tional Assessment of Anorexia/Cachexia Therapy (FAACT); and performance status via Karnofsky Performance Scale (KPS). Patients were randomized to receive either celecoxib 200 mg po bid or placebo for 3 weeks. Three weeks later, each patient returned for the same evaluation as on day 1. In this pilot study, no nutritional intervention was made. **Results:** Eleven patients have completed the study thus far. Seven have received placebo, while four have received active drug. Eight patients have head and neck cancers and three patients have cancer of the GI tract. All were male, with a mean age of 59.1 years. Interim unblinded analysis of the data reveals that, on average, patients taking celecoxib experienced weight gain of 1.0 kg (SE = 1.33), body mass index (BMI) increase of 0.31 (SE = 0.45), lean body mass percent (LBM%) increase of 0.28 (SE = 2.81), and improvement of FAACT score of 10 points (SE = 4). Those taking placebo experienced, on average, weight loss of 1.0 kg (SE = 1.63), BMI decrease of 0.56 (0.68), LBM% drop of 0.04% (SE = 1.60), and no improvement in FAACT score. **Conclusions:** Promising initial trends were seen in the administration of celecoxib to patients with cancer cachexia in this study, including gains in weight, BMI, LBM%, and QoL score. Future studies may examine cytokine and CRP levels and may include a nutritional intervention in studying the effect of anti-inflammatory therapy on cancer cachexia.

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AMAUROSIS FUGAX CAUSED BY THROMBOPHILIA-HYPOFIBRINOLYSIS IN CASES WITHOUT CAROTID ATHEROSCLEROSIS: THERAPY WITH COUMADIN-LOVENOX OR FOLIC ACID-B_6-B_{12} PREVENTS SUBSEQUENT TRANSIENT MONOCULAR PARTIAL BLINDNESS. C.J. Glueck, K. Golnik, P. Wang, Cholesterol Center, Jewish Hospital, Department of Ophthalmology, University of Cincinnati Medical Center, Cincinnati, OH.
In 8 men and 9 women (age 60 ± 14, all white) without ipsilateral atherosclerotic carotid plaque and with no other known causes of amaurosis fugax (AF), whose AF was associated with thrombophilia-hypofibrinolysis, we hypothesized that case-specific thromboprophylaxis (Coumadin-Lovenox, folic acid [5 mg]-B_6 [100 mg]-B_{12} [2,000 µg], aspirin, cessation of exogenous estrogens, glucophage [2.5 g]) would prevent subsequent episodes of transient monocular partial or total blindness. All 17 cases had ≥ 1 thrombophilic-hypofibrinolytic disorder thought to be etiologic for AF. Seven cases had MTHFR C677T homozygosity or C677T-A1298C compound heterozygosity, 5 4G4G PAI-1 homozygosity, 4 high factor VIII, 4 lupus anticoagulant, 4 the platelet glycoprotein PL A1/A2 mutation, 2 low free protein S, 2 high plasminogen activator inhibitor activity (PAI-Fx), 1 V Leiden heterozygosity, 1 prothrombin gene (PTG) heterozygosity, and 1 protein C deficiency. In 4 cases on Coumadin for 16,16, 21, and 98 months (1 PTG heterozygote, 1 protein C deficient [41%], 1 free protein S deficient [53%] with high factor VIII [157%], and 1 with high factor VIII [207%]), AF resolved, usually within 1 month of starting Coumadin, and the patients remained asymptomatic provided that the INR remained 2.5 or higher. In 1 case with low free protein S (28%), treated for 8 months of pregnancy and 1 month postpartum on Lovenox 80 mg/day, AF disappeared within 1 week, and she remained asymptomatic. In 3 cases with MTHFR C677T homozygosity treated with folic acid-B_6-B_{12} for 10, 15, and 29 months, AF resolved, usually within 1 month of starting therapy, and has not recurred. AF stopped within 1 month in 2 cases (1 high factor VIII 157%, 1 PAI-1 4G4G, PL A1/A2) when exogenous estrogens-SERMS were discontinued and has not recurred. The frequency of AF events was reduced in 2 cases on aspirin alone (1 PL A1/A2, I high VIII 157%) and AF events have remained less frequent over 5 and 11 months on aspirin. In 1 case with hypofibrinolysis (4G4G PAI-1 polymorphism, high PAI Fx, 31.7 IU/mL) treated with Glucophage (2.55 g/day), symptoms resolved within 1 month and have not recurred in 9 months on Glucophage. When AF occurs in the absence of carotid artery atherosclerosis or other known causes of AF, thrombophilia and/or hypofibrinolysis are nearly universal, reversible pathoetiologies.

