Touro University - California
Office of Research

February 27th, 2008
Mare Island, Vallejo
California
Welcome to the 7th Annual Research Day,

Learn what is new on research activities in the campus.

In the past few years Touro University-California has doubled its research facilities with the building of 3,600 square feet of new, state-of-the art laboratories. Ten researchers (barring students) presently work in these new laboratories which will host up to 18 investigators when full capacity is reached. A fully equipped GC-MS laboratory with 3 gas chromatographs-mass spectrometers, 2 HPLC machines, PCR thermocycler, Real Time PCR thermocycler, 2 cell culture labs are among the many new pieces of equipment purchased over the last year.

An NMR laboratory has been our latest addition (2007) to the growing infrastructure. Our faculty is funded by NIH R01, R21 and R21 grants as well as grants from the American Diabetes Association, JDRF, Pfizer, Lifescan and others by our intramural program.

3,600 square feet of laboratory space, including an electrophysiology patch clamp lab, an electrophysiology single-cell recording lab, a biochemistry/cell culture lab with a lipidology-ultracentrifuge unit, a gas detector X ray lab (partnership), animal facility (mice, rats and frogs), common equipment rooms, fluorescence microscopy unit with digital imaging equipment, Aperio system for digitizing slides, surgery and dark room. Seven full-time researchers (barring students) work in the area.

Our intramural grant program has allowed our veteran and new faculty to generate preliminary data that has resulted, a posteriori, in a Juvenile Diabetes Research Foundation and NIH grants received several of them.

We are blessed with our student body whose drive and willingness has served the research effort so well in the past and will surely continue. As we move forward, one of our goals is to develop a Master Program that would allow the productivity to grow exponentially.

We are working also in strengthening our partnerships and developing new ones, both at the local academic level (U.C.S.F., Gallo Institute, Buck Institute, U.C. Berkeley), with the industry and at the international academic level (Showa University, Japan, University of Sao Paulo and Santa Catarina, Brazil).

Clinical research, research in public health and education are fields towards which we are counting on expanding.

Please make sure you visit our webpages and learn more about faculty lab projects, opportunities, and publications.

A. Gugliucci, MD, PhD
Professor of Biochemistry and Research Director

We are grateful to Touro University for support, the Facilities and Food Service Departments, Ms Jennifer Taing and Alex Perez for putting together a classy Abstract Book and John Schulze and Jennifer Taing for printing so many posters with such quality.
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POSTER PRESENTATIONS
Quinidine and Cisapride Block of HERG Show Opposite Dependency on Extracellular Potassium Compared to Terfenadine and MK-499.

Barrows B, Foster T, Thakkar P, Cheung K, and Miller A.
Touro University College of Osteopathic Medicine, Vallejo, CA.

Background and Hypothesis: The human ether-a-go-go-related gene (HERG) encodes a voltage-gated potassium channel involved in terminating the ventricular action potential. Block of HERG can result in the lethal arrhythmia Torsade de Pointes, characterized by severely compromised cardiac output. A large number of pharmaceutical compounds still in use have been shown to block HERG. Previously published data has shown that HERG block by a number of compounds is reduced in increased extracellular potassium (K⁺). However, the mechanism behind this reduction in block by increased extracellular potassium is not well understood.

Methods: Block of HERG by quinidine, cisapride, terfenadine, and MK-499 were tested using two electrode voltage clamping of Xenopus oocytes in different extracellular potassium solutions.

Results: Increasing extracellular potassium from 0 mM K⁺ (no added potassium) to 20 mM K⁺ reduced quinidine and cisapride block of HERG. Quinidine block of HERG was reduced approximately 9 fold from an IC₅₀ of 2 μM in 0 mM K⁺ to an IC₅₀ of 17 μM in 20 mM K⁺. Cisapride block of HERG was reduced approximately 10 fold from an IC₅₀ of 0.13 μM in 0 mM K⁺ to an IC₅₀ of 1.24 μM in 20 mM K⁺. However, increasing extracellular potassium from 0 mM K⁺ to 20 mM K⁺ had the opposite effect on HERG block by terfenadine and MK-499. Increasing extracellular potassium from 0 mM K⁺ to 20 mM K⁺ increased HERG block by terfenadine approximately 3 fold from an IC₅₀ of 1 μM in 0 mM K⁺ to an IC₅₀ of 0.32 μM in 20 mM K⁺. Increasing extracellular potassium from 0 mM K⁺ to 20 mM K⁺ increased HERG block by MK-499 approximately 5 fold from an IC₅₀ of 2 μM in 0 mM K⁺ to an IC₅₀ of 0.43 μM in 20 mM K⁺.

Conclusions: Quinidine and cisapride block of HERG show the opposite dependency on extracellular K⁺ compared to terfenadine and MK-499. The mechanism behind this difference is not clear. However, previous data from this lab indicates that HERG block by quinidine and cisapride show a better correlation with the permeant ion species than with inactivation. Thus HERG block by quinidine and cisapride is greatest in solutions where the permeant ion is lowest, independent of the inactivation rate. This appears not to be the case for terfenadine and MK-499. One possibility is that HERG channel gating has a different influence on HERG block by terfenadine and MK-499 compared to HERG block by quinidine and cisapride. Consistent with this, terfenadine and MK-499 have been shown to be trapped in the channel after channel closure whereas quinidine and cisapride appear not to be trapped.
Performance on COMLEX 1 is an Outcome of the Touro University College of Osteopathic Medicine First and Second Year Curriculum

Glenn Davis  
Touro University-California, Vallejo, CA.

Background and Research Question: The first two years (OMS1 & 2) of the Touro University College of Osteopathic Medicine (TUCOM) curriculum should equip students to pass the first phase (COMLEX 1) of the licensure examination series, and the admissions process should select students likely to become licensed. It is intuitively obvious that variance in student achievement on COMLEX 1 first attempt results both from characteristics acquired during prior schooling, and those acquired at TUCOM during OMS1 & 2. What is not obvious is the relative importance of prior schooling represented by the admissions profile versus schooling experienced during OMS1 & 2, represented by the cumulative grade point average (gpa) at the end of OMS2. Explaining variance in COMLEX 1 scores will help illuminate the extent that performance on COMLEX 1 is an outcome of the TUCOM curriculum versus prior schooling.

Methods: A database of student characteristics was compiled from the TUCOM classes of 2001 - 2008. The database included six variables representing the outcome of prior schooling: Total MCAT, Verbal, Physical Science, and Biological Science MCAT sub scores, as well as undergraduate grade point average (gpa), and undergraduate science gpa. The database also included one variable representing the outcome of schooling at TUCOM: cumulative gpa at the end of OMS2, as well as the first attempt COMLEX 1 score. Linear regression analysis to the COMLEX 1 score was done for each of the 7 outcome variables. To help visualize the results, scatter plots were generated relating each variable to the first attempt COMLEX 1 score. All analysis was performed using SPSS 14.0 with missing data subject to listwise deletion, resulting in sample sizes ranging from n=726 for MCAT-Physical Science to n=797 for OMS2 gpa.

Results: 55% of the variance in first attempt COMLEX 1 scores is explained by the linear relationship to cumulative gpa at end of OMS2 (R Sq Linear = .548). Total MCAT explained 8% of variance (R Sq Linear = .079), MCAT – Biological Science explained 6% of variance (R Sq Linear = .062), and MCAT – Physical Science explained 4% of variance (R Sq Linear = .041). Undergraduate gpa, Undergraduate science gpa, and MCAT-Verbal each explained less than 2% of variance in first attempt COMLEX 1 scores. In total 77% of variance in first attempt COMLEX 1 scores is explained by the linear relationship to analyzed outcomes of schooling.

