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Thrombophilia, hypofibrinolysis, and alveolar osteonecrosis of the jaws

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Objectives. Our specific aim in 49 patients (42 women, 7 men) with osteonecrosis of the jaw was to determine whether thrombophilia (increased tendency to intravascular thrombosis) or hypofibrinolysis (reduced ability to lyse thrombi) were associated with this regional avascular necrosis.
Study design. Determinants of thrombosis and fibrinolysis were compared in healthy controls and in 42 women and 7 men who had biopsy-proven idiopathic osteonecrosis of the jaw with severe chronic jaw or facial pain syndromes and failure to respond to conventional medical and dental treatments.
Results. Of the 49 patients, 35 (71%) had thrombophilia or hypofibrinolysis and only 14 were normal. Thrombophilia as a sole coagulation defect was found in 10 patients, 7 with resistance to activated protein C and 3 with low protein C (deficiency of an antithrombotic protein). Hypofibrinolysis with low stimulated tissue plasminogen activator activity and high lipoprotein (a) (an atherogenic, hypofibrinolytic lipoprotein) were found as sole coagulation defects in seven and eight patients, respectively. Ten patients had mixed defects; 7 of these 10 had thrombophilia with resistance to activated protein C. Sinusoidal dilatation was a constant feature in maxillary and mandibular bone biopsies, suggesting venous occlusion with intramedullary hypertension. Marrow fibrosis and occasional fibrin plugs were additional microscopic features believed to impair venous drainage and to contribute to ischemic necrosis of the alveolar bone.
Conclusions. Primary thrombophilia and hypofibrinolysis appear to be common, heritable, pathophysiologic risk factors for idiopathic osteonecrosis of the jaws. These coagulation defects may also contribute to alveolar neuralgia, atypical odontalgia and facial neuralgia, idiopathic trigeminal neuralgia, and to treatment failures so often encountered in patients with alveolar osteonecrosis and disabling chronic facial and jawbone pain syndromes.
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Heritable thrombophilia (increased tendency toward intravascular thrombosis) and hypofibrinolysis (reduced ability to lyse thrombi) appear to be major pathophysiologic causes for idiopathic and secondary osteonecrosis of the femoral head in adults and for Legg-Perthes disease in childhood (pediatric idiopathic osteonecrosis).[1-7] The heritable thrombophilias and hypofibrinolysis are probably rather constant throughout adult life and include the following[1-7]:

1. Low levels of stimulated tissue plasminogen activator (tPA-Fx), the major stimulator of fibrinolysis, is often accompanied by high levels of plasminogen activator inhibitor (PAI-Fx), the major inhibitor of fibrinolysis leading to hypofibrinolysis.
2. Low levels of the antithrombotic proteins C or

S, leading to unopposed prothrombotic effects of factors Va and VIIIa (thrombophilia).

3. Resistance to activated protein C. Activated protein C fails to normally bind an abnormally configured factor Va, leading to unopposed prothrombotic effects of factor Va (thrombophilia).

4. High levels of the atherogenic, hypofibrinolytic lipoprotein, Lp(a).

In children and adults with osteonecrosis of the hip, it has been speculated that thrombophilia and hypofibrinolysis facilitate venous occlusion of the bone by fibrin clots, leading to venous (sinusoidal) hypertension within the cancellous bone.[1-8] Once the "ischemic threshold" is reached, cellular hypoxia presumably gives way to bone and marrow cell death.[1-8] Therapy with stanozolol, an anabolic-androgenic steroid that can normalize PAI-Fx, tPA-Fx, and Lp(a), when given before irreversible segmental collapse of the head of the femur may reverse hypofibrinolysis, facilitate normal venous drainage, and ameliorate osteonecrosis.[4]

Neuralgia-inducing cavitational osteonecrosis (NICO) of the jaw has been previously described[9-12] and has had no uniformly recognized pathoetiologic characteristics. However, on the basis of microscopic anatomy and pathologic findings,[9] it has been speculated that NICO results from thrombosis and subsequent fibrosis of veins and sinusoids responsible for outflow of blood from the jaws. Venous thrombosis then apparently leads to venous occlusion and an increase in intramedullary pressure that eventually results in hypoxia and bone cell death (osteonecrosis).[9] This is often compounded by the prothrombotic effects of local odontogenic infection, endodontic failures, tooth extraction, or endothelial trauma from other alveolar bone surgery.[9]

We studied 49 patients with atypical facial NICO of the jaw. Our specific aim was to evaluate whether, like osteonecrosis of the hip[1-7] and thrombophilia and hypofibrinolysis were common major pathophysiologic risk factors for regional avascular osteonecrosis and fat necrosis of cancellous bone.

MATERIAL AND METHODS

Patients

The 49 patients (42 women, 7 men) had well-documented, biopsy-proven idiopathic osteonecrosis of the jaw with concurrent severe chronic jaw or facial pain syndromes. At the time their coagulation parameters were studied in Cincinnati, all 49 patients had failed to respond to conventional medical and dental treatments including endodontic therapy, dental extraction, and surgical curettage of the diseased bone. Diagnostic and therapeutic biopsy and curettage of the diseased bone were carried out after these and other surgical procedures (sinus surgery, rhizotomy, trigeminal nerve block, radiofrequency neurolysis) had failed to alleviate the disabling facial or jaw pain. The patients were referred from the practices of three endodontic surgeons and one oral and maxillofacial surgeon who have special interests in the diagnosis and management of typical and atypical facial pain. The patients were evaluated in the sequence of their referral without selection bias and were compared to healthy normal controls.

