RESEARCH SUMMARIES

ENDOCRINE SOCIETY

Frontier research and groundbreaking studies

A Resource for Journalists

Research Summaries Book

Frontier research and groundbreaking studies presented during

The Endocrine Society's 96th Annual Meeting & Expo

ENDOCRINE SOCIETY

Research Summaries Book

ICE/ENDO 2014
June 21-24, 2014
McCormick Place West, Chicago, IL

Each day (Saturday through Tuesday) the newsroom (Room W176C) opens at 7:30 a.m.

HOW TO USE THIS BOOK

The ICE/ENDO 2014 Research Summaries Book is designed to facilitate media coverage of the joint meeting of the International Society of Endocrinology and the Endocrine Society. The highlighted abstracts contained in this book have been identified as those that would be of particular interest to journalists. Abstracts in the Research Summaries Book were selected from among the more than 3,000 abstracts that will be presented at ICE/ENDO 2014.

Each abstract in this book is presented in its original scientific form. A news summary of the research, which was prepared in coordination with the research teams, precedes each abstract. The summaries include additional background information on the area of research and, in many cases, the source of funding for the research. The news summaries appear on the left-hand pages and the original abstracts follow on the corresponding right-hand pages.

The indices are located at the end of the book and may be referenced by using abstract number, author's last name, topic or the date of the presentation. From clinical practice to basic science, ICE/ENDO 2014 offers the most comprehensive scientific program in the field of endocrinology.

The full ICE/ENDO 2014 program is available on the Endocrine Society's Web site at http://www.endocrine.org/endo-2014/program-and-events. For additional information about ICE/ENDO 2014 or the Endocrine Society, please contact:

Aaron Lohr
Director, Media Relations
Phone: 202.971.3654
Email: alohr@endocrine.org

Jenni Glenn Gingery
Manager, Media Relations
Phone: 202.971.3655
Email: jgingery@endocrine.org

The Endocrine Society
2055 L Street NW, Suite 600
Washington, DC 20036
Phone: 202.971.3636
Fax: 202.736.9705
www.endocrine.org

ENDO 2014 Embargo Policy

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For additional information, please contact Aaron Lohr, Director, Media Relations, at 240-482-1380 or alohr@endocrine.org

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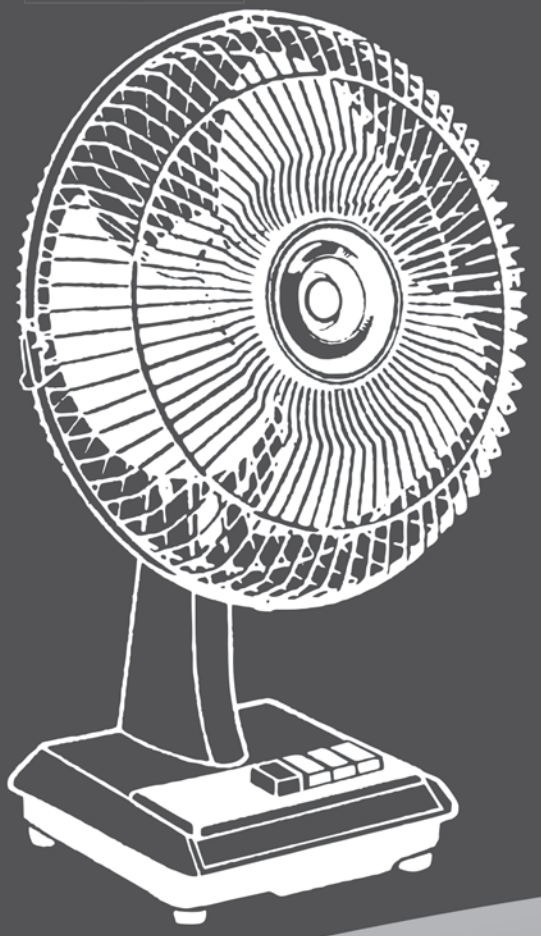

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Aaron Lohr | Director, Media Relations | Endocrine Society | 202.971.3654 | alohr@endocrine.org
Jenni Glenn Gingery | Manager, Media Relations | Endocrine Society | 202.971.3655 | jgingery@endocrine.org

THE ENDOCRINE SOCIETY'S

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ENDOCRINE SOCIETY

Clinical Trials

Date	Time	Session Type	Abstract	Event Title	Location Room #
Saturday, June 21st					
Saturday	11:15 am-11:30 am	Basic/Clinical	PP05-4	Liraglutide 3.0 Mg Reduces the Prevalence of Prediabetes and Delays Onset of Type 2 Diabetes in Overweight and Obese Adults: Results from Scale Obesity and Prediabetes, a Randomized, Double-Blind and Placebo-Controlled 56-Week Trial	W178
Saturday	11:30 am-1:00 PM	Translational	LB-OR01-1	Successful Treatment of Neonatal Micropenis and Bilateral Cryptorchidism Due to Hypogonadotropic Hypogonadism (HH) with 3-Month Daily Subcutaneous Injections of the Recombinant LH Plus FSH Preparation (Pergoveris®)	W475
Saturday	11:30 am-1:00 PM	Clinical	OR02-5	A Phase 2 Study of Chronocort®, a Modified Release Formulation of Hydrocortisone, in the Treatment of Adults with Classic Congenital Adrenal Hyperplasia	W190
Saturday	11:30 am-1:00 PM	Clinical/Translational	OR04-4	Impact of AMH Level on Chances for Ovulation in Pregnancy in Polycystic Ovary Syndrome II, a Multi-Center Randomized Clinical Trial	W192
Saturday	11:30 am-1:00 PM	Clinical/Translational	OR13-5	Vitamin-D Supplementation in Prediabetes Reduced Progression to type2 Diabetes through Decreased Insulin Resistance and Systemic Inflammation: An Open Label Randomized Prospective Study from Eastern India	W184
Saturday	1:00 PM-3:00 PM	Translational	LBSA-0270	Comparison of Laboratory and Imaging Methods Associated with Bone Metabolism in Patients with and without Renal Failure Under the Age of 45 Years with Elevated Parathormon Levels	Hall F
Saturday	1:00 PM-3:00 PM	Translational	LBSA-0571	Efficacy and Cardiac Safety of Short Term Weekly Levothyroxine Administration in Hypothyroid Patients on Replacement Therapy	Hall F
Saturday	1:00 PM-3:00 PM	Translational	LBSA-0737	Effect of Tolvaptan on Symptoms and Length of Stay in Hospitalized Patients with Dilutional Hyponatremia: Analysis of Salacia, a Prospective, Randomized Clinical Trial	Hall F
Saturday	1:00 PM-3:00 PM	Translational	SAT-0229	Correction of Vitamin D Deficiency in Critically Ill Patients: A Randomized Placebo-Controlled Trial	Hall F
Saturday	1:00 PM-3:00 PM	Translational	SAT-0232	Effects of Vitamin D Supplementation on Insulin Sensitivity and Beta Cell Function in Obese Adolescents	Hall F
Saturday	1:00 PM-3:00 PM	Translational	SAT-0233	Effect of Vitamin D Deficiency/Insufficiency Treatment on Insulin Resistance in Obese and Overweight Children	Hall F
Saturday	1:00 PM-3:00 PM	Translational	SAT-0236	Short Term Safety and Efficacy of High Dose Vitamin D Supplementation in Obese Adolescents with Vitamin D Deficiency	Hall F
Saturday	1:00 PM-3:00 PM	Translational	SAT-0239	Vitamin D Insufficiency May be a Casual Factor for Dyslipidemia	Hall F
Saturday	1:00 PM-3:00 PM	Translational	SAT-0240	Vitamin D Supplementation Improves Glycaemia in Vitamin D Deficient Nigerians with Diabetes Mellitus	Hall F
Saturday	1:00 PM-3:00 PM	Translational	SAT-0242	Vitamin D Treatment in Somalian Women Living in Sweden — a Randomized, Double-Blind, Placebo-Controlled Study	Hall F
Saturday	1:00 PM-3:00 PM	Translational	SAT-0544	A Comparative Study of Pre- and Postoperative Quantification of Upper Eyelid Retraction in Graves Orbitopathy Using Margin Reflex Distance and Digital Eyelid Image Processing Methods	Hall F
Saturday	1:00 PM-3:00 PM	Basic/Clinical	SAT-0683	Recombinant Human IGF-I Administration As an Alternative to Oral Glucose Tolerance Testing for Acromegaly Diagnosis	Hall F
Saturday	1:00 PM-3:00 PM	Basic/Clinical	SAT-0693	The Patro Adults Study of Omnitrope® for the Treatment of Adult Patients with Growth Hormone Deficiency: Latest Results	Hall F

Date	Time	Session Type	Abstract	Event Title	Location Room #
Saturday, June 21st					
Saturday	1:00 PM-3:00 PM	Clinical/Translational	SAT-0718	Short-Term Low Dose Growth Hormone (GH) Therapy Improves Insulin Sensitivity without Altering 24-Hour Cortisol Production Rates and Ectopic Fat Accumulation in GHDeficient (GHD) Adults	Hall F
Saturday	1:00 PM-3:00 PM	Clinical/Translational	SAT-0817	The Combination of Insulin-like Growth-Factor Receptor 1 (IGF1R) Antibody Cixutumumab and Mitotane As a First-Line Therapy for Patients with Recurrent/Metastatic Adrenocortical Carcinoma: A Multi-Institutional NCI-Sponsored Phase II Study	Hall F
Saturday	1:00 PM-3:00 PM	Clinical/Translational	SAT-0902	Changes in Total and Regional Fat Mass during Strength Training Were Inversely Associated with Improved Insulin Sensitivity Assessed By Euglycemic Hyperinsulinemic Clamp	Hall F
Saturday	1:00 PM-3:00 PM	Clinical/Translational	SAT-0925	Liraglutide 3.0 Mg Reduces the Prevalence of Prediabetes and Delays Onset of Type 2 Diabetes in Overweight and Obese Adults: Results from Scale Obesity and Prediabetes, a Randomized, Double-Blind and Placebo-Controlled 56-Week Trial	Hall F
Saturday	1:00 PM-3:00 PM	Clinical/Translational	SAT-0929	Safety and Tolerability of Liraglutide 3.0 Mg in Overweight and Obese Adults: The Scale Obesity and Prediabetes Randomized, Double-Blind, Placebo-Controlled 56-Week Trial	Hall F
Saturday	1:00 PM-3:00 PM	Clinical/Translational	SAT-0930	Effects of Liraglutide 3.0 Mg and 1.8 Mg on Body Weight and Cardiometabolic Risk Factors in Overweight and Obese Adults with Type 2 Diabetes Mellitus (T2DM): The Scale Diabetes Randomized, Double-Blind, Placebo-Controlled, 56-Week Trial	Hall F
Saturday	1:00 PM-3:00 PM	Clinical/Translational	SAT-0931	Liraglutide 3.0 Mg Improves Insulin Secretion and Action in Overweight and Obese Adults without Diabetes: Results from Scale Obesity and Prediabetes, a Randomized, Double-Blind and Placebo-Controlled 56-Week Trial	Hall F
Saturday	1:00 PM-3:00 PM	Clinical/Translational	SAT-0933	Beneficial Effects of Family-Based Multiprofessional Therapy on Obesity and Eating Behavior in Children Are Independent on Group or Individual Settings	Hall F
Saturday	1:00 PM-3:00 PM	Clinical/Translational	SAT-0937	Liraglutide 3.0 Mg Improves Body Weight and Cardiometabolic Risk Factors in Overweight or Obese Adults without Diabetes: The Scale Obesity and Prediabetes Randomized, Double-Blind, Placebo-Controlled 56-Week Trial	Hall F
Saturday	1:00 PM-3:00 PM	Clinical/Translational	SAT-0939	Meaningful and Sustained Improvements of Weight and Waist Circumference in Hypogonadal Men on Long-Term Treatment with Testosterone Undecanoate (TU) Injections Are Independent of Age: Observational Data from Two Registry Studies	Hall F
Saturday	1:00 PM-3:00 PM	Clinical/Translational	SAT-0940	Reductions of Weight and Waist Size in 362 Hypogonadal Men with Obesity Grades I to III Under Long-Term Treatment with Testosterone Undecanoate (TU): Observational Data from Two Registry Studies	Hall F
Saturday	1:00 PM-3:00 PM	Clinical/Translational	SAT-0941	Excessively Obese Hypogonadal Experience Substantial and Sustained Weight Loss upon Long-Term Treatment with Testosterone Undecanoate (TU) Injections: Observational Data from Two Registry Studies	Hall F
Saturday	1:00 PM-3:00 PM	Clinical	SAT-0985	Significance of Hypoglycemia in Patients with Type 2 Diabetes Mellitus in Primary Care	Hall F
Saturday	1:00 PM-3:00 PM	Clinical	SAT-0986	Safety and Efficacy of Empagliflozin Monotherapy in a 52-Week Study in Japanese Patients with Type 2 Diabetes Mellitus	Hall F
Saturday	1:00 PM-3:00 PM	Clinical	SAT-0987	Linagliptin Monotherapy Versus Initial Combination Therapy with Metformin in Patients with Newly Diagnosed Type 2 Diabetes (T2D): A Randomized Controlled Trial	Hall F