Conclusions: Performance on COMLEX 1 is an outcome of the TUCOM curriculum. Performance on COMLEX 1 is most completely explained as the outcome of all schooling including TUCOM OMS1 & 2, but cumulative gpa at the end of OMS2 alone explains much more variance in COMLEX 1 than the combined outcomes of prior schooling. Future studies should focus on discovering characteristics that explain the remaining 23% of variance in COMLEX 1 scores.
Induction of *Salmonella* Typhimurium prophages in response to environmental stress

*B. Elrod, K. Dominguez, and N. Garcia-Russell*

Basic Sciences Department, Touro University College of Osteopathic Medicine, Vallejo, CA,

**Background and Hypothesis:** The virulence of bacterial strains is determined by the expression of virulence factor genes located either on the chromosome or on transferable elements, such as prophages. The four prophages of *Salmonella enterica* serovar Typhimurium (Fels-1, Fels-2, Gifsy-1 and Gifsy-2) can be transferred to a new host and increase the recipient cell’s virulence. To investigate what influences these transfers, we quantified phage induction in *Salmonella* Typhimurium LT2 in response to different types of stress such as antibiotic treatment, fever and low nutrient availability.

**Methods:** The copy number of prophage genes was quantified by using quantitative Real-Time PCR and normalized to the copy number of *ansP*, a reference gene localized near the terminus of replication on the *Salmonella* chromosome. The copy number of *ilvG*, a bacterial gene localized close to the origin of replication, was also quantified to distinguish phage induction from chromosome replication.

**Results:** Our results show that not only the four prophages have different levels of spontaneous induction during exponential growth in rich media, they also respond differently to heat (43°C), antibiotic treatments (Mitomycin 2 µg/ml; Ampicillin at 2, 10, 50 and 100 µg/ml) and starvation (from 24 hours to 3 weeks).

**Conclusions:** These results suggest that in *Salmonella*, exposure to different types of environmental stress leads to variations in prophage induction and therefore to different pools of transferable virulence genes. Also, since prophage induction is commonly linked to the expression of the enclosed virulence genes, changes in prophage induction may lead to variation in bacterial virulence in response to specific environmental stress.

*This work is supported by Touro University*
Non-Invasive Measurement of Hepatic UDP-Glucose Turnover in Humans after a Fructose Diet.


1 Touro University-California, Vallejo, CA.
2 Dept. of Medicine, San Francisco General Hospital (SFGH), University of California San Francisco
3 Chemistry Dept., Pacific Union College, Angwin, California

Background and Hypothesis: This poster presents a non-invasive technique to measure UDP-Glucose turnover in humans after a high versus low fructose diet. This turnover reflects the dynamics of hepatic glycogen storage, a critical component of glucose control. Invasive techniques, such as splanchnic catheterization do not reveal the dynamics of the process and can only provide information regarding the net balances of metabolites across the liver. Furthermore, such techniques are not justified for research in humans. We hypothesize that a high fructose diet may impact UDP-glucose kinetic because animal studies have shown that fructose is a potent acute regulator of glycogen synthesis.

Methods: Healthy male volunteers were admitted to San Francisco General Hospital for an 18-day inpatient stay. Subjects were fed a complex carbohydrate (CHO) diet (50% energy from CHO, 35% from fat, and 15% from protein) for the first nine days. The last nine days consisted of an iso-energetic diet in which fructose was substituted for half of the CHO. During days 7 and 16, subjects underwent intensive stable isotope tracer and acetaminophen infusions to measure hepatic UDP-glucose flux in fasting and during a hyperinsulinemic-euglycemic clamp. Deuterium-labeled galactose (D-galactose-1d) was used to label UDP-glucose, which in turn was sampled by acetaminophen serving as a “pharmacological probe”. Acetaminophen is conjugated with UDP-glucose in the liver to form acetaminophen glucuronide (GlcUA) which is subsequently excreted in the urine. High pressure liquid chromatography (HPLC) was utilized to detect and isolate the labeled GlcUA from urine samples using a fraction collector. The GlcUA was collected and derivatized for gas chromatography/mass spectrometry (GC/MS). The flux of UDP-glucose was calculated by the tracer dilution method.

Preliminary Results: When monitoring the changes of UDP-glucose fluxes during the transition from fasting to hyperinsulinemic-euglycemic clamp, we observed a 20 to 36% flux increases after nine days of a complex carbohydrate diet. However, only a 4 to 12% increases after nine days of a fructose rich diet.

Conclusions: This method quantifies the amount of glucose stored as glycogen in both fasting states and after three hours of hyperinsulinemic-euglycemic clamp. Our preliminary data suggest a diminished hepatic glycogen storage capacity after a fructose rich diet. The non-invasive technique can be used in both healthy control and subjects with metabolic disease such as diabetes and hepatic steatosis. Further development of this method should allow the estimation of hepatic glucose uptake.

Supported by Touro University.
Hypochlorous acid (HOCl) is a potent inactivator of human proteins responsible for protection against thrombosis and LDL oxidation: a study on plasminogen and paraoxonase 1.

Alejandro Gugliucci and John Schulze.
Glycation, Oxidation and Disease Laboratory, Touro University-California, Vallejo, CA, USA

Background. Myeloperoxidase (MPO), released from degranulated neutrophils, has been considered an important pathophysiological factor in oxidative stress. Through generation of hypochlorous acid it plays a key bactericidal role, however, if it goes unchecked, its activity may lead to inactivation of important proteins. This may occur in the inflammatory microenvironment of the atheroma plaque. Oxidation of amino acid residues such as tyrosine, leading to the formation of 3-chlorotyrosine, has been recently shown to inactivate paraoxonase-1 (PON-1) in HDL. Plasminogen is an important check for thrombus formation, possesses 25 tyrosine residues and has been previously shown by us to be inactivated by nitration.

Hypothesis. We hypothesized that plasminogen can be also be inactivated by HOCl in a similar way as PON-1 is, and this inhibition can be counteracted by cysteine.

Methods. Human plasminogen (10 µmol/L) or human HDL prepared by sequential flotation ultracentrifugation were incubated in PBS containing 2 mmol/L CaCl₂, pH 7.4, at 37°C for up to 3 h in the presence or absence of freshly prepared HOCl (0-1000 µmol/L). After extensive dialysis, streptokinase-activated plasmin activity was kinetically measured using a synthetic pNA substrate and PON-1 activity was kinetically measured using paraoxon as a substrate. SDS-PAGE gels were run to monitor protein aggregation/fragmentation and Western blots (anti-3 chlorotyrosine antibodies) allowed for monitoring of protein adduct formation.

Results: We confirm inactivation of PON-1 in HDL which achieves over 95% inhibition at 1 mmol/L (IC 120 µmol/L). This correlates with changes in molecular weight and 3-chlorotyrosine formation. When plasminogen was incubated under the same conditions plasmin activity (generated by streptokinase) is reduced in a time and concentration dependent fashion (IC 40 µmol/L). Inhibition reaches a plateau of 70% inhibition at 50-100 µmol/L. Cysteine and taurine protected both proteins from inactivation in a concentration dependent fashion.

Conclusions: This study addressed the effects of HOCl on 2 key players in the overall process of atherogenesis. Neutrophils can secrete HOCl at 100 µmol/L. Our data on quick functional inactivation of plasminogen by chorination, at IC concentrations 3 times lower than those needed for PON-1, adds a new pathophysiological dimension to our previous work showing plasminogen as a target for peroxynitrite damage. They suggest that MPO and HOCl may also be implicated in impaired fibrinolysis. New therapeutic approaches in atherosclerosis and diabetes should limit the formation of HOCl, taurine and thiols may prove beneficial.

