

# *Changes in salivary composition of chemically dependent subjects*

## *Cambios en la composición salival de personas químicamente dependientes*

Luciana Lyra, Universidade Federal do Paraná, Curitiba, Brazil, [lulyra@hotmail.com](mailto:lulyra@hotmail.com)  
William Bellani, Universidade Federal do Paraná, Curitiba, Brazil, [william.bellani@gmail.com](mailto:william.bellani@gmail.com)  
Carolina E. Mazur, Universidade Federal do Paraná, Curitiba, Brazil, [carolmazur6@hotmail.com](mailto:carolmazur6@hotmail.com)  
João A. Brancher, Pontifícia Universidade Católica do Paraná, Curitiba, Brazil, [jabrancher@hotmail.com](mailto:jabrancher@hotmail.com)  
Antonio Adilson S. de Lima, Universidade Federal do Paraná, Curitiba, Brazil, [antollima@gmail.com](mailto:antollima@gmail.com)  
José Miguel Amenábar, Universidade Federal do Paraná, Curitiba, Brazil, [jamenaba@gmail.com](mailto:jamenaba@gmail.com)

### **ABSTRACT**

*Chemically dependent subjects may present relevant changes in the volume and composition of salivary fluid because the secretion of the salivary glands is controlled by the parasympathetic and sympathetic system. The aim of this study was to compare the salivary concentration of total proteins, amylase, urea, calcium, phosphate and flow rate between chemically dependent and non-chemically dependent subjects. Saliva flow rate, calcium, phosphate, total protein, amylase and urea concentrations were measure in both groups: chemical dependent group (n=27) and control group (n=27). Saliva samples, from the chemically dependents, were taken one day before the beginning of the detoxification treatment. Statistical analysis was undertaken using t-test. The salivary flow and the urea concentration did not present statistically significant difference between the groups. However, total proteins, amylase, calcium and phosphate concentrations were statistically higher on the chemical dependents group. Saliva composition seems to be modified by the chronic use of alcohol and illicit drugs.*

### **KEYWORDS**

*Saliva, alcohol, cannabis, cocaine, salivary composition, substance-related disorders, substance dependence, drugs*

### **RESUMEN**

*Los dependientes químicos pueden presentar cambios relevantes en el volumen y la composición de la saliva, debido a que la secreción de las glándulas salivales es controlada por el sistema parasimpático y simpático. El objetivo de este estudio fue comparar la concentración salival de proteínas totales, amilasa, urea, calcio, fosfato y la velocidad de flujo salival entre personas con dependencia química y no dependientes. Cada grupo fue formado por 27 participantes. La velocidad del flujo salival y las concentraciones de calcio, fosfato, proteína total, amilasa y urea se midieron en ambos grupos. Las muestras de saliva de los dependientes químicos se tomaron un día antes de comenzar el tratamiento de desintoxicación. El análisis estadístico se realizó por medio del test t de student. El flujo salival y la concentración de urea no presentaron diferencias estadísticamente significativas entre los grupos. Sin embargo, las concentraciones de proteínas totales, amilasa, calcio y fosfato fueron estadísticamente mayores en el grupo de dependientes químicos. El uso crónico de alcohol y de drogas ilícitas provocan modificaciones en la composición salival.*

### **PALABRAS CLAVE**

*Saliva, alcohol, cannabis, cocaína, composición salival, desórdenes asociados a sustancias, dependencia a sustancias, drogas*

Recibido: 17 junio, 2019

Aceptado para publicar: 5 diciembre, 2019

Lyra, L., Bellani, W., Mazur, C. E., Brancher, J. A., Adilson, A. & Amenábar, J. M. (2020). Changes in salivary composition of chemically dependent subjects. *Odontología Vital*, 1(32), 63-70 <https://doi.org/10.59334/ROV.v1i32.381>

## INTRODUCTION

Chemical dependency, which includes both alcoholism and drug addiction, is a primary illness characterized by the dependence to a mood-altering chemical (Kalivas & Volkow, 2005). A chemically dependent person is not able to stop drinking or using a drug despite serious social and health consequences.

It is possible that chemically dependent subjects may present relevant changes in the volume and composition of the salivary fluid because the secretion of the salivary glands is controlled by the parasympathetic and sympathetic systems, simultaneously (Carpenter, 2013; Proctor & Carpenter, 2007) which can be affected by alcohol, drugs or both (Aps & Martens, 2005; Enberg, Alho, Loimaranta, & Lenander-Lumikari, 2001; Newlin, 1995). Those changes can be responsible for the disturbances on the integrity of the enamel, periodontal tissues and oral mucosa (Antoniazzi et al., 2018; Cho, Hirsch, & Johnstone, 2005; da Fonseca, 2009; Rawal, Tatakis, & Tipton, 2012; Reddy et al., 2012; Sordi, Massochin, Camargo, Lemos, & Munhoz, 2017).

