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Prevalence of Panoramically Imaged Carotid Atheromas in Alcoholic Patients With Chronic Pancreatitis and Comorbid Diabetes

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Abstract

Purpose: Men with alcohol-related chronic pancreatitis (ARCP) resulting in type 3c diabetes mellitus (DM) are at a uniquely elevated risk of adverse ischemic events given the role of inflammation in both the underlying disease processes and atherosclerosis. We hypothesized that their panoramic images would show a prevalence of calcified carotid artery atheromas (calcified carotid artery plaques [CCAPs]) significantly more often than a general population of similarly aged men.

Patients and Methods: We implemented a retrospective observational study. The sample was composed of male patients older than 30 years having panoramic images. The predictor variable was a diagnosis of ARCP-DM, and the outcome variable was the prevalence rate of CCAPs. The prevalence of CCAPs among the patients with ARCP-DM was then compared with that of a historical general population composed of similarly aged men. Descriptive and bivariate statistics were computed, and the P value was set at.05.

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Results: Of the 32 men (mean age, 61.7 ± 11.2 years) with ARCP-DM, 8 (25%) (mean age, 63.3 ± 4.80 years) had atheromas (CCAPs). There was a statistically significant (P <.05) association between a diagnosis of ARCP-DM and the presence of an atheroma on the panoramic image in comparison with the 3% rate manifested by the historical general-population cohort. The presence or absence of classic atherogenic risk factors within the ARCP-DM cohort failed to distinguish between individuals with and individuals without atheroma formation on their panoramic images.

Conclusions: The results of this study suggest that CCAP, a risk indicator for future adverse cardiovascular events, is frequently seen on the panoramic images of male patients with ARCP-DM. Dentists treating male patients with the disorder must be uniquely vigilant for the presence of these lesions.

Alcohol-related chronic pancreatitis (ARCP) is frequently associated with diabetes mellitus (DM), also occasionally referred to as “type 3c diabetes,” with a lifetime diabetes risk as high as 50% to 75%. Although the pathophysiology is not known, compromised β-cell function arising from pancreatic fibrosis and an inflammatory milieu are observed. Reduced insulin sensitivity also may play a role, and limited data from euglycemic clamp studies have suggested a potential role of whole-body and/or hepatic insulin resistance. Chronic pancreatitis and comorbid (80%) DM frequently develop among European,[1,2] Asian,[3,4] and North American[5] men after many years of heavy alcohol and nicotine use.[6,7] These 2 agents act synergistically to produce an inflammatory-fibrotic reaction that causes vascular ischemic atrophy of pancreatic acinar cells, which secrete digestive enzymes, and islet cells, which secrete insulin and glucagon for optimal control of glucose levels.[8–10] The ensuing diabetic condition[11] engenders an associated atherogenic lipid profile that, in concert with the underlying inflammatory process, heightens the risk of vascular occlusive disease. Some investigators have claimed that the disease complex causes microvascular complications manifesting as retinopathy and renal dysfunction,[12–14] whereas others have denoted macrovascular disease as evidenced by myocardial infarction (MI) and peripheral vascular disease.[15–18] In addition, studies in Taiwan and Denmark have recently shown a strong association of the disease complex with concomitant ischemic stroke.[19,20]

These latter findings suggest that dentists may have an opportunity to participate in this debate and assist in identifying high-risk individuals (estimated to represent almost 10% of all patients with previously diagnosed type 2 diabetes[21]) by assessing their panoramic images for evidence of calcified carotid artery plaques (CCAPs) (Fig 1), a validated “risk factor” for future adverse cerebrovascular events.[22,23] Specifically, dental researchers have reported that these panoramically imaged lesions are evidenced approximately 3% of the time among older men and, when present, herald future adverse cardiovascular and cerebrovascular events.[23,24]

Given the controversy as to the loci of atherosclerotic disease and given that there have not been any previously reported studies evaluating panoramic images for the presence of CCAPs among individuals with ARCP-DM, we undertook this project. Its specific purpose was to determine the prevalence rate of CCAPs among older male military veterans having the symptom complex diagnosed by endocrinologists and gastroenterologists. The prevalence rate of CCAPs in this cadre of patients was hypothesized to be significantly

greater than that previously reported (3%) among a general population of men attending an ambulatory dental clinic.[23]