Study protocol, and clinical and dental evaluation

At the initial visit, a detailed medical and family history was systematically obtained including questions focusing on known risk factors for secondary osteonecrosis, such as long-term corticosteroid use, sickle cell trait, alcoholism, traumatic fracture, systemic lupus erythematosus, and dysbaric exposure.[1-3, 7, 8] The patients' history of facial pain and their medical and surgical therapies for facial and jaw pain were systematically recorded. In addition, the patients' histories of dental surgery including endodontic therapy, extractions, bone biopsies, and treatment for odontogenic or osseous infections were provided by the referring oral and endodontic surgeons.

Study protocol, laboratory methods

After an Institutional Research Committee-approved protocol, signed informed consent was obtained. After a 12-hour fast and with the patients seated for 5 to 10 minutes, blood was drawn from the antecubital vein. This was done between the hours of 8 and 10 AM to minimize circadian influence on fibrinolytic activity.[13, 14] After discarding the first 3 ml, blood was collected in 5 ml 0.13 M (3.8%) sodium citrate Vacutainer tubes and immediately placed in wet ice for transport to the laboratory. Laboratory personnel were blinded as to the severity and duration of the patients' osteonecrosis of the jaw. For measures of stimulated tPA-Fx, the major stimulator of fibrinolysis, blood was collected in 5 ml Stabilyte tubes (American Diagnostica, Greenwich, Conn.) containing an acidified citrate anticoagulant solution that preserves the level of tPA activity.[13, 14]

With the patient remaining seated during a standard stimulus (10 minutes of venous occlusion at 100 mm Hg with a blood pressure cuff[1, 13, 14]), citrated blood was again collected (as aforementioned) for measurement of stimulated tPA-Fx. Within 60 minutes of collection, the blood samples were centrifuged at 2000g for 20 minutes at 4° C. Platelet-poor plasma was snap-frozen and stored at –70° C until processed (approximately 1 week).

TPA-Fx[15, 16] (Biopool Spectrolyse [fibrin], American Diagnostica) and PAI-Fx[17] (Biopool Spectrolyse pL, American Diagnostica), the major inhibitor of fibrinolysis, were measured by chromogenic assays.

Protein C[18] (Asserachrom Protein C, American Bioproducts, Parsippany, N.J.) and protein S[19] (Asserachrom Protein S, American Bioproducts) were measured antigenically by enzyme-linked immunosorbent assay. Resistance to activated protein C[21, 21] (activated human protein C, American Diagnostica, and PIT automate, American Bioproducts) was measured functionally by clotting technique (ST4 clot detection system, American Bioproducts).

Lp(a) was measured by immunoprecipitin analysis,[13] and levels ≥25 mg/dl were considered high. Fasting plasma lipids were measured as previously described.[13]

Triglycerides ≥250 mg/dl and LDL cholesterol >160 mg/dl were identified as high, and HDL cholesterol <35 mg/dl was identified as low.[1]

Laboratory personnel were blinded as to the severity and duration of the patient's pain and the time lapsed since osteonecrosis was diagnosed.

Statistical methods

Patients' stimulated tPA-Fx levels were compared with those of 29 adult normolipidemic controls who were sampled during our recent studies of Lp(a) and fibrinolytic activity.[13] Patients' measures of resistance to activated protein C were compared with those of 27 normal healthy hospital and blood bank personnel. Patients' protein C and Lp(a) levels were compared with those of 36 and 90 healthy subjects (spouses and unrelated family members) sampled in family studies of Legg-Perthes disease.[3] It was not possible to obtain all of the measures of coagulation in a single control group or to match controls versus patients, one by one, by age, sex, and race. However, age and race distributions of the controls were very comparable with those of the patients. Moreover, in adults, the major coagulation measures do not differ by age, sex, and race.[1, 4]

Chi-squared analyses[22] were used to compare patients and controls; p values ≤0.05 were considered to be statistically significant.

RESULTS

Clinical and dental characteristics

Mean (standard deviation, SD) age of the 49 patients (42 women, 7 men) was 45 ± 12 years (mean, 45 for women; 46 for men). None of the 49 patients had historic or clinical evidence for diseases that could predispose to secondary osteonecrosis,[1, 2, 5, 6, 23] such as sickle cell trait, alcoholism, systemic lupus erythematosus. Two patients (4%) had major jaw trauma or osteotomy for reconstruction. Eight patients (16%) had, however, received long-term (>1 month) corticosteroid therapy (>10 mg prednisone/day, which could predispose to secondary osteonecrosis[1]) for a variety of medical indications including asthma (n = 2), allergic rhinitis (n = 4), and chronic sinusitis (n = 2). Corticosteroids in these eight patients had not been used, however, to treat autoimmune disease, which could possibly be associated with elevated anti-phospholipid antibodies.[6] The corticosteroid therapy had antedated the diagnosis of osteonecrosis by 15 ± 12 years and not been given as an approach to ameliorate jaw pain in these eight patients. None of the patients had received long-term chlorpromazine, which may be associated with elevated serum antiphospholipid antibodies.

None of the patients had evidence of suppurative osteomyelitis, although seven had at one time or another received intravenous antibiotics as therapy for presumptive osteomyelitis. None of the patients exhibited any signs of active infection at the time that we measured their fibrinolytic and thrombophilic profiles.

The mean ± SD age of onset of severe jaw or atypical facial pain was 40 ± 13 years. The mean (SD) duration of the jaw or atypical facial pain was 7 ± 5 years; the range was 1 to 21 years. All patients had severe chronic facial and jaw pain syndromes, and 80% of them required long-term pain relief with narcotics including oral morphine sulfate and methadone. Twenty patients (41%) were totally disabled by chronic facial or jaw pain. Only 2 of the 49 patients had jaw or facial pain relief after repetitive curettage. Maxillary sinusotomy with antral curettage of chronic inflammatory tissues and polyps had been performed on nine patients (18%) (four patients more than once) with concomitant chronic sinusitis on the side of their facial pain but with only temporary relief.