Some studies have shown that salivary constituents, such as proteins, calcium, phosphate, potassium, bicarbonate, IgA, lysozyme and lactoferrin may undergo changes in their concentrations due to the abuse of alcohol (Enberg *et al.*, 2001; Waszkiewicz *et al.*, 2017; Waszkiewicz, Zalewska-Szajda, Zalewska, Waszkiewicz, Szajda, Repka, Szulc, Kpka, *et al.*, 2012; Waszkiewicz, Zalewska-Szajda, Zalewska, Waszkiewicz, Szajda, Repka, Szulc, Kpka, *et al.*, 2012; Waszkiewicz, Zalewska, Szajda, Szulc, *et al.*, 2012; Waszkiewicz, Zalewska, Szajda, Waszkiewicz, *et al.*, 2012).

Nevertheless, there are no studies evaluating if the salivary composi-

tion of patients with an alcohol or illicit drug dependency is altered. The objective of this study was to compare the salivary concentration of proteins, amylase, urea, calcium, phosphate and flow rate between chemically dependent and non-chemically dependent subjects.

## MATERIALS AND METHODS

### Ethical approval

The study's protocol was approved by the Research Ethics Committee of the Federal University of Paraná, Brazil (Approval number: 84071). All the participants received detailed information concerning the nature and the procedures involved in the study and signed informed consent forms.

### Subject's selection

Twenty-seven volunteers, males, aged between 18 and 50 years old, with alcohol dependence and drug addiction, attending the Institute for Research and Treatment of Alcohol (Campo Largo, Paraná, Brazil) were recruited. All the participants were going to begin the detoxification program.

The control group consisted of 27 healthy males, 18-50 years of age, recruited from the Police Academy of Curitiba, Paraná, Brazil. These participants did not have alcohol dependence nor reported the use of drugs. Only healthy volunteers were accepted for this group, and individuals with any regular medication, substance-related addiction or illness were excluded from the study.

### Saliva Collection

Saliva samples, from the chemically dependent group, were taken one day before the detoxification treatment started.

Stimulated saliva was collected between 09:00 A.M. and 11:00 A.M. in a quiet room, free from external interferences. The participants were previously instructed to refrain from eating, drinking, or cleaning their teeth for 2 hours before the collection process. The saliva sample was obtained with the use of paraffin film in order to perform a five-minute stimulation. Then, they spit their saliva into a sterile container (Sterile Universal Collector - J.PROLAB 80 ml). The sample volumes were measured gravimetrically according to the method of Banderas-Tarabay et al., (1997) using a precision balance (MARTE AM200, Santa Rita do Sapucaí/MG, Brazil) and the samples were immediately frozen at -20 °C until further analysis. All the samples were processed within 7 to 10 days.

### Biochemical Analysis

All the samples were centrifuged at 2,600g for 10 min at 4°C to remove cellular and food debris and none of them were contaminated with blood. Calcium and phosphate concentrations were determined by colorimetric testing. (Calcio Liquiform, Labtest diagnostica, Lagoa Santa/MG, Brazil; Fósforo, Labtest diagnostica, Lagoa Santa/MG, Brazil). Determination of protein concentration was carried out using Coomassie blue with bovine serum albumin as the standard. Urea and amylase concentrations were analyzed using enzymatic colorimetric test kits (Urea UV Liquiform, Labtest diagnostica, Lagoa Santa/MG, Brazil and Amilase, Labtest diagnostica, Lagoa Santa/MG, Brazil). All biochemical analyses were done 3 times for each saliva sample using a spectrophotometer (S-2000 UV - VIS, SP, Brazil).

### Statistical analysis

The results were expressed as mean  $\pm$  standard deviation. Statistical analysis was undertaken

**Table 1. Age, alcohol and illicit drugs use (quantity and duration) by groups**

Age: mean years (SD)	Chemically dependent (27)	Control (27)
<b>Alcoholic beverage</b>	37.56 (10.70)	38.15 (11.12)
Use (n)	27	0
Quantity, ml/day (SD)	1598.62 (660.72)	
Duration, years (SD)	21.92 (12.05)	
<b>Cocaine</b>		
Use (n)	27	0
Quantity, mg/day (SD)	60.4 (30.7)	
Duration, years (SD)	11.62 (8.82)	
<b>Smoke Cocaine</b>		
Use (n)	13	0
Quantity, mg/day (SD)	66.6 (22.5)	
Duration, years (SD)	7.46 (4.20)	
<b>Cannabis</b>		
Use (n)	13	0
Quantity, g/week (SD)	6.84 (2.72)	
Duration, years (SD)	13.15 (8.45)	

using Student's t test for independent samples. A p-value <0.05 was accepted to be statistically significant. Statistical analysis was performed with Statistical Package for the Social Sciences for Windows (SPSS, version 20.0, SPSS Inc., Chicago, IL, USA).