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STROMELYSIN-1 5A/6A AND eNOS T-786C POLYMORPHISMS, MTHFR C677T AND A1298C MUTATIONS, AND CIGARETTE-CANNABIS SMOKING: A PILOT STUDY OF GENE-ENVIRONMENT PATHOPHYSIOLOGICAL ASSOCIATIONS WITH BUERGER'S DISEASE. C.J. Glueck, M. Haque, M. Winiarska, S. Dharashivkar, R.N. Fontaine, B. Zhu, P. Wang, Cholesterol Center, Jewish Hospital, Cincinnati, OH.
Buerger's disease (BD) etiologies are poorly understood. Beyond smoking cessation, medical-surgical treatments have limited success. We hypothesized that mutations associated with arterial vasospasm (stromelysin-1 5A/6A, eNOS T-786C) and C677T-A1298C methylenetetrahydrofolate reductase (MTHFR) interacted with cigarette-cannabis smoking, reducing vasodilatory nitric oxide (NO), promoting arterial spasm-thrombosis. Of 19 smoking BD patients (13 men [2 siblings], 6 women, 18 Caucasian, 1 African American), compared to 200 healthy Caucasian controls, BD patients were more likely to have 6A6A stromelysin-1 homozygosity (7/19 [37%] vs 46/200 [23%]) and to have eNOS T-786C homozygosity (3/19 [16%] vs 22/200 [11%]), but these patient-control differences were not significant, $p = .4$, 0.5. C677T MTHFR homozygosity or compound C677T-A1298C heterozygosity did not differ in patients vs controls (6/19 [32%] vs 70/200 [35%]), $p = .8$. In 9 patients who stopped and 1 who continued smoking, all stromelysin-1 5A/6A and/or eNOS heterozygotes-homozygotes, lower limb gangrenous ulcers, and intractable ischemic rest pain with arterial occlusion progressed despite conventional medical therapy, threatening amputation. In these 10 patients, to increase vasodilatory NO via endothelial NO synthase, L-arginine (15 g/day) was given, along with folic acid 5 mg, vitamin B_6 (100 mg), and B_{12} (2,000 µg/day) to optimize homocysteine metabolism and reduce asymmetric dimethylarginine, a NO synthase inhibitor. Unexpectedly quickly and strikingly, within 8 weeks to 8 months on L-arginine-folic acid, all 10 treated patients improved with uniform pain reduction, ulcer healing, and in 5, full recovery of previously absent peripheral pulses. In smokers homo-heterozygous for stromelysin-1 5A/6A, eNOS T-786C, and C677T-A1298C MTHFR mutations, we speculate that the development and severity of BD are related to a gene-environment vasospastic interaction with reduced NO-mediated vasodilatation. Increasing NO production by L-arginine while optimizing homocysteine metabolism by folic acid-B_6-B_{12} may have therapeutic benefit. Further blinded, placebo-controlled studies are needed to determine whether our observations can be generalized to larger BD cohorts.