Well before the diagnosis of osteonecrosis of the jaw but after development of chronic jaw and facial pain and with the goal to reduce disabling pain, seven (14%) patients underwent neurosurgery (alcohol blocks, trigeminal branch rhizotomy) without relief of pain (five patients more than once). No ischemic side effects were reported from these procedures.

Fourteen (33%) of the 42 women took supplemental estrogens; 3 also took progestins.

Histopathologic findings

All patients presented with intramedullary disease that was visibly or tactually abnormal at surgery. The affected marrow was characterized by abundant and multifocal reticular fatty degeneration (marrow fi-

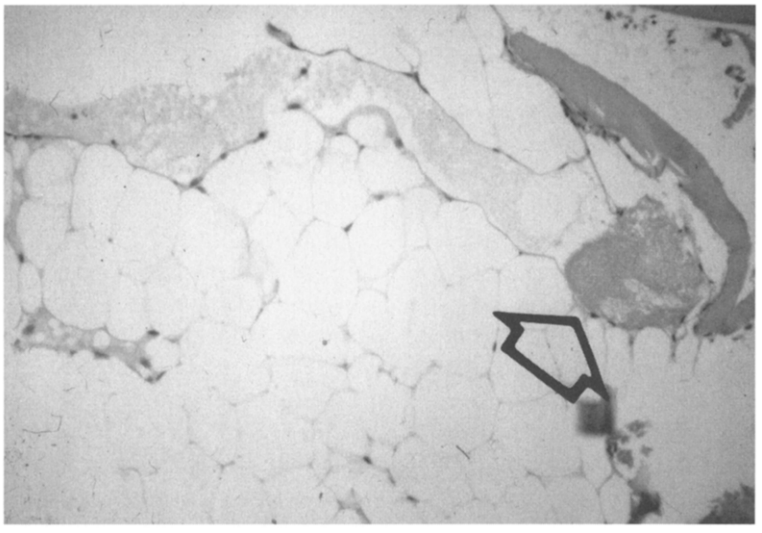

Fig. 1. Sinusoid/vein is seen to be dilated approximately 8 times normal diameter and contains an intravascular plug of fibrin/platelets *(arrow)*. Delaminated bone fragments are seen in the upper right hand corner, but the fatty marrow is otherwise minimally involved at the light microscopic level. (Original magnification ×100.)

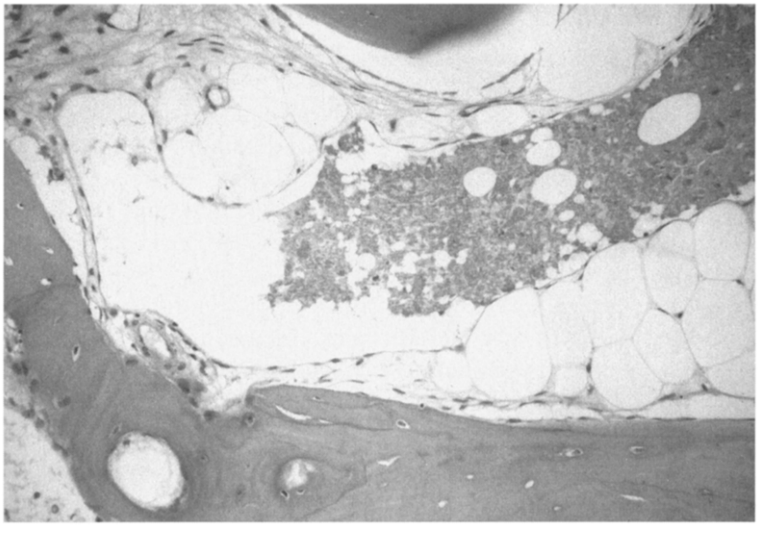

Fig. 2. Photomicrograph shows extremely dilated sinusoid filled with calcific necrotic debris and fat globules presumably forced into the lumen from degenerating tissues surrounding the vascular channels. Numerous osteocytes are missing from the trabeculum in the lower portion of the photograph. (Original magnification ×100.)

brosis, fibroplasia), with or without small numbers of lymphocytes and plasma cells. Neutrophils, eosinophils, and histiocytes were rare. Remaining adipocytes varied in size but were usually small and surrounded by an amorphous eosinophilic material in addition to the fibrosis. Marrow sinusoids were usually dilated but not filled with erythrocytes. Marrow vessels occasionally contained fibrin/platelet thrombi or fat globules (Figs. 1 and 2). Adjacent bone demonstrated focal loss of osteocytes, much more than would be seen in routine preparations of normal bone, microcracking, actual delamination, and prominent reversal (cement) lines.

Marrow necrosis was also a characteristic feature of the tissue samples, often with the formation of "oil cysts" and occasionally associated with areas of presumed microinfarction with numerous extravasated, pale-staining, or "ghost" erythrocytes. Calcific fat

Table I. Forty-nine patients with osteonecrosis of the jaw

Patient coagulation abnormality group	*Coagulation abnormalities*			*Coagulation abnormalities admixed with primary coagulation defect*			
	Total	*Alone*	*Mixed*	*APCR*	*High Lp(a)*	*Low tPA-Fx*	*Low C*
Resistance to activated protein C	14	7	7	—	3	3	2
High Lp (a)	14	8	6	2	—	2	2
Low stimulated tPA-Fx	11	7	4	3	1	—	0
Low protein C	7	3	4	2	2	0	—
No abnormalities	14	—	—	—	—	—	—

necrosis was often seen in aggregated globules that contained slivers or shards of delaminated, resorbing, nonviable bony trabeculae (NICO globules); these are virtually pathognomonic for ischemic osteonecrosis.[9] Even when NICO globules were not present, large areas of marrow often contained calcific necrotic detritus. In the typical case, very little normal marrow was present.

