Prevalence of sublingual varices in patients with cirrhosis and the correlation with nitrogen compounds

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Objective. The aim of this study was to verify the presence and severity of sublingual varices in patients with cirrhosis and the correlation between these varices and nitrogen compounds (i.e., ammonia, urea and nitric oxide) in blood and saliva.

Study Design. This is a case-control observational study of 52 patients with cirrhosis and 52 normoreactive individuals, aimed at assessing the presence (degrees 0 and 1) and severity (mild, moderate, and severe) of sublingual varices. Medical records of the patients with cirrhosis, including complications of cirrhosis, were also obtained. Blood and saliva were collected to evaluate the presence of nitrogen compounds by means of automated enzymatic colorimetric assays.

Results. The cirrhosis group had a higher prevalence (n = 39; 75%) compared with controls (n = 22; 42.3%) as well as higher severity (moderate n = 12 [23.1%]; and severe n = 16 [30.0%]) ($P = .001$ and $P < .001$, respectively). Of the 39 patients with cirrhosis and sublingual varices, 84.6% had gastroesophageal varices. No correlations were found between the presence/severity of sublingual varices and cirrhotic complications/nitrogen compounds.

Conclusions. The prevalence and severity of varices were higher in the cirrhosis group, but no correlations between the presence/severity of sublingual varices and nitrogen compounds were found. (Oral Surg Oral Med Oral Pathol Oral Radiol 2020;129:39−44)

Hepatic cirrhosis is histologically characterized by the substitution of liver parenchyma for fibrosis and regenerative nodules.[1] With the increase of intrahepatic obstruction, vascular resistance to portal blood flow is increased and results in the main complication of cirrhosis: portal hypertension.[2] In an attempt to circumvent the increase in portal vein pressure, varices and splanchnic collaterals are formed through the reopening and dilation of local extrahepatic vascular channels originating from collapsed embryonic veins or neoformation of vessels associated with increased angiogenic factors, such as vascular endothelial growth factor.[3] Because these newly formed vessels are highly resistant, decompression is still inadequate, and thus, the endogenous release of vasoactive agents (e.g., nitric oxide) is necessary for the maintenance of this collateral circulation.[4]

Nitric oxide is a molecule that has been described as being essential and indispensable for the maintenance of splanchnic vasodilation in patients with cirrhosis and portal hypertension. With its increased bioavailability and free diffusion through the cellular membrane, nitric oxide acts by increasing the production of cyclic guanosine monophosphate by guanylate cyclase activation, which consequently causes relaxation of smooth muscle cells.[5]

Numerous varices and collateral veins develop as a result of portal hypertension and can be present virtually in the whole body. That is the reason they are called *collateral* or *portosystemic veins.* However, there are anatomic areas with greater portosystemic confluence, such as intrathoracic manifestations that characteristically develop through the coronary vein, resulting in esophageal or paraesophageal varices.[6]

The fragile and thin walls of these vessels can be easily disrupted and lead to episodes of upper gastrointestinal (GI) bleeding, resulting in morbidity and mortality caused by cirrhosis.[7] Esophagogastroduodenoscopy is the gold standard method for the diagnosis of these varices. However, less invasive diagnostic methods have been increasingly used, such as serum ammonia for the prediction of the presence and severity of gastroesophageal varices.[8-10]

Because the formation of varices in patients with cirrhosis can occur in the entire GI tract, the oral cavity may be affected as well. The ventral surface of the tongue and the floor of the mouth are the regions most

Statement of Clinical Relevance

The diagnosis of esophageal varices helps determine cirrhosis progression, and the diagnosis of sublingual varices can be an auxiliary tool for the early diagnosis of esophageal varices and to evaluate the severity of liver disease.

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Received for publication Jun 18, 2019; returned for revision Sep 13, 2019; accepted for publication Sep 14, 2019.

