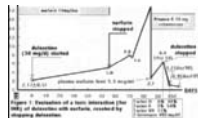


with INR 6.4, 39 days after stopping warfarin, factors II, VII, and X had low values; LFTs and fibrinogen remained normal. On day 94, duloxetine was stopped, and by day 98, INR had fallen to 1.2, with factor II increasing to 48% and factor X to 54%. On day 105, INR was 0.9. The metabolism of warfarin involves several CYP450 isoenzymes (CYP 1A2, 2D6, 2C9, 2C19, and 3A4). Duloxetine inhibits CYP1A2 and CYP2D6 and could potentially interact with warfarin. Duloxetine is also highly protein bound in plasma (> 90%) and when given with warfarin, another highly protein-bound drug, could displace warfarin, possibly resulting in a toxic effect. Our case emphasizes the need to closely monitor for the toxic drug interactions between the 2 drugs.



40

HEREDITARY THROMBOPHILIAS MEDIATING ARTERIAL THROMBOTIC EVENTS.

Q. Khalil, D. Aregawi, M. Winiarska, M. Agloria, J. Munjal, M. Haque, P. Wang, C.J. Glueck. Cholesterol Center, Jewish Hospital, Cincinnati, OH.

In 10 normolipidemic patients with 1 or more myocardial infarctions (MI) < age 45, 8 of whom had MI < age 35 years, we speculated that hereditary thrombophilias promoted arterial thrombosis. Thrombophilias studied by PCR included G1691A factor V Leiden, G20210A prothrombin, MTHFR C677T-A1298C, and platelet glycoprotein PL A1/A2 mutations, with serologic studies of ACLA IgG and IgM, the lupus anticoagulant, proteins C, S, and antithrombin III, homocysteine, and factors VIII and XI. Hypofibrinolysis studies included the 4G4G plasminogen activator inhibitor 1 mutation, plasminogen activator inhibitor activity (PAI-Fx), and Lp(a). Cases were compared to healthy normal controls (239 for PCR, 75 for serologic measures). At study entry, without diet-pharmacotherapy, 10 normolipidemic patients with one or more MI < 45 were selected by LDL cholesterol (LDLC) < 130 mg/dL, HDL cholesterol (HDLC) > 35 in men and > 40 mg/dL in women, and triglycerides (TG) < 200 mg/dL. In these 10 normolipidemic patients (7 men, 3 women, 9 white, 1 black, 1 smoker, 2 diabetic), mean \pm SD age was 46 \pm 13, BMI 26.0 \pm 2.8, LDLC 90 \pm 31, HDLC 49 \pm 10, and TG 93 \pm 35 mg/dL. Factor V Leiden heterozygosity was present in 2 of 10 (20%) cases vs 8 of 239 (3%) controls ($p = .055$). High factor VIII (> 150%) was present in 4 of 7 (57%) cases vs 0/36 controls ($p = .0003$). Of 14 hyperlipidemic patients having an arterial event < age 45 (6 MI, 1 coronary artery bypass graft, 1 angioplasty, 2 ischemic stroke, 4 TIA), 8 men, 6 women, 12 white, 2 other, 6 smokers, 3 diabetic, 1 smoker and diabetic, mean \pm SD age was 40 \pm 8, BMI 31.3 \pm 6.5, LDLC 105 \pm 42, HDLC 38 \pm 9, and TG 243 \pm 203 mg/dL. Four of these 14 cases (29%) had high factor VIII (> 150%) vs 0/36 controls ($p = .004$), 2 of 11 (18%) had high factor XI (> 150%) vs 0/61 controls ($p = .022$), and 5 of 13 (38%) had hypofibrinolytic high PAI-Fx (> 21.1 U/mL) vs 4/61 (7%) controls ($p = .007$). In both normo- and hyperlipidemic patients sustaining an arterial thrombotic event before age 45, and especially before age 35, we speculate that heritable thrombophilias (factors VIII, XI, factor V Leiden) or hypofibrinolysis (PAI-Fx) may contribute to endothelial damage or altered hemostatic equilibrium and thus promote arterial thrombotic events. In patients with thrombophilia and/or hypofibrinolysis-mediated arterial thrombotic events before age 45, we speculate that thrombophilia might have value in secondary prevention of subsequent arterial thrombotic events.

41

ROSUVASTATIN ACCEPTABILITY, EFFICACY, AND SAFETY IN HYPERCHOLESTEROLEMIC PATIENTS UNABLE TO TOLERATE OTHER STATINS.

Q. Khalil, M. Winiarska, M. Agloria, J. Munjal, M. Haque, D. Aregawi, P. Wang, C.J. Glueck, Cholesterol Center, Jewish Hospital, Cincinnati, OH.