Date	Time	Session Type	Abstract	Event Title	Location Room #
Saturday, June 21st					
Saturday	1:00 PM-3:00 PM	Clinical	SAT-0988	Control of Oral Advanced Glycation Endproducts (AGEs) By Sevelamer Carbonate Improves Glucose Metabolism and Albuminuria in Stage 2-4 Diabetic Kidney Disease (DKD)	Hall F
Saturday	1:00 PM-3:00 PM	Clinical	SAT-0989	Breakfast Replacement with a Low Glycemic Index Liquid Formula in Type 2 Diabetes: A Cross-over Clinical Trial	Hall F
Saturday	1:00 PM-3:00 PM	Clinical	SAT-0990	Impact of Prescribed and Monitored Medium-Intensity Exercise on Diabetes, Obesity, Cardiovascular Profiles and Quality of Life	Hall F
Saturday	1:00 PM-3:00 PM	Clinical	SAT-0991	Dapagliflozin Reduces HbA1c and Systolic Blood Pressure in Patients with Type 2 Diabetes: Subgroup Analysis Based on Patient Characteristics	Hall F
Saturday	1:00 PM-3:00 PM	Clinical	SAT-0992	In African American Men with Dygsycemia and Vitamin D Deficiency, Vitamin D Supplementation for 1 Year MAY Improve Insulin Sensitivity and Glycemic Status. DATA from a Randomized Controlled Trial of Vitamin D Intervention at Veteran Administration (DIVA, NCT01375660)	Hall F
Saturday	1:00 PM-3:00 PM	Clinical	SAT-0993	Glycemic Effect of Sweetener, Sweete GI-0 in Peoples with Glucose Intolerance	Hall F
Sunday, June 22nd					
Sunday	11:15 am-11:30 am	Translational	PP17-1	Long-Term Safety of Growth Hormone (GH) Replacement in Adults with GH Deficiency (GHD) Following Cure of Acromegaly — a Kims (Pfizer International Metabolic Database) Analysis	W192
Sunday	11:15 am-11:30 am	Clinical	PP22-4	Residual Fracture Risk Following Sequential Teriparatide-Bisphosphonate Therapy in Patients with Very High Risk Osteoporosis	W181
Sunday	11:30 am-1:00 PM	Translational	LB-OR02-6	Empagliflozin Reduces Blood Pressure in Patients with Type 2 Diabetes and Hypertension: A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial (EMPA-REG BP™)	W471
Sunday	11:30 am-1:00 PM	Basic/Translational	OR16-5	A Randomized, Double-Blind, Placebo-Controlled, Crossover Study to Evaluate the Effect of a Melanocortin Receptor 4 (MC4R) Agonist, RM-493, on Resting Energy Expenditure (REE) in Obese Subjects	W179
Sunday	11:30 am-1:00 PM	Clinical/Translational	OR17-5	Efficacy and Safety of Oral Octreotide in Acromegaly: Results of a Multicenter Phase III Trial in 155 Patients	W192
Sunday	11:30 am-1:00 PM	Clinical	OR22-1	Effect of Denosumab Treatment in Postmenopausal Women with Osteoporosis: Eight-Year Results from the Freedom Extension, Phase 3 Clinical Trial	W181
Sunday	11:30 am-1:00 PM	Clinical	OR22-2	Denosumab for the Treatment of Men with Low Bone Mineral Density: 24-Month Results from the Adamo Trial	W181
Sunday	11:30 am-1:00 PM	Clinical/Translational	OR23-6	The Impact of Perioperative Hyperglycemia in Patients with and without Diabetes Undergoing Coronary Artery Bypass Surgery	W185
Sunday	1:00 PM-3:00 PM	Translational	LBSU-1079	High Dose Vitamin D Supplementation for 12 Months Improves Insulin Sensitivity and Glucose Disposition Indices in African American Men with Hypovitaminosis D and Dysglycemia: Results of the D-Vitamin Intervention in Veteran Administration (DIVA) Randomized Clinical Trial (RCT)	Hall F
Sunday	1:00 PM-3:00 PM	Translational	LBSU-1080	Empagliflozin (EMPA) for ≥76 Weeks As Add-on to Pioglitazone with or without Metformin in Patients with Type 2 Diabetes (T2DM)	Hall F

Date	Time	Session Type	Abstract	Event Title	Location Room #
Sunday, June 22nd					
Sunday	1:00 PM-3:00 PM	Translational	LBSU-1081	Empagliflozin (EMPA) Monotherapy for ≥76 Weeks in Drug-Nai¨ve Patients with Type 2 Diabetes (T2DM)	Hall F
Sunday	1:00 PM-3:00 PM	Translational	LBSU-1082	Empagliflozin (EMPA) for ≥76 Weeks As Add-on to Metformin in Patients with Type 2 Diabetes (T2DM)	Hall F
Sunday	1:00 PM-3:00 PM	Basic	SUN-0056	Pharmacokinetic Profile of 50 Mg and 100 Mg Doses of Subcutaneous Testosterone Enanthate Administered with the Novel Jet-Injector™	Hall F
Sunday	1:00 PM-3:00 PM	Basic	SUN-0058	Adherent CPAP Improves Erectile and Sexual Function and Quality of Life in Men with OSA and Erectile Dysfunction (ED): A Randomised Sham Controlled Study	Hall F
Sunday	1:00 PM-3:00 PM	Clinical	SUN-0085	Hypogonadal Patients with Crohn's Disease Benefit from Treatment with Testosterone — Data from an Ongoing, Long-Term, Observational Registry Study	Hall F
Sunday	1:00 PM-3:00 PM	Clinical	SUN-0090	The Pharmacokinetics of Different Doses and Dosing Regimens of Testosterone Undecanoate Injection for the Treatment of Male Hypogonadism	Hall F
Sunday	1:00 PM-3:00 PM	Clinical	SUN-0097	Metabolic Syndrome Parameters in Hypogonadal Men on Long-Term Treatment with Testosterone Undecanoate (TU) Injections Improve Independently from Age: Observational Data from Two Registry Studies	Hall F
Sunday	1:00 PM-3:00 PM	Clinical	SUN-0102	Oral Contraception Versus Low-Dose Pioglitazone-Spironolactone-Metformin (PioSpiMet)	Hall F
Sunday	1:00 PM-3:00 PM	Clinical/Translational	SUN-0163	Androgen Replacement in Boys with 47,XXY Klinefelter Syndrome: Influence on the Testicular Phenotype	Hall F
Sunday	1:00 PM-3:00 PM	Clinical	SUN-0220	The Effect of Long-Term Whey Protein Supplementation on Bone Mineral Density and Body Composition in Older Adults: A Randomized, Double-Blind, Controlled Trial	Hall F
Sunday	1:00 PM-3:00 PM	Clinical	SUN-0251	Residual Fracture Risk Following Sequential Teriparatide-Bisphosphonate Therapy in Patients with Very High Risk Osteoporosis	Hall F
Sunday	1:00 PM-3:00 PM	Translational	SUN-0333	Role of Metformin on Recurrence-Free Survival in Neuroendocrine Tumors	Hall F
Sunday	1:00 PM-3:00 PM	Clinical	SUN-0446	Improved Treatment Satisfaction in Patients with Type 1 Diabetes Mellitus Treated with Insulin Glargine Vs Neutral Protamine Hagedorn Insulin	Hall F
Sunday	1:00 PM-3:00 PM	Clinical	SUN-0452	Quality of Life Assessment in Patients with Graves' Ophthalmopathy Randomized to Treatment with Rituximab Vs. Placebo	Hall F
Sunday	1:00 PM-3:00 PM	Clinical/Translational	SUN-0589	Long-Term Safety of Growth Hormone (GH) Replacement in Adults with GH Deficiency (GHD) Following Cure of Acromegaly — a Kims (Pfizer International Metabolic Database) Analysis	Hall F
Sunday	1:00 PM-3:00 PM	Clinical/Translational	SUN-0597	Utilizing Health Information Technology to Study Clinical Aspects of Diagnosis and Treatment of Patients with Acromegaly: Developing the Acromedic (Acromegaly Multi-site Electronic Data Innovative Consortium) Database	Hall F
Sunday	1:00 PM-3:00 PM	Clinical	SUN-0850	Underlying Mechanisms of Extreme Type 5 Hyperlipoproteinemia in a North American Cohort	Hall F

Date	Time	Session Type	Abstract	Event Title	Location Room #
Sunday, June 22nd					
Sunday	1:00 PM-3:00 PM	Clinical	SUN-0878	Modulation of Leptin to Adiponectin Ratio in EMPOWIR (Enhance the Metabolic Profile of Women with Insulin Resistance), a Randomized Clinical Trial of Normoglycemic Women with Midlife Weight Gain, Waist Gain, and White-Coat Hypertension (Syndrome W)	Hall F
Sunday	1:00 PM-3:00 PM	Clinical/Translational	SUN-0895	Improvement of Metabolic Syndrome (MetS) Parameters in 362 Obese Hypogonadal Men upon Long-Term Treatment with Testosterone Undecanoate (TU) Injections: Observational Data from Two Registry Studies	Hall F
Sunday	1:00 PM-3:00 PM	Clinical/Translational	SUN-0897	Oral Administration of Gelesis100, a Novel Hydrogel, Significantly Decreases Body Weight in Overweight and Obese Subjects	Hall F
Sunday	1:00 PM-3:00 PM	Basic/Translational	SUN-0912	Resistin and Obesity	Hall F
Sunday	1:00 PM-3:00 PM	Basic/Translational	SUN-0921	Resistance Training Improves Metainflammation and Body Composition in Obese Adolescents	Hall F
Sunday	1:00 PM-3:00 PM	Clinical	SUN-1000	Effects of One Year Testosterone Versus Anastrazole Treatment on Physiological Functions in Hypogonadal Older Men	Hall F
Monday, June 23rd					
Monday	11:15 am-11:30 am	Clinical	PP40-3	Once Weekly Dulaglutide Enhances -Cell Function Compared to Metformin in Patients with Type 2 Diabetes (T2DM)	W185
Monday	11:15 am-11:30 am	Clinical	PP40-4	Effects on Glycemic Control and Weight of a Widely Available Weight Control Program Tailored for People with Type 2 Diabetes: Six-Month Results	W185
Monday	11:30 am-1:00 PM	Clinical	OR27-4	International Randomized, Double-Blind, Placebo-Controlled, Phase 3 Study of Linsitinib (OSI-906, L) in Patients (pts) with Locally Advanced or Metastatic Adrenocortical Carcinoma (ACC)	W196
Monday	11:30 am-1:00 PM	Clinical/Translational	OR40-5	Improved Oral Glucose Tolerance in Prediabetics and Type 2 Diabetics (T2D) in a Pilot Clinical Trial Testing a Novel Gastrointestinal (GI) Microbiome Modulator	W185
Monday	1:00 PM-3:00 PM	Clinical	MON-0013	Contrasting Effects of Aromatase Inhibition and Testosterone Therapy in Men with Severe Obesity: A Randomised Clinical Trial	Hall F
Monday	1:00 PM-3:00 PM	Clinical	MON-0019	Long-Term Treatment with Testosterone Undecanoate (TU) Injections Improves Urinary and Sexual Functions and Quality of Life (QoL) Independent of Age	Hall F
Monday	1:00 PM-3:00 PM	Clinical	MON-0147	Safety and Efficacy Results of a 6 Month, Randomized, Multi-Center Trial of a Novel Long-Acting Rhgh (VRS-317) in Naïve to Treatment, Pre-Pubertal Children with Growth Hormone Deficiency (GHD)	Hall F
Monday	1:00 PM-3:00 PM	Clinical	MON-0196	Cinacalcet Normalizes Serum Calcium in a Randomized, Placebo-Controlled Clinical Study in Patients with Primary Hyperparathyroidism Unable to Undergo Parathyroidectomy	Hall F
Monday	1:00 PM-3:00 PM	Clinical	MON-0209	Paricalcitol Therapy Improves Hyperparathyroidism in Patients with X-Linked Hypophosphatemia: Results from a One-Year Randomized Controlled Trial	Hall F
Monday	1:00 PM-3:00 PM	Clinical	MON-0210	Effect of Four Monthly Doses of a Human Monoclonal Anti-FGF23 (Fibroblast Growth Factor 23) Antibody (KRN23) on Quality of Life in X-Linked Hypophosphatemia (XLH)	Hall F

Date	Time	Session Type	Abstract	Event Title	Location Room #
Monday, June 23rd					
Monday	1:00 PM-3:00 PM	Basic	MON-0383	The Relationships Between Thyroid Function Tests and Insulin Receptor Substrate Gene Polymorphisms in Patients with Metabolic Syndrome	Hall F
Monday	1:00 PM-3:00 PM	Clinical/Translational	MON-0475	Minimum Dosage of Methimazole at Discontinuation Is a Strong Index for Predicting Remission of Graves' Disease	Hall F
Monday	1:00 PM-3:00 PM	Clinical/Translational	MON-0477	Antithyroid Drug Therapy Holds Good for Recurrent Graves' Disease	Hall F
Monday	1:00 PM-3:00 PM	Clinical/Translational	MON-0480	An Efficiency and Safety of Short-Term Prednisone Treating to Moderate and Severe Subacute Thyroiditis	Hall F
Monday	1:00 PM-3:00 PM	Clinical/Translational	MON-0635	The Most Common Endocrine Disease in the Clinic Is Often Forgotten	Hall F
Monday	1:00 PM-3:00 PM	Clinical/Translational	MON-0636	Childhood Craniopharyngioma — Changes of Treatment Strategies in the Multinational Prospective Trials Kraniopharyngeom 2000/2007	Hall F
Monday	1:00 PM-3:00 PM	Clinical	MON-0656	Impact of a Mindfulness-Based Stress Reduction Program on Depressive and Anxiety Symptomatology, Stress and Cortisol Levels and the Quality of Life in Premenopausal Patients with Polycystic Ovary Syndrome	Hall F
Monday	1:00 PM-3:00 PM	Clinical	MON-0663	Persistent Weight Loss in Patients Treated with Mifepristone (MIFE) for Cushing's Syndrome: Results from the Seismic & Long Term Extension Studies	Hall F
Monday	1:00 PM-3:00 PM	Clinical	MON-0664	A Pilot Study Assessing the Use of Continuous Subcutaneous Hydrocortisone Infusion in the Treatment of Congenital Adrenal Hyperplasia: Preliminary Data	Hall F
Monday	1:00 PM-3:00 PM	Clinical/Translational	MON-0715	Study Design of a Phase II Trial of Subcutaneous Pasireotide Alone or Combined with Cabergoline in Patients with Cushing's Disease	Hall F
Monday	1:00 PM-3:00 PM	Clinical/Translational	MON-0726	An Acromegaly, Open-Label, Multi-Center, Safety Monitoring Program for Treating Patients with SOM230 (pasireotide) LAR Who Have Need to Receive Medical Therapy (ACCESS)	Hall F
Monday	1:00 PM-3:00 PM	Bench to Bedside	MON-0823	Circadian Cortisol and Growth Hormone Profiles in Patients with Addison's Disease: A Comparison of Continuous Subcutaneous Hydrocortisone Infusion with Conventional Glucocorticoid Replacement Therapy	Hall F
Monday	1:00 PM-3:00 PM	Basic/Clinical	MON-0927	The Effects of Consumption Levels of Fructose and Fructose Containing Sugars on Circulating Glucose, Insulin, Leptin, and Active Ghrelin	Hall F
Monday	1:00 PM-3:00 PM	Clinical	MON-0953	Once Weekly Dulaglutide Enhances □-Cell Function Compared to Metformin in Patients with Type 2 Diabetes (T2DM)	Hall F
Monday	1:00 PM-3:00 PM	Clinical	MON-0955	Effects on Glycemic Control and Weight of a Widely Available Weight Control Program Tailored for People with Type 2 Diabetes: Six-Month Results	Hall F
Monday	1:00 PM-3:00 PM	Clinical	MON-0985	How Much Is Too Much? Outcomes in Patients Using High-Dose Insulin Glargine	Hall F

