43,3	14	46,7
Total	30		15		15	

Information: f = Total

The results show that 2 research subjects who experienced hyposalivation were female, and 1 research subject who experienced hyposalivation was male.

Salivary flow rates in all study subjects based on average, below average and hyposalivation

Table 2. Saliva Flow Rate on All Subjects by Normal Category. Under Normal and Hyposalivation

gory, order fromut and rryposativation					
Saliva Flow Rate Category	f	%			
Normal (>30mL)	14	46,7			
Below normal (0,1≤x≤0,3)	13	43,3			
Hyposalivation (<0,1)	3	10			
Total	30	100			

Information: = f = total - % = Percentage

categories can be seen in Table 2. below:

Table 2. above shows, 14 people (46.7%) of the study subjects had a standard salivary flow rate of> 0.3 mL/min, 13 people (43.3%) of the study subjects had a salivary flow rate below normal even though they had not entered hyposalivation and 3 (10%) subjects experienced hyposalivation. The results of the study in Table 3. Show that 3 subjects who experienced hyposalivation consisted of 2 subjects with moderate diabetes control (HbA1C 8.9% and 8.2%) and 1 person who had poor diabetes control (HbA1C) 14.6%). The results showed that the average salivary flow rate in study subjects experiencing hyposalivation was 0.07 mL/min with an average of 5 years of diabetes and with an average HbA1C value of 10.57. The long history of diagnosed diabetes, the description of diabetes control (HbA1C value), and the salivary flow rate in subjects experiencing hyposalivation can be seen in Table 4.3 below:

Table 3. Overview of Diabetes Diagnosis, HbA1C Value, and Saliva Flow Rate in Research Subjects that Have

Hyposalivation						
Subject No.	Duration	HbA1C	Saliva flow rate			
	Diagnosed	(%)	(mL/minute)			
	Diabetes (year)					
11	5	8,9	0,06			
20	4	8,2	0,08			
30	6	14,6	0,08			
Average rate	5	10,6	0,07			

A description of the average salivary flow rate, the average diagnosed with diabetes mellitus and the average HbA1C value in all study subjects can be seen in Table 4. below:

Table 4. Overview of Average Salivary Flow Rate, Average Length of Diagnosis of Diabetes Mellitus, and Average
HbA1C Value in All Research Subjects

	Normal Below		Hyposalivation
		normal	
Average saliva flow rate	0,44	0,19	0,07
(mL/minute)			
Average diag- nosed Diabetes	6,6	5,6	5
Mellitus (An- nually)			
Average HbA1C	7,3	7,9	10,5

The results showed that the average salivary flow rate in patients with type 2 diabetes mellitus whose regular salivary flow rate was 0.44 mL/min with an average diagnosis of diabetes mellitus stipe 2 for 6.6 years and with an average HbA1C value of 7, 3 While the average salivary flow rate in people with diabetes who have decreased salivary flow but not in the hyposalivation category is 0.19 mL/

min with an average diagnosis of diabetes mellitus stipe 2 for 5.6 years and with an average HbA1C value of 7, 9 while the average salivary flow rate in patients with type 2 diabetes mellitus that has decreased salivary flow but not yet included in the hyposalivation category is the category of salivary flow rate and xerostomia in all study subjects can be seen in Table 5. below:

Table 5. Groups of Saliva and xerostomia Flow Rates in All Research Subjects

Salivary flow rate	Xerostomia			Without xerostomia			
	f (%)	Gender	f (%)	Gender			
		Р	L			Р	L
Normal (> 0,3 ml)	9 (30)	7	2	5	(16,7)	-	5
Below normal	7 (23,3)	3	4	6 (20)	3	3	
$(0,1 \text{ ml} \le n \le 0,3 \text{ ml})$							
Hyposalivation (< 0,1)	3 (10)	2	1		-	-	-
Total	19	12	7	11		3	8

Information: f = total % = percentage P= Female L = Male

The results showed 19 people (63.3%) of the study subjects stated xerostomia. From all research subjects who reported xerostomia, it was proven that 3 people (15.8%) of the research subjects experienced hyposalivation.

Seven people (36.8%) even though they have not experienced hyposalivation, the salivary flow rate is below average. In comparison, 9 people (47.4%) other subjects do not experience hyposalivation, and the salivary flow rate is still normal.