Thrombophilic and hypofibrinolytic defects

Of the 49 patients, only 14 (29%) (11 women, 3 men) had normal values for resistance to activated protein C, protein C, protein S, Lp(a), and stimulated tPA-Fx, whereas 35 (71%) of the patients had one or more coagulation defects (Tables I and II). Of these 35 patients, 25 had a single coagulation defect (7 with resistance to activated protein C, 3 with low protein C, 7 with low stimulated tPA-Fx, 8 with high Lp(a) [Tables I and II). Ten patients had mixed coagulation defects (Table II). In 7 of these 10 patients, resistance to activated protein C was accompanied by another coagulation defect (Table II).

Of the 35 NICO patients with thrombophilia/hypofibrinolysis (Table II), 2 had extraosseous evidence of thrombosis (deep venous thrombosis of the legs), none had osteonecrosis of the femoral head or other bones. There was a history of thrombosis in 12 (34%) of the 35 families of the 35 NICO patients with thrombophilia/hypofibrinolysis and a history of osteonecrosis of the hip in 7 (20%) of these families.

Resistance to activated protein C

There were 14 patients with resistance to activated protein C (APCR) (Tables I and II), a thrombophilic trait that was much more common in patients (29%) than in controls (0%), $X^2 = 9.46$, $p = 0.002$. Of the 14 patients with resistance to activated protein C, 7 had this defect as their sole coagulation defect; in the other 7 patients, APCR was accompanied by low protein C in 2, by low stimulated tPA-Fx in 3, and by high Lp(a) in 3 (Tables I and II).

Of the 14 patients with APCR, 12 were women; 7 (58%) were taking supplemental estrogens. The 12 women with APCR were more likely to be taking estrogens (58%) than were the 11 women with no thrombophilic/hypofibrinolytic traits (2 of 11, 18%) ($X^2 = 3.9$, $p = 0.05$), or the 30 woman with osteonecrosis who did not have resistance to activated protein C (7 of 30, 23%) ($X^2 = 4.7$, $p = 0.03$).

Low protein C

Seven patients had low protein C, a deficiency of an antithrombotic protein that was much more common in patients (14%) than in controls (0%) ($X^2 = 5.6$, $p = 0.018$. Of the seven patients with low protein C, three had this trait as a sole coagulation defect, whereas four had low protein C and a second coagulation defect (two with high Lp(a), two with APCR (Tables I and II).

High Lp(a)

Fourteen patients, 29% of the osteonecrosis cohort, had high Lp(a) (Table I) not significantly greater ($p > 0.1$) than controls (20%). Of these 14, 8 had high Lp(a) as a sole coagulation defect, whereas 6 had a second coagulation defect (2 with APCR, 2 with low protein C, 2 with low stimulated tPA-Fx) (Tables I and II).

Low stimulated tPA-Fx

Eleven patients had low stimulated tPA-Fx (Table I), a hypofibrinolytic trait that was slightly but not significantly more common in patients (22%) than in controls (7%) ($X^2 = 3.17$, $p = 0.075$). In seven of these patients, the low stimulated tPA-Fx was the sole coagulation defect, whereas three had concurrent resistance to activated protein C and one had high Lp(a) (Tables I and II).

Patients with neither thrombophilia nor hypofibrinolysis

Fourteen patients (11 women, 3 men) had no coagulation defects; they had normal APCR, Lp(a), protein C, protein S, stimulated tPA-Fx, and PAI-Fx

Table II. Forty-nine patients with osteonecrosis of the jaw

				Normal range[1-3, 5, 6]					
Age	*Sex*	*ID*	*Group*	*APCR ≥2.0*	*Lp (a) <25 mg/dl*	*PC-Ag >70%*	*tPA-Fx >2.28 IU/ml*	*PAI-Fx <26.9 U/ml*	*PS-Ag >70%*
55	F	9	APCR	**1.590**	1	89	2.60	2.90	110
45	F	12	APCR	**1.890**	17	81	8.49	15.40	73
51	F	38	APCR	**1.441**	1	140	6.10	13.00	100
66	F	42	APCR	**1.980**	17	99	14.00	21.60	95
36	F	44	APCR	**1.500**	7	130	8.30	9.00	80
41	F	45	APCR	**1.890**	6	92	2.40	11.10	79
28	F	49	APCR	**1.530**	1	87	3.70	12.30	100
45	M	2	High Lp (a)	2.041	**74**	70	6.74	8.80	134
52	F	10	High Lp (a)	2.294	**45**	130	10.38	9.40	120
45	F	19	High Lp (a)	2.667	**33**	80	10.62	1.90	126
49	F	24	High Lp (a)	2.970	**26**	126	11.55	6.50	85
45	F	33	High Lp (a)	2.300	**85**	132	6.00	17.60	110
36	F	36	High Lp (a)	—	**38**	116	7.32	8.80	120
41	F	37	High Lp (a)	2.177	**46**	98	5.59	10.60	87
74	F	39	High Lp (a)	2.220	**35**	134	9.70	23.80	170
27	F	1	Low C	2.474	1	**57**	11.41	6.70	140
38	F	17	Low C	2.570	1	**60**	8.51	7.70	76
39	F	21	Low C	2.597	14	**50**	11.90	6.20	85
51	F	15	Low tPA	2.372	1	88	**0.53**	**40.00**	144
29	F	16	Low tPA	2.571	1	110	**0.31**	**69.00**	130
35	F	27	Low tPA	2.430	10	140	**0.37**	**55.80**	130
37	F	28	Low tPA	2.620	6	140	**1.74**	18.90	96
34	F	29	Low tPA	2.750	1	89	**1.71**	21.40	90
74	M	31	Low tPA	2.640	14	138	**0.31**	23.20	160
31	F	34	Low tPA	2.362	1	77	**2.18**	3.70	91
37	F	11	Mixture	2.410	**35**	**67**	2.50	1.80	**66**
41	F	18	Mixture	**1.945**	11	**53**	11.65	8.00	75
22	M	22	Mixture	**1.800**	21	**60**	4.70	12.10	80
48	F	30	Mixture	2.388	**94**	108	**2.19**	18.00	80
37	F	40	Mixture	**1.490**	11	140	**1.30**	12.90	126
46	F	41	Mixture	**1.700**	27	98	3.30	13.00	130
63	F	43	Mixture	**1.890**	1	132	**0.90**	17.40	140
49	M	46	Mixture	**1.800**	**56**	114	**1.50**	24.40	156
40	F	47	Mixture	2.600	**45**	68	5.70	25.30	100
58	F	48	Mixture	**1.570**	**39**	116	3.70	18.60	100
61	F	3	Normal	2.560	1	73	9.53	1.80	87
33	M	4	Normal	2.240	1	91	3.40	39.60	82
60	M	5	Normal	2.600	18	88	6.33	15.40	120
56	F	6	Normal	2.080	21	104	6.66	12.20	166
45	F	7	Normal	2.560	1	90	4.55	11.60	87
24	F	8	Normal	2.198	1	85	15.06	5.70	92
39	M	13	Normal	2.810	7	114	9.26	17.40	126
67	F	14	Normal	2.620	6	89	11.80	7.60	90
38	F	20	Normal	2.626	12	104	5.80	16.10	140
46	F	23	Normal	2.960	11	87	2.44	18.40	89
56	F	25	Normal	2.750	18	114	4.64	18.00	140
41	F	26	Normal	2.559	17	144	7.49	26.40	220
38	F	32	Normal	2.750	18	104	3.38	7.40	95
50	F	35	Normal	2.380	10	200	2.44	10.70	198