2212-4403/$-see front matter
https://doi.org/10.1016/j.oooo.2019.09.009

susceptible to the formation of varices because of an extensive submucosal venous plexus.[11] Although the etiology of sublingual varices is not well defined, some studies have reported an association with older age groups, cardiovascular diseases, smoking, diabetes, and denture wear.[12-15] With regard to the association between sublingual varices and portal hypertension, only 3 cases have been reported in the literature.[16-18]

Therefore, our objective was to assess in patients with cirrhosis the prevalence and severity of sublingual varices and their possible association with nitrogen compounds (i.e., ammonia, urea, and nitric oxide) in blood and saliva.

MATERIALS AND METHODS

Study design and patients

A case-control study was conducted from September 2016 to July 2018 at the Special Care Dentistry Centre of the University of São Paulo School of Dentistry. The study included consecutive patients with cirrhosis who were on the liver transplantation waiting list and normoreactive individuals accompanying the patients with cirrhosis. A sample size calculation was performed by using the software Epiinfo, version 7.1. Data were obtained from the study by Hedström et al.,[12] who reported the prevalence of sublingual varices in 47.5% of patients with hypertension compared with 18.3% in normotensive individuals. Therefore, considering an alpha value of 5%, a beta value of 90%, and a 1:1 ratio of cases and controls, the ideal sample for the present study was determined to be 52 patients in each group.

This study was approved by the local research ethics committee and conducted according to the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) recommendations for observational studies

Clinical examination

Clinical examination of the patients consisted of anamnesis and physical examination. Data on gender, age, smoking, etiology of cirrhosis, MELD (model of end-stage liver disease) score, and selected complications of cirrhosis (i.e., gastroesophageal varices, upper GI bleeding, and grade 1 ascites—mild, only visible on ultrasonography) were collected from anamnesis and confirmed by laboratory tests or medical records. Jaundice, hepatic encephalopathy (West Haven criteria), edema, and directly visible ascites (grade 2—moderate symmetric distention; and grade 3—marked distention) were identified during physical examination of the patient.

Physical examination was performed in a dental outpatient setting under artificial light, and the patients underwent an oral mucosal examination for the clinical diagnosis of varices. The examination sites included the tongue, floor of the mouth, and buccal and labial mucosae. Sublingual varices were categorized by using the criteria established by Hedström and Bergh,[13] who graded the presence of varices as degree 0 = absent, a few or non-visible varices; and degree 1 = moderate or severe varices. The varices were also categorized on the basis of severity: mild = no varices or small-sized ones; moderate = medium- or large-sized varices; and severe = presence of venous lakes.

Two evaluators (N.T.D. and A.O.G.) made the diagnosis of varicose veins, and the third evaluator (K.L.O.) was consulted only in the case of any divergence of opinions. The calibration of the examiners was performed in 2 steps. The first training was performed in lux, consisting of slide projection images of different individuals with sublingual varices. After 1 week, the images were reassessed, and the examiners were to agree on at least 80% of the diagnoses. In the second phase (pilot study), 10 patients who did not participate in the research were independently examined by an experienced "gold standard" examiner and the other study examiners. After 2 weeks, the same patients were re-examined. Inter- and intraexaminer agreement values were calculated by using the kappa index ($\kappa = 0.818$ and $\kappa = 0.863$, respectively). The results supported an acceptable methodology.

Blood and saliva sample collection

During the clinical examination, samples of peripheral blood and saliva were collected from patients with cirrhosis. The patients were instructed to avoid ingesting food or beverages and avoid performing any oral hygiene for 60 minutes before saliva collection. Mouth rinse with distilled water was performed for 30 seconds before collection, and all the saliva produced during the subsequent 10 minutes was collected into a Falcon tube. The collected saliva was immediately transferred to safe-lock tubes (Protein LoBind Microcentrifuge Tubes; Eppendorf, Hamburg, Germany) before being frozen at −80°C for later biochemical analyses.

Blood was collected by means of venous puncture and then stored in a tube containing a clot activator, remaining at rest for 30 minutes at 4°C. After centrifugation at 3000 rpm for 15 minutes, the resulting serum was stored in safe-lock tubes (Protein LoBind Microcentrifuge Tubes; Eppendorf, Hamburg, Germany), in a freezer at −20°C for later biochemical analyses.