Patients and Methods

STUDY DESIGN AND PATIENT SAMPLE

To address the research question, we designed and implemented a retrospective cross-sectional study. The study was conducted in accordance with the Declaration of Helsinki guidelines. The study protocol was approved by the Institutional Review Board of the Veterans Affairs Greater Los Angeles Healthcare System, and the need for informed consent from each patient was waived given the retrospective nature of the project and its use of deidentified patient data. The medical center's electronic medical records and digital dental image library dating between January 1, 2000, and December 31, 2017, were accessed and reviewed. Chosen for further scrutiny were the charts and images of all male patients having a diagnosis of chronic pancreatitis and a classically positioned panoramic imaging study obtained to diagnose dental disease.

Patients diagnosed with ARCP-DM were determined by use of *International Classification of Diseases, Ninth Revision and/or International Classification of Diseases, Tenth Revision* coding in the Veterans Affairs electronic medical records. Demographic data (age, gender), ARCP risks and/or effects (history of smoking, pancreatic polypeptide titer), comorbid DM disease state (fasting glucose and hemoglobin A_{1c} [HbA_{1c}] levels), treatment (oral antihyperglycemic agents, insulin), and additional atherogenic risk factors identified (hypertension, dyslipidemia) were all obtained from the participants' electronic medical records. Furthermore, the senior author (A.H.F.) reviewed the medical records of each study patient and determined convincing historical information and medical diagnostic testing data to substantiate the comorbid diagnoses and medication regimens.

Our study's inclusion criteria mandated that the following elements be present: *1*) a documented history of alcoholism that was determined to be the etiologic agent for the diagnosis of chronic pancreatitis; *2*) development of the diabetic condition as a result of the pancreatitis; *3*) determination of the diagnoses by a gastroenterologist or endocrinologist; and *4*) an acceptable panoramic image that included the area of interest, that is, 2.5 cm inferior and 2.5 cm posterior to the cortical rim of the midpoint of the mandibular angle. The presence of CCAPs was jointly determined by 2 oral and maxillofacial surgeons certified by the American Board of Oral and Maxillofacial Surgery using the American Academy of Oral and Maxillofacial Radiology–sponsored training packet for identification of carotid artery calcifications on panoramic radiographs.[25] Consistent with these guidelines, radiopaque lesions in a verticolinear orientation relative to the hyoid bone, as well as parallel to the cervical vertebrae in the region of the intervertebral space between C3 and C4, were identified as CCAPs. Special attention was directed to ruling out confounding radiopaque lesions that also were often visualized proximate to the carotid vessels such as calcified triticeous cartilage or superior cornu of the thyroid cartilage.[26] In addition, to ensure the precision and accuracy of the data, we excluded cases in which there were any diagnostic discrepancies between the 2 clinicians.

STUDY VARIABLES AND DATA SOURCE RETRIEVAL

The primary measurement was the prevalence of calcified carotid artery atheromas on the panoramic images of male patients with ARCP having comorbid diabetes. Also assessed was the severity of comorbid diabetes as determined by the lists of medications used for its control.

DATA ANALYSIS

A similarly aged group of patients previously reported on by the senior author[23] and representing a general population of male veterans was compared with patients with ARCP for the prevalence of the presence of CCAPs using the χ^2 test. In addition, in the current study group, both the CCAP-positive and CCAP-negative groups were compared by the Fisher exact test or *t* test depending on the type of variable being analyzed. Group differences in the prevalence of hypertension, prevalence of smoking history, prevalence of dyslipidemia, oral DM medication, and insulin treatment were tested with Fisher exact tests and a logistic regression model. On the other hand, the *t* test was used for the comparison of mean values of age and body mass index (BMI) to determine whether either of these was different between the CCAP-positive and CCAP-negative groups. If assumptions of equality of variance in the standard deviation and normality of data distribution (required for the *t* test) were not met, as in the measures of HbA_{1c} and the international normalized ratio (INR), the Mann-Whitney *U* test—a nonparametric test equivalent to the parametric *t* test—was performed on these variables.

Data were recorded in a deidentified fashion and entered into a standardized electronic database, and all statistical tests were performed with SPSS Statistical Analysis Software (version 17.0; SPSS, Chicago, IL). Statistical comparison of the prevalence rate for the presence of CCAPs was performed by the Fisher exact test, where the *P* value level of significance was set at.05. All analyses were conducted by use of a 2-sided test with α set at. 05.