## RESULTS

The mean age of the chemically dependent group was  $37.56 \pm 10.70$  years, while the control group showed  $38.15 \pm 11.12$  years. None of the participants of the control group reported the use of alcohol or illicit drugs. On the other hand, all subjects in the addiction group confirmed using alcohol and cocaine. Also, 48% of these participants used to smoke cocaine or cannabis. The quantity and duration of the consumption are presented in Table 1.

Salivary flow and urea concentration did not show statistically significant differences between groups, however, total proteins, amylase, calcium and phosphate concentration were higher on the chemically dependent group. Table 2 shows the comparison of the analyzed variables.

## DISCUSSION

The results of the study show alterations of the salivary composition among the chemically dependent subjects. Several studies have reported the dangerous character of alcohol and illicit drugs, as well as their physiological consequences in short and long terms (Cho et al., 2005; Gossop, Manning, & Ridge, 2006; Pateria, de Boer, & MacQuilán, 2013; Singh et al., 2017). On the other hand, there are no studies evaluating the salivary composition on chemically dependent subjects, or they were not found during the literature review made for this research.

**Table 2. Comparison of the salivary variables between the groups.**

	Chemically dependent (27)	Control (27)	p-value
<b>Saliva flow rate, ml/min (SD)</b>	$0.94 \pm 0.80$	$0.84 \pm 0.42$	0.595
<b>Total protein, mg/mL (SD)</b>	$0.45 \pm 0.31$	$0.28 \pm 0.22$	0.022
<b>Amylase, U/dL (SD)</b>	$766.7 \pm 6.6$	$753.6 \pm 28.3$	0.035
<b>Urea, mg/mL (SD)</b>	$3.04 \pm 2.67$	$3.05 \pm 2.26$	0.988
<b>Calcium, mg/mL (SD)</b>	$0.12 \pm 0.06$	$0.050 \pm 0.04$	< 0.0005
<b>Phosphate, mg/mL (SD)</b>	$0.78 \pm 0.22$	$0.55 \pm 0.17$	< 0.0005

Student's t test for independent samples, p<0.05

Alcohol acts as a central nervous system (CNS) depressant and its effects are potentially deleterious and irreversible to the CNS (Ron & Barak, 2016). There is an increase in the synthesis and release of noradrenaline through the blood vessels (Koob, 1992). The salivary fluid becomes thicker due to the sympathetic adrenergic stimulus by increasing the effects of sympathetic nervous activity (Carpenter, 2013). Consequently, saliva may present lower fluidity and higher secretion of proteins and calcium, as observed in the study.

Cannabis also affects the CNS in a similar way to alcohol. It has depressant and psychomimetic effects. Muscarinic receptors, from acetylcholine, are coupled to G protein and produce excitatory and stimulatory effects of salivary gland secretion, known as parasympathetic stimulation (Proctor & Carpenter, 2014). The abusive use of cannabis results in anticholinergic activity such as a blockage of the effects of acetylcholine on muscarinic M3 receptors (Ralevic, 2003), that may decrease salivary secretion. Therefore, this constant sympathetic stimulation leads to the production of viscous saliva, low in quantity and but rich in proteins and inorganic electrolytes (Aps & Martens, 2005). This may also explain the difference found between groups, in the total protein and calcium concentration.

On the other hand, cocaine (crack) is a sympathomimetic drug of indirect action, since it blocks the transport of noradrenaline, serotonin and dopamine in the synaptic cleft, occurring prolongation of the user's euphoric sensation (Dackis & O'Brien, 2001). It inhibits the capture of catecholamines by noradrenaline and dopamine transporters to noradrenergic nerve terminals, intensifying the effects of sympathetic nervous activity (Riezzo *et al.*, 2012). These

may induce changes in the saliva flow rate. While some authors reported that saliva flow does not change (Woyceichoski *et al.*, 2013), but others had found a significant association between the use of crack and a reduced salivary flow (Antoniazzi *et al.*, 2018). In the present study we did not see any difference on stimulated salivary flow between groups.