Determination of concentrations of nitrogen compounds in saliva and blood

Concentrations of nitric oxide, ammonia, and urea in saliva and blood were determined by using automated enzymatic colorimetric assays, respectively—EnzyChrom Nitric Oxide Synthase Assay; EnzyChrom

Ammonia Assay Kit; and EnzyChrom Urea Assay Kit (BioAssay Systems, Hayward, CA). These were performed according to the manufacturers' recommendations. A Stat Fax 2100 microplate reader (Awareness Technology) was used to read the samples.

Statistical analysis

Data were analyzed by using the Statistical Package for Social Science for Windows, version 20.0 (SPSS Inc., Chicago, IL). Descriptive analysis was carried out, and the Kolmogorov-Smirnov test was applied to confirm the nonparametric distribution. In the bivariate analysis, Pearson's χ^2 test, Fisher's exact test, Mann-Whitney U test, Kruskal-Wallis test, and the linear association test were performed to determine the relationships between the independent variables and the outcomes, as well as group comparisons. All statistical tests were performed at a significant level of 5% ($P < .05$).

RESULTS

Evaluation of demographic characteristics of the 52 study patients with cirrhosis and the 52 normoreactive controls showed a higher male gender predilection (in both groups) and mean ages of 51.6 and 46.8 years in the former and latter groups, respectively. Six patients in the cirrhosis group reported being smokers. None of these variables showed statistically significant differences between the groups (Table I).

The characterization of the study group relied on data regarding current disease and complications of cirrhosis to confirm that all patients had portal hypertension, with the majority presenting with a previous history of jaundice (n = 33; 63.5%) and upper GI bleeding (n = 26; 50%). Currently, 46 patients (88.5%) had gastroesophageal varices; 38 (73.1%) had hepatic encephalopathy; 30 (57.7%) had ascites; and 27 (51.9%) had peripheral edema. The most common causes of cirrhosis were alcoholism (n = 15; 28.8%); hepatitis C (n = 9; 17.3%); and cryptogenic cirrhosis (n = 9; 17.3%), followed by autoimmune hepatitis (n = 7; 13.6%); nonalcoholic steatohepatitis (n = 5; 9.6%); schistosomiasis (n = 2; 3.9%); and others (n = 5; 9.6%). The MELD score was 17.02 (± 4.80).

With regard to the presence of sublingual varices, the study group had a higher prevalence (n = 39; 75%) compared with the control group (n = 22; 42.3%) and also greater severity (moderate = 12 [23.1%] and severe = 16 [30%]) ($P = .001$ and $P < .001$, respectively) (Table II). Among the patients in the study group with sublingual varices (n = 39), we identified gastroesophageal varices in 84.6% (n = 33); peripheral edema in 56.4% (n = 22); ascites in 52.3% (n = 20); hepatic encephalopathy in 74.4% (n = 29); and upper GI bleeding in 56.4% (n = 22). No statistically significant correlations were found between these complications of cirrhosis and the presence (ascites, $P = .194$; peripheral edema, $P = .343$; hepatic encephalopathy, $P = .729$; gastroesophageal varices, $P = .632$; and upper GI bleeding, $P = .199$) or severity of sublingual varices (ascites, $P = .843$; peripheral edema, $P = .493$; hepatic encephalopathy, $P = .762$; gastroesophageal varices, $P = .969$; and upper GI bleeding, $P = .340$)

Among the 52 patients of the cirrhosis group, 35 agreed to have their blood and saliva collected for the measurement of ammonia, nitric oxide, and urea concentrations. The levels of urea and nitric oxide in blood and saliva were positively correlated, whereas ammonia had no correlation with its serum and salivary levels or with other nitrogen compounds. Quantitative changes in the levels of nitric oxide reflect alterations in other nitrogen compounds because it positively correlates with all the others in both blood and saliva (Table III).