Results

A cohort of 32 men (mean age, 61.7 ± 11.20 years) diagnosed with ARCP and comorbid DM were enrolled for study. Consistent with the alcoholic etiology of ARCP and the development of comorbid DM, both the INR (mean, 1.21 ± 0.55) and the HbA_{1c} level (mean, 7.94 ± 1.94) were elevated. Similarly, consistent with the underlying disorders were the prevalence of hypertension (90.6%), dyslipidemia (84.4%), and smoking history (75%). Among this cohort, 8 of the 32 participants (25%) showed an atheroma (CCAP) on their panoramic radiographic images (Table 1). This prevalence rate (25%) was significantly greater (*P* =.0004) than the 3% rate evidenced by a previously studied group of similarly aged men (N = 295; mean age, 69.3 years) attending an outpatient dental clinic (Table 2). The current study, however, failed to identify any significant differences in the extent of atherogenic risk factors (age; BMI; HbA_{1c}; INR; prevalence of hypertension, smoking history, or dyslipidemia; and form of diabetic medication) between individuals with and without atheroma formation on their panoramic images (Table 3). Furthermore, logistic regression models used to predict the presence or absence of CCAPs by using age, BMI,

HbA_{1c}, INR, prevalence of hypertension, prevalence of smoking history, prevalence of dyslipidemia, oral DM medication, or insulin treatment similarly failed to identify a statistically significant relationship with these covariates.

Discussion

The results of our study documented a significant association between ARCP with comorbid diabetes and calcified carotid atheromas in the cervical distribution as viewed on panoramic images. These lesions are a risk factor for ischemic stroke; thus our findings are very consistent with 2 recent studies showing an enhanced risk of cerebrovascular disease in patients with chronic pancreatitis.[19,20,27] These macrovascular lesions likely resulted from both the inflammatory component of the underlying disorder and the associated metabolic disorder. Specifically, cytokines such as tumor necrosis factor a in the pancreatic tissues spill over into the systemic circulation and promote an atherogenic milieu (increased permeability of endothelial cells, monocyte adhesion, macrophage differentiation, vascular smooth muscle cell proliferation, foam cell formation, and calcification of vascular cells).[28–35] Further promoting the atherogenic process is the comorbid diabetic environment characterized by hyperglycemia, with a deficiency in vascular protective high-density lipoprotein level and heightened oxidative modification of the admittedly lower low-density lipoprotein level.[36,37]

The time interval from onset of the disease complex (ARCP-DM) to the development of mature calcified atheromas (CCAPs) visible on panoramic images remains unknown; however, we do know that when these lesions are denoted in large populations of male patients free of ARCP-DM, they are risk factors for future stroke and “risk indicators” for future MI. Specifically, in a previously published study, we followed 46 men (mean age, 66 years) with CCAPs on their panoramic images and a like number of vascular risk–matched controls lacking radiographs until an adverse event, as an endpoint, developed.[24] A total of 20 events (MI [6], stroke [3], revascularization procedure [6], angina requiring hospitalization [3], and transient ischemic attack [2]) occurred in 12 study-group patients and 6 events (MI [1], stroke [1], revascularization procedure [1], hospitalization for angina[2], and transient ischemic attack [1]) occurred in 5 control-group patients (P =.006). A somewhat similar study conducted in Sweden was recently published (2018). Among a group (N = 562) of community-residing males (median age 61) who had just suffered a first myocardial infarction 32.7% evidenced either unilateral or bilateral CCAP on their PI versus 26.5% of age and gender matched controls (odds ratio, 1.24; 95% confidence interval, 1.03 to 1.48; P =.022) who did not have a cardiac event.[38]

ARCP with comorbid diabetes is a clinically important disease complex. The progression from acute pancreatitis to chronic pancreatitis with diabetes to pancreatic cancer is a complex process that is characterized by a progressive desmoplastic reaction and an associated inflammatory injury to pancreatic cells. Although the fibrotic and inflammatory processes of pancreatitis are mainly restricted to the exocrine pancreas, resulting over time in pancreatic enzyme insufficiency, there is relative sparing of the is-lets of Langerhans and their insulin-producing β cells that mainly occur in the tail of the pancreas.[39] Thus, the most consistently observed defects in type 3c diabetes include abnormal islet responses,

particularly decreased insulin and pancreatic polypeptide secretion. Conflicting studies have been published regarding the potential role of peripheral insulin resistance in the pathogenesis of type 3c diabetes. Never-theless, the inflammatory environment appears to compromise β-cell function, and progressive fibrosis results in eventual loss of β islet cells.