Supported by Touro University-California
Developing a cell-based assay to test anti-HIV therapeutics

Evan Hermel, Miriam Gochin
Touro University-CA, Vallejo CA

The leading cause of infectious disease-mediated morbidity and mortality is infection by the human immunodeficiency virus (HIV), the causative pathogen of AIDS. HIV infects CD4+ T lymphocytes by using viral gp120 to bind to the CD4 and CCR5 receptors, followed by viral gp41-induced fusion with the host cell membrane. Interrupting these molecular interactions would prevent infection and the concept has led to the development of an FDA-approved CCR5 inhibitor, Maraviroc®, and one anti-fusion therapeutic, T20, (Fuseon). However, T20 is a peptide therapeutic, which requires it to be injected, and it is marketed at considerable cost. Therefore, the development of additional small molecules as entry inhibitors would greatly affect the treatment or prevention of AIDS. To test novel anti-HIV therapeutics, we developed a luciferase-based cellular assay using modified HeLa cells. Our assay utilized 48-well tissue culture plates and two cell lines: HL2/3 (containing HIV-tat+gp160) and TZM-bl (containing luciferase+CD4). Culture conditions were optimized for control inhibitors (T20 and soluble CD4), cell numbers, and incubation times.
In Vitro Transdermal Iontophoretic Delivery of Penbutolol Sulfate

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**INTRODUCTION** Penbutolol, [1-\(\alpha\)-butylamino-3-(2-cyclopentylphenoxy) propan-2-ol] (Figure 1) is a non-cardioselective \(\beta\)-adrenoreceptor blocking agent and used for the treatment of hypertension (1, 2). Penbutolol is mainly metabolized to 4-hydroxypenbutolol in humans (3). The conventional dosage form for penbutolol is tablet which has limitations including hepatic first-pass metabolism, high incidence of adverse effects due to variable absorption profile and poor patient compliance. Transdermal delivery offers an alternative mode of drug administration (4). A stable plasma drug concentration can be maintained over a prolonged period (5). However few drugs can penetrate the excellent barrier provided by the stratum corneum. Over the past few decades, iontophoresis has attracted considerable interest as a method of enhancing transdermal drug delivery. Iontophoresis involves the use of a low-level electric current to drive ionized drug molecules into or through the skin (Banga, 1998, Kalia et al 2004, Dixit et al 2007)

The major advantage of iontophoresis is that transcutaneous drug permeation can be controlled by varying the externally applied current (Meidan et al, 2003)

The aim of the present research was to investigate transdermal iontophoretic delivery of penbutolol sulfate across porcine ear skin in vitro.

**EXPERIMENTAL METHODS** In vitro permeation of penbutolol sulfate by iontophoresis was conducted using vertical Franz diffusion cells (Permegear, Bethlehem, PA) and pig ear skin as a membrane. The receptor chamber was filled with phosphate buffered saline and temperature was maintained at 37 °C. Skin was mounted between the donor and receptor chambers. Donor chamber area was 1.77cm\(^2\) while receptor compartment volume was 15ml. The donor chamber was filled with 1ml of 17mg/ml penbutolol sulfate in phosphate buffered saline. For iontophoresis, Ag (Sigma Aldrich) and Ag/AgCl (In vivo Metrics, CA) electrodes were used as anode and cathode respectively. The Ag electrode was placed in the donor chamber such that the electrode was immersed in the solution approximately 5 mm from the skin surface (Chaturvedula et al 2005). Anodal iontophoresis was used since penbutolol is positively charged. The AgCl electrode was placed in the sampling port of the receptor chamber. A constant current power source (Phoresor II Model PM 850, Iomed, Salt lake City, UT, USA) was connected to the electrodes and current (0.1, 0.2 or 0.3mA) applied. Samples were collected at 2, 4, 6, 8, 10, 24 hours and analyzed by HPLC. Control experiments were also carried out by placing drug solutions into donor compartments without applying iontophoresis.

Penbutolol was assayed at 271 nm. The mobile phase comprising 30% acetonitrile and 70% water with 0.025% trifluoroacetic acid was delivered at a flow rate of 1ml/ml. The injection volume was 10\(\mu\)l and the limit of detection was 10ng/ml. Waters HPLC system equipped with ultraviolet (Waters 2487 dual absorbance) and fluorescence (Waters 2475 multi wavelength) detectors, Autosampler (Waters 717), binary pump (Waters 1525) and a reversed phase (Sunfire, Waters C\(_{18}\) 5\(\mu\)m 4.6x 100 mm) column was used.

**RESULTS AND DISCUSSION** The present investigation was carried out in order to assess transdermal permeation of penbutolol sulfate across porcine ear skin. An HPLC method was developed for penbutolol assay. Transdermal flux of penbutolol sulfate across porcine ear skin was studied using vertical Franz diffusion cells.

Iontophoresis (0.11mA/cm\(^2\), 0.17mA/cm\(^2\) and 0.22mA/cm\(^2\)) for 6 hours resulted in a net transport of 87.36\(\mu\)g/cm\(^2\), 150.51\(\mu\)g/cm\(^2\) and 201.13\(\mu\)g/cm\(^2\) respectively. Iontophoresis significantly (P<.05) increased the permeability of penbutolol sulfate across pig ear skin in comparison with passive delivery. There was a 2.20-(0.11mA/cm\(^2\)), 3.26 (0.17mA/cm\(^2\)) and 4.28-fold (0.22mA/cm\(^2\)) enhancement in transcutaneous flux values.

**CONCLUSION** There was a statistically significant increase in transdermal steady-state flux enhancement of penbutolol sulfate after iontophoretic application compared to passive delivery (7.65 \(\mu\)g/cm\(^2\)). The results presented here serve as initial evidence for the potential of iontophoresis to enhance transcutaneous delivery of penbutolol sulfate.

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Age-related differences in modulation of HSP70 induction and transport in cerebral cortex in the R6/2 transgenic mouse model of Huntington’s Disease (HD)

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Background: Heat shock proteins (HSP) are expressed by cells in response to environmental stressors and are well known for their role as molecular chaperones which aid in the folding and targetting of cellular proteins. They are known to co-localize with the intracellular and intranuclear inclusions which are hallmarks of HD cellular pathology, and are thought to play a protective role. Because transport mechanisms exist to move HSP across cell membranes, and thus between cells, both intracellular and extracellular HSP may play a role in HD pathogenicity.

Method: To test the hypothesis that HSP production and transport across cell membranes is altered in Huntington's disease, we examined intracellular and extracellular HSP levels in cerebral cortex of R6/2 transgenic (mut) or wildtype (WT) age-matched littermate control mice following exposure to an oxidative stressor at asymptomatic (18-25 days) and symptomatic (>80 days) ages. Cerebral cortex from mut and WT was microdissected into low-Ca2+ (1mM) ice-cold oxygenated artificial cerebrospinal fluid (aCSF) Ca2+ containing 1mM kynurenic acid. Tissue was then divided into approximately equal parts and incubated in oxygenated aCSF (containing 2mM CaCl2) with low-density lipoprotein (LDL, control) or oxidized-LDL (ox-LDL, stressor) for 24h. Tissue samples were homogenized and analyzed for intracellular Hsc70/Hsp70 (iHSP) using standard Western blot (immunoblot) techniques (mouse anti-HSP70 [Sigma], goat anti-mouse, alkaline phosphatase conjugate [Bio-Rad]). Incubation aCSF was collected and analyzed for extracellular Hsp70 (eHSP) using an ELISA [Stressgen] protocol.

Results: In asymptomatic WT, ox-LDL treatment decreased iHSP to 63±7% and increased eHSP by 5±1Kg/mg tissue compared to LDL treated samples. In asymptomatic mut, ox-LDL had no effect on iHSP (100±6%) but decreased eHSP by 2.4±3Kg/mg tissue. Thus, ox-LDL treated mut tissue retained relatively more iHSP than WT (p=0.002) while the eHSP70 was decreased compared to WT (p=0.01).

In symptomatic WT, ox-LDL decreased iHSP to 81.0±8.94% and increased eHSP by 3.25±2.24Kg/mg tissue compared to LDL treated samples. In symptomatic mut, ox-LDL also decreased iHSP to 68.6±9.90% and increased eHSP by 4.63±2.4Kg/mg tissue; iHSP and eHSP were not significantly different between HD and WT (p=0.37 and p=0.868, respectively).