Although the median values of urea in blood and saliva were higher in patients with sublingual varices, these correlations were not statistically significant (Table IV). In addition, no statistically significant correlation was found between the severity of sublingual varices and the amount of nitrogen compounds (Table V).

Table I. Distribution of age, gender, and smoking habits of the patients with cirrhosis and controls

Variables	*Groups*		*P*
	Controls n (%)	*Patients n (%)*	
Age in years	46.8 ± 11.1	51.6 ± 13.8	.053*
Gender			.671†
Male	37 (71.2)	35 (67.3)	
Female	15 (28.8)	17 (32.7)	
Smoker			
No	46 (88.5)	36 (69.2)	
Former smoker	06 (11.5)	10 (19.2)	.063‡
Yes	00 (0.0)	06 (11.5)	

*Mann-Whitney test.
†χ^2 test.
‡Linear association test.

Table II. Severity of the sublingual varices in the patient and control groups

Severity of sublingual varices	*Groups*		*P*
	Controls n (%)	*Patients n (%)*	
Mild	42 (80.8)	24 (46.2)	< .001
Moderate	05 (9.6)	12 (23.1)	
Severe	05 (9.6)	16 (30.8)	

$P = \chi^2$ and linear association tests.

Table III. Correlation between nitrogen compounds in blood and in saliva of patients with cirrhosis (n = 35)

	Nitric oxide in saliva (U/L)	*Nitric oxide in blood (U/L)*	*Urea in blood (mg/dL)*	*Urea in saliva (mg/dL)*
Nitric oxide in saliva (U/L)	–	R = 0.418 *P* = .012	R = 0.397 *P* = .018	R = 0.400 *P* = .017
Urea in saliva (mg/dL)	R = 0.400 *P* = .017	NS	R = 0.627 *P* < .001	–
Nitric oxide in blood (U/L)	R = 0.418 *P* = .012	–	NS	NS

NS, no significance; *P,* significance; *R,* Pearson's correlation coefficient.

Table IV. Presence of sublingual varices and concentrations of nitrogen compounds in saliva and blood

Variables	*Sublingual varices*	*Median*	*Rank*	*P**
Ammonia (mg/dL) – saliva	Degree 0	1.17	0.67–1.41	.428
	Degree 1	0.89	0.49–1.82	
Ammonia (mg/dL) – blood	Degree 0	1.33	0.50–1.54	.154
	Degree 1	1.15	0.46–1.50	
Nitric oxide (U/L) – saliva	Degree 0	19.92	10.10–41.04	.132
	Degree 1	15.29	5.55–40.74	
Nitric oxide (U/L) – blood	Degree 0	7.27	4.35–15.27	.286
	Degree 1	6.09	4.35–13.12	
Urea (mg/dL) – saliva	Degree 0	31.68	24,07–38,65	.954
	Degree 1	31.88	16.12–85.15	
Urea (mg/dL) – blood	Degree 0	44.48	30.93–55.67	.052
	Degree 1	50.95	31.09–99.09	

*Mann-Whitney test.

DISCUSSION

The prevalence of sublingual varices has been estimated to range from 26% to 55.8%,[12,19,20] with some factors, such as arterial hypertension, denture wearing, and, particularly, older age, being directly associated with their presence and high prevalence. In our study, both the prevalence and severity of sublingual varices were much higher in patients with liver cirrhosis compared with controls. It should be emphasized that the prevalence rates observed in patients with cirrhosis (75%), mean age 51.6 years, were only comparable with those of patients age greater than 70 years.[13,20,21]

Overall, varicose veins of lower extremities, as well as gastroesophageal and lingual veins, have a similar etiopathogenesis because they have been associated

Table V. Severity of sublingual varices and concentrations of nitrogen compounds in saliva and blood