Date	Time	Session Type	Abstract	Event Title	Location Room #
Tuesday, June 24th					
Tuesday	9:30 am-11:00 am	Clinical	OR43-1	The First Multi-Dose Trial of a Human Anti-FGF23 (Fibroblast Growth Factor 23) Antibody (KRN23) in Adults with X-Linked Hypophosphatemia (XLH)	W181
Tuesday	9:30 am-11:00 am	Clinical	OR43-5	Increased Risk for Vertebral Fractures with Long-Term Observation in Mild Primary Hyperparathyroidism: Five Year Data from the Scandinavian Investigation of Primary Hyperparathyroidism (SIPH)	W181
Tuesday	9:30 am-11:00 am	Translational	OR53-1	Defects in Aldosterone Signaling Exacerbate Sodium Loss at Birth in Preterm Infants: Prime Results from the Premaldo Study	W183 BC
Tuesday	9:30 am-11:00 am	Clinical	OR54-3	ABC Goal Attainment in Patients with Type 2 Diabetes Mellitus in US Primary Care	W190

Presentations

Saturday, June 21, 2014

ENDOCRINE SOCIETY

OR04-2: Blood kisspeptin level test may identify which pregnant women are at high risk for miscarriage

Measuring pregnant women's blood kisspeptin levels early in their pregnancy may effectively predict their risk of miscarriage, a new study finds. The results will be presented Saturday at ICE/ENDO 2014, the joint meeting of the International Society of Endocrinology and the Endocrine Society in Chicago.

"We show that, even in women with no symptoms of miscarriage, a single blood test for kisspeptin more accurately predicted the risk of miscarriage compared with the hCG [human chorionic gonadotropin] levels that were measured at the same time," said lead study author Ali Abbara, MBBS BSc MRCP, clinical research fellow in the Department of Investigative Medicine at Imperial College London, United Kingdom. "Being better able to identify women at high risk of miscarriage may allow for improved monitoring and management of these pregnancies."

Miscarriage affects 1 in 5 pregnancies, and most miscarriages occur early in pregnancy, before the woman is able to carry her fetus for 24 weeks. Kisspeptins are peptides encoded by the KISS1 gene, which is highly prevalent in the placenta. Kisspeptins circulating in the blood increase dramatically during normal human pregnancy, to several thousand times non-pregnancy levels, which makes them a novel predictive marker for assessing the risk of later complications.

This is the first study showing that a single plasma kisspeptin level test during early pregnancy can identify the risk for miscarriage in women who have no symptoms. Dr. Abbara and his colleagues evaluated plasma kisspeptin levels in 993 asymptomatic pregnant women who were, on average, 11 weeks pregnant and were visiting their doctor for a routine prenatal exam at an urban academic obstetric center.

The women provided a single blood sample and the researchers measured each woman's levels of kisspeptin and hCG (a hormone commonly used to diagnose possible miscarriage and other abnormalities) and compared them.

The researchers found that, in women who miscarried, blood kisspeptin levels, corrected for gestation at time of blood test, were 60% lower than the levels in women who later had healthy pregnancies. Compared with hCG, which was 36% lower in women who miscarried, blood kisspeptin levels more accurately predicted future miscarriage.

They also found that plasma kisspeptin over 1,306 picomoles per liter was strongly associated with a lower risk of miscarriage.

"Future work will assess whether it is possible to intervene to prevent miscarriage in women identified as being at high risk of this complication by a low blood kisspeptin level," Dr. Abbara observed.

The Medical Research Council UK, National Institute for Health Research, Wellcome Trust, funded this study.

# # #

OR04-2: Plasma Kisspeptin Measurement during Early Pregnancy Is a Highly Predictive Marker of Subsequent Miscarriage

Ali Abbara. *Imperial College London*

Ali Abbara[1], Channa Nalin Jayasena[2], Chioma Izzi-Engbeaya[1], Alexander N Comninos[1], Richard A Harvey[3], Juan Gonzalez Maffe[4], Subair Sarang[5], Zainab Ganiyu-Dada[6], Ana Padilha[7], Mandish Dhanjal[8], Catherine Williamson[9], Lesley Regan[8], Mohammad A. Ghatei[2], Stephen R. Bloom[2] and Waljit S. Dhillo[2], (1) Investigative Medicine, Imperial College London, United Kingdom, (2) Investigative Medicine, Imperial College London, London, United Kingdom, (3) Biochemistry, Imperial College NHS Trust, London, (4) Clinical Trial Unit, Imperial College London, London, (5) Investigative Medicine, Imperial College London, (6) Investigative medicine, Imperial College London, london, United Kingdom, (7) Biochemistry, Imperial College NHS Trust, (8) Obstetrics and Gynaecology, Imperial College NHS Trust, (9) Obstetrics and Gynaecology, King's College London

Background: The kisspeptins are a group of peptides encoded by the KISS1 gene, which is highly expressed in the placenta. Circulating levels of kisspeptin rise dramatically during normal human pregnancy, reaching levels several thousand-fold higher when compared with levels found outside of pregnancy. Plasma kisspeptin levels measured during early pregnancy may therefore represent a novel predictive marker for assessing the risk of subsequent pregnancy complications. Miscarriage (pregnancy loss prior to 24 weeks of gestation) is the most common complication of pregnancy, affecting 1 in 5 pregnancies.

Objective: To determine whether a single measurement of plasma kisspeptin in asymptomatic women attending their antenatal booking visit predicts miscarriage risk.

Study Design: Prospective cohort study in single tertiary obstetric centre in London.

Participants: We recruited 993 asymptomatic pregnant women attending their routine antenatal booking visit (mean gestation of 11.2 weeks (range 5.9-29.0) between 2010 and 2012.

Main Outcome Measures: Plasma kisspeptin and serum hCG were measured during the routine booking antenatal visit and pregnancy outcome was prospectively recorded.

Results: Plasma kisspeptin levels were highly correlated with the gestational week of pregnancy ($r^2=0.57$; $P<0.0001$). Gestational age-corrected (multiples of median; MoM) plasma kisspeptin levels were 60.4% lower ($P<0.001$), and MoM hCG was 36.1% lower ($P<0.001$) in women who were later diagnosed with miscarriage when compared with women who did not miscarry. Plasma kisspeptin >1306 pmol/L was strongly associated with a reduced risk of miscarriage, even after adjusting for age, body mass index, gestational age, smoking and blood pressure (Odds Ratio 0.13 [CI 0.08-0.22], $P=0.0001$). Plasma kisspeptin had a higher diagnostic performance for miscarriage when compared with hCG (ROC area under curve: 0.899±0.025, plasma kisspeptin; 0.775±0.040, serum hCG, $P<0.01$ vs. plasma kisspeptin).

Conclusion: This is the first study demonstrating that a single plasma kisspeptin measurement taken during early pregnancy provides a highly predictive marker for identifying asymptomatic pregnant women with subsequent miscarriage.

Presentation Date: Saturday, June 21
Presentation Time: 11:30 a.m.-1:00 p.m.
Location: Room W192

OR07-1: Sleep and mood improves after substantial weight loss

Obese adults who lose at least 5 percent of their body weight report that they sleep better and longer after six months of weight loss, according to a new study. The results will be presented Saturday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

"This study confirms several studies reporting that weight loss is associated with increased sleep duration," said the study's lead investigator, Nasreen Alfaris, MD, MPH, a fellow in the Department of Medicine at the Perelman School of Medicine at the University of Pennsylvania, Philadelphia.

In addition, the study found that weight loss at 6 months improved sleep quality, as well as mood, regardless of how the individuals lost the weight.

The 390 study subjects participated in the Practice-Based Opportunities for Weight Reduction at the University of Pennsylvania (POWER-UP) trial. This 2-year study, funded by the National Institutes of Health, compared three behavioral interventions for weight loss in obese adults treated in primary care practices.

Subjects (311 women and 79 men) were randomly assigned to one of three programs that provided varying amounts of support to achieve the same diet and exercise goals. The groups were: (1) usual care, in which subjects received printed educational materials during quarterly visits with their primary care provider; (2) brief lifestyle counseling, which included quarterly visits with their primary care provider, combined with brief meetings with lifestyle coaches; or (3) enhanced brief lifestyle counseling, with meal replacements or weight loss medications added to the second intervention.

The researchers evaluated changes in weight, sleep duration and quality, and mood after 6 and 24 months of treatment. They compared subjects who lost 5 percent or more of their original body weight with those who lost less than 5 percent, regardless of their group assignment. The analyses controlled for several subject variables, including sex and age.

At month 6, subjects in both lifestyle counseling groups lost more weight on average (brief counseling: 7.8 lb; enhanced counseling: 14.7 lb) than those in the usual care group (4.4 lb), Alfaris reported.

Examining all three groups together, subjects who lost at least 5 percent of their weight at month 6 reported that they gained an average of 21.6 minutes of sleep a night, compared with only 1.2 minutes for those who lost less than 5 percent. Likewise, subjects who lost >5% of initial weight reported greater improvements on measures of sleep quality and mood (i.e., symptoms of depression), compared with subjects who lost <5%.

Only improvements in mood remained statistically significant at 24 months, according to Alfaris.

"Further studies are needed to examine the potential effects of weight regain in diminishing the short-term improvements of weight loss on sleep duration and sleep quality," she said.

# # #

OR07-1: Effect of Behavioral Weight Loss on Sleep and Mood: Results from the POWER-up Trial

Nasreen Alfaris. *University of Pennsylvania*

Nasreen Alfaris, MD, MPH[1], Jesse Chittams, MS[2], Lisa Diewald, MS, RD, LDN[2], Marion Vetter, MD[3] and Thomas Wadden, PhD[1], (1) Center for Weight and Eating Disorders, University of Pennsylvania, philadelphia, PA, (2) Center for Weight and Eating Disorders, University of Pennsylvania, Philadelphia, PA, (3) Center for Weight and Eating Disorders, Univ of Pennsylvania, Philadelphia, PA

Little is known about the effects of intentional weight loss on sleep quality or sleep duration in obese individuals not selected for obstructive sleep apnea. This study examined the issue in 390 subjects (M age=51.5±11.5 yr, BMI=38.5±4.7 kg/m2, 75.4% female) who participated in a 2-yr randomized trial of behavioral weight loss in primary care (POWER-UP study). As reported previously[1], subjects were randomized to: 1) Usual Care; 2) Brief Lifestyle Counseling (LC); or 3) Enhanced Brief LC, all of which were delivered by physicians and medical assistants in the primary care practices. The three interventions provided subjects different amounts of support to achieve the prescribed diet (1200-1800 kcal/d) and activity (180 min/wk) goals. This study reports changes at months 6 and 24 in weight, sleep quality and duration (assessed by the Pittsburgh Sleep Quality Index questionnaire [PSQI]), and mood, measured by the Patient Health Questionnaire-8 (PHQ-8). Data were analyzed by mixed effects general linear models. Changes in sleep and mood also were compared in subjects who lost ≥5% vs <5% of initial weight, regardless of original group assignment. At month 6, subjects in the three groups lost a mean (SEM) of 2.0±0.5, 3.5±0.5, and 6.6±0.5 kg, respectively; all three groups differed significantly from each other ($p<0.05$). There were no significant differences between groups in sleep duration, PSQI scores, or mood, although the latter two values declined (favorably) over time ($p<0.05$). At month 24, subjects in Enhanced Brief LC lost more weight than Usual Care (-4.6±0.7 vs -2.0±0.5 kg, $p<0.05$) and reported more favorable changes in sleep duration (+13.8±9.0 vs -9.0±9.0 min; $p<0.05$). There were no differences between groups on PSQI or mood scores, but both values declined (favorably) over time ($p<0.05$). When examining participants who lost ≥5% vs <5% of initial weight, regardless of original group assignment, at month 6 sleep increased by 21.6±7.2 min in the former group, compared with 1.2±6.0 min for those losing <5% ($p<0.05$). Similarly favorable changes, with greater weight loss, were observed on the PSQI (-1.6±0.2 vs -0.4±0.2, $p < 0.001$) and PHQ (-2.5±0.4 vs -0.1±0.3, $p<0.0001$). At month 24, however, only the differences between the two groups on mood (PHQ) remained significant ($p<0.05$), and at no time were significant differences observed between the two weight loss categories on sleep duration. The present findings indicate that losing ≥5% of initial weight is associated with significant short-term (6 month) self-reported improvements in sleep quality and mood. Further study is needed of the possible effects of weight regain, as observed in this study, in mitigating short-term improvements in sleep quality.