The results showed that 16 subjects (53.3%) stated xerostomia but did not experience hyposalivation consisting of 10 women and 6 men. Eleven people (36.7%) of the study subjects did not experience either hyposalivation or xerostomia, composed of 11 female and 3 male. The use of dentures, emotional disturbances, smoking habits, and menopause in research subjects experiencing hyposalivation along with

the value of DMF-T can be seen in Table 5. The results showed that 3 subjects who experienced hyposalivation consisted of 2 people (66.6%) who had experienced menopause and 1 person (33.3%) research subjects experienced emotional disturbances. There was only 1 person (33%) of the study subjects who experienced hyposalivation, who did not use dentures, did not experience emotional disorders, did not have smoking habits, and did not experience menopause.

The DMF-T index in all four subjects of this study was 13.7. Based on the results of the study in Table 4.6, two people (6.7%) of the study subjects had cervical caries. Both of these subjects, one subject experienced hyposalivation and one other subject did not experience hyposalivation, but the subject's salivary flow rate was below average, which is below 0.3 mL/min. Both of these subjects both had an 8.2% HbA1C value that was included in the moderate diabetes control category.

Table 6. Use of Dentures, Emotional Disorders, Smoking Habits, and Menopause Conditions in Hyposalivated					
Subjects and DMF-T values					

No.	Denture	Emotional Smoking Menopause Menstruation DMF-T		Without xerostomia			
		Disorder					
11	-	+	-	+	-	15	L
20	-	-	-	-	-	21	5
10	-	-	-	+	-	5	
		Index DMF-T	13,7				
	Information: (+)	= Yes			-	-	-
	(-)	= No		11		3	8

Table 7. HbA1C values of research subjects experiencing cervical caries

Sequence	HbA1C score (%)	Saliva Flow Rate
No.		(mL/minute)
20	8,2	0,08
16	8,2	0,16

# **DISCUSSION**

Hyposalivation is a condition of decreasing salivary flow rate which can be measured objectively through measurement of salivary flow rate. <sup>14</sup> Someone stated experiencing hyposalivation if the total unstimulated salivary flow rate is <0.1 mL/min measured for 5 minutes using the spitting method. <sup>13,15</sup> The results showed the prevalence of hyposalivation in patients with type 2 diabetes mellitus in RSUP Dr Hasan Sadikin Bandung is 10 per cent. percentage values can be classified into. <sup>16</sup> 0 %= No, 1-25 % = Low, 26-49 %= Low enough, 50 % = half, 51-76 %= High, 77-99 %= Very high, 100 %= Complete.

Based on the assessment classification, according to Arikunto (1998), it can be concluded that the prevalence value resulting from this study is included in the low category, which is 10 per cent. <sup>16</sup> Besides, there is 43.3 per cent of research subjects who have salivary flow rates that are already included in the category in below-average although not yet included in the hyposalivation category, which is  $\leq 0.3$  ml/min and  $\geq 0.1$  ml/min. This shows that 53.3 per cent of the study subjects had a saliva flow rate below average ( $\leq 0.3$ ). The results of this study are by the theory that diabetics can have decreased salivary flow due to polyuria, lack of hydration or a pathological condition in the salivary glands. <sup>6-7</sup>

The results show the average value of total unstimulated salivary flow rate in the subject of hyposalivation (n = 3) was 0.07 ml/min. This value is below the hyposalivation value of <0.1 ml/min.  $.^{13,15}$  This shows that the degree of hyposalivation experienced by the research subjects is quite significant.

The results showed the more extended the diagnosis of type 2 diabetes mellitus did not show a decrease in salivary flow. This is not following the theory that in patients with type 2 diabetes mellitus, prolonged hyperglycemia can trigger significant fluid loss through urine. If this happens continuously, the body can lose a lot of fluids, and the body's fluid balance becomes negative (dehydration).<sup>4</sup>

A decrease in total body fluids can cause a decrease in both intracellular and extracellular fluid volume. A reduction in the composition of body fluids by as much as 8 per cent can cause a reduction in the flow rate of saliva by 100 per cent. However, other theories say dehydration alone cannot cause changes in salivary gland function. The mechanism of salivary secretion in people with diabetes mellitus is influenced by complications such as diabetic angiopathy and diabetic neuropathy that affect the sympathetic function of the autonomic nervous system and block the parasympathetic nervous system. 18

The results showed that the worse a person's diabetes control, the lower the flow rate of saliva. This is following the theory in patients with diabetes mellitus changes in the process of salivary secretion that may be influenced by metabolic control. <sup>19</sup> Oral complications that occur in people with diabetes mellitus usually occur in patients with diabetes mellitus that is not controlled or poorly controlled. <sup>7</sup>