Conclusion: As the WT mice age, there is no significant difference in stressor-induced iHSP or eHSP (p=0.162 and p=0.964, respectively). However, as mut mice age and become symptomatic, stressor-induced iHSP levels were significantly decreased while eHSP levels were significantly increased when compared to WT controls (p=0.017 and p=0.002, respectively).
Investigation of the role of β-catenin on optic axonal pathfinding and growth cone behavior

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Background and Hypothesis: In the retino-tectal circuit, optic axons navigate a specific path from the retina to the tectal midbrain. β-catenin is a cytoplasmic adaptor protein involved in the Cadherin and Wnt signaling pathways known to regulate the development of optic axons. We investigated how interactions of the N-terminal domain of β-catenin with α-catenin (required for Cadherin adhesion) and GSK-3β (involved in Wnt signaling) control pathfinding and growth cone morphology of optic axons.

Methods: We overexpressed two deletion mutants of the N-terminal domain of β-catenin in ventral optic axons in living Xenopus tadpoles. One deletion mutant contained both the α-catenin and the GSK-3β binding sites of the N-terminal domain of β-catenin (NTERM), and the second deletion mutant contained only the GSK-3β binding site (β-cat107). Using epi-fluorescence microscopy, we studied how these mutants altered pathfinding and growth cone morphology of optic axons in living tadpoles and brain preparations.

Results: Images of dorsal tecta from living tadpoles showed that NTERM increased the waviness of optic axons whereas β-cat 107 straightened optic axonal trajectories. Examination of whole brain preparations confirmed these observations and revealed that NTERM also perturbed the adhesions found in optic axonal growth cones.

Conclusions: These data suggest that the interactions of β-catenin with α-catenin and GSK-3β exert opposing effects on the waviness of the optic axonal path. Moreover, interactions of β-catenin with α-catenin are required for normal growth cone morphology and adhesions.

Supported by an intramural grant from Touro University.
Transient Hyperglycemia in Non-Diabetic Subjects During a Modified Oral Glucose Tolerance Test: Possible Relationship to Fasting Period

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Background and Hypothesis: As part of a broader study comparing the effects of low vs. moderate intensity aerobic exercise on the moderation of postprandial glycemia (see Philbin et. al. Poster), a group of non-diabetic subjects underwent a modified Oral Glucose Tolerance Test (OGTT) while at rest (Methods). The purpose of the non-exercising OGTT was to obtain an individualized baseline of each subject’s ability to metabolize a normalized glucose load at rest for later comparison to glycemia profiles obtained while the subject performs various protocols of cycling exercise. This presentation reports early results related to a small group of subjects who have completed the non-exercising OGTT glycemia profile.

Methods: Utilizing a consumer model blood glucose metering system (TheraSense: Freestyle Freedom™), capillary blood samples were collected from the fingertips of non-diabetic subjects recruited from the TU-CA campus student body and staff (n = 4; 2 male & 2 female) and assayed for a period of 130 minutes at 10-20 min. intervals before, during, and after consuming between 52-76 gms of glucose (Dex4® Glucose Tablets; 4 gms/tablet). Glucose load was standardized at 0.5 gm/lb lean body mass and ingested at a rate of ≈1 tablet/30 sec. along with a proportional water volume (3-4 ml/gm glucose). Each subject’s fasting blood glucose level was assayed just prior to ingestion of glucose tablets. Sedentary OGTT data was collected while subjects were seated or standing in a stationary position. It is noteworthy (see Results) that for convenience, subjects were required to fast (water-only) for a period of only 4-6 hours prior to the scheduled OGTT instead of the current standard of “at least 8-10 hrs but not greater than 16 hrs”. Glycemia results were plotted to form a graphical profile of the glycemia response to the glucose load. Parameters indicative of relative glycemic exposure were evaluated and compared to normal standards including: (1) peak glycemia level, (2) 2-hr post-glucose glycemia level, & (3) total hyperglycemia exposure.

Results: All subjects possessed normal fasting blood glucose levels (92.3 mg/dL ±8.3) prior to the OGTT (normal range: 80-100 mg/dL). As expected, a rise in blood glucose was evident within 10-20 min. after glucose ingestion (20 min:152.3 mg/dL ±19.3). Surprisingly, as the testing period progressed each subject began to display abnormally elevated blood glucose levels. Average values between 40-80 min. all exceeded 200 mg/dL with an average peak value reached at 60 min. (224.5 mg/dL ±27) (normal peak <160-170 mg/dL). From this point, levels gradually declined although the extrapolated 2-hr average value near the end of the monitoring period exceeded 130 mg/dL (130 min: 130.3 gm/dL ±20.9) (normal 2 hr value <140 mg/dL). Interestingly, when the identical OGTT was repeated in one subject after a standard 8-10 hr fast, the subject’s glycemia profile remained within normal limits.

Conclusions: Based on these limited data, results indicate the importance of a sufficient fasting period prior to OGTT evaluation. Data also offers a possible model to study the dynamics of the insulin response to mild hyperglycemia using healthy non-diabetic subjects.
De Novo Lipogenesis, Lipid, and Carbohydrate Metabolism in Non-Alcoholic Fatty Liver Disease


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Background and Hypothesis: Non-alcoholic fatty liver disease (NAFLD) is the most common liver ailment in developed countries, affecting up to one third of the population. Its prevalence is rising and seems to parallel the global increase in obesity and type 2 diabetes. Untreated, more serious risks of NAFLD could develop such as cirrhosis and metabolic complications including insulin resistance, hyperglycemia and atherogenic dyslipidemia. The etiology of NAFLD in humans is not well understood but recent studies suggest that hepatic conversion of carbohydrate (CHO) to lipids (de novo lipogenesis, DNL) may be a key mechanism. In previous studies, we have demonstrated that fructose stimulates DNL, whereas infusion of an isocaloric amount of glucose does not. We hypothesize that hepatic DNL is a major contributor to steatosis and that reduction of DNL in the liver will improve hepatic and extra-hepatic insulin sensitivity, and that these changes will be associated with reductions in liver and muscle fat after a 8-week dietary intervention. The study consists of two aims. Aim 1: To test the hypothesis that individuals with steatosis as a result of NAFLD, have higher rates of hepatic DNL, increased hepatic and extra-hepatic insulin resistance and impaired glucose control when compared to non-steatotic controls. Aim 2: To test the hypothesis that diet induced reductions in DNL, liver and muscle fat will be accompanied by parallel improvements in hepatic and extra-hepatic insulin sensitivity and glycemic control.

Methods: Aim:1 A total of 40 subjects with steatosis and 20 non-steatotic controls matched for sex, ethnicity, age, and body mass index (BMI) will be recruited. Each subject will undergo a 4-day inpatient study, while consuming a controlled, weight-maintaining diet corresponding to their usual intake of fructose and other simple sugars. State-of-the-art stable isotope methods will be used to compare fractional and absolute rates of hepatic DNL, apolipoprotein B100 (apoB100) turnover and very low density lipoprotein triglyceride (VLDL-TG) production, as well as whole-body lipolysis under both fasting and fed conditions. Hepatic and extra-hepatic insulin sensitivity will be measured using hyperinsulinemic-euglycemic clamps and stable isotope tracer studies of endogenous glucose production. Liver and muscle fat will be measured by proton magnetic resonance spectroscopy, visceral fat by magnetic resonance imaging and total lean and fat mass by dual-energy X-ray absorptiometry. Aim 2: We will perform a randomized study in which 20 steatotic subjects whose intake of fructose and simple sugars accounts for ≥15% of total energy intake will be stratified by sex and ethnicity. Each subject will be assigned to one of two low-fat energy-restricted dietary regimens for six weeks, followed by a 2-week weight maintenance period, at the end of which all the studies described in Aim 1 will be repeated. The diets will differ only in their ratio of complex to simple CHO. One of the experimental diets will maintain the amount of simple CHO, including fructose, whereas the other will substitute complex CHO for fructose and simple sugars.

Conclusions: Although we expect both diets to reduce liver and muscle fat and decrease fasting insulin levels because of the energy deficit, we hypothesize that the magnitude of the reduction in liver and muscle fat content and hepatic insulin resistance will be greater with the diet containing complex CHO when compared to the conventional diet, rich in fructose. If our trial demonstrates a beneficial effect of reduction of hepatic CHO fluxes in steatotic patients, these findings could impact on the development of clear dietary guidelines to minimize hepatic CHO channeling, DNL and possibly the development of pharmacological inhibitors of hepatic CHO uptake.