Presentation Date: Saturday, June 21
Presentation Time: 11:30 a.m.-3:00 p.m.
Location: Room W183 BC

OR13-5: Raising low vitamin D levels lowers risk of prediabetes progressing to diabetes

Vitamin D and calcium supplementation along with diet and exercise may prevent Type 2 diabetes in prediabetic individuals who have insufficient vitamin D in their bodies, a study from India suggests. The results will be presented Saturday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

Vitamin D deficiency has been linked to prediabetes, which is a blood glucose, or sugar, level that is too high but not high enough to be considered diabetes. It is unclear, however, if bringing low vitamin D blood levels to normal through supplementation will affect progression to diabetes.

In the new study, every unit increase in vitamin D level after supplementation of the vitamin decreased the risk of progression to diabetes by 8 percent, the authors reported.

"Without healthy lifestyle changes, nothing works to prevent diabetes in at-risk individuals," said the lead author, Deep Dutta, MD, DM, a research officer at the Institute of Postgraduate Medical Education & Research and Seth Sukhlal Karnani Memorial Hospital in Calcutta, India. "However, our results are encouraging because the addition of vitamin D and calcium supplements is easy and low in cost."

"If our results are confirmed in a large multicenter trial," Dutta said, "vitamin D supplementation would provide us with a new tool in the armamentarium of diabetes prevention strategies."

The West Bengal chapter of the Research Society for the Study of Diabetes in India funded this study. Of 170 individuals with prediabetes who had not taken vitamin D supplements in the past six months, 125 had vitamin D deficiency or insufficiency, which the researchers defined as a vitamin D blood level (25-hydroxyvitamin D) of 30 nanograms per milliliter (ng/mL) or less. These 125 study subjects were randomly assigned to one of two treatment groups. In the first group, 68 subjects received ready-to-mix, powdered vitamin D3 (cholecalciferol, D-Rise sachets, USV Ltd., Mumbai, India) at a dose of 60,000 International Units (IU) once weekly for eight weeks and then monthly. They also received a daily 1,250-milligram calcium carbonate tablet.

The other group of 57 subjects received only calcium supplements. Both groups received advice to eat a healthy, calorie-appropriate diet and to engage in brisk exercise for 30 minutes each day.

The researchers analyzed results for subjects who had at least a year of follow-up tests. After an average of nearly two years and four months' follow-up, only six of 55 subjects (10.9 percent) in the group that received vitamin D plus calcium supplementation had become diabetic, whereas diabetes developed in 13 of 49 individuals (26.5 percent) in the calcium-alone group. Blood sugar levels reportedly became normal in about twice as many people in the vitamin D group as in the group that did not get vitamin D supplementation: 23 of 55 subjects versus 10 of 49 subjects, respectively (41.8 percent versus 20.4 percent).

At the end of the study, those who received vitamin D supplementation had much higher vitamin D levels in the blood and lower fasting blood glucose levels compared with the other group. Every unit (1 ng/mL) increase in vitamin D in the body was associated with a 5.4 percent increased chance of reversal to normal blood sugar levels, Dutta reported.

He said the greater reversal to normal blood sugar in the vitamin D group presumably occurred through improvements in their insulin resistance and inflammation.

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OR13-5: Vitamin-D Supplementation in Prediabetes Reduced Progression to type2 Diabetes through Decreased Insulin Resistance and Systemic Inflammation: An Open Label Randomized Prospective Study from Eastern India

Deep Dutta. *Institute of Post Graduate Medical Education & Research*

Deep Dutta, MD, DM[1], Samim Ali Mondal, MSc[2], Indira Maisnam, MD, DM[3], Satinath Mukhopadhyay, MD, DM[4] and Subhankar Chowdhury, MD, DM[3], (1) Endocrinology & Metabolism, Institute of Post Graduate Medical Education & Research (IPGMER) and Seth Sukhlal Karnani Memorial (SSKM) Hospital, Calcutta, West Bengal, India, (2) Biochemistry, Institute of Post Graduate Medical Education & Research (IPGMER) and Seth Sukhlal Karnani Memorial (SSKM) Hospital, Calcutta, India, (3) Endocrinology & Metabolism, Institute of Post Graduate Medical Education & Research (IPGMER) and Seth Sukhlal Karnani Memorial (SSKM) Hospital, Calcutta, India, (4) Endocrinology and Metabolism, Institute of Postgraduate Medical Education & Research (IPGMER) and Seth Sukhlal Karnani Memorial (SSKM) Hospital, Calcutta, India

Objective: Indian individuals with prediabetes (IPD) have one of the highest rates of progression (≈18% per year) to type2 diabetes (T2DM). Since vitamin-D deficiency has been linked to prediabetes, we aimed to evaluate role of vitamin-D supplementation on progression to T2DM and/ or reversal to normoglycemia in IPD.

Methods: IPD with persistent impaired fasting glucose (IFG) or impaired glucose tolerance (IGT) over 2 oral glucose tolerance test (OGTT), without any severe co-morbid state or drug intake, having serum 25-OH-vitamin-D (25OHD) ≤30ng/ml were randomized into Group-A [received vitamin-D (cholecalciferol 60,000 U once weekly for 8 weeks then monthly) and calcium (1250mg of calcium carbonate/day equivalent to elemental calcium 500mg) supplementation] and Group-B (received calcium only). IPD with serum 25OHD>30ng/ml were also followed with calcium supplementation (Group-C). All received therapeutic lifestyle modification. OGTT, insulin, 25OHD, lipids, interleukin-6 (IL6), tumor necrosis factor-α (TNF-α) and hsCRP were done at baseline and annually. Data from IPD with at least 1-year follow up were analyzed. The trial is registered with clinical trial registry of India at ctri.nic.in (CTRI/2011/091/000192).

Results: 1946 individuals were initially screened, of which 498 underwent OGTT-1 and 301 underwent OGTT-2. 125 out of 170 finally included IPD (73.52%) had 25OHD ≤30ng/ml. Mean follow-up in Group-A (n=55), B (n=49) and C (n=32) was 28.2±8.83, 29.15±7.69 and 27.51±7.8 months respectively. 25OHD had significant correlation with HOMA2-IR (r=-0.42; P=0.004), TNFα (r=-0.31; P=0.03) and hsCRP (r=-0.31; P=0.03), after adjusting for BMI.

At the end of study, Group-A IPD had significantly higher serum 25OHD (p<0.001), lower FBG (p=0.023), 2hPGBG (p<0.001), TNFα (p=0.002) and IL-6 (p=0.0005) as compared to Group-B and C. Group-A IPD as compared to Group-B had significantly lower progression to diabetes (6/55 vs. 13/49; P=0.04), and higher reversal to normoglycemia (23/55 vs. 10/49; P=0.02). Cox regression revealed baseline 25OHD [Exp(B)=0.921; P=0.049] and 2hPGBG [Exp(B)=1.033; P=0.014] independently predicted progression to diabetes. Hypertension [Exp(B)=0.416; P=0.043] and baseline 25OHD [Exp(B)=1.054; P=0.046] predicted reversal to normoglycemia.

Conclusion: Vitamin-D supplementation in IPD decreased the rate of progression to diabetes and increased reversal to normoglycemia, presumably by an improvement in IR and systemic inflammation.

Presentation Date: Saturday, June 21
Presentation Time: 11:30 a.m.-1:00 p.m
Location: Room W184

OR13-1: Vitamin D can lower weight and blood sugar via the brain

Vitamin D treatment acts in the brain to improve weight and blood glucose (sugar) control in obese rats, according to a new study being presented Saturday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

"Vitamin D deficiency occurs often in obese people and in patients with Type 2 diabetes, yet no one understands if it contributes to these diseases," said Stephanie Sisley, MD, the study's principal investigator and an assistant professor at Baylor College of Medicine, Houston. "Our results suggest that vitamin D may play a role in the onset of both obesity and Type 2 diabetes by its action in the brain."

"The brain is the master regulator of weight," Sisley said. A region of the brain called the hypothalamus controls both weight and glucose, and has vitamin D receptors there.

In this study funded by the National Institutes of Health, Sisley and partners at the University of Cincinnati delivered vitamin D directly to the hypothalamus. The investigators administered the active, potent form of vitamin D—called 1,25-dihydroxyvitamin D3—to obese male rats through a cannula (thin tube) surgically inserted using anesthesia into the brain's third ventricle. This narrow cavity lies within the hypothalamus. Rats recovered their presurgery body weight, and the researchers verified the correct cannula placement.

The animals received nothing to eat for four hours, so they could have a fasting blood sugar measurement. Afterward, 12 rats received vitamin D dissolved in a solution acting as a vehicle for drug delivery. Another 14 rats, matched in body weight to the first group, received only the vehicle, thus serving as controls. One hour later, all rats had a glucose tolerance test, in which they received an injection of dextrose, a sugar, in their abdomen, followed by measurement of their blood sugar levels again.

Compared with the control rats, animals that received vitamin D had improved glucose tolerance, which is how the body responds to sugar. In a separate experiment, these treated rats also had greatly improved insulin sensitivity, the body's ability to successfully respond to glucose. When this ability decreases—called insulin resistance—it eventually leads to high blood sugar levels. Two of insulin's main effects are to clear glucose from the bloodstream and decrease glucose production in the liver. In this study, vitamin D in the brain decreased the glucose created by the liver.

In a separate experiment of long-term vitamin D treatment, the researchers gave three rats vitamin D and four rats vehicle alone for four weeks. They observed a large decrease in food intake and weight in rats receiving vitamin D compared with the group that did not get vitamin D. Over 28 days, the treated group ate nearly three times less food and lost 24 percent of their weight despite not changing the way they burned calories, study data showed. The control group did not lose any weight.

"Vitamin D is never going to be the silver bullet for weight loss, but it may work in combination with strategies we know work, like diet and exercise," Sisley commented.

She said more research is necessary to determine if obesity alters vitamin D transport into the brain or its action in the brain.

# # #

OR13-1: CNS Vitamin D Improves Glucose Tolerance, Hepatic Insulin Sensitivity, and Reverses Diet-Induced Obesity

Stephanie Sisley. *Baylor College of Medicine*

Stephanie Sisley, MD, Pediatrics, Baylor College of Medicine, Houston, TX, Randy Seeley, PHD, Dept of Internal Medicine, Division of Endocrinology, Univ of Cincinnati, Cincinnati, OH and Darleen Sandoval, PhD, University of Cincinnati, Cincinnati, OH

Low vitamin D levels have been correlated to both obesity and the development of type 2 diabetes (T2DM) (1, 2), although no causative mechanisms have been established. Vitamin D receptors are present in the hypothalamus (3), a region important in both weight and glucose regulation. The role of these receptors, though, is unknown. We tested the hypothesis that vitamin D can act in the brain to improve glucose tolerance and weight gain in diet-induced obese animals. 1,25-dihydroxyvitamin D3, the active form of vitamin D, improved glucose tolerance in DIO rats when given into the third cerebral ventricle (i3vt) 1 hour prior to an intraperitoneal glucose tolerance test. During a hyperinsulinemic euglycemic clamp, i3vt 1,25-dihydroxyvitamin D3 acutely improved whole body insulin sensitivity, as demonstrated by an 8-fold higher glucose infusion rate in vitamin D treated animals compared to vehicle treated animals (13.19±0.96 vs. 1.55±0.62 mg/kg/min; $P < 0.0001$; $n \geq 4$ per group). I3vt vitamin D3 suppressed hepatic glucose production to 50% of vehicle treated animals (7.36±1.98 vs. 16.40±2.82 mg/kg/min; $P = 0.03$). This correlated with a 9-fold decrease in the expression of phosphoenolpyruvate carboxykinase (PEPCK), a key enzyme in hepatic gluconeogenesis, in vitamin D treated animals (12.67±6.86 vs. 118.3±66.61 ratio of PEPCK:L32; $P = 0.009$). No changes occurred between groups in glucose clearance (13.59±0.97 vs. 9.96±1.67 mL/kg/min; $P = 0.08$). Although i3vt 1,25-dihydroxyvitamin D3 did not change food intake when given acutely, chronic administration dramatically reduced food intake (179.71±11.27 vs. 484.29±28.84 g/28 days; $P < 0.0001$; $n \geq 3$ per group) and body weight (509.87±9.43 vs. 670.21±38.05 g; $P = 0.014$) of DIO animals on a high fat diet without changes in energy expenditure. These results demonstrate the ability of vitamin D to act within the brain to dramatically alter glucose homeostasis and weight maintenance in DIO rats and suggest that vitamin D may play a large role in the onset of both obesity and T2DM.

Results expressed as mean±SEM.

Presentation Date: Saturday, June 21
Presentation Time: 11:30 a.m.-1:00 p.m.
Location: Room W184

SAT-0966: Gender-based treatment needed for cardiovascular risk factors in diabetes

Women with Type 2 diabetes and high cholesterol are less likely than their male peers to reach treatment goals to lower their "bad" cholesterol, or low-density lipoprotein (LDL) cholesterol, despite access to cholesterol-lowering medication, a Canadian study finds. The results will be presented on Saturday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

Although other research has shown a similar gender gap in reduction of LDL cholesterol among adults with diabetes, the new study found that access to medication is not responsible for this difference. All patients, who were in a database from pharmacies in four Canadian provinces, had social insurance and could afford their medications, according to the study's principal investigator, Pendar Farahani, MD, MSc, an endocrinologist at Queen's University, Kingston, Ontario.

The finding that women were not able to lower their so-called bad cholesterol sufficiently is a concern, Farahani noted. Abnormal cholesterol levels are a risk factor for heart disease and stroke, as is diabetes.

"Women with diabetes have a considerably higher rate of cardiovascular-related illness and death than men with diabetes," Farahani said. "This pattern is likely related to poorer control of cardiovascular risk factors."

To evaluate whether biological sex influenced the results of cholesterol-lowering drug treatment, the investigators included nearly equal numbers of men and women (101 and 97) in their study. The average age for men was 65 years and for women was 63. All patients had Type 2 diabetes and had filled prescriptions for statin medication to treat high cholesterol between 2003 and 2004.