Abnormal values in bold.

(Tables I and II). These 14 patients did not differ ($p > 0.1$) from the 35 patients who had one or more coagulation defects with respect to the percentage disabled by their osteonecrosis (36% versus 43%), the percentage taking narcotics (79% versus 80%), or the percentage who had taken corticosteroids >1 month (29% versus 25%). Two of the 11 women (18%) with neither thrombophilia nor hypofibrinolysis were taking estrogens; this is fewer but not significantly less than the 13 (42%) of 31 other women with a coagulation defect who were taking estrogens ($X^2 = 2.0$, $p = 0.16$).

Long-term (≥1 month) corticosteroid therapy

Of the eight patients who had received corticosteroids for ≥1 month (at a dose ≥10 mg prednisone/day), a stimulus for secondary osteonecrosis,[1] three had APCR or low protein C, three had high Lp(a) or low tPA-Fx, and two had no coagulation defects. Thus there were no predominant coagulation defects ($p > 0.1$) among corticosteroid users.

Lipids and lipoprotein cholesterols

The percentage of patients with high triglyceride (≥250 mg/dl), low HDL cholesterol (<35 mg/dl), or high LDL cholesterol (≥160 mg/dl) did not differ ($p > 0.1$) between the four groups of patients with coagulation defects and those without defects. Overall, the prevalence of high triglycerides (12%), low HDL cholesterol (8%), or high LDL cholesterol (14%) did not differ significantly from that expected, 10% for each lipid.

DISCUSSION

On the basis of our previous findings[1-6] and those of others[7] that thrombophilia and hypofibrinolysis appear to be major causes for osteonecrosis of the hip in adults and in children, we speculated that we would observe a similar mix of coagulation disorders in patients with idiopathic osteonecrosis of the jaw. We had previously found coagulation disorders in 87% of 30 adults with osteonecrosis of the hip.[1] Nine of 12 patients with idiopathic osteonecrosis had exceptionally high levels of the major inhibitor of fibrinolysis, PAI-Fx, and could not normally elevate the major stimulator of fibrinolysis, tPA-Fx, after venous occlusion for 10 minutes at 100 mm Hg (familial hypofibrinolysis).[1] Three of the 12 patients with idiopathic osteonecrosis had both normal PAI-Fx and normal stimulated tPA-Fx. These 3 patients and 14 of the 18 patients with secondary osteonecrosis[1] had high levels (>20 mg/dl) of Lp(a), an atherogenic hypofibrinolytic lipoprotein.[13, 14] We concluded that hypofibrinolysis mediated by high PAI-Fx appeared to be a common cause of idiopathic osteonecrosis, whereas high Lp(a) apparently played a major etiologic role in secondary osteonecrosis.[1]

Subsequently we studied two groups of children (8 and 44 patients) with idiopathic osteonecrosis of the hip (Legg-Perthes disease).[2, 3, 24] In the group of eight, 63% of the patients had a coagulation abnormality; three have low protein C, one had low protein S, and one had hypofibrinolysis.[2] In the group of 44, we found that 82% of the children had heritable coagulation abnormalities including resistance to activated protein C, low protein C or S, high Lp(a), or low tPA-Fx with high PAI-Fx.[3, 24]

In the current study, 71% of 49 patients with osteonecrosis of the jaw had coagulation abnormalities, compared with 87% of adults[1] and 63% and 82% of two groups of children with osteonecrosis of the hip.[2, 3, 24] Of the 49 patients with osteonecrosis of the jaw, 29% had resistance to APCR versus 0% in controls ($p = 0.002$), and 14% had low protein C versus 0% in controls ($p = 0.018$). Hence, two heritable[2, 21] thrombophilic traits, resistance to activated protein C and low protein C, were associated with osteonecrosis of the jaw. Of the women with resistance to activated protein C, 58% were taking supplemental estrogens, a larger percentage than the 18% of women with osteonecrosis of the jaw but no coagulation defect ($p = 0.05$). Although it is possible that supplemental estrogens might produce acquired APCR, it is more likely that thrombophilia in patients with heritable APCR is amplified by concurrent estrogen therapy.[25] In patients with underlying heritable APCR, we speculate that supplemental estrogen may amplify[25] the APCR-mediated increased tendency to thrombosis,[21] increasing the likelihood of osteonecrosis and other manifestations of thrombosis.