ORAL AND MAXILLOFACIAL SURGERY IMPLICATIONS

Given that vascular disease is also a frequent comorbid illness with diabetes, oral and maxillofacial surgeons reviewing the panoramic images of these individuals need to be mindful of the presence of calcified carotid artery atherosclerotic lesions. Such lesions, when observed by these imaging systems, have been shown to herald adverse cardiovascular events; therefore, these patients should be referred to their primary care physicians for further evaluation. Furthermore, when one is planning surgical procedures, it is prudent to obtain a preoperative INR and platelet count given that the vast majority of persons with this complex disorder are or were heavy imbibers of alcohol. Specifically, advanced alcoholic liver disease results in reduced production of coagulation factors and depletion of vitamin K because of malnutrition. Further compromising the hemostatic process is an often-accompanying thrombocytopenia, which arises from both alcohol's suppression of platelet production by the bone marrow and platelet sequestration in an often-enlarged spleen resulting from portal hypertension. Recent research findings, however, have shown that among patients with concomitant deficiencies in coagulation factors and platelets, local measures consisting of primary closure of the surgical sites, application of fibrin sponges, and use of oral tranexamic acid rinses may sufficiently achieve hemostasis if the INR is less than 2.5 and the platelet count is greater than 40,000/μL of blood.[40] Hematologic consultation is suggested for patients having more extreme concomitant deficiencies. Issues of DM-related delayed healing and increased risk of postoperative infections after exodontia have recently been addressed in 2 contemporaneous prospective studies, in which neither cohort of diabetic patients (mixed group of patients with type 1 and type 2 diabetes, with the other group limited to patients with type 2 diabetes) showed enhanced risk compared with healthy control patients.[41,42] Of note, prophylactic antibiotics were not administered in either study.

The patients in our study (N = 32) evidenced INR values that ranged from 0.9 to 3.7 and platelet counts that ranged from 70,000/mL to 330,000/mL. In this cohort, 13 men (mean age, 62.8 years; range, 43 to 86 years) had dentoalveolar surgical procedures (ie, soft and hard tissue biopsy, extraction of erupted teeth [mean, 4.75; range, 1 to 12], and alveoloplasty) performed by use of local anesthesia with a vasoconstrictor, which was usually staged over several visits (mean, 3; range, 1 to 9). The hemostatic profile of these individuals showed a mean INR of 1.2 (range, 0.9 to 2.6) and a mean platelet count of 215,000/mL (range, 70,000/mL to 330,000/mL). Postoperative hemostasis was achieved at the completion of each procedure, and none of the patients had postoperative bleeding despite the fact that some had a prolonged INR and relatively lower platelet count. Of note, in 9 of the 12 patients having exodontia, alveolar osteitis developed, in 1 or more extraction sockets, requiring anodyne dressing placement and, when the diagnosis was equivocal, a 7-day course of antibiotics (amoxicillin, 500 mg 3 times a day, or clindamycin, 150 mg 4 times a day). Of these 9 individuals, 5 were insulin dependent.

Our study had limitations and strengths. The main limitations were the small sample size; data derived from a single center; and the retrospective cross-sectional design, which prevented us from proving a causal relationship between ARCP with comorbid DM and CCAPs. Furthermore, the small sample size may have precluded the differentiation of CCAP-positive from CCAP-negative patients based on the presence or absence of classic atherogenic risk factors. Conclusions drawn from our data, among older male veteran patients with the disease complex, should be considered with caution before extending them to a general population with the same complex because older male veterans have been shown to consistently have uniquely high levels of medical comorbidities.[43] In terms of study strengths, this is the first study to be published in the literature, to our knowledge, that describes this disease entity as well as having identified a role for the profession in detecting the disorder's systemic manifestations by determining the occurrence and prevalence of CCAPs on the panoramic images of older male patients with the illness.