With treatment, only 64 percent of women lowered their LDL cholesterol to the recommended level compared with 81 percent of men, the investigators reported. The average LDL cholesterol level was 2.39 millimoles per liter (mmol/L) among women and 2.07 mmol/L for men.

At the time of the study, the Canadian Diabetes Association recommended that people with diabetes achieve an LDL cholesterol level of 2.5 mmol/L or less (now 2.0 mmol/L). In the U.S., LDL cholesterol goals are ideally below 100 milligrams per deciliter (mg/dL), the equivalent of less than 2.59 mmol/L, according to the American Diabetes Association.

The study did not explore the reasons why women had poorer LDL cholesterol. However, past research supports that women have poorer adherence to taking their statin medicine. Farahani said statins theoretically appear to have somewhat dissimilar pharmacological properties in a woman's body than a man's, which might explain why women typically have more bothersome side effects such as muscle pain.

Despite their differences in LDL cholesterol, male and female subjects reportedly achieved similar long-term control of their blood glucose, or sugar, as measured by a hemoglobin A1C level of 6.8 percent for each group. Most people with diabetes should have an A1C below 7 percent.

"Additional clinical investigations of the reasons for gender differences are needed to eliminate fundamental inequalities between men and women in the treatment and prevention of cardiovascular disease in patients with diabetes," Farahani said. "The findings suggest the need for gender-based evaluation and treatment of cardiovascular risk factors in these patients."

# # #

SAT-0966: Gender Gap for LDL-C Goal Achievement Amongst Patients with Diabetes and Dyslipidemia

Pendar Farahani. *Queen's University*

Pendar Farahani, MD, MSC, Division of Endocrinology, Department of Medicine, Queen's University, Kingston, ON, Canada and Mitchell Levine, MD, MSc, Center for Evaluation of Medicines, McMaster University

Background: Women with diabetes have a considerably higher risk of cardiovascular related morbidity and mortality than men with diabetes.

Objective: To investigate LDL-C goal attainment amongst men versus women with diabetes and dyslipidemia.

Method: A sub-cohort of patients with diabetes was identified amongst patients with dyslipidemia on lipid-lowering pharmacotherapy in a Canadian database from primary care settings. HgbA1c and components of fasting lipid profile for men and women with diabetes were compared using ANOVA. Chi-square was used for LDL-C goal attainment comparison between men and women.

Results: 101 men and 97 women with dyslipidemia and diabetes were identified in the database. Average age was 65 (9) [mean (SD)] and 63 (11) years-old for men and women, respectively. No significant differences for HgbA1c was detected between men [6.8% (1.3)] and women [6.8% (1.0)] as an indicator of blood glucose management (P-value: 0.30). However, only 64% of female patients achieved LDL-C goal in comparison to 81% of male patients (P-value: 0.003). Average LDL-C on lipid lowering pharmacotherapy was 2.07 (0.76) mmol/l amongst men and 2.39 mmol/l amongst women.

Conclusion: This study demonstrated women with diabetes are more likely than men to have a LDL-C above treatment goals. However, this pattern of gender gap was not observed for HgbA1c goal attainment. The concept of gender gap is useful for identifying at-risk groups for prevention and treatment efforts.

Presentation Date: Saturday, June 21
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

SAT-0937: Diabetes drug, liraglutide, improves risk factors for heart disease

Treatment with the diabetes drug liraglutide, in combination with diet and exercise, led to a significant reduction in weight and improved a number of cardiovascular risk factors, including high blood pressure and high cholesterol, according to a multicenter study. The results, from more than 3,700 overweight and obese nondiabetic adults, will be presented Saturday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

"If these improvements continue over time, they may result in a lower risk of heart disease," said the study's principal investigator, Carel Le Roux, MD, PhD, Diabetes Complications Research Centre, University College Dublin.

The drug is undergoing testing at a 3 milligram (mg) dose for long-term weight management as part of the SCALE™ (Satiety and Clinical Adiposity—Liraglutide Evidence in Nondiabetic and Diabetic Subjects) Obesity and Prediabetes trial. Liraglutide currently is marketed as Victoza® in 1.2 mg and 1.8 mg injectable doses for adults with Type 2 diabetes to help control blood glucose (sugar) when used along with diet and exercise. The drug does not have approval for weight loss, according to its manufacturer, Denmark-headquartered Novo Nordisk, which sponsored the study.

The study included 3,731 nondiabetic obese adults and overweight adults who had at least one other risk factor for diabetes and heart disease, such as prediabetes, high blood pressure or high cholesterol. As part of the study's weight loss efforts, all subjects exercised and ate 500 fewer calories per day than usual. In addition, they were randomly assigned, in a 2-to-1 ratio, to a once-daily injection with either 3 mg of liraglutide (2,487 subjects) or placebo (1,244 subjects) for 56 weeks. Neither the subjects nor the investigators knew who received the active drug.

On average, individuals treated with liraglutide 3 mg lost 5.4 percent more of their body weight, achieving a total of 8 percent, and nearly 1.7 more inches (4.2 centimeters) around their waist than did those who received placebo, the investigators reported.

Compared with the placebo group, liraglutide-treated subjects also experienced better improvements in blood pressure and levels of all fasting lipids (blood fats), including LDL ("bad") cholesterol, HDL ("good") cholesterol, triglycerides and total cholesterol, according to Le Roux. These improvements, he said, resulted in a greater reduction in net use of blood pressure drugs and lipid-lowering medications in the liraglutide 3 mg group than in the placebo group.

In general, the researchers found liraglutide 3 mg to have a safety profile that was similar to that found in previous clinical trials of the drug in individuals with Type 2 diabetes treated with lower doses.

"Current obesity treatment options are limited," Le Roux said. "There is a need for new treatment options for people who struggle with obesity and obesity-related diseases that can help in reducing their weight."

# # #

Note: For results from the SCALE Obesity and Prediabetes trial of liraglutide's role in reducing the frequency of prediabetes and delaying onset of Type 2 diabetes, see News Summary SAT-0925.

SAT-0937: Liraglutide 3.0 Mg Improves Body Weight and Cardiometabolic Risk Factors in Overweight or Obese Adults without Diabetes: The Scale Obesity and Prediabetes Randomized, Double-Blind, Placebo-Controlled 56-Week Trial

Carel Le Roux. *University College Dublin*

Carel Le Roux, MD, PhD, Diabetes Complications Research Centre, University College Dublin, Dublin, Ireland, Arne Astrup, MD, University of Copenhagen, Frederiksberg C, Denmark, Ken Fujioka, MD, Department of Endocrinology, Scripps Clinic, La Jolla, CA, Frank Lyons Greenway III, MD, Pennington Biomed Res Ctr, Baton Rouge, LA, Alfredo Halpern, MD, Endocrinology, Universidade Sao Paulo, Sao Paulo, Brazil, Michel Krempf, MD, PhD, School of Medicine, Hopital Nord - Laennec, Nantes, France, David C Lau, MD PhD, University of Calgary, Calgary, AB, Canada, Rafael Violante Ortiz, MD, Internal Medicine, Instituto Mexicano del Seguro Social, Cuidad Madero, Tamaulipas, Mexico, John Wilding, DM, FRCP, Department of Obesity and Endocrinology, University of Liverpool, Liverpool, United Kingdom, Christine Bjørn Jensen, MD, PhD, GLP-1 & Obesity, Novo Nordisk A/S, Søborg, Denmark and F Xavier Pi-Sunyer, MD, MPH, St Luke's Roosevelt Hosp, New York, NY

Obesity is a chronic disease associated with multiple progressive comorbidities including hypertension, dyslipidemia, type 2 diabetes and atherosclerosis. A 5-10% weight loss has been shown to improve weight-related comorbidities. This phase 3 trial investigated the effects of liraglutide 3.0 mg, as adjunct to diet and exercise, on weight loss (primary endpoint) and cardiometabolic risk factors (waist circumference, blood pressure, triglycerides, HDL cholesterol and other biomarkers).

Individuals (BMI ≥27 kg/m2 with ≥1 comorbidity or ≥30 kg/m2) were advised on a 500 kcal/day deficit diet and exercise program and randomized 2:1 to once daily sc liraglutide 3.0 mg (n=2487) or placebo (n=1244). Randomization was stratified by prediabetes status (ADA 2010) and BMI. Data are shown for the full analysis set (exposed individuals with ≥1 post-baseline assessment) with LOCF. The trial has an ongoing 2-year extension for participants with prediabetes. Clinicaltrials.gov ID: NCT01272219.

Baseline characteristics were: age 45.1 years, 78.5% female, body weight 106.2 kg, BMI 38.3 kg/m2, 61.2% with prediabetes). At week 56, individuals treated with liraglutide 3.0 mg (n=2437) achieved more weight loss (8.0%, least square mean) than those treated with placebo (n=1225; 2.6%) (estimated treatment difference [ETD] -5.4% [95%CI 5.8; -5.0]; p<0.0001). Weight loss was accompanied by reductions in mean waist circumference (ETD 4.2 [-4.7; -3.7] cm), systolic BP (ETD -2.8 [3.6; -2.1] mmHg) and diastolic BP (ETD 0.9 [-1.4; -0.4] mmHg) for liraglutide vs placebo (all p<0.001). Mean pulse was increased at week 56 with liraglutide 3.0 mg vs placebo (ETD 2.5 [1.9; 3.0] beats/min, p<0.0001). Improvements in all fasting lipids were seen with liraglutide 3.0 mg vs placebo: triglycerides (ETD -9% [-12; -7]), total cholesterol (-2% [3; 1]), VLDL cholesterol (-9% [11; -7]) (all p<0.0001); LDL cholesterol (-2% [-4; -1]) and HDL cholesterol (+2% [1; 3]) (both p<0.01); and free fatty acids (-4% [-7; -1]) (p<0.05). Improvements in concentrations of high-sensitivity C-reactive protein (ETD -30% [34; 26]), plasminogen activator inhibitor-1 (-21% [-26; -17]) and adiponectin (+8% [5; 12]) (all p<0.0001) were also observed with liraglutide 3.0 mg vs placebo. No treatment effects on fibrinogen or urinary albumin:creatinine ratio were seen. Liraglutide led to a greater reduction in net use of anti-hypertensive (odds ratio [OR] 1.7, p<0.0001) and lipid-lowering (OR 1.5, p=0.02) medications, while maintaining greater beneficial effects on BP and lipids at week 56 compared to placebo.

In conclusion, weight loss with liraglutide 3.0 mg, as adjunct to diet and exercise, produced improvements in a wide range of cardiometabolic risk factors, including inflammatory markers, in overweight or obese individuals, which if sustained in the long term may be associated with reduced cardiovascular events.

Presentation Date: Saturday, June 21
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

SAT-0925: Diabetes drug appears to work for weight management, reversing prediabetes

Nondiabetic obese and overweight people lose more weight, are more likely to reverse prediabetes and are slower to develop Type 2 diabetes when they take the diabetes drug liraglutide in addition to dieting and exercising, a new study finds. The results of the multicenter study will be presented Saturday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

Study subjects who received a 3-milligram (3-mg) dose of liraglutide lost an average of 8 percent of their body weight (18.7 pounds), compared with just 2.6 percent (6.2 pounds) for subjects receiving a placebo, or "dummy" drug, the investigators reported.

"An 8 percent weight loss is as good as with any weight loss drug on the market," said F. Xavier Pi-Sunyer, MD, MPH, the study's principal investigator and an endocrinologist at St. Luke's-Roosevelt Hospital Center in New York City.

Liraglutide is an injectable prescription medicine marketed at lower doses as Victoza® to improve blood sugar (glucose) in adults with Type 2 diabetes when used along with diet and exercise. The drug is not approved for weight management, according to its manufacturer, Denmark-based Novo Nordisk, which sponsored this study, called the SCALE™ (Satiety and Clinical Adiposity-Liraglutide Evidence in Nondiabetic and Diabetic Subjects) Obesity and Prediabetes trial.

The study included 3,731 obese adults and overweight adults who had at least one other risk factor for heart disease, such as prediabetes, high blood pressure or high cholesterol. As part of their weight loss efforts, all subjects exercised and ate 500 fewer calories than usual. In addition, they were randomly assigned, in a 2-to-1 ratio, to a once-daily injection with either 3 mg of liraglutide or placebo for 56 weeks. Neither the subjects nor the investigators knew who received the active drug. Subjects who received liraglutide started at a dose of 0.6 mg, which gradually was increased to 3 mg, to minimize side effects, such as nausea.

The study had two arms. In the first arm, which included 1,446 adults who did not have prediabetes, 959 received liraglutide and 487 got the placebo. For the second arm, among 2,285 individuals with prediabetes, liraglutide went to 1,528 of them and placebo to 757.

Among subjects who had prediabetes at the beginning of the study (arm 2), blood sugar levels reverted to normal in nearly 70 percent of those receiving liraglutide versus 32 percent of people in the placebo group, according to the abstract. Liraglutide also lowered the chance of prediabetes developing in adults who started the study with normal blood sugar levels, with 7 percent becoming prediabetic compared with nearly 20 percent of those receiving placebo.

Study data also showed that Type 2 diabetes developed in three times as many people receiving placebo as those who took liraglutide (14 subjects versus four, respectively).

"The delay in progression to Type 2 diabetes with liraglutide use is likely due to increased weight loss," Pi-Sunyer said.

The SCALE Obesity and Prediabetes trial is continuing for two more years for the prediabetic subjects in arm 2. Twelve-week results show that liraglutide treatment continues to sustain the weight loss, Pi-Sunyer reported.

