G	#	AC 1/2	AS 1/2	ASBP 1/2	PP 1/2	RPPHG 1/2	%SCA 1/2
C	100	16/6	6/6	110/110	40/40	9/9	1/1
L1	50	16/25	6/14*	111*131*	40/51*	23*/24	0/21*
L2	50	16/16	6/6	110/111	40/40	23*/8	1/1
M	50	24*/16	15*/6	126*/110	50*/40	21*/9	20*/1
Md	50	32*/16	26*/7	136*/114	56*/40	22*/8	35*/1
MdS	50	45*/17	42*/7	147*/116	67*/40	21*/9	58*/2

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CALCIUM THERAPY CAUSES PROGRESSION OF CORONARY STENOSIS IN TYPE A WOMEN. R. Barndt, S. Jagtap, N. Mina, A. Stavrakis, A.Y. Cho, M. Castandi, Bethel Public Service Clinic, Downey, CA; Drexel University College of Medicine, Philadelphia, PA; Detroit, MI; Los Angeles, CA.
Our pilot study (PS) shows calcium therapy (Rx) causes systolic hypertension (SBP > 120 mm Hg) and coronary stenosis (CS) in type A women (TA) on calcium hormonal replacement therapy (CHRRx). Low systolic time intervals (STI < 40) and TA behavior were predicted in general population screening by a significant (Sig* at $p < .01$ by t-test = TT) rise in pulse pressure (PP) to handgrip (RPPHG > 15 mm Hg at 5 PSI, 3 minutes). Both identify high adrenergic neurovascular tone (ANVT with STI = PEP/LVET × 100%). STI predicted TA behavior test results ($r = .98$, $p < .001$). In prospective studies, normal TA women were randomized into two groups (G1, G2) with type B (TB) women as controls (C). G1, G2, and C had normal systolic blood pressures (SBP = 110 ± 10), with no significant coronary stenosis by ultrasonography using methods previously reported by our clinic (see Table below) at time 1 (T1 = start). General population screening revealed 40% of the population (500/1250) on CHRRx had systolic hypertension and Sig* PP increase predictive of Sig* %CS by previous PS equations. G3 was randomly selected (200 of 500) TA women on CHRRx for 10 years versus TB behavioral C, also on therapy for 10 years. All study patients were age 55 ± 5 years old and had LDL < 130, HbA_{1c} < 6.1, Hgb > 13, normal serum tryglycerides (< 145 mg%), and normal C-reactive protein levels and were nonsmokers. All Gs were treated each day (qd) with 1,500 mg calcium, 0.625 mg estrogen, and 2.5 mg progesterone with informed consent. G2 and G3 also had Rx (Rx2) qd of amitriptyline 10 to 50 mg, Tenormin 13 to 100 mg, and diltiazem CD 240 to 360 mg to reduce ANVT, SBP, STI, and systemic vascular resistance (SVR) to CG levels. Serial measurements were made at T1 and T2 (1/2) (T2 = 6 years) in all Gs (G3 = 10 years). Serial measurements were made of SBP, PP, RPPHG, STI, SVR, AS (aortic stiffness), AC (aortic collagen = %AC/area), and maximum %CS with ultrasonic measurements by methods previously reported by our clinic in standard units. In PS, the greatest degree of stenosis and change was found in the left anterior descending (LAD). Quality of life (QL 1–100) was assessed. Data were placed into a blind matrix for analysis later. Prospective results by G analysis: G means shown. See Table. Where * = Sig difference from CG at $p < .01$. ** = Sig change from T1 to T2 at $p < .02$ both by TT. G1 reveals **Sig progression of AC and maximum %CS in the LAD. Multiple regression analysis revealed SBP and SVR (reflected by STI) as the Sig** risk factors predictive of CS (mR = 0.97, $p < .001$ in G1 at T2 and G3 at T1). G2 (a matched G to G1) on Rx2 demonstrates *Sig prevention of progression of AC and %CS compared with G1. G3 at T2 shows Sig** regression of AC and %CS due to SBP, SVR, and STI reduction to C levels. This study demonstrates that systolic hypertension (SBP > 120) and high SVR are significant vascular risk factors during CHRRx in TA women. Thus, control of SBP (< 121 mm Hg), SVR (< 1,600 standard units), and STI (> 45) is necessary for the prevention or regression of AC and %CS during calcium Rx.