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The GSK-3β and α-catenin binding regions of β-catenin exert opposing effects on the terminal ventral optic axonal projection

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Background and Hypothesis: In the retino-tectal circuit, optic axons extend from the retina to the tectal midbrain where they project into specific synaptic targets. β-catenin is a cytoplasmic adaptor protein involved in the Cadherin and Wnt signaling pathways that regulate the development of optic axons. Here we dissect how interactions of the N-terminal domain of β-catenin with α-catenin (required for Cadherin adhesion) and GSK-3β (involved in Wnt signaling) control development of terminal optic axonal projections.

Methods: We overexpressed two deletion mutants of the N-terminal domain of β-catenin in ventral optic axons in living Xenopus tadpoles. One deletion mutant contained both the α-catenin and the GSK-3β binding sites of the N-terminal domain of β-catenin (NTERM), and the second deletion mutant contained only the GSK-3β binding site (β-cat107). We used epi-fluorescence and confocal microscopy to compare the effects of these mutants on terminal pathfinding, targeting and branching of ventral optic axons in the dorsal tectum of living tadpoles.

Results: Expression of NTERM in ventral optic axons dispersed their paths into tectum and induced anterior and lateral shifts in their targeting locations in the dorsal tectum. In contrast, β-cat 107 compressed the ventral optic axonal trajectories and shifted the synaptic targeting locations of ventral optic axons medially and posteriorly. In addition, NTERM expressing ventral optic axons formed arbors that were wider than controls whereas β-cat 107 axonal arbors were narrower compared to controls.

Conclusions: These data suggest that the interactions of β-catenin with α-catenin and GSK-3β exert opposing effects on the dispersion of terminal projections of ventral optic axons.

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Drug Discovery of HIV-1 gp41 inhibitors

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Introduction

HIV-1 gp41 mediates viral fusion and as such is a key viral therapeutic target. Although the peptide T20 has been approved by the FDA as a gp41 inhibitor, its poor pharmacokinetic profile and related dosing requirements limit its clinical use. We have successfully designed a fluorescence based high throughput screening assay for gp41 drug discovery. With the help of this assay, we further explored new small molecule lead compounds which could inhibit gp41, and which have the inherent potential to be developed into an orally bio-available drug. Several new compounds have been synthesized and tested.

Experiment

All reagents for organic synthesis were purchased from Sigma-Aldrich. Reactions were monitored by TLC. The products were purified by either PTLC, silica gel column chromatography or HPLC. Activity was tested by our own high throughput assay.

Results and Discussion

We successfully synthesized several new small molecule lead compounds which test active against HIV gp41. Preliminary results reveal that compound WD-86 has 0.2µM binding activity, which makes it currently the highest affinity small molecule gp41 inhibitor known. Looking forward, we will continue to optimize WD-86 in order to achieve the low nM affinity required for a good drug.
Poster Presentations

Clinical Sciences
Low Adiponectin Levels are Associated with Diabetes and Pre-diabetes Among Latino Subjects

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Background and Hypothesis: Adiponectin, a hormone secreted exclusively by adipocytes, is reduced in obesity and in insulin-resistant states. Individuals with elevated adiponectin levels have been shown to be at decreased risk of developing Type 2 DM in a study of Pima Indians [1] and also among Caucasians [2]. This study investigates the utility of low levels of adiponectin as a marker for concurrent pre-diabetes or DM among Latino individuals age 45 and over (a population at high risk of DM).

Methods: Men and women age 45 and over were recruited from Latino communities in Solano County and Sonoma County, California. Serum total adiponectin levels were measured using an ELISA system (Mercodia AB). Additionally, a 2-hour oral glucose tolerance test was performed on all subjects after an overnight fast, utilizing a 75-gram glucose load.

Results: Results are reported for 48 subjects. Age range was 45-83. 22 subjects (45.8%) had abnormal glucose metabolism: 15 (31.3%) had pre-diabetes (impaired fasting glucose and/or impaired glucose tolerance), and 7 (14.6%) had previously undiagnosed DM. A low adiponectin level was defined as a level below the mean for subjects with normal glucose metabolism. As a means of identifying either pre-diabetes or DM in these subjects, low adiponectin level had a sensitivity of 82%, specificity 35%, positive predictive value 51%, and negative predictive value 69%.

Conclusions: In this sample of Latino men and women age 45 and over, a low adiponectin level appears to be a sensitive marker for pre-diabetes or diabetes. This is further evidence to support the role of adiponectin in the pathophysiology of Type 2 diabetes.

References:
Changes in Pharmacist-Provided Medication Therapy Management Services: Analysis of One Innovative Company's MTM Service Claims Over Time

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Background and Hypothesis: Medication Therapy Management (MTM) was introduced by Congress in the recent Medicare Prescription Drug, Improvement, and Modernization Act (MMA) of 2003. MTM describes services to be provided by pharmacists to ensure patients receive the best outcomes from their medication therapy. The objective of this study was to characterize changes in medication therapy management (MTM) interventions across time, including identification of trends associated with the provision of pharmacist-provided MTM services and evaluation of potential cost savings from avoidance in healthcare utilization resulting from pharmacist-provided MTM services.

Methods: Medication therapy management claims from a multi-state MTM company were analyzed across a seven-year time period. Data extracted from each claim included patient demographic information (e.g., age and gender), specific information about the medication triggering the intervention (e.g., therapeutic class and therapy type), and specific information about the service provided (e.g., reason, MTM action, MTM intervention result, and estimated cost avoidance (ECA)). In addition, pharmacy payment information was extracted, so that along with ECA, an estimated return on investment for each claim could be calculated.

Results: A selected subsample containing over 75,000 MTM claims submitted by pharmacists in 47 states from years 2000 through 2006 were analyzed. The reason for pharmacist-provided MTM intervention moved away from new/changed drug therapy to cost efficacy management, while actions shifted from patient education/follow up to provider consultations (P<.01). Services also shifted towards claims involving chronic type medications and away from acute type medications (P<.01), resulting in significant changes in the therapeutic classes and older patients being served (P<.01). These trends resulted in higher pharmacy reimbursements, greater cost avoidance, and larger average returns on investment per claim across time (P<.01).

Conclusions: MTM interventions over a seven-year period evolved from the provision of traditional patient education involving acute medications towards consultation-type services for chronic medications. These shifts suggest the provision of MTM services will be increasingly vital as the population ages. Further, these trends suggest that pharmacists will be provided with increasing opportunities to provide MTM services and receive higher reimbursements for performing these services.
Hypothesis: Intervention with gabapentin and Osteopathic Manipulative Medicine (OMM) can improve the symptoms of Fibromyalgia. These treatments can decrease the number and severity of tender points (TPs) and the overall pain level. Subjects will have improved quality of life and increased function.

Methods: Subjects between the ages of 18 and 65 with Fibromyalgia symptoms were recruited from Solano, Sonoma and Contra Costa counties. Subjects who met inclusion criteria were enrolled, randomized to an arm and monitored at eight weekly intervals, receiving treatment during weeks 2-7. Treatment interventions consisted of OMM only, gabapentin only or combined therapy of OMM and gabapentin.

Results: 12 subjects completed the study. Subjects had 21% less tender TPs at the end of the study and could tolerate 12% more pressure on their 4 worst TPs. Subjects had 25% less pain and 32% more days of feeling good at the end of the study. Subjects had a 31% decrease in negative symptoms/treatment reactions. Subjects considered themselves moderately ill when they began treatment, with a 26% improvement by the final visit.

Conclusions: Preliminary results show some promising treatment options for Fibromyalgia patients. We look forward to continued enrollment to increase the sample size to 100 to complete the study.