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SAT-0925: Liraglutide 3.0 Mg Reduces the Prevalence of Prediabetes and Delays Onset of Type 2 Diabetes in Overweight and Obese Adults: Results from Scale Obesity and Prediabetes, a Randomized, Double-Blind and Placebo-Controlled 56-Week Trial

F. Xavier Pi-Sunyer. *St. Luke's Roosevelt Hospital*

F Xavier Pi-Sunyer, St Luke's Roosevelt Hosp, New York, NY, Arne Astrup, University of Copenhagen, Frederiksberg C, Denmark, Ken Fujioka, Department of Endocrinology, Scripps Clinic, La Jolla, CA, Frank Lyons Greenway III, Pennington Biomed Res Ctr, Baton Rouge, LA, Alfredo Halpern, Endocrinology, Universidade Sao Paulo, Brazil, Michel Krempf, School of Medicine, Hopital Nord - Laennec, Nantes, France, David C Lau, University of Calgary, Canada, Carel Le Roux, Diabetes Complications Research Centre, University College Dublin, Ireland, Rafael Violante Ortiz, Internal Medicine, Instituto Mexicano del Seguro Social, Cuidad Madero, Tamaulipas, Mexico, Christine Bjørn Jensen, GLP-1 & Obesity, Novo Nordisk A/S, Søborg, Denmark and John Wilding, Department of Obesity and Endocrinology, University of Liverpool, United Kingdom

Obesity is associated with prediabetes, a significant risk factor for development of type 2 diabetes mellitus (T2DM) and its accompanying complications. This trial investigated the effects of liraglutide 3.0 mg, as adjunct to diet and exercise, on weight loss (primary endpoint), prediabetes prevalence and onset of T2DM (ADA 2010 criteria) over 56 weeks. The effects of liraglutide 3.0 mg cessation were investigated in a subsequent 12week re-randomized period. Adults (BMI ≥27 kg/m2 with ≥1 comorbidity or ≥30 kg/m2) were advised on a 500 kcal/day deficit diet and exercise program and randomized 2:1 to once-daily s.c. liraglutide 3.0 mg or placebo. Randomization was stratified by prediabetes status (ADA 2010 criteria). At week 56, individuals without prediabetes and on liraglutide 3.0 mg were re-randomized 1:1 to liraglutide 3.0 mg or placebo (diet and exercise continued). The trial has an ongoing 2-year extension for individuals with prediabetes. Clinicaltrials.gov ID: NCT01272219.

Of 3731 randomized individuals (age 45.1 years, 78.5% female, body weight 106.2 kg, BMI 38.3 kg/m2, 61.2% with prediabetes), 71.9% on liraglutide 3.0 mg and 64.4% on placebo completed 56 weeks. At week 56, individuals on liraglutide 3.0 mg (n=2432) had lost 8.0% (8.4 kg) of body weight compared to 2.6% (2.8 kg) on placebo (n=1220) (estimated treatment difference [ETD] 5.4% [5.6 kg], p<0.0001, LSmeans, full analysis set with LOCF, ANCOVA).

Liraglutide 3.0 mg improved fasting and post-load glycemia compared to placebo (ETD FPG 6.9 mg/dL, PG [OGTT, area under the curve] 36.4 h*mg/dL, HbA1c 0.23 %-points; p<0.0001 for all). Accordingly, of those with prediabetes at screening, more individuals had reverted to normoglycemia on liraglutide 3.0 mg (69.7%) than on placebo (32.1%) at week 56 (estimated odds ratio [OR] 4.85, p<0.0001, LSmeans, logistic regression). Likewise, of those with normoglycemia at screening, more individuals had progressed to prediabetes on placebo (19.9%) than on liraglutide 3.0 mg (6.9%) at week 56 (OR 3.3, p<0.0001). Few individuals developed T2DM during treatment, but more did so on placebo (14 individuals, 1.3 events/100 patient years of exposure [PYE]) than on liraglutide 3.0 mg (4 individuals, 0.2 events/100 PYE) (OR 0.12, p=0.0003).

From week 56 to 68, individuals re-randomized from liraglutide 3.0 mg to placebo regained more weight (2.9%) than individuals staying on liraglutide 3.0 mg (0.7%) (ETD 2.2%, p<0.0001), and more individuals progressed to prediabetes on placebo (from 8.0% to 22.4%, observed means) than on liraglutide 3.0 mg (from 9.1% to 8.6%) (p<0.0001). No individuals developed T2DM. In conclusion, consistent with the combined effects on body weight and glycemia, liraglutide 3.0 mg, as adjunct to diet and exercise, was superior to placebo in reducing the prevalence of prediabetes and T2DM after 56 weeks of treatment. Continued treatment was required to sustain these effects.

Presentation Date: Saturday, June 21
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

SAT-0414: Possible new weapon found for fighting some types of breast cancer

Researchers believe they have discovered one reason why some women with estrogen receptor-positive breast cancer may respond poorly or only temporarily to estrogen-blocking drugs such as tamoxifen. Results of a new study, which will be presented Saturday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago, point to a previously unrecognized role of the androgen receptor.

Although this receptor (protein) is expressed in nearly all prostate cancers, it also is expressed in most breast cancers. Now scientists have found that estrogen receptor alpha—a main driver of estrogen-fueled breast cancer—may rely on the androgen receptor for its function.

In a study funded by the U.S. Department of Defense Breast Cancer Research Program, Jennifer Richer, PhD, from the University of Colorado Anschutz Medical Campus in Aurora, and her colleagues studied 192 women with estrogen receptor-positive breast cancers. They found that women were 4.4 times more likely to have a cancer recurrence during tamoxifen treatment when their main tumor had a high ratio (2:1 or greater) of androgen receptor-positive cells to estrogen receptor-positive cells.

“Women with breast cancer do not routinely receive testing for the androgen receptor,” Richer commented.

The investigators hypothesized that maximal estrogen receptor activity depends on the androgen receptor’s nuclear localization. This process, Richer said, involves the receptor moving itself and the hormone molecule, to which it is bound, inside the nucleus of a cell, where the receptor “does its important business.”

Richer and her co-workers then tested a new anti-androgen drug called enzalutamide, which is approved for treatment of prostate cancer. Unlike older anti-androgen drugs, which allow the androgen receptor to go to the cell’s nucleus, enzalutamide inhibits the ability of androgen receptors to enter the nucleus, Richer said.

“If the androgen receptor is outside the nucleus, both estrogen and androgen driven tumor growth is inhibited,” she explained.

In preclinical models (human cells and mice) of estrogen receptor-positive breast cancers that also were positive for the androgen receptor, enzalutamide treatment inhibited both androgen- and estrogen-controlled tumor growth, Richer reported. Further, the combination of enzalutamide and tamoxifen decreased estrogen-driven tumor growth better than either drug alone.

Another study by Richer’s team, to be presented Monday (OR38-2), found that breast cancers that are estrogen receptor negative (“triple negative”) can also rely on the androgen receptor for growth. In preclinical models of estrogen receptor-negative tumors, enzalutamide treatment decreased tumor growth by 85 percent, according to the abstract.

“Our research suggests that the androgen receptor may serve as a therapeutic target in both estrogen receptor-positive and negative breast cancers,” Richer said.

# # #

SAT-0414 : Androgen Receptors in Estrogen Receptor Positive Breast Cancer

Jennifer Richer. *University of Colorado Anschutz Medical Campus*

Jennifer K Richer, PhD, Dept. of Pathology, University of Colorado Anschutz Medical Campus, Aurora, CO, Nicholas D'Amato, Ph.D., Pathology, University of Colorado Anschutz Medical Campus, Nicole Spoelstra, B.S., University of Colorado Anschutz Medical Campus, Marc B Cox, PHD, Dept of Biological Sciences, Univ of Texas at El Paso, El Paso, TX and Anthony Elias, MD, Medical Oncology, Univ of Colorado Anschutz Medical Campus, Aurora, CO

Background: The androgen receptor (AR) is widely expressed in breast cancer, but its role, particularly in estrogen receptor positive (ER+) tumors is not fully understood. In a cohort of 192 women with ER+ breast cancers, we found that a high ratio (≥2.0) of AR to ER percent cells positive by IHC indicated an over four fold increased risk for failure while on tamoxifen (HR=4.43). In preclinical cell line models of ER+/AR+ breast cancer, DHT is proliferative in vitro and in vivo, and anti-androgens such as bicalutamide (bic) and enzalutamide (enza) inhibit DHT-mediated proliferation. Surprisingly enza, a new generation AR inhibitor that decreases ligand-mediated nuclear translocation, decreased E2-mediated proliferation of ER+ breast cancer cells, while bic does not. Hypothesis: We hypothesized that nuclear localization of AR is necessary for maximal E2-mediated ER activity and proliferation, and targeting AR with Enz or other agents that impede AR nuclear entry will inhibit growth of ER+/AR+ human breast cancer cell lines and decrease tumor burden in preclinical models. We also postulated that if tamoxifen and enza inhibit E2-mediated proliferation by different means, the combination would result in additive or synergistic tumor shrinkage in vivo. Results: Both Enz and MJC13, which inhibits AR release from heat shock proteins, thereby impeding its nuclear translocation, blocked E2-induced proliferation of ER+AR+ breast cancer cell lines, while Bic did not. Both DHT and to a lesser extent, E2 treatment, induced nuclear translocation of AR, and Enz inhibited AR nuclear localization in both instances, while Bic did not. In vivo, ENZ inhibited growth of MCF7 xenografts as effectively as tamoxifen, and the combination of the two agents gave an additive effect. Conclusions: Our results suggest that AR plays a previously-unrecognized role in E2-mediated ER activity in ER+/AR+ breast cancer. Enz or other agents that inhibit AR nuclear localization, may serve as effective therapeutics in ER+/AR+ breast cancers. Furthermore, Enz may be useful when combined with traditional anti-estrogens.

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Presentation Date: Saturday, June 21
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

SAT-0367: Soy supplements appear to be safe and beneficial in diabetic men

Soy protein supplements, which contain natural estrogens, do not reduce testosterone levels in men with Type 2 diabetes who already have borderline-low testosterone, according to a new study. The results will be presented Saturday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

"Because soy contains phytoestrogens that are similar to the female hormone estrogen, it was not known whether consumption of soy could reduce testosterone levels in men with Type 2 diabetes, who are at increased risk of low testosterone," said the study's lead investigator, Thozhukat Sathyapalan, MD, an endocrinologist researcher at Hull York Medical School, University of Hull, Hull, U.K.

"It was important to know this because prior studies have found that daily consumption of soy reduces the risk of Type 2 diabetes and heart problems. Our study found that soy protein and phytoestrogen supplementation is safe in diabetic men and may improve their diabetes control and their risk factors for heart disease," Sathyapalan said.

Their study included 210 men ages 55 to 70 who had Type 2 diabetes and a borderline-low total testosterone level: less than or equal to 12 nanomoles per liter (nmol/L) or 345.8 nanograms per deciliter. For three months, the men ate two cereal bars a day, each containing 30 grams of soy protein. The bars in one group of 100 men contained 66 milligrams of soy phytoestrogens, which is equivalent to the amount in soy supplements or in a typical Southeast Asian diet. The second group of 100 men received soy protein bars in which phytoestrogens were removed. Patients were asked to avoid eating foods containing soy.

The men had testosterone blood tests before and after treatment at the same time of day. Both groups experienced an increase in total testosterone level, the investigators reported. On average, testosterone level increased from 9.8 to 11.3 nmol/L in the soy protein-phytoestrogen group and from 9.2 to 10.3 nmol/L in the group receiving only soy protein.

Sathyapalan said it is unclear why testosterone levels rose, but it could be a direct effect of soy.

Soy protein with phytoestrogens also improved diabetes control much better than did soy protein alone. Specifically, the first group significantly lowered their fasting blood glucose (sugar) levels and hemoglobin A1c, a measure of blood sugar control over the past three months, as well as fasting insulin levels and estimated insulin resistance, which showed an improved use of the hormone insulin. Neither group lost or gained weight, according to Sathyapalan.

In addition, the phytoestrogen-containing soy protein reportedly led to better improvements in certain cardiovascular risk factors, he said. These included triglycerides—a type of fat in the blood—and high-sensitivity C-reactive protein, which measures inflammation in the body and is a predictor of heart disease risk. Total cholesterol and "bad" (LDL) cholesterol levels rose (worsened) in both groups but not enough to be statistically significant, according to Sathyapalan.

Both soy protein supplements significantly improved diastolic blood pressure (the bottom number in a blood pressure reading) but not systolic blood pressure (the top number).

The study received funding from the Food Standards Agency, which is responsible for food safety in the U.K.

# # #

SAT-0367: The Effect of Soy Phytoestrogens on Cardiovascular Risk Markers in Men with Type 2 Diabetes and Subclinical Hypogonadism — a Randomised Double Blind Parallel Study

Thozhukat Sathyapalan. *Hull York Medical School*

Thozhukat Sathyapalan, MBBS, MD, FRCP Edin, Department of Academic Endocrinology, Diabetes and Metabolism, Hull York Medical School, Hull, United Kingdom, Eric S Kilpatrick, MBBS, MD, FRCPath, Clinical Biochemistry, Hull and East Yorkshire NHS Trust, Hull, United Kingdom, Alan S Rigby, Centre for Cardiovascular and Metabolic Research, Hull York Medical School, Hull, United Kingdom, Natalie J Thatcher, Food Standards Agency, London, United Kingdom and Stephen L Atkin, MBBS, MD, PhD, Department of Medicine, Weill Cornell Medical College Qatar, Doha, Qatar

Background: The effect of soy on testosterone levels in men with compensated hypogonadism is unknown, though increased habitual intake of soy phytoestrogens has been associated with a reduced risk of both type 2 diabetes (T2DM) and cardiovascular disease.

Materials and Methods: A randomised double-blind, parallel study was undertaken with 210 T2DM men aged between 55 – 70 years with a total testosterone level ≤12nmol/L but with normal gonadotrophins. They were randomised either to preparation 1 (30g soy protein with 66mg of phytoestrogens) or preparation 2 (30g soy protein alone without any phytoestrogens; less than 300 parts per billion by serial ethanol washing) for 12 weeks. Endothelial function was measured using the endopat 2000. The primary outcome was the change in total testosterone levels, whilst the secondary outcome was the change in cardiovascular risk markers.