G	#	SBP 1/2	RPP 1/2	STI 1/2	SVR 1/2	AS 1/2	PP 1/2	AC 1/2	%CS 1/2	QL 1/2
1	56	110/142**	15*/22**	33*/24**	1540*/1700**	6/17**	40/62**	17/37**	0/32**	60*/65**
2	75	108/110	15*/9**	34*/50**	1500*/1232**	6/6	40/40	17/17	1/0	96/94
3	200	151*/113**	23*/10**	24*/46**	2225*/1280**	30*/8**	71*/43**	48*/20**	62*/2**	62*/92**
C	100	111/110	10/9	53/52	994/1009	6/6	40/40	17/17	0/1	98/97

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PARADOXICAL CHANGES IN INSULIN TOLERANCE IN MICE WITH NONALCOHOLIC FATTY LIVER DISEASE INDUCED BY SEDENTARY ACTIVITY AND AN AMERICAN FAST FOOD–TYPE DIET. M. Basaranoglu, L.H. Tetri, E.M. Brunt, B.A. Neuschwander-Tetri, Saint Louis University, St. Louis, MO.
Nonalcoholic fatty liver disease (NAFLD) is one of the most prevalent forms of chronic liver disease in the United States. Insulin resistance plays a central role in both the development and progression of NAFLD. Contributing factors to this may include the increasingly sedentary lifestyle of the population and increased consumption of a high-fat diet and high-fructose corn syrup (HFCS). The aim of this study was to characterize the glucose and insulin tolerance of sedentary mice fed a diet similar in composition to commonly consumed fast food (FFD). **Methods:** Male C57/BL6 mice ($n = 10$ in each treatment group) were fed ad libitum a FFD diet containing trans-fats (Harlan-Teklad, 43% of calories from fat) and water containing HFCS equivalent (6 g/kg/d) or standard chow and water. To promote sedentariness in the FFD group, the cages' wire racks were removed. The insulin tolerance tests were performed after 6 hours of food deprivation at 4, 8, and 12 weeks of feeding; regular human insulin (1 U/kg) was injected intraperitoneally, and blood glucose was measured at 0, 20, 40, and 60 minutes. Glucose tolerance test was performed at 8 weeks by the administration of glucose 1 g/kg intraperitoneally after 12 hours of food deprivation. Blood glucose was measured at 0, 20, 40, 60, and 150 minutes. **Results:** Hepatic steatosis increased progressively over 8 weeks in a distinctly zone 1 to zone 3 distribution pattern, similar to pediatric NAFLD. At 8 weeks, the triglyceride content of the FFD livers was 24 μg/mg (SD 8.0) and the control triglyceride content was 8.2 μg/mg (SD 1.6) ($p <$ .01). Baseline fasting glucose levels were higher in the FFD mice than controls throughout the study period (at weeks 4, 8, and 12; $p < .05$). As shown in the Table below, the blood glucose levels after insulin injection were paradoxically lower in FFD mice than controls in mice fed for 4 and 8 weeks; in contrast, the blood glucose levels after insulin injection in mice fed the FFD for 12 weeks were higher than controls, suggesting impaired glucose tolerance developed by this later time point in sedentary mice fed the FFD. Glucose tolerance testing showed substantially higher glucose levels in the FFD mice after 8 weeks of feeding, indicating earlier onset of impaired glucose tolerance than insulin resistance. The differences were significant at 20, 40, 60, and 150 minutes ($p < .01$). **Conclusions:** The increased insulin responsiveness following 4 or 8 weeks but not 12 weeks of sedentary activity and feeding FFD might indicate initially increased insulin sensitivity or, alternatively, impaired insulin clearance or impaired counterregulatory mechanisms against low glucose levels. After 12 weeks, impaired insulin responsiveness was found. These findings might be explained by the following: (1) the unique metabolism of fructose in the liver because fructose is a precursor for triglyceride synthesis and only a small amount of fructose enters into the systemic circulation, (2) impaired insulin clearance, (3) increased oxidant stress in the liver, (4) impaired islet cell function in the pancreas, or (5) insulin resistance develops in the liver and adipose tissue earlier than in muscle. Because insulin tolerance testing is a measure of muscle glucose uptake, it is also possible that increasing fat content in muscle over time might cause peripheral insulin resistance by week 12 in this model.

Insulin Tolerance Test Glucose, % of Time 0 (± SD)

	20 min	40 min	60 min
FFD-4 wk	42 ± 15*	36 ± 15*	42 ± 12*
Ctrl-4 wk	62 ± 14	69 ± 13	87 ± 27
FFD-8 wk	54 ± 23*	42 ± 22*	46 ± 19
Ctrl-8 wk	78 ± 34	64 ± 25	78 ± 44
FFD-12 wk	55 ± 5	50 ± 11	56 ± 12*
Ctrl-12 wk	56 ± 18	41 ± 19	33 ± 10

*$p < .05$.