Statins as a class are well tolerated. We assessed acceptability, efficacy, and safety of rosuvastatin in 57 euthyroid patients with primary high LDL cholesterol (LDLC) who, serially, could not tolerate most other statins or cholesterol-lowering drugs, primarily because of myocytosis. Of the 57 patients, 44 could not tolerate atorvastatin, 27 simvastatin, 15 pravastatin, 7 fluvastatin, 2 lovastatin, 1 Vytorin, 10 WelChol, 5 Zetia, 2 TriCor, and 2 Niaspan. Rosuvastatin (5 mg/day)-diet was given to 24 patients (3 men, 21 women, 21 white, 3 black, 3 type 2 diabetics, mean \pm SD age 61 \pm 9 years, BMI 31.7 \pm 4.2, LDLC 179 \pm 32 mg/dL). On rosuvastatin 5 mg-diet for a median of 5 months, weight fell 3.0 \pm 7.7 lb ($p = .016$), LDLC fell 76 \pm 35 mg/dL ($p < .0001$) to 103 \pm 31 mg/dL, with median percent change -47%. Adjusted for changes in body weight, decrements in LDLC remained significant, LS mean \pm SE -75 \pm 8 mg/dL, $p < .0001$. None of the 24 patients discontinued the 5 mg rosuvastatin, muscle symptoms were minor to absent, and there were no upward changes in liver function tests (≥ 3 times the laboratory upper normal limit), or in CPK (≥ 10 times the laboratory upper normal limit). Rosuvastatin (10 mg/day) was given to 33 patients, 16 men, 17 women, 31 white, 1 black, 1 other, 9 smokers, 4 type 2 diabetics, mean \pm SD age 59 \pm 10 years, BMI 31.1 \pm 5.2, and LDLC 178 \pm 53 mg/dL. On therapy for a median of 11 months, body weight fell 3.1 \pm 6.8 lb ($p = .014$), LDLC fell 80 \pm 49 mg/dL ($p < .0001$) to 96 \pm 38 mg/dL, median percent change -48%. Adjusted for body weight change, decrements in LDLC remained significant, LS mean \pm SE -82 \pm 11 mg/dL, $p < .0001$. None of the 33 patients discontinued the 10 mg rosuvastatin, muscle symptoms were minor to absent, and there were no upward changes in liver function tests (≥ 3 times the laboratory upper normal limit), or in CPK (≥ 10 times the laboratory upper normal limit). Since rosuvastatin is not metabolized by the 3A4 isoenzyme of the cytochrome P450 enzyme system and is < 10% metabolized by the 2C9 isoenzyme, we speculate that its acceptability, efficacy, and safety in hypercholesterolemic patients unable to tolerate other statins are related to reduced interactions with other drugs known to inhibit CYP 450 enzymes. By contrast, atorvastatin, lovastatin, and simvastatin are metabolized through the 3A4 pathway and fluvastatin through 2C9, common pathways for many other drugs, facilitating drug-drug interactions, which may be expressed clinically as muscle symptoms, leading to discontinuance of the statin. Rosuvastatin's LDLC lowering potency often facilitates reaching LDLC goals by use of low doses, 5 or 10 mg/day.

42

ADIPONECTIN RECEPTORS ARE NOT MODULATED BY SHORT-TERM THIAZOLIDINEDIONE THERAPY.

P. Kishore, W. Li, J. Tonelli, K. Zhang, P.E. Scherer, M. Hawkins, Albert Einstein College of Medicine, Bronx, NY.

The fat-derived protein adiponectin enhances insulin action in rodents and its plasma levels are correlated with insulin sensitivity in humans. Adiponectin levels are reduced in obesity and type 2 diabetes mellitus (T2DM) and increased by thiazolidinediones (TZDs) in

concert with improved insulin action. Two adiponectin receptors (AdipoR1 and AdipoR2) have recently been cloned. We examined the expression of these receptors in human adipose tissue and whether they are also regulated by TZDs. Gene expression was quantified by real-time rt-PCR in subcutaneous (Sub) and omental (Om) adipose tissue from 10 non-diabetic patients (7 F/3 M, age 38 \pm 3 years, BMI 31.6 \pm 1.5 kg/m², range 23-38) undergoing elective abdominal surgery. In a subgroup ($n = 5$), adipocytes and stromal cells were immediately separated by collagenase. RNA copy numbers (plasmid standard curves, normalized to GAPDH) of AdipoR1 were universally {223}10-fold higher than AdipoR2, and expression of AdipoR1 was similar in Sub and Om, while AdipoR2 expression was higher in Om. While adiponectin gene expression was specific to adipocytes, the receptors were expressed in both adipocytes and stromal cells (adipocytes:stromal cell ratio = 5:4). We then studied the effects of short-term pioglitazone (45 mg daily for 21 days) vs placebo on AdipoR1/R2 gene expression and insulin action (insulin clamp studies) in 11 T2DM subjects (9 M/2 F, age 49 \pm 3 years, HbA_{1c} 9.7 \pm 0.7%, BMI 32 \pm 2 kg/m²). There was no correlation between baseline insulin action and expression of AdipoR1/R2 in muscle or fat. While pioglitazone increased adiponectin expression \approx 2-fold in Sub fat and improved both hepatic and peripheral insulin action, it did not affect expression of either receptor in fat or muscle. There were also no correlations between changes in insulin action and changes in receptor expression with pioglitazone in individual subjects. This was in contrast with a remarkably tight correlation ($r^2 = .93$) between improved hepatic insulin action and increase in the active high-molecular-weight form of adiponectin. **Conclusions:** Both adiponectin receptor subtypes are expressed in human fat, with AdipoR1 being much more abundant. Unlike adiponectin, the receptors are expressed in both adipocytes and stromal adipose cells and are not affected by TZDs. Additionally, receptor expression did not correlate with insulin action at baseline or in response to pioglitazone. Further study is warranted to determine the physiologic significance of these receptors in humans.