Results: The baseline parameters were comparable between the two groups. There was a significant increase in serum total testosterone with both preparation 1 (9.83 ± 0.21 vs. 11.34 ± 0.36nmol/L p value <0.01) and preparation 2 (9.22 ± 0.23 vs. 10.33 ± 0.3nmol/L; p value <0.01) . There was a significant reduction in HbA1c (52.71 ± 1.19 vs. 50.16 ± 1.26 mmol/mol; p value =0.01), fasting glucose (7.93 ± 0.21 vs. 6.45 ± 0.15 mmol/L; p value <0.01), fasting insulin (19.78 ± 1.72 vs. 8.98 ± 0.63 μIU/mL; p value <0.01) and HOMA-IR (7.23 ± 0.73 vs. 2.59 ± 0.2; p value <0.01) after preparation 1 that was significantly greater than that for the preparation2. There were no changes in weight after either preparation.

Triglycerides (1.67 ± 0.09 vs. 0.87 ± 0.04 mmol/L; p value-<0.01) and hsCRP (3.13 ± 0.46 vs. 0.69 ± 0.11; p value -<0.01) reduced significantly with preparation 1. Diastolic blood pressure reduced significantly after both preparation 1 (80.86 ± 0.99 vs. 78.22 mmHg; p value 0.03) and preparation 2 (80.01 vs. 78.06 mmHg; p value 0.05) preparation. There were no changes in systolic blood pressure for either group. There was a significant increase in reactive hyperemia index (RHI) (1.30 ± 0.06 vs. 2.35 ±0.08) with preparation 1 where as there was a significant reduction with preparation 2(1.92 ± 0.08 vs. 1.25 ± 0.25).

Conclusions: Soy protein with and without 66 mg phytoestrogen per day significantly improved testosterone levels in men with type 2 diabetes and low testosterone levels after 12 weeks. There was a significant improvement in cardiovascular risk markers including glycemic control, triglycerides and hsCRP with soy protein and phytoestrogen combination compared to supplementation with soy protein alone.

Presentation Date: Saturday, June 21
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

SAT-0733: Veterans with blast traumatic brain injury may have unrecognized pituitary dysfunction

In soldiers who survive traumatic brain injury from blast exposure, pituitary dysfunction after their blast injury may be an important, under-recognized, and potentially treatable source of their symptoms, a new study finds. The results will be presented in a poster Saturday, June 21 at ICE/ENDO 2014, the joint meeting of the International Society of Endocrinology and the Endocrine Society in Chicago.

"Our study suggests that deficiencies in the pituitary's growth hormone and testosterone are commonly seen after blast traumatic brain injury, especially in patients who are overweight. Because multiple symptoms common with blast traumatic brain injury are also seen with growth hormone and testosterone deficiencies, perhaps treating these hormone deficiencies will help improve the symptom burden and quality of life for these veterans," said lead study author Jeffrey S. Taylor, MD, endocrinology fellow at Virginia Commonwealth University Medical Center in Richmond, Virginia.

Blast traumatic brain injury (bTBI) is increasingly common in military personnel returning from combat. A common consequence of bTBI in general is pituitary hormone dysfunction, which can occur even without mechanical head trauma and can interfere with the soldier's recovery, long-term health, and overall well-being. A soldier's depression, post-traumatic stress disorder (PTSD), and certain medications may further complicate diagnosing possible pituitary dysfunction, so it often goes unrecognized and untreated.

Expanding on their prior research of the incidence of pituitary dysfunction in male post-bTBI veterans, Dr. Taylor and his colleagues looked at 37 male veterans who had been exposed to combat-related blasts. They evaluated them for bTBI and tested them for hormone dysfunction while screening for and minimizing their use of medications that might interfere with their lab tests.

Of these veterans, 23 had mild and 2 had moderate TBI. Overall, 27% were obese and almost all the men had PTSD. Their exposure to the blast ranged from 2 to 113 months prior to the time their blood samples were taken.

The most common finding involved growth hormone deficiency and hypogonadism associated with low testosterone, especially in their overweight patients, suggesting that these hormone deficiencies occur frequently after bTBI and that treating them may improve their symptoms.

The authors called for further study to address several challenges.

"One challenge in diagnosis is that certain medications commonly used for these patients can interfere with needed laboratory testing. Another is that, although our data suggest that growth hormone deficiency and hypogonadism occur frequently after bTBI, these conditions also appear to be strongly associated with obesity. PTSD and depression may also affect pituitary function. Further study is needed to clarify the extent to which these conditions affect diagnosing true pituitary dysfunction among bTBI survivors and to determine if hormone replacement will benefit them," Dr. Taylor said.

This study was a continuation of a pilot study presented at the Endocrine Society National meeting in 2012. Genentech, Inc. funded the study.

# # #

SAT-0733: Anterior Pituitary Dysfunction in Male Military Veterans with Blast Traumatic Brain Injury

Jeffrey Taylor. *Virginia Commonwealth University*

Jeffrey S Taylor, MD, Endocrine Division, Virginia Commonwealth University Medical Center, Richmond, VA, Amy Denise Anderson, DO, Department of Medicine, Division of Endocrinology, University of Virginia, Charlottesville, VA, Shane McNamee, MD, Physical Medicine, McGuire Veterans Affairs Medical Center, Richmond, VA and Robert A Adler, MD, Dept of Endo 111-P, McGuire Vet Affairs Med Ctr, Richmond, VA

Purpose: Blast traumatic brain injury (bTBI) is increasingly common in military personnel. Many symptoms seen after bTBI are also seen with pituitary dysfunction, a known consequence of other TBI. Depression, post-traumatic stress disorder (PTSD), and certain medications complicate diagnosing pituitary dysfunction in this population. Here, we expand our prior study on the incidence of pituitary dysfunction in post-bTBI male veterans, while limiting the confounding factors of antiepileptic and opioid medication use.

Methods: Male veterans (n=37) with a history of blast exposure were evaluated by blinded TBI staff for presence and severity of TBI. Subjects taking antiepileptics (other than valproate) or opioids (other than low-dose tramadol) within 2 months were excluded. On day 1, fasting morning serum cortisol, LH, FSH, total testosterone (TT), SHBG, FT4, PRL, and IGF-1 levels were obtained, followed by an ACTH-stimulated cortisol level. On day 2, GH response to glucagon stimulation, 1-2mg IM based on weight, was assessed over 240 minutes. Bioavailable testosterone (BT) was calculated.

Results: Of 37 subjects with blast exposure, 23 had mild and 2 had moderate TBI. 27% were obese (BMI >35). Nearly all had PTSD. Time from blast exposure to sample collection was 2 to 113 months. 41% of mild and all moderate TBI subjects had low serum TT vs 33% of blast-exposed only subjects. Far fewer subjects in all 3 groups had low BT levels. 90% of obese subjects had low serum TT vs 22% of non-obese subjects. 93% of all subjects with low TT had low or inappropriately normal gonadotropins. 45% of mild and all moderate TBI subjects had low peak GH response to glucagon vs 25% of blast-exposed only subjects. 80% of obese subjects had a low peak GH response to glucagon vs 26% of non-obese subjects.

Conclusions: Pituitary dysfunction after bTBI may contribute to post-TBI symptom burden. Though underdiagnosed, treatment may improve recovery and quality of life. These data suggest that hypogonadism and GH deficiency are seen frequently after bTBI. However, these deficiencies also appear to be strongly associated with obesity. PTSD and/or depression may also affect pituitary function. Further investigation is needed to clarify the extent to which these confounders affect diagnosing true pituitary dysfunction in the bTBI population and to determine if hormone replacement is beneficial.

Presentation Date: Saturday, June 21
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

SAT-0018: Polycystic ovary syndrome is tied to increased risk of type 2 diabetes, independent of body mass index

Women with polycystic ovary syndrome are at increased risk for Type 2 diabetes mellitus (T2DM), and this risk appears to be independent of body mass index (BMI), a new study finds. The results will be presented in a poster session Saturday, June 21, at ICE/ENDO 2014, the joint meeting of the International Society of Endocrinology and the Endocrine Society in Chicago.

The large group of young women in the study with PCOS had a very high risk of Type 2 diabetes, even at a young age, and their risk was independent of obesity, the usual key cause of T2DM.

"Polycystic ovary syndrome (POCS) is a common and complex condition that must now be recognized to have not only reproductive features but also important metabolic features, including a high risk of diabetes at a young age, independent of obesity," said lead study author Helena Jane Teede, MBBS, FRACP, PhD, professor of Women's Health and director of the Monash Centre for Health Research and Implementation of the School of Public Health and Preventive Medicine of Monash University in Clayton, Victoria, Australia.

In the United States, an estimated 5 to 6 million women have PCOS and women with this condition are at high risk for diabetes, infertility, depression and poor quality of life.

"With the dramatic rising prevalence of diabetes in the general population, this work highlights the need for greater awareness, targeted screening and intervention in high-risk groups, including young women with PCOS. It highlights the need for recognition of PCOS as a metabolic condition with implications beyond the ovary and it supports the current calls for a change in the name of the condition to better reflect the diverse health consequences," Professor Teede said.

To examine the prevalence of T2DM and the impact of obesity in reproductive-aged women with and without PCOS, Professor Teede and her colleagues studied a large longitudinal, community-based cohort of young women and analyzed longitudinal data from the Australian Longitudinal Study on Women's Health (ALSWH).

From Australia's national health insurance database, the researchers randomly selected 6,384 women who lived in the community and asked them to self-report whether they had PCOS and T2DM. The women, ranging in age from 34 to 37 years, were younger than the age recommended for diabetes screening and were in their reproductive years, when undetected diabetes in pregnancy may lead to poor outcomes for mothers and their babies.

The researchers found that type 2 diabetes was roughly 5 times more prevalent among the women with PCOS than among those without PCOS. Overall, 8.8% (561 women) had PCOS, and 3.8% of this 8.8% had T2DM. By contrast, among the women who did not have PCOS, only 0.8% had T2DM. This high risk of T2DM in PCOS was independent of obesity.

The National Health and Medical Research Council of Australia and Monash University funded the study, and the Australian Government funded the Longitudinal Study for Women's Health (ALSWH).

# # #

SAT-0018: Longitudinal Risk of Type 2 Diabetes in Reproductive-Aged Women with Polycystic Ovary Syndrome

Helena Jane Teede. *Monash University*

Anju Elizabeth Joham, MBBS, FRACP, Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Clayton VIC, Australia, Sanjeeva Ranasinha, MEpid, MSc(ApplStat), Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Clayton VIC, Australia, Sophia Zoungas, MBBS, FRACP, PhD, Monash Centre for Health Research and Implementation, School of Public Health and Preventive Medicine, Monash University, Monash University, Clayton VIC, Australia and Helena Jane Teede, MBBS, PhD, FRACP, Monash Centre for Health Research and Implementation, School of Public Health & Preventive Medicine, Monash University, Clayton VIC, Australia

Context: Polycystic ovary syndrome (PCOS) affects 9-21% of women. PCOS has been associated with an increased risk of type 2 diabetes (T2DM), however the independence of this risk and the impact of body mass index (BMI) is unclear.

Objective: To assess the prevalence of T2DM and the impact of obesity in young reproductive-aged women with and without PCOS, in a community-based cohort.

Design: Longitudinal analysis of data from the Australian Longitudinal Study on Women's Health (ALSWH).

Setting: General community

Participants: Women were randomly selected from the national health insurance database. Standardised data collection occurred at 6 survey time points (years 1996, 2000, 2003, 2006, 2009 and 2012). Longitudinal data from 6384 women who responded to surveys 4, 5 and 6 were examined for this study.

Main outcome measures: Self-reported PCOS and T2DM

Results: In survey 6 in women aged 34 to 37 years, PCOS prevalence was 8.8% (95% CI 8.0 – 9.6) and the prevalence of T2DM was 3.8% in women with PCOS and 0.8% in women without PCOS respectively ($p<0.001$). On univariate regression analysis, both PCOS and BMI were associated with increased odds of T2DM. A mutivariable random effects logistic regression model to examine the longitudinal association between T2DM and PCOS adjusting for BMI, age, hypertension, smoking and demographic factors revealed that both PCOS and longitudinal BMI were independently associated with increased odds of T2DM (OR 3.5, 95% 1.6-7.9, $p=0.002$ and OR 1.08 per BMI unit, 95% CI 1.03-1.12, $p<0.001$ respectively). A significant interaction was observed between PCOS and BMI for this outcome. Further sensitivity analysis by PCOS status, showed that BMI did not independently impact on the risk of T2DM in women with PCOS (OR 1.0, 95% CI 0.9-1.1, $p=0.93$), but that BMI mediated the risk of T2DM in women without PCOS (OR 1.10 per BMI unit, 95% CI 1.05-1.15, $p<0.001$).

Conclusions: In the largest longitudinal, community-based cohort of reproductive-aged women, increased risk of T2DM in PCOS was shown to be independent of BMI. Regular screening and implementation of preventive measures are warranted in women with PCOS.

Presentation Date: Saturday, June 21
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

SAT-0926: Among weight loss methods, surgery and drugs achieve highest patient satisfaction

Obese and overweight Americans who have tried losing weight report far greater overall satisfaction with weight loss surgery and prescription weight loss medications than with diet, exercise and other self-modification methods, an Internet survey finds. The results will be presented Saturday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

"This finding may mean that diet and exercise alone just don't work for a lot of people," said Z. Jason Wang, PhD, the study's principal investigator and director of Health Economics and Outcomes Research at Eisai in Woodcliff Lake, N.J.

The company funded the study, an analysis of data from more than 39,000 respondents to the 2012 National Health and Wellness Survey.

"Drug treatment and bariatric surgical procedures should be considered an integral part of weight management for eligible patients to achieve better treatment satisfaction, which may in turn help patients achieve and maintain better long-term weight loss," Wang said.