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PLASMINOGEN ACTIVATOR INHIBITOR ACTIVITY, 4G5G POLYMORPHISM OF THE PLASMINOGEN ACTIVATOR INHIBITOR 1 (PAI-1) GENE, AND FIRST-TRIMESTER MISCARRIAGE IN WOMEN WITH POLYCYSTIC OVARY SYNDROME. C.J. Glueck, L. Sieve, B. Zhu, P. Wang, Cholesterol Center, Jewish Hospital, MDL Laboratories, Cincinnati, OH.
We assessed whether hypofibrinolytic plasminogen activator inhibitor (PAI-Fx) was independently associated with first-trimester miscarriage in 430 women with polycystic ovary syndrome (PCOS) who had previous pregnancies. We hypothesized that Glucophage optimizes live births in women with PCOS by lowering PAI-Fx before conception and further lowering PAI-Fx in the first trimester of pregnancy. We also assessed whether PAI-Fx levels were independently related to PAI-1 genotype and to modifiable risk factors, BMI, insulin, and triglyceride (TG). By stepwise logistic regression with the dependent variable being previous pregnancy outcomes at 3 levels (live birth pregnancies only [$n = 208$], both one or more 1 live births and ≥ one or more first-trimester miscarriages [$n = 111$] or first-trimester miscarriages only [$n = 71$]), and explanatory variables PAI-1 genotype, PAI-Fx, insulin, HOMA IR, BMI, and TG, PAI-Fx was positively associated with first-trimester miscarriage, $p = .004$. For each 5 IU/mL increment in PAI-Fx, the risk being in an adverse first-trimester miscarriage category increased, odds ratio 1.12, 95% CI 1.04 to 1.20. Prospectively, from pretreatment to the last preconception visit on Glucophage, in 30 women who subsequently had live births, PAI-Fx fell 44% but rose 19% in 23 women with first-trimester miscarriage, $p = .03$. In the 30 women with live birth pregnancies, median PAI-Fx fell continuously from pretreatment through the first trimester (from 16.8 to 6.7 IU/mL), while PAI-Fx was either unchanged or rose in women with first-trimester miscarriage. Of the 921 PCOS women who had 4G5G data, 718 (78%) had 4G4G-4G5G genotypes vs 87/126 (69%) normal female controls ($\chi^2 = 4.95$, $p = .026$). The 4G-allele frequency was 53% in PCOS women vs 46% in controls ($\chi^2 = 4.3$, $p = .04$). By stepwise regression, positive independent determinants of PAI-Fx included BMI (partial $R^2 = 10.6\%$, $p < .0001$), insulin (partial $R^2 = 2.8\%$, $p < .0001$), TG (partial $R^2 = 1.1\%$, $p = .0009$), and PAI-genotype (partial $R^2 = 1\%$, $p = .0011$). The PAI-1 gene 4G polymorphism is more common in PCOS than normal women, and, in concert with obesity, hyperinsulinemia and hypertriglyceridemia, contributes to treatable, hypofibrinolytic, miscarriage-promoting, high PAI-Fx. Preconception and first-trimester decrements in PAI-Fx on Glucophage are associated with live births, whereas increments or no change in PAI-Fx despite Glucophage appear to be associated with first-trimester miscarriage.

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GROWTH, MOTOR, AND SOCIAL DEVELOPMENT IN BREAST- AND FORMULA-FED INFANTS OF METFORMIN-TREATED WOMEN WITH POLYCYSTIC OVARY SYNDROME. C.J. Glueck, M. Salehi, L. Sieve, P. Wang, Cholesterol Center, Jewish Hospital, Cincinnati, OH.
Objectives: In a prospective, 6-month study of 61 breast- and 50 formula-fed infants born to 92 PCOS mothers, all of whom took metformin throughout pregnancy, our hypothesis was that metformin during lactation vs formula would have no adverse effects on infants' growth, motor-social development, and intercurrent illness. **Study Design:** Growth, motor-social development, and illness requiring a pediatrician visit were prospectively assessed in 61 nursing infants (21 male, 40 female) and 50 formula-fed infants (19 male, 31 female) born to 92 PCOS mothers taking a median of 2.55 g metformin/day throughout pregnancy and lactation. **Results:** Within gender, at 3 and 6 months of age, weight, height, and motor-social development did not differ ($p \geq .06$) between breast- and formula-fed infants. No infants had retardation of growth, motor, or social development. Intercurrent illnesses did not differ in 30% of breast- and 22% of formula-fed infants by 3 months ($p = .4$) and in 46% and 34% by 6 months ($p = .2$). **Conclusions:** Growth, motor-social development, and intercurrent illnesses in breast- and formula-fed infants from metformin-treated PCOS mothers did not differ; metformin during lactation appears to be safe and effective in the first 6 months of infancy.