43

GROWTH HORMONE SECRETION AMONG HIV-INFECTED PATIENTS: EFFECTS OF GENDER, RACE, AND FAT DISTRIBUTION.

P. Koutkia, K. Eaton, S.M. You, J. Brey,* S.K. Grinspoon, Massachusetts General Hospital Program in Nutritional Metabolism and Neuroendocrine Unit, Harvard Medical School, Boston, MA; *General Clinical Research Center, Massachusetts Institute of Technology, Cambridge, MA.

Objective: To determine the effects of gender, race, and fat redistribution on growth hormone (GH) secretory patterns in HIV-infected patients. **Design:** We investigated GH responses to GHRH + arginine stimulation testing in HIV-infected subjects with fat redistribution, comparing HIV-infected males ($n = 139$) and females ($n = 25$) to non-HIV-infected male ($n = 25$) and female ($n = 26$) control subjects similar in age, BMI, and race. **Methods:** A standard growth hormone releasing hormone (GHRH) GHRH + arginine stimulation test [GHRH 1 μ g/kg and arginine (0.5 g/kg, maximum dose 30 g)] was performed, and fat redistribution was assessed by anthropometric measurements. **Results:** Waist to hip ratio (WHR) was markedly different between male HIV-infected and control subjects and between female HIV-infected and control subjects (0.99 \pm 0.01 vs 0.91 \pm 0.01, $p < .0001$ for males and 0.94 \pm 0.02 vs 0.85 \pm 0.01, $p = .0001$ for females, HIV vs controls, respectively, in each comparison). HIV-infected women had significantly higher peak GH in response to GHRH + arginine (36.4 \pm 7.3 vs 18.9 \pm 2.0 ng/mL, $p = .003$) and GH area under the curve (AUC) (2,678.8 \pm 593.3 vs 1,283.8 \pm 133.4 mg/dL*min, $p < .001$) compared to HIV-infected men. Among men, a cutoff of 7.5 ng/mL for peak GH response on the GHRH + arginine test achieved good specificity and sensitivity and optimally separated the HIV and control groups (eg, the failure rates were 37% vs 8%, $p = .004$, respectively). Among women, no specific cutoff could be determined to separate the HIV and control subjects. Non-Caucasians demonstrated a higher GH AUC response compared to Caucasians among the HIV-infected male subjects. In stepwise regression modeling WHR was most significantly related to peak GH in response to GHRH + arginine in HIV-infected men. **Conclusions:** HIV-infected men with fat redistribution have significantly reduced GH peak responses and increased failure rates to standardized GH stimulation testing in comparison to healthy male control subjects and to HIV-infected women of similar age and BMI. GH secretion is related to gender and race in HIV-infected patients.

44

DIFFERENTIAL PERISPINAL OXYGEN SATURATION DURING NEONATAL AND PEDIATRIC AORTIC COARCTATION REPAIR.

KA. Krajewski, J. Henson, H.L. Edmonds Jr, A. Sehic, E.H. Austin III, M.E. Mitchell, University of Louisville, Louisville, KY.

Background: We describe a critical observation during a novel use of near-infrared spectroscopy (NIRS) for aortic coarctation repair in children. Although NIRS has been used in adults to assess tissue oxygen saturation changes in the perispinal microvasculature during repair of thoracoabdominal aneurysms, its use has not been described in infants. The purpose of this study was to characterize tissue oxygen saturation at the T10 level in neonates and children undergoing repair of aortic coarctation. **Methods:** Ten neonates (< 30 days old) and 4 children (ages 4 to 11 years) with aortic coarctation were enrolled in the study. Cerebral and perispinal regional oxygen saturations (C-rSO₂ and S-rSO₂) were measured by NIRS sensors (SomaSensors, Somanetics Corp., Troy, MI) placed on the left forehead and lower thoracic dorsal midline at the level of T10. All measurements were made at 1-minute intervals. Ten baseline measurements were made on each patient prior to incision. These were averaged and all subsequent values are reported as percent change from baseline. **Results:** Neonates demonstrated significant percent drop in S-rSO₂ from baseline during each minute following application of cross-clamp while there was no significant change in saturation in older children. Neonates demonstrated return to baseline saturation after cross-clamp removal in all cases. **Conclusions:** Spinal oximetry in the smallest children is interpretable. Neonates with severe aortic coarctation exhibit a significant drop in lower body tissue saturation during cross clamp, a drop that is not seen in older children. These findings suggest that collateral blood supply after the neonatal period in children with severe coarctation, that clamp times are more critical in the neonate, and may explain postoperative issues with visceral ischemia and reperfusion.