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Advanced oxidation protein product levels in end-stage renal disease patients decrease after hemodialysis while myeloperoxidase levels increase

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Background: An increase in myeloperoxidase (MPO) during hemodialysis (HD) has been previously reported. Advanced oxidation protein products (AOPP) seem to be, at least in part, causally related to MPO activity and have been shown to be highest in patients undergoing HD. The present study was designed to show the concomitant effects of HD on MPO, as well as homocysteine (Hcys), in a cohort of end stage kidney disease (ESKD) patients with normal triglyceride levels.

Methods: Pre and post dialysis levels of MPO, AOPP and Hcys were determined in 35 HD patients (HD for 1-19 years), together with the standard chemical panels. Advanced oxidation protein products (AOPP): Determination of AOPP is based on spectrophotometric detection according to Witko-Sarsat et al. For low molecular weight AOPP, serum was, ultrafiltered through 10 Kda cut-off Amicon filters and processed without further dilution. Myeloperoxidase: Myeloperoxidase mass was determined in plasma by ELISA employing a kit from Mercodia (Mercodia AB Uppsala, Sweden). Briefly, it is based on a sandwich technique on which two monoclonal antibodies are directed against separate antigenic determinants on the molecule. Peroxidase labeled secondary MPO antibodies are used in the second step after capture. The reaction is developed with 3,3',5,5' tetramethylbenzidine and read as an endpoint colorimetric reaction. Homocysteine: Measurement of homocysteine was performed by ELISA using a kit “Homocysteine test” from BioRad, (Hercules, CA, USA). Briefly, protein-bound Hcys is reduced to free Hcys and is enzymatically converted to S-adenosyl-L-homocysteine (SAH) in a separate step prior to the immunoassay.

Results: This is the first study to focus on the concurrent variation of AOPP and MPO in pre and post dialysis samples from ESKD patients. We confirm the post dialysis increase in MPO shown previously by others, from 27.4 ± 12.2 to 37.8 ± 12.9 µg/l, p < 0.0001. The novelty of our data is that we show a positive effect of HD on the concentration of AOPP from 34.2 ± 12.1 to 25.3 ± 11.2 µmol/L (average 35%, range 0-50%, p < 0.0001) which parallels in magnitude the change seen for homocysteine; from 37.2 ± 12.0 to 28.5 ± 11.8 µmol/L (p < 0.0001). This decrease is not accompanied by measurable significant changes in triglycerides, which rules out previously reported interferences. The effect, present in all the patients enrolled, does not correlate with the effectiveness of dialysis to clear creatinine and urea and cannot be explained by changes in albumin concentration. No significant concentrations of dialyzable low molecular AOPP were found.

Conclusion: Our results show dissociation between release of MPO during dialysis and decrease in AOPP, suggesting increased catabolism of AOPP during HD which points to a positive effect of HD on the delicate oxidant-antioxidant state of these patients. This should be weighted against other pro-oxidant effects that have also been shown to occur previously. More research on AOPP catabolism is therefore warranted.

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Lack of Effectiveness of Low-Dose Filgrastim (G-CSF) in TAC Breast Cancer Chemotherapy

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Background and hypothesis: Filgrastim, a granulocyte colony-stimulating factor (G-CSF), is used for the treatment and prevention of febrile neutropenia in patients receiving cancer chemotherapy. The standard dose of filgrastim is 5 mcg/kg/day, which is typically rounded to 300 mcg/day or 480 mcg/day based on patient weight. The objective of this study is to retrospectively review the differences between low-dose filgrastim (150 mcg/day) versus standard-dose filgrastim in preventing febrile neutropenia and hospitalizations in breast cancer patients receiving the TAC breast cancer chemotherapy regimen.

Methods: A single center retrospective data analysis was performed involving 22 adult female breast cancer patients who concurrently received the TAC chemotherapy regimen and low-dose filgrastim from March 2004 to February 2007. Data from this study was compared to previously published data in which patients received standard-dose filgrastim.

Results: More patients developed febrile neutropenia in the low-dose filgrastim group compared to the standard-dose group (31.8% vs. 7.5% respectively, p=0.0014; RR=4.24). More patients were hospitalized due to febrile neutropenia in the low-dose filgrastim group compared to the standard-dose group (31.8% vs. 6.5% respectively, p<0.001; RR=4.89). More chemotherapy cycles resulted in febrile neutropenia in the low-dose filgrastim group compared to the standard-dose group (6.7% vs. 1.2% respectively, p<0.001; RR=5.58).

Conclusion: Compared to standard-dose filgrastim, low-dose filgrastim resulted in a significantly greater incidence of febrile neutropenia, hospitalizations due to febrile neutropenia, and chemotherapy cycles with febrile neutropenia. Standard-dose filgrastim appears superior to low-dose filgrastim in breast cancer patients receiving the TAC chemotherapy regimen.
Effects of dietary fructose versus glucose on de novo lipogenesis in overweight and obese human subjects

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Background and Hypothesis: The increased prevalence of obesity and type 2 diabetes in the United States and many other parts of the world is associated with increased fructose intake (i.e. high fructose corn syrup). Most, if not all, of the fructose from one’s diet is metabolized in the liver (90-100%); on the other hand, glucose is mostly metabolized in extra-hepatic tissues (80%). Also, fructose is metabolized faster than glucose because it bypasses the early steps of glycolysis. Any excess dietary carbohydrate (CHO) that is not metabolized or stored is converted to fat by the process of de novo lipogenesis (DNL) in the liver. Preliminary studies have shown that fructose consumption leads to higher levels of triglycerides and atherogenic apolipoprotein (ApoB) in the blood. The effects of a fructose versus glucose diet on fractional hepatic DNL in overweight and obese human subjects were examined.

Methods: Subjects were admitted to the UC Davis School of Medicine/Sacramento Veterans Affairs Medical Center General Clinical Research Center (GCRC) for a double-blinded diet intervention study to evaluate lipid metabolism. Subjects were fed a non-lipogenic complex carbohydrate (CHO) diet (55% energy from CHO, 30% fat, 15% protein) for the first three weeks (baseline period), followed by an isoenergetic rich in simple sugar diet in which either glucose or fructose was substituted for 25% of the CHO. During the baseline period and in the final two weeks of the intervention phase, subjects underwent intensive stable isotope tracer infusions to measure DNL in the fasted and fed states. Triglycerides were isolated from very low density lipoproteins (VLDL) and subsequently derivatized to methyl palmitate esters for gas chromatography/mass spectrometry (GC/MS) analysis. The data was then used to calculate fractional DNL by applying mass isotopomer distribution analysis (MIDA).

Results: Fasting fractional DNL (the percent of newly synthesized fat from the liver) was similar with each diet (~11%). However, in the fed state, during which subjects (n=3) were given fructose as part of meals, fractional DNL was increased by an average of 31.6% when compared to meals in which CHO was complex.

Conclusions: Our results indicate that two diets with the same macronutrient composition but different types of carbohydrate (fructose vs. glucose) affect hepatic DNL in different ways. The data show that fractional hepatic DNL is significantly increased with fructose consumption, elevating triglyceride levels in blood which potentially can lead to atherogenesis, insulin resistance, and other harmful conditions. Nonetheless, more studies are necessary to evaluate the health consequences of chronic high fructose feeding.

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In vitro and in vivo antioxidant effects of toasted (maté tea) Ilex paraguariensis beverages: preliminary results

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Background. Yerba Maté (Ilex paraguariensis) is a native and widely consumed South American plant. It contains high concentrations of phenolic compounds that respond for its high antioxidant activity in vitro and in vivo. Mate has gained popularity in the USA in the last few years, especially in Northern California. A recent prospective clinical study conducted over 11 years, has shown, for the first time that green tea consumption is associated with reduced mortality due to cardiovascular disease and to all causes. Our previous in vitro studies show that green mate extracts contain much higher levels of polyphenols and are more effective than green tea or red wines as free radical quenchers and protectors of proteins, lipoproteins and cells from oxidative stress. Other authors have recently shown that mate extracts can inhibit the progression of atherosclerosis in cholesterol-fed rabbits. Maté tea (less bitter and favored in Sao Paulo and Rio de Janeiro, Brazil) is obtained by roasting the mate leaves and, up to now, there are no published results indicating if the roasting process might affect maté tea in vivo antioxidant activity. Acrolein, an advanced lipoxidation product, has been shown to inactivate paraoxonase (PON-1), a key LDL protector from oxidation. No study addressing the potential protective effect of mate has been reported.