In conclusion, we found that older male patients with ARCP with comorbid DM are significantly more likely to evidence calcified carotid artery atheroma on their panoramic images than a similarly aged general population of the same gender. We further conclude that surgeons must become familiar with the clinical correlates associated with the disease complex (poor compliance with lifestyle advice and medications given the underlying addiction to alcohol and tobacco) given its increasing prevalence among younger individuals worldwide.[44,45] Our specialty has an opportunity during imaging procedures to collaborate with the patient's primary care physician in possibly diagnosing evidence of ischemic vascular disease. Future larger cohort studies to investigate this association could provide an important predictor for cardiovascular disease and chronic pancreatitis.

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FIGURE 1.

Panoramic image of an 82-year-old male patient with alcohol-related chronic pancreatitis–associated diabetes mellitus. The image, which has been digitally enhanced with the manufacturer's provided software, shows bilateral calcified carotid artery plaques (arrows) situated anterior to the interspace between the third and fourth cervical vertebrae (C3 and C4). Abbreviation: L, left.

Table 1.

CHARACTERISTICS OF PATIENTS WITH ALCOHOL-RELATED CHRONIC PANCREATITIS–ASSOCIATED DIABETES (N = 32)

	Data
Age, yr	
Mean ± SD	61.69 ± 1120
Range	31–86
BMI	
Mean ± SD	25.19 ±5.59
Range	14.94–39.50
HbA_{1c} level	
Mean ± SD	7.94 ± 1.94
Range	5.2–13.4
INR	
Mean ± SD	1.21 ±0.55
Range	0.9–3.7
Platelet count, per mL	
Mean ± SD	216,940 ± 66,740
Range	70,000 – 333,000
Prevalence of CCAPs, n (%)	8 (25.0)
Prevalence of hypertension, n (%)	29 (90.6)
Prevalence of smoking history, n (%)	24 (75.0)
Prevalence of dyslipidemia, n (%)	27 (84.4)
Oral DM treatment, n (%)	17 (53.1)
Insulin treatment, n (%)	22 (68.8)

Abbreviations: BMI, body mass index; CCAP, calcified carotid artery plaque; DM, diabetes mellitus; HbA_{1c}, hemoglobin A_{1c}; INR, international normalized ratio.

Table 2.

PREVALENCE OF CALCIFIED CAROTID ARTERY ATHEROMAS ON PANORAMIC IMAGES OF MEN WITH ALCOHOL-RELATED CHRONIC PANCREATITIS–ASSOCIATED DIABETES MELLITUS IN COMPARISON WITH HISTORICAL GENERAL-POPULATION COHORT

	CCAP Present	CCAP Absent	*P* Value
Current study, n	8 (25%)	24 (75%)	*P* =.0004
Historical cohort study, n	10 (3%)	285 (97%)	

Abbreviation: CCAP, calcified carotid artery plaque.

Table 3.

COMPARISON OF DIFFERENT FACTORS BETWEEN PATIENTS WITH CCAPS AND PATIENTS WITHOUT CCAPS

Variable	CCAP Present (n = 8)	CCAP Absent (n = 24)	*P* Value
Age, yr			
Mean ± SD	63.25 ± 4.77	61.17 ± 12.69	.656
Range	56–69	31–86	
BMI			
Mean ± SD	25.03 ± 4.37	25.24 ± 6.02	.928
Range	20.40–30.92	14.94–39.50	
HbA_{1c} level			
Mean ± SD	7.55 ± 1.69	8.07 ± 2.03	.827
Range	5.2–10.0	5.9–13.4	
INR			
Mean ± SD	1.58 ± 1.02	1.09 ±0.15	.477
Range	0.9–3.7	0.9–1.5	
Platelet count			
Mean ± SD, per mL	214,500 ± 92,890	217,750 ±58,100	.836
Range	70,000 – 333,000	102,000 – 333,000	
Prevalence of hypertension, n (%)	8 (100.0)	21 (87.5)	.555
Prevalence of smoking history, n (%)	7 (87.5)	17 (70.8)	.642
Prevalence of dyslipidemia, n (%)	8 (100.0)	19 (79.2)	.296
Oral DM medication, n (%)	3 (37.5)	14 (58.3)	.423
Insulin treatment, n (%)	7 (87.5)	15 (62.5)	.380

Abbreviations: BMI, body mass index; CCAP, calcified carotid artery plaque; DM, diabetes mellitus; HbA_{1C}, hemoglobin A_{1C}; INR, international normalized ratio.