In our previous studies, we did not have the laboratory assay for APCR available. Recently,[24] we found that 15 (34%) of 44 children with Legg-Perthes disease had APCR. APCR was the sole coagulation defect in 20% of these 15 children; APCR was often accompanied by low protein C, low protein S, high Lp(a), and low tPA-Fx.[24] These findings in children with Legg-Perthes disease[24] were similar to the current study in which APCR was found in 29% of patients with osteonecrosis of the jaw and was often accompanied by low protein C, by high Lp(a), or by low tPA-Fx.

Although not statistically significant, hypofibrinolysis (low stimulated tPA-Fx) was more likely to

occur in the patients with osteonecrosis of the jaw than in controls (22% versus 7%, $p = 0.075$). In 3 of the 11 patients with low tPA-Fx, low tPA-Fx was accompanied by high levels of PAI-Fx, the major inhibitor of fibrinolysis. Two of these 3 patients also had high levels of triglyceride (367 and 422 mg/dl), compared with those reported by Van Veldhuizen[7] and consistent with our previous observation that triglyceride levels are major independent determinants of PAI-Fx, and through this relationship, of hypofibrinolysis.[13]

Fourteen patients had high Lp(a), an atherogenic putatively hypofibrinolytic lipoprotein.[13, 14] However, the patients with osteonecrosis of the jaw were not more likely than controls to have high Lp(a) (≥25 mg/dl, 29% versus 20%). We speculate that the local intramedullary hypofibrinolytic effect of Lp(a) might be amplified in the closed space of the jawbone or femur,[1, 2] whereas systemic measures of fibrinolytic activity may, therefore, still be normal in patients with high Lp(a).[13, 14]

Preliminary studies of anticardiolipin antibodies (aCLA) have been completed in 39 of these 49 patients and in all 14 patients without other thrombophilic or hypofibrinolytic traits.[6] Eight of these 14 patients (57%) had elevated aCLA (1 with high IgM alone, 2 with high IgG alone, 4 with high IgA alone, and 1 with high IgA and IgG).[6] Because high aCLA are thrombophilic,[6] only 6 (12%) of the 49 patients with osteonecrosis of the jaws had neither thrombophilic nor hypofibrinolytic traits. ACLA were high in 12 (31%) of the 39 patients in whom they were measured.[6]

All 49 patients failed to respond to conventional endodontic or exodontic therapy, and only 2 had lasting pain relief (>1 year) after curettage of the diseased cancellous bone. We speculate that chronic inflammation[26-30] and immunogenic reactions to xenobiotics[31-33] in jawbones could potentiate the putative intramedullary thrombophilic or hypofibrinolytic traits of our patients. These adverse conditions are not usually found in other bones, and when coupled with underlying coagulation disorders, may amplify thrombosis and hypofibrinolysis thus perpetuating osteonecrosis.

Osteonecrosis of the alveolar bone of the jaw, as in the current study, appears to have a close and putatively causal association with chronic facial pain[9]; when undiagnosed it can leave the patient with a sense of hopelessness and even hysteria. Long-term chronic facial pain arising from an osteonecrotic lesion in the jaw might induce reactive depression. Severe depression and thoughts of suicide were common in this cohort. The pain associated with osteonecrosis of the jaws is often medically catastrophic; 41% of our patients were totally disabled by chronic jaw and facial pain and 80% required daily narcotic therapy for pain relief. It is exceptionally difficult to determine how much of the chronic facial pain in patients with biopsy-proven osteonecrosis of the jaw is pathoanatomic and how much might be related to or caused by depression, hysteria-conversion reactions, or even malingering.

Although many of our patients had undergone psychological counseling and psychotherapy before seeing us, we did not require psychiatric evaluation as part of our work-up. Psychotherapy and psychological support networks are often necessary for long-term comprehensive management when the pain is refractory to treatment.

Long-term follow-up studies[10] report 73% success in relieving the pain associated with osteonecrosis when surgical curettage of the diseased jawbone is carried out in a prescribed manner. Patients with NICO who do not experience pain relief after surgical curettage might have a chronic predisposition to microcirculatory disturbances because of the aforementioned risk factors[9] for secondary osteonecrosis, or because of an underlying thrombophilia or hypofibrinolysis, as detected in 71% of our patients. In these cases, surgical curettage of the jawbone may improve the pain temporarily, but as long as there is a systemic thrombophilic/hypofibrinolytic risk factor present, we speculate that the venostasis is likely to recur as the cancellous bone attempts to regenerate. In addition, if surgical treatment is performed many years after the onset of symptoms, alterations in the nervous system may decrease the likelihood of pain relief from surgery.[34, 35]

Our current study demonstrated that thrombophilia or hypofibrinolysis or both were present in 35 (71%) of 49 patients with "idiopathic" osteonecrosis of the jaws, patients whose facial pain was not relieved by medical therapy, surgical curettage, and in some cases not even by neurosurgical ablative procedures. Of the 14 (29%) patients who were "normal" (had no coagulation defects), 8 (57%) were found to have high levels of anticardiolipin antibodies (aCLA) in new, preliminary data from this cohort.[6] If the high aCLA levels are confirmed by follow-up and family studies,[6] then 43 of 49 (88%) of this cohort would have thrombophilic or hypofibrinolytic traits. We postulate that thrombophilic and hypofibrinolytic risk factors in osteonecrosis of the jaw function in a fashion similar to their role as pathophysiologic risk factors for osteonecrosis of the hip in adults and in children.[1-8] In

the presence of increased likelihood of thrombosis or reduced clot lysis, it appears that the vascular networks of the hip[1, 2] or jaws are unable to reinitiate normal blood perfusion in such a way as to support normal new bone formation. As summarized by Bouquot,[9]