Hypotheses: 1) Mate tea drinking in a healthy student population produces changes in circulating lipoproteins favoring anti-atherogenic profiles 2) Mate protects paraoxonase in HDL from in vitro inactivation by acrolein.

Material and methods: 1) Blood samples of five female volunteers (staff members School of Nutrition, USP, Brazil) were obtained at three different times: before drinking the tea (t₀), after one hour (t₁) and after one week of daily consumption (t₂) of mate tea. The isolated LDL was oxidized with CuSO₄ and incubated at 37°C for up to 6h. Next, the concentration of malondialdehyde (measured by TBARs methodology) and conjugated dienes (lag time) were evaluated, using spectrophotometric methods. 2) HDL isolated from pooled serum (no intervention), was incubated for 3 h at 37°C with 0-500 µmol/L acrolein with and without addition of green and roasted Ilex paraguariensis extracts (0-20 µl/mL). After extensive dialysis, PON-1 activity was kinetically measured using paraaxon as a substrate.

Results: In our ongoing in vivo study, there was a reduction in the TBARS formation on LDL: t₀= 4.90± 0.32 µmol/g ptn; t₁= 4.12 ± 0.35, p=0.018; t₂= 3.85 ± 0.78 p=0.05 and an increase in the oxidation retarding capacity (lag time): t₀ = 32.50 ± 11.60 min; t₁ = 50.78 ± 36.24 min. p=0.006; t₂ = 57.55 ± 39.34 min p=0.01, in both periods (t₁ and t₂) when compared to t₀. Our in vitro study shows that acrolein inactivates PON-1 (IC 50 250 µM/L) and mate blocks the effect in a concentration dependent fashion, reaching 60% protection at 10 µl/mL (p < 0.001).

Conclusion. Our preliminary data support the contention that the consumption of roasted mate reduces LDL oxidation in a similar manner as we have previously shown for green mate. Moreover, it protects PON-1 from inactivation by acrolein, a key carbonyl present in sites of inflammation. Given the impact of oxidative stress and lipoprotein metabolism on human pathology, the huge economical burden of atherosclerosis and coronary artery disease, our in vitro data and the aforementioned studies, we believe a larger, cross-over, randomized exploratory clinical trial to evaluate the putative lipid lowering and anti-oxidative efficacy of this herb is warranted.

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“Poiseuille's Panacea”: a New Direction in Osteopathic Manipulation of the Thorax

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Background and Hypothesis: Poiseuille (1846) described the variables that affect the flow of fluid through a tube. While most variables (tube length, fluid pressure, viscosity) affect the flow in a linear relationship (double the tube length and the pressure must double, or the flow will cut in half), one variable stands out: the radius of the tube affects the flow to the 4th power. If the radius is doubled, the same flow can be maintained with one-sixteenth of the pressure. We propose that this identifies the radius as the pre-eminent factor to address over a broad variety of clinical disease: Asthma, Hypertension, Pulmonary Hypertension, Atherosclerosis, COPD (Chronic Obstructive Pulmonary Disease). Indeed, pharmacotherapy for these conditions emphasizes the dilation of blood vessels and airways. We propose that increases in the radius of blood vessels and airways can also be obtained through manipulation: specifically by manipulation that expands the anatomic structure containing the vessels/airways. We propose that an expansion of the thorax will translate to proportional increases in all the vessel/airway lumens within the thorax, and to measurable improvements in airflow & blood flow. We suggest that the benefits of this approach go beyond those obtained by traditional OMT directed to restore costo-vertebral motion.

Methods: Students were recruited from the TUCOM-CA Class of 2010, and introduced to McCombs' protocol for manual thoracic expansion. Measurements of thoracic circumference were made at the 10th thoracic segment/xiphoid process. Peak Expiratory Flow was measured with a hand-held Peak Flow Meter.

Results: On 9 January 2008, our first student subject was treated by Drs Towne & McCombs. OMT increased his thoracic excursion by 4.5 cm, and his “easy normal” by 2.8 cm. His peak flow increased by 10 lpm, a clinically insignificant finding in an asymptomatic subject. One week later, the subject had lost 1.1 cm of “easy normal” circumference, maintaining 1.7 cm of the 2.8 cm increase gained through OMT. When this approach was applied by students to each other, gains in thoracic circumference were less, and in some cases reduced. The greatest gains were obtained by those students most practiced in the techniques.

Conclusions: The 3.3% increase in “easy normal” circumference would, if proportionally translated to increases in the lumens of his thoracic vessels & airways, reduce the pressure within them (or increase the flow through them) by 13%. Our clinical experiences at St Lukes Hospital support the view that these structural changes are both possible and beneficial. Measurements of thoracic circumference are less reliable than desired, and acquisition of a spirometer (on order) will more reliably document the benefits of OMT for thoracic expansion, especially in the ill.
Prevalence of Diabetes in an HIV+ population

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BACKGROUND: Infection with HIV has been associated with an increased incidence of hyperglycemia and insulin resistance. There is a greater rate of whole-body proteolysis in HIV+ subjects. Proteolysis contributes to HIV hyperglycemia by providing amino acids for gluconeogenesis. Furthermore, subcutaneous fat is almost completely absent and visceral fat increased in persons with HIV lipodystrophy. Visceral adipose tissue area correlates inversely with whole-body glucose uptake into muscles. Several studies demonstrate significant increase in insulin resistance with the use of antiretroviral therapy. Epidemiological studies have reported that about 1.4 million people in Tanzania are living with HIV/AIDS in a population of 32 million. The country is also experiencing a rapid rise in the burden of diabetes. In the 1980s, the prevalence of type 2 diabetes was among the lowest in the world, but now 300,000-350,000 of Tanzania's 32 million people have diabetes.

OBJECTIVE: To investigate the association between HIV and Diabetes in a Tanzanian population by studying the prevalence of diabetes in HIV+ population and the relationship between (1) age, (2) sex, (3) antiretroviral therapy use, (4) endemic diseases, and (5) stage of HIV with the occurrence of Diabetes.

METHODS: A total of 64 HIV infected patients were screened for diabetes mellitus using glucose test strip/meter at an outpatient HIV clinic; of which 22 were males and 42 were females. Data was obtained regarding past medical history, family history of diabetes, antiretroviral therapy use, and infection with 3 of the most common endemic diseases to the region: Malaria, TB, and Schistosomiasis.

RESULTS: Of the 64 subjects, 1 (1.56%) individual (F) was found to have diabetes, and 2 individuals (3.12%) were found to have prediabetes (1F, 1M). 3.12% of the subjects with diabetes/prediabetes were below the age of 45 and 1.56% were above age of 45. 80% of the subjects were at stage 4 of HIV, 12.3% were at stage 3 of HIV, and 7.7% were at stage 2 of HIV. 64% of the subjects gave history of malaria; 15.6% of the subjects gave history of TB; and 10.9% of the subjects gave history of Schistosomiasis. Of the 65 HIV+ individuals, 67.2% were on highly active antiretroviral therapy and of the 67.2% none were diagnosed with diabetes.

CONCLUSION: The prevalence of Diabetes among the HIV infected subjects is 1 out of 64 (1.56%), which is not significant enough to make an association between HIV and diabetes. Age and sex are independent factors in the association between HIV and diabetes, however, a greater pool of participants is needed to validate this outcome. Malaria, TB and Schistosomiasis are endemic to the population and show no relationship to the incidence of diabetes. There is no association between antiretroviral drug use and insulin resistance in this population. The small population size limits the accuracy of the study and an increase in the number of participants is needed for reliable data analysis.
Elevated D-Lactate Concentrations in Serum and Urine of Diabetic Patients

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Background: Metabolic disturbances in diabetes mellitus lead to increased D-lactate production, which also indicates enhanced formation of other, harmful metabolites. Accurate determination of D-lactate is challenging because of the presence of its stereoisomer, L-lactate at much higher concentrations.