The results showed 15.8 per cent of research subjects who stated xerostomia, proved to have hyposalivation. The other thirty-six point eight per cent, although they have not experienced hyposalivation, the salivary flow rate is below average, while the other 47.4 per cent of research subjects do not experience hyposalivation and the salivary flow rate is still normal. The number of subjects experiencing impaired salivary flow rate (research subjects who experienced hyposalivation and research subjects who had saliva flow rates below normal) was 52.6 per cent. This shows that xerostomia is a symptom of decreased salivary flow.<sup>7</sup>

The research subjects who experienced xerostomia but did not experience hyposalivation can be influenced by other factors, such as gender and psychological factors. The results showed that research subjects who experienced xerostomia consisted of 63.2 per cent of women and 36.8 per cent of men. This indicates that xerostomia is more common in women, and in accordance with the theory that women experience xerostomia with a higher prevalence according to statistics than men. <sup>20</sup>

Xerostomia is subjective, with no changes in salivary flow. In patients like this, xerostomia is often related to psychological factors. All research subjects who experienced emotional disturbances, all have experienced xerostomia. All subjects who experience emotional distress and xerostomia, apparently only 25 per cent who experience hyposalivation. Subjects who experienced hyposalivation, only 33.3 per cent said they were experiencing emotional disorders. It can be concluded that xerostomia is subjective and is associated with psychological factors.

The state of menopause is often associated with salivary gland dysfunction, which causes xerostomia, increasing in women who have experienced menopause. Observation shows the contrary to changes in flow rate and salivary composition. In general, the salivary flow does not decrease significantly compared to women who have not yet menopause.<sup>21</sup> this is evident in the results of the study, subjects who had experienced menopause consisted of 85.7 per cent had xerostomia, and 14.3 per cent had no xerostomia. All subjects had experienced menopause and had xerostomia, 33.3 per cent had

hyposalivation, 16.7 per cent had a low salivary flow rate below 0.3 ml/min, and the other 50 per cent had an average salivary flow rate. Besides, all subjects who had experienced menopause and did not experience xerostomia, all of them were proven not to experience hyposalivation. Subjects who experienced hyposalivation, 66.7 per cent had experienced menopause. It can be concluded that the prevalence of xerostomia increases in women who have experienced menopause but is not accompanied by a significant decrease in salivary flow.

The results showed the DMF-T index of subjects experiencing hyposalivation (n = 3) was 13.7. This value is above the DMF-T index for samples without hyposalivation, which is 11.7. This shows that patients who experience hyposalivation, they are more at risk of caries than patients who do not experience hyposalivation. It shows that it is consistent with the theory that there is a direct relationship between reduced saliva and the presence of caries and halitosis, caries in such situations usually occur quickly.<sup>22</sup>

Another theory states the main complication of xerostomia is the occurrence of dental caries. This process is increasing as evidence that there is a decrease in oral irrigation and the inability to clean food from the oral cavity quickly, especially glucose or acid. Besides, salivary and electrolyte proteins that inhibit cariogenic microorganisms and buffer oral acid are reduced.<sup>7</sup>

Other theories also suggest that microbial changes in the oral cavity have also been linked to hyposalivation, an increase in the number of microbial flora of the oral cavity has been observed in patients with hyposalivation, and may be related to an increased incidence of dental caries, periodontitis, and candidiasis.<sup>8</sup>

The DMF-T index value between subjects experiencing hyposalivation and subjects who are not suffering hyposalivation were 13.7 and 11.7. The saliva pH of diabetics tends to be acidic due to an increase in sugar levels in the saliva, increasing the colonization of bacteria that have enzymes to metabolize sugar or carbohydrates into lactic acid. These bacteria include lactobacilli and Streptococcus mutans. When the number of one of these bacteria increases, the acidic substance produced from the fermentation of sugar or carbohydrates increases and causes the pH of

saliva to become acidic due to the influence of the material. <sup>19</sup> Increased pH in the oral cavity causes an increase in tooth demineralization, which results in the onset of dental caries. This shows that subjects without hyposalivation also have a high risk of caries. Besides, the difference in the DMF-T index in patients experiencing hyposalivation and not experiencing hyposalivation can also be caused by their habits in maintaining oral hygiene before and after being diagnosed with type 2 diabetes mellitus because caries is a result of a long process. <sup>8</sup>

The results showed 6.7 per cent of the study subjects had cervical caries, and both of them had an 8.2 per cent HbA1C value that was included in the category of moderate diabetes control. One subject experienced hyposalivation, and the other still had an average salivary flow rate even though it has been involved in the low salivary flow rate. Factors that influence the occurrence of increased erosion and cervical caries are hyposalivation so that the power of mouth cleaning by saliva is reduced.<sup>23</sup> Tooth decay can be progressive even in a well-preserved oral cavity.<sup>1</sup>

# CONCLUSION

Based on the research conducted, it can be concluded that the prevalence of hyposalivation in patients with type 2 diabetes mellitus in the Endocrinology Installation of the Internal Medicine Division of Dr Hasan Sadikin Hospital in October 2011 is low.