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EFFECT OF ACETALDEHYDE UPON CATHEPSIN G AND MAST CELL CHYMASE: NON–RENIN-ANGIOTENSIN SYSTEM IMPLICATIONS. A.S. Brecher, R.C. Dubord, Bowling Green State University, Bowling Green, OH.
Hypertension is commonly observed in alcoholics. Both the renin-angiotensin system and the non–renin-angiotensin system (NRAS) have been implicated in the dynamics for the maintenance of blood pressure. Acetaldehyde has earlier been reported to enhance the generation of the rate-limiting angiotensin I (Ang I) in bilaterally nephrectomized rat plasma and to inhibit the activity of several angiotensinases (A, B, and M) in human serum, thereby promoting a hypertensive set of reactions. In the current study, the effect of acetaldehyde upon cathepsin G and mast cell chymase has been investigated. Acetaldehyde at 223.5 down to 11.2 mM concentrations enhanced cathepsin G activity at all levels employed in a statistically significant manner. Since cathepsin G is one of several enzymes transforming Ang I into Ang II and is also capable of cleaving Ang II directly from angiotensinogen, it is suggested that alcoholism, which will generate exogenous acetaldehyde from ingested alcohol, may be a contributory factor for an elevated cathepsin G activity and, consequently, hypertension via the NRAS. Mast cell chymase activity also is elevated upon exposure to 440 mM acetaldehyde and is diminished with 27 mM acetaldehyde. Since both enzymes also degrade Ang II, degradative effects may be partially neutralized.

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EFFECT OF POLYAMINES UPON BLOOD COAGULATION: POSSIBLE IMPLICATIONS IN ALCOHOLICS. A.S. Brecher, G.E. Reeves, J.N. Poulimenos, K.D. Gray, Bowling Green State University, Bowling Green, OH.
Polyamines such as protamine sulfate have been widely used clinically to neutralize the anticoagulant effect of excessive heparin. Protamine itself exhibits concentration-dependent anticoagulant and procoagulant effects. This laboratory has earlier reported that acetaldehyde exerts synergistic prolongation of the anticoagulant effect of heparin upon prothrombin time (PT). In the current investigation, it is seen that acetaldehyde, the primary metabolite of ethanol metabolism, reacts synergistically with protamine to effect a prolongation of PT beyond the individual effects of acetaldehyde and protamine on the PT. In an analogous study, the effect of polylysine (1-4K) and acetaldehyde upon activated partial thromboplastin time (APTT) was studied. It was observed that the polylysine (PL) prolonged APTT. When PL was preincubated with plasma at RT for 15 minutes, followed by a further 15 minutes with acetaldehyde, an additional prolongation time was observed. When acetaldehyde was preincubated with plasma prior to the addition of PL, a synergistic APTT was noted. When a PL-acetaldehyde mixture was preincubated prior to the addition to plasma, a drastic reduction in the prolongation of APTT was seen, suggesting that PL and acetaldehyde may detoxify one another by a Schiff base reaction under highly specific conditions.

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LEPTIN REGULATES ADIPOSE TISSUE LIPOGENESIS THROUGH HYPOTHALAMIC PATHWAYS THAT REQUIRE PI3K BUT ARE INDEPENDENT OF STAT3 SIGNALING. C. Buettner, E.D. Muse, A. Pocai, M. Myers, L. Rossetti, Mount Sinai Medical Center, New York and Bronx, NY.
Adipose tissue metabolism is a major factor in the control of body fat mass. In the long term, the size and the metabolism of our adipose depots have a pivotal impact on glucose fluxes and insulin resistance. A better understanding of the regulatory pathways that control body adiposity will improve our understanding of the association between obesity and insulin resistance, with implications for the pathophysiology and treatment of diabetes. Leptin regulates fuel partitioning by promoting lipid oxidation and protein synthesis and by curtailing lipogenesis, resulting in a selective loss of adiposity while preserving lean body mass. Here we examined whether the central administration of leptin modulates the expression of key lipogenic enzymes in visceral fat pads. Because insulin and glucose can also alter the expression of these genes and central leptin is known to affect both, all rats received a 6-hour infusion of leptin or vehicle into the mediobasal hypothalamus (MBH) while the circulating glucose and insulin levels were kept constant at basal levels in all groups (pancreatic basal insulin clamp). Central administration of leptin to conscious rats markedly down-regulated the adipose tissue expression of several key lipogenic enzymes, including acetyl-CoA carboxylase (ACC), stearoyl