Variables	*Severity of sublingual varices*	*Median*	*Interquartile interval*	*P**
Ammonia (mg/dL) – saliva	Mild	1.03	0.53–1.59	.374
	Moderate	1.25	0.68–1.82	
	Severe	0.86	0.49–1.31	
Ammonia (mg/dL) – blood	Mild	1.25	0.50–1.54	.684
	Moderate	1.10	0.46–1.41	
	Severe	1.21	0.55–1.47	
Nitric oxide (U/L) – saliva	Mild	17.26	5.55–41.04	.952
	Moderate	15.63	8.96–40.74	
	Severe	15.56	9.65–36.13	
Nitric oxide (U/L) – blood	Mild	5.93	4.35–15.27	.820
	Moderate	6.09	5.13–7.01	
	Severe	6.26	4.91–13.12	
Urea (mg/dL) – saliva	Mild	33.18	16.12–61.51	.409
	Moderate	28.96	23.68–45.04	
	Severe	33.61	21.24–85.15	
Urea (mg/dL) – blood	Mild	49.80	30.93–85.54	.394
	Moderate	48.82	31.09–55.44	
	Severe	51.85	44.01–99.09	

*Kruskal-Wallis test.

with dilation caused by loss of vessel wall elasticity, malfunctioning of venous valves, and increase in venous pressure.[13,22]

We initially believed that a correlation might exist between sublingual and gastroesophageal varices because they have a similar etiology and are located in nearby anatomic regions. However, this was not confirmed in our investigation. One possibility for this lack of correlation would be the anatomy of venous drainage. The submucous venous plexus of periesophageal veins drains into the lower thyroid veins in its cervical portion, into the azygos and hemiazygos veins in its thoracic portion, and into the gastric veins in its lower portion (abdominal), thus connecting with the portal venous system.[23,24]

However, sublingual veins drain into the internal jugular vein, which connects with the subclavian vein to form the brachiocephalic vein, which, in turn, ends in the superior vena cava.[25]

Even though there is no recognized anastomosis between lingual vein drainage and portal circulation,[16] decompensated cirrhosis accounts for hyperdynamic circulation. More specifically, the presence of pervasive vascular hyporeactivity that is characterized by a decrease in peripheral vascular resistance, an average arterial pressure, the expansion of plasma volume, and an increase in cardiac output and heart rate[26] all lead to cirrhotic cardiomyopathy.[27]

Because sublingual varices have been widely associated with cardiovascular conditions,[12-14,19] it is possible that their presence in patients with cirrhosis may be related to a more severe systemic condition.

In the present study, however, known clinical characteristics of cirrhotic decompensation, such as ascites and hepatic encephalopathy,[28] were not found to be correlated with the presence of sublingual varices. Ammonia and urea were not found to be positively correlated with the presence of sublingual varices despite both having been involved in cases of hepatic encephalopathy.[29]

Nitric oxide, a known vasodilator classically linked to the triggering and maintenance of hyperdynamic circulation,[26] had no systemic (blood) or local (saliva) presence correlated with the presence or severity of sublingual varices. Data on nitrogen compounds (i.e., urea, nitric oxide, and ammonia) were found to be consistent because their serum levels positively correlated with their salivary levels. Individually, none of the nitrogen compounds, in blood or saliva, was positively correlated with the presence of lingual varices.

The lack of association between nitrogen compounds and sublingual varices was not observed for gastroesophageal varices. The literature has been reporting that increased serum levels of ammonia and nitric oxide are linked to the presence of gastroesophageal varices, whereas that of urea is linked to their bleeding. This association is so close that some authors have already been suggesting that these compounds should be used as a noninvasive method for the early diagnosis of these varicosities.[8-10,30]

CONCLUSIONS

Although sublingual varices are statistically more prevalent and more severe in patients with cirrhosis than in healthy controls, it was not possible to verify the existence of any factor that could be correlated with higher prevalence or severity of these varicosities in patients with cirrhosis. We believe that this significant qualitative and quantitative increase of sublingual varices possibly opens a pathway to investigate the links to the severity of this liver disease and early diagnosis of gastroesophageal varices.

FUNDING

This work was supported by Fundação de Amparo à Pesquisa do Estado de São Paulo– FAPESP (grant # 2017/18938-6); Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq).

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