Stimulated saliva provides information about the secretory capacity of the salivary glands. The salivary composition is influenced by the taste and mechanical stimulus (Carpenter, 2013). The acid stimulus may interfere with the buffer capacity and cause precipitation of certain salivary proteins and calcium (Dawes, 1984). In order to avoid alterations in the salivary composition in this study it was used only a mechanical stimulation with insipid wax.

The significant increase of total proteins, amylase, calcium and phosphate found in the saliva of the chemically dependent group may be explained by the control of the central and autonomic nervous system in the salivary glands (Proctor & Carpenter, 2014). Secretion of the salivary glands is qualitatively and quantitatively modified in the presence of sympathetic and parasympathetic nervous stimulus (Aps & Martens, 2005) and both, alcohol and illicit drugs influence the response of the sympathetic system (Koob, 1992; Magura & Rosenblum, 2000; Oliére, Joliette-Riopel, Potvin, & Jutras-Aswad, 2013).

The salivary parameters that presented statistical differences (total proteins, amylase, calcium and phosphate) are related to the autonomic nervous mechanism in the salivary secretion (Proctor & Carpenter, 2014). The nerve fibers of the sympathetic system release noradrenalin that binds  $\alpha$  and  $\beta$

adrenergic receptors.  $\beta$  -receptors, whose second messenger is cyclic AMP (cyclic adenosine monophosphate) stimulates the precipitation of enzymes and proteins. There is an increase in permeability of the membranes of acinar cells, which contain zymogen granules that stores proteins that are liberated in high amounts (Castle & Castle, 1998; Proctor, 2016; Turner & Sugiyama, 2002). That is why  $\beta$ -adrenergic stimulus results in increased protein (Turner & Sugiyama, 2002) and salivary phosphate concentration (Beal, 1991).

The  $\alpha$ -adrenergic receptors activate P substance, a peptidergic receptor that acts as mediator of the nervous stimulus, present in the acinar cell membrane. This increases the levels of calcium and the quantity of salivary, by potentiating the effect of acetylcholine (Aps & Martens, 2005; Proctor, 2016), which can explain why the salivary calcium concentration in the chemical dependent group was higher.

Urea is a normal component of saliva and it is passively diffused from blood (Macpherson & Dawes, 1991; Thorn, Prause, & Oxholm, 1989). The results of the biochemical analysis of urea showed no significant difference between the two groups. The urea concentration is dependent on the salivary flow (Thorn *et al.*, 1989) and since there was no variation of the salivary flow between the groups, it can be expected that urea concentration remained the same.

In this study, all the participants of the chemically dependent group reported that they used cocaine as well as alcohol and sometimes cannabis. This is an important limitation of the study, because it makes very difficult to draw specific conclusions for each substance and it is impossible to discern if the modifications in saliva composi-

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tion are due to the use of alcohol, a specific drug or the combination of all of them. On the other hand, it is extremely difficult to select chemically dependent users who consume only one kind of drug.

### **CONCLUSION**

Saliva composition can have an impact in oral health, and it seems to be altered on the chemically dependent subjects. Future studies with larger samples and analysis of other salivary constituents should be performed, as well as longitudinal follow-up to verify if the changes continue in the long term.

**Acknowledgments:** We thank the Coordination for the Improvement of Higher Level Education Personnel (CAPES) for the postgraduate scholarship for LL, WB and CEM. ■■■

#### Autores

Luciana Lyraa, William Bellania, Carolina E. Mazura, João A. Brancherb, Antonio Adilson S. de Limaa, José Miguel Amenábara

a) Stomatology Department, Universidade Federal do Paraná, Curitiba, Paraná, Brazil.

b) Department of Biological Sciences, Pontifícia Universidade Católica do Paraná, Curitiba, Paraná, Brazil

Luciana Lyra:

lulyra@hotmail.com

William Bellani:

lulyra@hotmail.com

Carolina E. Mazur:

carolmazur6@hotmail.com

João A. Brancher:

jabrancher@hotmail.com

Antonio Adilson S. de Lima:

antollima@gmail.com

José Miguel Amenábar:

jamenaba@gmail.com

Corresponding Author:

José Miguel Amenábar

Posgraduate Program in Dentistry, Universidade Federal do Paraná, Curitiba, Paraná, Brazil Av. Prof. Lothário Meissner, 632 – Jardim Botânico 80210-170 Curitiba, PR. Tel: +55(41) 3360-4024 / Fax: +55(41) 3360-4134. jamenaba@gmail.com

BRASIL



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