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CHANGES IN WEIGHT, PAPILLEDEMA, HEADACHE, VISUAL FIELD, AND LIFE STATUS IN RESPONSE TO DIET AND METFORMIN IN WOMEN WITH IDIOPATHIC INTRACRANIAL HYPERTENSION. C.J. Glueck, K.C. Golnik, D. Aregawi, N. Goldenberg, L. Sieve, P. Wang. Cholesterol Center, Jewish Hospital, University of Cincinnati, College of Medicine, Ophthalmology Department, Cincinnati, OH.
We hypothesized that metformin (MET)-diet would improve signs-symptoms of idiopathic intracranial hypertension (IIH) in women who also had polycystic ovary syndrome (PCOS) or hyperinsulinemia without PCOS. We prospectively assessed changes in weight, papilledema, headache, visual fields, and life status on 2.25 g MET-diet or diet alone for > 4 months in 75 women with IIH, 43 also having PCOS. Life status was graded by a self-reported 1–5 scale (1-well; 2-unwell, usual activities; 3-poor, usual activities; 4-poor, no usual activities; 5-totally disabled). Conventional Rx for IIH was maintained unchanged during MET-diet Rx. The diet was hypocaloric (1,500 cal/day if BMI ≥ 25, 2000 cal/day if BMI < 25), high protein (26% of calories), low-carbohydrate (44%). Of the 43 PCOS cases, 31 received MET-diet, 12 diet only (not tolerate MET). Of the 32 cases without PCOS, 15 were hyperinsulinemic and received MET-diet, and 17 received diet alone. (*$p < .05$,**< .01 vs baseline, within group).

			Hyperinsulinemic	
Group (n)	*PCOS +/MET2 (12)*	*PCOS+/MET+ (31)*	*PCOS2/MET2 (17)*	*PCOS2/MET+ (15)*
Baseline BMI	41.6	39.7	35.1	33.0
Follow-up (months)	11.1	14.0	21.2	16.3
% Weight change	−2.5%	−6.5%**	−2.9%	−2.9%*
Papilledema at baseline	10 (83%)	28 (93%)	13 (81%)	13 (87%)
Papilledema at follow-up	3 (25%)**	7 (23%)**	7 (44%)*	4 (29%)**
Headache at baseline	10 (91%)	25 (83%)	14 (87%)	14 (93%)
Headache at follow-up	6 (50%)	20 (65%)	10 (62%)	10 (67%)
Visual fields (%better/same/worse)	38/50/13%	75/17/8%	57/43/0%	46/46/ 8%
Life status baseline → follow-up	2.8 → 1.0	3.0 → 1.5**	2.5 → 2.0	1.5 → 2.0

The greatest % weight loss occurred in diet-MET groups. MET ($p = .012$) and baseline BMI ($p = .019$) were predictors for weight loss. Papilledema improved in all 4 groups. The most marked improvement in life status ($p = .004$) was seen in the 31 women with PCOS on diet-MET. Since ≈50% of women with IIH have PCOS, and since weight loss is central to IIH treatment, diet-MET is a novel approach to treat IIH in women with concurrent PCOS or hyperinsulinemia without PCOS.