Hypothesis: D-Lactate is higher in plasma and urine of diabetic patients than in controls.

Methods: Lactate (both D and L isomers) was purified from serum and urine of diabetic and control patients by deproteinization and ion exchange chromatography. Next, lactate was derivatized to its propylamine-heptafluorobutyric anhydride for gas chromatography/mass spectrometry (GC/MS) analysis. The derivatized lactate isomers were separated and quantified by GC/MS, using a chiral column (Rt-βDEXcst, Restek Corp.) and chemical ionization mode. By using standard D-lactate and L-lactate preparations, we ascertained that this assay procedure did not lead to racemization of the lactate isomers. Glucose, L-lactate, HbA1c and creatinine were determined by standard clinical laboratory methods. Results are expressed as means ± S.D. Statistical significance of differences between diabetic and control patients were determined by Student’s t-test.

Results: The study included 14 diabetic patients and 11 control subjects. The diabetics displayed both hyperglycemia (10.9 ± 4.1 vs. 5.2 ± 1.0 mmol/L, p<0.001) and elevated HbA1c (8.1 ± 1.4 vs. 5.1 ± 0.2 %, p<0.001). L-Lactate, a normal metabolite, was in the normal range in the sera of both groups (1.9 ± 0.5 and 2.1 ± 0.8 mmol/L), but it was markedly increased in the urine of diabetics (0.99 ± 0.45 vs. 0.59 ± 0.28 mmol/L, p<0.03).

Our main finding was the more than two-fold increase of D-lactate in diabetic patients both in the serum (56 ± 32 umol/L vs. 24 ± 19 μmol/L, p<0.012; note that the units are micromoles/L) and the urine (410 ± 350, vs. 130 ± 100 μmol/L, p<0.02). While normal urine did not contain detectable amounts of glucose, several urine samples from diabetics contained substantial amounts (up to 1 g/dL). In order to exclude the possibility of bacterial production of D-lactate from glucose in the urine of diabetics, the samples were shown to be free of bacterial contamination by means of a nitrite assay. The difference in urinary D-lactate remained unchanged after correction for glomerular filtration rates based on creatinine clearance.

Conclusions: Our study confirmed the increased production of D-lactate in diabetic patients, using a highly specific procedure for the separation of this trace metabolite from its - much more abundant - stereoisomer, L-lactate. This finding is relevant to the complications of diabetes which have been attributed, at least in part, to protein glycation. Methylglyoxal, a precursor of D-lactate, is one of the most aggressive glycation agents. Elevated D-lactate levels indicate enhanced production of methylglyoxal, and thus enhanced protein glycation.

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Determination of VO2pk to Normalize Relative Exercise Intensity of Subjects During Recumbent Cycling Exercise

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Background and Hypothesis: Exercise is an effective intervention for management of postprandial hyperglycemia in Type 2 diabetics. Current guidelines recommend 150 min/wk of moderate intensity (exertion) aerobic exercise. However, moderate intensity exercise (e.g. brisk jogging) can be too rigorous for many obese and debilitated diabetics. Although lower intensity exercise (e.g. leisurely walking) is more practical, its relative effectiveness for hyperglycemia control is unclear. The purpose of this study is to examine the HYPOTHESIS that low intensity cycling exercise performed after a glucose load reduces hyperglycemia exposure at least as effectively as moderate intensity exercise. To necessarily normalize exercise intensity between study subjects of varying age, gender, and fitness level, each subject performed a peak O2 consumption (VO2pk) test to estimate their own unique target exercise intensity parameters required for the study (see Methods). Results from this aspect of the study are presented here.

Methods: Non-diabetic volunteers recruited from the TU-CA campus student body and staff were evaluated (n = 8; 4 male & 4 female). VO2 rate (ml O2/min./kg body wt) was measured by indirect calorimetry (Korr® CardioCoach®-PLUS Fitness Assessment Instr.). VO2pk values were determined for each volunteer during a single bout of progressive resistance (30-245 Watts), constant speed (60 rpm) stationary recumbent cycling exercise (StarTrac Pro®). Based on software extrapolated data, an exercise “fitness” profile of each subject was generated correlating VO2 rate with heart rate and calorie expenditure rate. Profiles were then used to identify the appropriate Target Heart Rate range & Cycling Resistance Level for each individual corresponding to the defined Low Intensity (30% VO2pk) & Moderate Intensity (70% VO2pk) levels evaluated in the study.

Results: Average VO2pk rate attained during the testing procedure by all subjects (n=8) was 36.2 ±7.9 ml O2/kg/min. As expected, VO2pk was higher in male (43.7 ±1.9 ml O2/kg/min) compared to female (28.6 ±6.5 ml O2/kg/min) subjects. VO2pk rates corresponded to peak heart rate values of 152 ±10.8 bpm and 142 ±10.8 bpm in male and female subjects, respectively. Based on VO2pk values and other data, 30% and 70% VO2pk values were approximated: For male subjects 30%VO2pk values ranged from 11.7-14.1 ml/kg/min (Target HR range: 80-110 bpm) and 70%VO2pk values from 27.4-30.5 ml/kg/min (Target HR range: 125-150 bpm). For female subjects 30%VO2pk values ranged from 6-11.2 ml/kg/min (Target HR range: 85-105 bpm) and 70%VO2pk values from 13.9-26.2 ml/kg/min (Target HR range: 120-150 bpm).

Conclusions: Based on anthropometric characteristics, VO2pk results are generally consistent with published values expected from subjects examined in this study. Data will be used to validate results testing the hypothesis of the study described above.
Cross-cultural implementation of Diabetes Shared Medical Appointments and Continuous Quality Improvement Among the Uninsured Latino Population

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Background and Hypothesis: Based on the 2005 CDC report, 20.8 million people in the US have diabetes. Among them, Latinos experience disproportionately high rates of type 2 diabetes. This trend exacerbates over time, with the rates of severe diabetic complications being up to six times higher among Latinos. Compelling scientific evidence indicates that lifestyle changes can prevent or delay the occurrence of type 2 diabetes in high-risk groups. Yet it is imperative to consider linguistic and cultural components when designing and implementing an intervention for a specific patient population. Thus it is necessary to create a systematic way to review, pilot, and select health program for a specific patient population.

Methods: Subjects were recruited from Clínica Tepati’s diabetic patient population, a non-profit community clinic serving the underserved monolingual Spanish-speaking patients in Sacramento County. The Shared Medical Appointment (SMA) model of patient education was adopted for Clínica’s Latino diabetic population through: 1) selection of diabetes educational material and assessment tools in Spanish, 2) validation of all survey tools in a Spanish-speaking low-literacy Latino immigrant population, and 3) training interested medical students and providers in the health education components of diabetes care. Continuous Quality Improvement (CQI) methods such as control charts and Plan-Do-Study-Act (PDSA) cycles were used to specifically tailor the SMA program to the Clinic’s unique structure, patient population, and mission. Both patient and provider feedback was collected to assist with weekly modifications and PDSA reports. Finally, the program was set up for quantitative evaluation using pre-test/post-test analysis in order to assess its long-term impact on patients’ health outcomes.

Results: The introduction of SMA model of diabetes care has reduced average clinic time by about 70 minutes compared to the same time period in the past two years. This reduction in clinic time not only increased clinic’s overall efficiency, but it allowed for better use of volunteered medical staff’s time and reduced patient waiting time. Control charts on variables “start time” and “end time” indicate that the overall implementation process has been “in control”, thus suggesting a working integration of the new diabetes program into Clínica’s existing structure.

Conclusions: Although the principles of SMA have not been previously used among the Latino patient population, our results indicate that it was a good starting framework for a diabetes program. This study has also shown that the CQI PDSA process can be effectively used in developing and implementing interventions to culturally and linguistically unique patient population. Furthermore, it was demonstrated that culturally appropriate and linguistically validated information is an absolute requirement for effective teaching and quality healthcare.