# **REFERENCES**

- Silverman S, Eversole LR, Truelove EL. Essential of Oral Medicine. Canada: BC Decker Inc; 2002. 84-92 pp.
- Sousa MG, Costa Ade L, Roncalli AG. Clinical study of the oral manifestation and related factors in type 2 diabetic patients. Braz J Othorhinolaryngol. 2011;77(2):145-152.
- 3. Ganong WF. Buku Ajar Fisiologi Kedokteran. Jakarta: EGC. 1995. 216-218 pp.
- Little JW. Dental Management of the Medically Compromised Patient. 7<sup>th</sup> Ed. St. Louis, Missouri: Mosby Elsevier. 2008. 212-222 pp.
- 5. Saraf S. Textbook of Oral Pathology. 1st Ed. New Delhi: Jaypee Brothers Medical Publisher

- (P) Ltd; 2006. 130-132 pp.
- Greenberg MS, Glick M. Burket's Oral Medicine Diagnosis and Treatment. 10<sup>th</sup> Ed. Philadelphia: BC Decker Inc. 2003. 235- 238; 563-568 pp.
- 7. Guggenheimer J, Moore PA. Xerostomia: etiology, recognition and treatment. JADA; 2
- Khovidhunkit. Xerostomia, hyposalivation, and oral microbiota in type 2 diabetic patients: A preliminary study. J Med Assoc Thai. 2009;92(9):1220-8.
- Fox PC, Eversole LR. Diseases of The Salivary Gland. Essentials of Oral Medicine. Editors: Silverman S, Eversole LR, Truelove EL. London (England): B.C. Decker Inc; 2002. 260-276 pp.
- Scully, Crispian. Oral and Maxilofacial Medicine: The Basis of Diagnosis and Treatment. 2<sup>nd</sup> Ed. St. Louis: Elsevier Limited. 2008. 93-95 pp
- 11. Sastroasmoro S. Dasar-Dasar Metodologi Penelitian Klinis Edisi ke-2. Jakarta: Perpustakaan Nasional RI: Katalog Dalam Terbitan (KDT). 2002. 80-85 pp.
- 12. Levine, David M. Statistic For Managers. 5th Ed. New Jersey: Pearson Education, Inc. 2008. 268-271 pp.
- 13. Navazesh M, Kumar SK; University of Southern California School of Dentistry. Measuring salivary flow: challenges and opportunities. J Am Dent Assoc. 2008 May;139 Suppl:35S-40S. DOI: 10.14219/jada.archive.2008.0353
- 14. Nederfors T. Xerostomia and hyposalivation. Adv Dent Rest. 2000. 14;48-56 pp.
- 15. Navazesh M. Saliva as A Diagnostic Fluid. New York: The New York Academy of science. 1993. 72-76 pp.
- 16. Arikunto. Prosedur Penelitian. Edisi ke-5. Jakarta: Rineka Cipta; 1998. 109 pp.
- 17. Vernillo A. Dental considerations for the treatment of patients with diabetes mellitus. JADA. 2003. 134; 24-33.
- 18. Quirino MR1, Birman EG, Paula CR. Oral manifestations of diabetes mellitus in controlled and uncontrolled patients. Braz Dent J. 1995;6(2):131-6.
- 19. Karjalainen K. Periodontal disease, dental caries, and saliva in a relation to clinical charactheristic of diabetes. Oulu University Library. JADA; 2000. 1-20 pp.
- Nederfors T. Xerostomia and hyposalivation.
   Adv Dent Res. 2000 Dec;14:48-56. DOI: 10.1177/08959374000140010701

- 21. Miles T, Nauntofte S, Birgitte, Peter S. Clinical Oral Physiology. Quintessence Publishing: Books. 2004. 298 pp
- 22. Silvestre FJ, Minguez MP, Suñe-Negre JM. Clinical evaluation of a new artificial saliva in
- spray form for patients with dry mouth. Med Oral Patol Oral Cir Bucal. 2009;14(1):8-11.
- 23. Ranakusuma AB. Metabolik Endokrinologi Rongga Mulut. UI-Press: Jakarta. 1992. 58-65 pp.