> the similarity between NICO and ischemic osteonecrosis is so strong as to lend considerable credence to the theory that NICO also results from poor vascular circulation of the jaws, albeit often compounded by a local odontogenic infection. . . . There is evidence that chronic odontogenic infections . . . can initiate intraosseous ischemia via increased intraosseous edema and collapse of venous drainage vessels, in addition to other local damage from the release of inflammatory mediators. . . . There is also evidence that chronic intraosseous ischemia produces the initial compromised state and a superimposed odontogenic infection promotes a more active necrosis of the bone.[9]

Better recognition of the histopathologic findings of osteonecrosis, as in this and other[36] studies, should stimulate diagnostic evaluation of thrombosis and fibrinolysis.

If we presume that thrombophilia and hypofibrinolysis are part of the etiologic framework for NICO as well as for adult and pediatric idiopathic osteonecrosis,[1-7] it may be possible to extrapolate from the very limited experience with osteonecrosis of the hip[4] and to reverse the Lp(a), high PAI, or low protein C mediated coagulation defects with stanozolol. In the early stages of osteonecrosis,[4] stanozolol therapy may normalize fibrinolysis, and hence facilitate resumption of normal venous drainage, reduction of intramedullary venous hypertension, normal osseous oxygenation, and cessation of bone necrosis. In cases of long duration, stanozolol therapy[4] may prove to be an important adjunct to jaw surgery if taken for several months before and after local curettage or block resection of the compromised bone. Because resistance to activated protein C can be treated with warfarin sodium (Coumadin),[21] it may be possible to prevent or ameliorate osteonecrosis of the jaw in patients with this heritable trait and to encourage normal regeneration of bone. In aggregate, these medical therapies might, speculatively, reduce the extraordinary chronic severe jaw and facial pain syndromes experienced by patients with NICO. In addition to stanozolol[4] or Coumadin[21] when indicated, additional consultation with a neurosurgeon or oral surgeon skilled in diagnostic local anesthetic blocks should help determine on which trigeminal nerves to perform a local alcohol block, cryotherapy, or peripheral neurectony. Careful consideration of risk and benefit should be given to neurosurgery procedures that denervate already vascularly compromised trigeminal tissues because of the possibility of enlarging the ischemic zone.[37-39]

The intramedullary environment of the jaws is unique in the human skeleton because of the presence of teeth and their supporting structures. The fact that the jaw contains large sensory nerve trunks and marrow tissues that are commonly infected by a wide variety of pathogenic microorganisms adds further to its uniqueness. Distinct regions of alveolar bone may undergo osteonecrosis as the ischemic threshold is exceeded in the cellular elements of the cancellous bone.[9, 10] Both systemic and local risk factors may interfere with the microcirculation and nutrition of the trabecular bone and the sensory nerve trunks encased within. Primary osteonecrosis is often termed *idiopathic* when the cause for the avascular necrosis is unknown. Our current study suggests that thrombophilia and hypofibrinolysis may have an etiologic role for the idiopathic osteonecrosis seen in many patients with NICO in a fashion similar to their role as pathophysiologic risk factors for idiopathic femoral head necrosis in adults and children.[1-8] Thrombophilia and hypofibrinolysis may contribute not only to the genesis of atypical facial neuralgia but also to the treatment failures so often encountered in such patients.

REFERENCES

1. Glueck CJ, Freiber R, Glueck HI, et al. Hypofibrinolysis: a common, major cause of osteonecrosis. Am J Hematol 1994;45:156-66.
2. Glueck CJ, Glueck HI, Greenfield D, et al. Protein C and S deficiency, thrombophilia, and hypofibrinolysis 1994;35: 383-8.
3. Glueck CJ, Crawford A, Roy D, Frelberg R, Glueck H, Stroop D. Association of antithrombotic factor deficiencies and hypofibrinolysis with Legg-Perthes disease. J Bone Joint Surg Am 1996;78:3-13.
4. Glueck CJ, Freiberg R, Glueck HI, Tracy T, Stroop D, Hamer T. Idiopathic osteonecrosis, hypofibrinolysis, high plasminogen activator inhibitor, high lipoprotein (a), and therapy with Stanozolol. Am J Hematol 1995;48:213-2.
5. Glueck CJ, Glueck HI, Mieczkowski L, Tracy T, Speirs J, Stroop D. Familial high plasminogen activator inhibitor with hypofibrinolysis: a new pathophysiologic cause of osteonecrosis? Thrombosis Haemostasis 1993;69:460-5.
6. Gruppo R, Glueck CJ, MaMahon RE, et al. Anticardiolipin antibodies and osteonecrosis of the jaws [abstract]. J Invest Med 1995;43:459.
7. Van Veldhuizen PJ, Neff J, Murphey MD, Bodensteiner D, Skikne BS. Decreased fibrinolytic potential in patients with idiopathic avascular necrosis and transient osteoporosis of the hip. Am J Hematol 1993; 44:243-8.
8. Jones JP. Intravascular coagulation and osteonecrosis. Clin Orthop 1992;277:41-54.
9. Bouquot JE, Roberts AM, Person P, Christian J. Neuralgia-inducing cavitational osteonecrosis (NICO) osteomyelitis in

224 jawbone samples from patients with facial neuralgia. Oral Surg Oral Med Oral Pathol 1992;73:307-19.
10. Bouquot JE, Christian J. Long-term effects of jawbone curettage on the pain of facial neuralgia. J Oral Maxillofac Surg 1995;53:387-97.
11. Chang CC, Greenspan A, Gershwin ME. Osteonecrosis: current perspectives on pathogenesis and treatment. Semin Arthritis 1993;23:47-69.
12. Chuong R, Piper MA. Avascular necrosis of the mandibular condyle-pathogenesis and concepts of management. Oral Surg Oral Med Oral Pathol 1993;75:428-32.
13. Glueck CJ, Glueck HI, Tracy T, Speirs J, McCray C, Stroop D. Relationships between lipoprotein(a), lipids, apolipoproteins, basal and stimulated fibrinolytic regulators, and D-dimer. Metabolism 1993;42:236-46.
14. Glueck CJ, Glueck BI, Tracy T, Speirs J, McCray C, Stroop D. Inheritance conjointly contributing to fibrinolysis and hyperlipidemia. Metabolism 1993;42:1410-9.
15. Rånby M, Norrman B, Wallén P. A sensitive assay for tissue plasminogen activator. Thromb Res 1982;27:743-9.
16. Rånby M, Sundell IB, Nilsson TK. Blood collection in strong acid citrate anticoagulant used in a study of dietary influence on basal tPA activity. Thromb Haemost 1989;62:917-22.
17. Chmielewska J, Rånby M, Wiman B. Evidence for rapid inhibitor to tissue plasminogen activator in plasma. Thromb Res 1983;31:427-36.
18. Amiral J, Boyer C, Rothchild C, Wolf M. Determination of protein C by an immunoenzymatic assay. In: Witt I, ed. Protein C: biochemical and medical aspects. Berlin: Walter de Gruyter, 1983:67-9.
19. Amiral J, Adam M, Plassart V, Minard F, Vissac AM. Immunoassays for the measurement of protein S. In: Gaffney PJ, ed. Fibrinolysis: current prospects. London: John Libbey, 1988: 125-8.
20. Sochynsky CL, Joyner KA, Ortel TI. Clinical note: a method for testing APC resistance in thrombotic patients. Am Clin Lab 1994;13:26-7.
21. Svensson PJ, Dahlback B. Resistance of activated protein C as a basis for venous thrombosis. N Engl J Med 1994;330:517-22.
22. Sndedcor GW, Cochran WG. Statistical methods. 7th ed. Ames, Iowa: Iowa State University Press, 1980:1-507.
23. Mankin Jt{. Nontraumatic necrosis of bone (osteonecrosis). N Engl J Med 1992;326:1473-9.
24. Glueck CJ, Crawford A, Roy D, Freiberg R, Glueck H, Stroop D. Familial thrombophilia, hypofibrinolysis, and hiqh lipoprotein(a): pathophysiologic etiologies of Legg-Perthes disease [Abstract]. J Invest Med 1005;43(suppl2):233.
25. Glueck CJ, McMahon RE, Bouquot JE, et al. Resistance to activated protein C, estrogens, and osteonecrosis of the jaws [Abstract]. J Invest Med 1995;43(suppl2):234.
26. Barkhodar RA, Hussain MZ, Hayashi C, Detection of interleukin-1 beta in human periapical lesions. Oral Surg Oral Med Oral Pathol 1992;73:334-6.
27. Hargreaves KM, Troullos ES, Dionne RA, Schmidt EA, Schafer SC, Joris JL. Bradykinin is increased during acute and chronic inflammation: therapeutic implications. Clin Pharmacol Ther 1988;44:613-21.
28. Lerner UH. Regulation of bone metabolism by the kallikrein-kinin system, the coagulation cascade, and the acute phase reactants. Oral Surg Oral Med Oral Pathol 1994;78:481-93.
29. Safavi KE, Rosscuendo EF. Tumor necrosis factor identified in periapical tissue exudates of teeth with apical periedontitis. J Endodon 1991;17:12-3.
30. Wannafors K. Vascular changes after experimentally induced inflammation in the mandible. Int J Oral Mxillofac Surg 1989;18:79-82.
31. Kawakami T, Nakamura C, Eda S. Effects of the penetration of a root canal filling material into the mandibular canal: 1. Tissue reaction to the material. 2. changes in the alveolar nerve tissue. Endod Dent Traumatol 1991;15:539-43.
32. Hata G, Nishikana I, Kawazoe S, Toda T. Systemic distribution of ^{14}C labelled formaldehyde applied in the root canal following pulpectomy. J Endodon 1989;15:539-43.
33. Spangberg LSW. N2, formaldehyde, and milk. Oral Surg Oral Med Oral Pathol 1994;77:551.
34. Dray A, Urban L, Dickenson A. Pharmacology of chronic pain. Trends Pharmacol 1994;15:190-7.
35. Dubher R. Neuronal plasticity and pain following peripheral tissue inflammation or nerve injury. Proceedings of the 6th World Congress on Pain. In: Bond MR, Charlton JE, Woolf CJ, eds. Pain research and clinical management. Vol 4. Amsterdam, The Netherlands: Elsevier, 1991:263-76.
36. Sweet DE, Madewell JE. Osteonecrosis: pathogenesis. In: Resnick D, ed. Diagnosis of bone and joint disorders. 3rd ed. Philadelphia: WB Saunders, 1995:3445-9.
37. Fardy MJ, Patton DW. Complications associated with peripheral alcohol injections in the management of trigeminal neuralgia. Br J Oral Maxillofac Surg 1994;32:387-91.
38. Goodnight JW, Calcaterra T. Trigeminal trophic syndrome: a report of two cases and review. Am J Otol 1994;15:219-22.
39. Dunlap CL. Post-rhizotomy periodontal atrophy. J Periodontal 1995;66:301-2.

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