Wang and his co-worker, Sharoo Gupta, MS, from Kantar Health in Princeton, N.J., analyzed survey responses for 22,927 obese adults (50 percent women) and 19,121 overweight or obese adults who had at least one weight-related health problem (44 percent women). (Approximately 2,900 obese individuals were included in both groups, according to Wang.)

They found that 58.4 percent of obese people were not currently taking any steps to lose weight. Wang said this finding suggests "a dire need to better educate the public about the health consequences of obesity and the importance of addressing the problem with their doctors."

Among obese individuals who were trying to lose weight, 2.3 percent reported that they underwent weight loss surgery, such as gastric bypass or laparoscopic gastric banding, or they were taking prescription weight loss medication. Together, these people made up the "Surgery/Rx" group. The other 39.3 percent of obese respondents reported using a self-modification method, which included diet, exercise, weight management programs, and over-the-counter weight loss drugs or supplements.

The percentage of obese respondents who reported being extremely or very satisfied with their weight loss method was 39.3 percent in the Surgery/Rx group versus only 20.2 percent in the group that used self-modification methods, Wang reported. Treatment satisfaction was about the same between those using medication and those who had surgery, he said.

The researchers observed similar findings in the overweight respondents, with 44.4 percent of the Surgery/Rx group being extremely or very satisfied with their treatment compared with 19.7 percent of participants who used self-modification.

Wang's company, Eisai, makes the prescription weight loss medication, lorcaserin (marketed as Belviq). Kantar Health administers the annual National Health and Wellness Survey.

# # #

SAT-0926: Satisfaction with Different Weight Loss Methods Among Obese Patients: An Analysis of the 2012 U.S. National Health and Wellness Survey

Zhixiao Wang. *Eisai, Inc.*

Zhixiao Wang, PhD, Health Economics & Outcomes Research, Eisai, Inc., Woodcliff Lake, NJ and Shaloo Gupta, MS, Health Outcomes Practice, Kantar Health, Princeton, NJ

Background: Obesity has been associated with significant burden and can negatively affect patients' quality of life. Different weight loss (WL) methods are available and may lead to different results. Treatment satisfaction is not only associated with the effectiveness of the WL method, but can be a driver for long-term compliance and commitment, which is essential in weight management. The objective of this study was to explore treatment satisfaction associated with different WL methods.

Methods: Data were obtained from the 2012 National Health and Wellness Survey (NHWS). The NHWS is an annual Internet-based survey, using stratified random sampling to ensure demographic representativeness of the adult U.S. population (N=71,157). Patients were categorized as had a WL procedure (e.g., gastric bypass, LAP-BAND@) or using a prescription medication for WL (Sur/Rx), vs. using self-modification WL techniques (e.g., diet, exercise, over-the-counter medication, weight management programs, and WL supplements). Sur/Rx patients were matched on demographics, comorbidities, insurance status, smoking and alcohol use, obesity class, and had non-WL surgery in the past 12 months to self-modification patients, via propensity scores (1:2). Overall satisfaction with current WL methods (1 [extremely dissatisfied] to 7 [extremely satisfied]) was assessed. Chi-square tests and ANOVAs were used to determine significant differences after matching.

Results: Of the 22,927 obese (BMI≥30) patients, 58.4% took no current action to lose weight, 2.3% were in the Sur/Rx group and 39.3% were in the self-modification group. The average age was 50.6 (SD=15.3), 50.0% were female. The Sur/Rx group reported being extremely/very satisfied more frequently than the self-modification group (39.3% vs. 20.2%, $p<0.001$). There was no difference in treatment satisfaction between those using Rx and those whom had a surgical procedure ($p>0.05$). Similar results were found in overweight and obese patients (BMI≥27) with ≥1 weight related comorbidity (type 2 diabetes, hypertension, or dyslipidemia). Satisfaction was higher for the Sur/Rx group vs. the self-modification group (44.4% vs. 19.7%, $p<0.001$).

Conclusion: Almost 60% of the obese U.S. population did not take steps to lose weight, suggesting the need for more education on obesity awareness/prevention. Among those who took measures to lose weight, satisfaction with WL methods was greater for the Sur/Rx vs. the self-modification group.

Presentation Date: Saturday, June 21
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

Presentations

Sunday, June 22, 2014

ENDOCRINE SOCIETY

LBSU-1076: Gut microbe levels are linked to Type 2 diabetes and obesity

People with Type 2 diabetes or obesity have changes in the composition of their intestinal micro-organisms—called the gut microbiota—that healthy people do not have, researchers from Turkey have found. They will present the results Sunday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

The study lends support to other recent reports that have found an association between specific bacterial species in the human digestive system and obesity and diabetes, according to lead investigator Yalcin Basaran, MD, an endocrinologist from Gulhane Military Medical Academy School of Medicine, Ankara, Turkey.

"The gut microbiota may be used as an important marker to determine the risk of these metabolic diseases—obesity and diabetes—or it may become a therapeutic target to treat them," Basaran said.

The human digestive system contains an estimated 10 trillion to 100 trillion bacteria and other microscopic organisms, with each person housing at least 160 different species of organisms, according to Basaran. Some researchers now believe that this community of microbes in the human gut contributes to the onset of low-grade inflammation, which in turn may affect body weight and glucose (sugar) metabolism.

Basaran and his fellow researchers sought to identify the relationship between the gut microbe composition and obesity and Type 2 diabetes. Their study included 27 severely obese adults (20 men and seven women) whose body mass index, or BMI, exceeded 35 kg/m2, as well as 26 adults (18 men and eight women) with newly diagnosed Type 2 diabetes and 28 healthy control subjects (22 men and six women). All subjects were between 18 and 65 years of age, and all provided stool samples. None of the participants had taken antibiotics within the past three months, and none was currently taking medications, according to the investigators.

Fecal analysis using a molecular biology technique showed that several of the most common types of bacteria in the gut were present at considerably lower levels in the obese and diabetic groups, compared with healthy controls. These reductions ranged from 4.2 to 12.5 percent in the obese patients and 10 to 11.5 percent in the diabetic patients, Basaran reported.

In addition, statistical analysis found that bacterial counts related to certain metabolic variables. BMI, a measure of weight and height, and hemoglobin A1c, a measure of blood sugar control over the past three months, influenced levels of the most common gut bacterial species, Firmicutes. Waist circumference, a measure of abdominal fat, and hemoglobin A1c affected levels of another bacterial species: Bifidobacteria, a type of Actinobacteria. Finally, both weight and fasting blood glucose level influenced levels of a third species, Clostridium leptum.

"Further studies should be carried out to elucidate if the gut microbial changes are a cause or effect of metabolic diseases," Basaran said. "Manipulation of intestinal bacteria could offer a new approach to manage obesity and Type 2 diabetes."

# # #

LBSU-1076: Comparison of Gut Microbiota in Obese, Diabetic and Healthy Control Individuals

Yalcin Basaran. *Gulhane Military Medical Academy School of Medicine*

Yalcin Basaran[1], Abdullah Taslipinar[1], Sinasi Erol Bolu[1], Mehmet Ali Saracli[2], Turker Turker[3], Coskun Meric[1], Cem Haymana[1], Kamil Baskoy[1], Mustafa Dinc[1], Ferhat Deniz[4], Mahmut Yazici[1], Aydogan Aydogdu[1], Alper Sonmez[1] and Omer Azal[1], (1) Department of Endocrinology, Gulhane Military Medical Academy School of Medicine, Ankara, Turkey, (2) Department of Microbiology, Gulhane Military Medical Academy School of Medicine, Ankara, Turkey, (3) Department of Public Health, Gulhane Military Medical Academy School of Medicine, Ankara, Turkey, (4) Department of Endocrinology, GATA HAYDARPASHA Training Hospital, Istanbul, Turkey

The worldwide prevalence of obesity and type 2 diabetes is a growing epidemic problem. The accumulating evidence indicates that, in addition to genetic susceptibility and environmental factors, changes in the gut microbial composition may be responsible for that increase. The human microbiota consist of as many as 10 to 100 trillion microorganisms. This represents at least 10 fold more cells than those in the human body. It is predicted that each individual harbors at least 160 such species from a total of 1000 to 1150 prevalent bacterial species.

We designed a prospective study to identify the relation between the gut microbiota composition and these metabolic conditions. 27 morbidly obese individuals, 26 patients with newly diagnosed diabetes and 28 healthy control subjects were included in the present study. Fecal samples of the participants were analyzed by quantitative real-time PCR for the presence of Bacteroidetes, Firmicutes, Bifidobacteria (Actinobacteria) and Clostridium Leptum (Firmicutes).

Bacteroidetes concentrations were similar between the three groups and there were no significant differences in the fecal Bifidobacteria, Firmicutes and Clostridium Leptum levels among the obesity and diabetic groups. However, Bifidobacteria, Firmicutes and Clostridium Leptum counts were significantly lower in patients with obesity and diabetes, compared to healthy control individuals. Logistic regression analysis showed that metabolic parameters, such as BMI and HbA1c, waist circumference and HbA1c, and finally weight and FBG were independent risk factors for reduced proportions of Firmicutes, Bifidobacteria and Clostridium Leptum, respectively.

These findings support that both obesity and diabetes may be associated with compositional changes in the intestinal microbial composition. All these results suggest that the gut microbiota can be used as an important marker, helping to determine the risk and etiopathogenesis of aforementioned metabolic disorders.

Presentation Date: Sunday, June 22
Presentation Time: 1-3:00 p.m.
Location: Hall F

LBOR02-1: Growth hormone defect may protect against diabetes and cancer in unique Ecuador population

People who lack growth hormone (GH) receptors also appear to have marked insulin sensitivity that prevents them from developing diabetes and lowers their risk for cancer, despite their increased percentage of body fat, new research finds. The results will be presented as a late-breaking abstract Sunday, June 22, at ICE/ENDO 2014, the joint meeting of the International Society of Endocrinology and the Endocrine Society in Chicago.

"We have shown that people who, due to a genetic defect, are unable to respond to growth hormone have an increased sensitivity to insulin that safeguards them from developing Type 2 diabetes, which is associated with overweight, even if they have increased body fat content. They also have reduced risk for developing cancer," said lead study author Jaime Guevara Aguirre, MD, professor of diebetology and endocrinology at Universidad San Francisco de Quito in Quito, Ecuador.

"In the presence of the largest pandemic of obesity, diabetes and associated comorbidities, including cancer, knowledge of the mechanisms influencing insulin sensitivity and resistance appears relevant," said Dr. Guevara Aguirre.

Growth hormone is produced in the pituitary gland and helps stimulate growth. Insulin is a hormone secreted by the pancreas that controls the level of the sugar glucose in the blood and permits cells to use glucose for energy. In the most common form of diabetes, type 2, the pancreas produces insulin, but cells throughout the body do not respond normally to it.

Previous research by Dr. Guevara Aguirre and colleagues reported the absence of diabetes and protection from cancer in a unique group of people from southern Ecuador who have growth hormone receptor deficiency (GHRD).

They showed that, even if these people were overweight or obese, they did not have diabetes, while 5% of their relatives had diabetes. They also showed that the overnight fasting concentrations of insulin in their blood were much lower than in their relatives, indicating that their bodies had increased sensitivity to insulin.

This report continues that work and explores the effects of lifelong absence of GH and the relationships between body composition, hormonal status and disease risk in a larger population.

The researchers studied 27 adults with GHRD and 35 comparably overweight control study participants and found that the adults with GHRD had a consistently greater mean percentage of body fat — ~50% — and a lower ratio of lean to fat. Their fasting insulin, 2-hour blood glucose, Very-low-density lipoprotein (VLDL), and triglyceride levels were all significantly lower, indicating their sensitivity to insulin, and their cholesterol (C), high-density lipoprotein (HDL) and low-density lipoprotein (LDL) were also elevated.

The authors called for further research to explore the detailed metabolism of this unique group of people and their normal relatives to find exactly where in the complex metabolic cycle the lack of growth hormone is having an effect, which may lead to focused treatment for Type 2 diabetes.

The Instituto de Endocrinologia Metabolismo y Reproducción (IEMYR) in Quito, Ecuador, provided the main funding for the study.

# # #

LBOR02-1: Enhanced Insulin Sensitivity in Subjects with Absent Growth Hormone Receptor Signaling Despite Increased Body Fat Content

Jaime Guevara-Aguirre. *Universidad San Francisco de Quito*

Jaime Guevara Aguirre, MD[1], Arlan L Rosenbloom, MD[2], Priya Balasubramaniam, PhD[3], Enrique Teran, MD[1], Marco Guevara Aguirre, MD[4], Jannette Saavedra, MD[4], Patricio Procel, MD[4] and Valter D Longo, PhD[3], (1) Universidad San Francisco de Quito, Quito, Ecuador, (2) Pediatrics, University of FL College of Medicine, Gainesville, FL, (3) Andrus Gerontology Center, University of Southern California, (4) Instituto de Endocrinologia IEMYR

We have reported absence of diabetes and protection from cancer in a unique cohort with growth hormone receptor deficiency (GHRD) from southern Ecuador (1). This report presents further information about the effects of lifelong absence of GH action, providing insight into the relationship of body composition, hormonal status, and disease risk. We propose that the absence of GH action is associated with marked insulin sensitivity that prevents the development of diabetes and reduces the risk for cancer, despite increased percentage body fat. We studied carbohydrate, lipid, and adipocytokine concentrations in an adult population of 27 GHRD and 35 comparably overweight control subjects, metabolic responses to a standard breakfast in 7 GHRD and 11 control subjects, and oral glucose tolerance tests (OGTT) in 7 GHRD and 7 controls. Despite matching for age & BMI, GHRD subjects had consistently greater mean % body fat (~50%) and lower lean/fat per DXA. Fasting insulin, 2 hour blood glucose, VLDL, and triglyceride levels were all significantly lower in the 27 subjects with GHRD, indicative of insulin sensitivity; both cholesterol (C) and HDL were elevated with comparable C/HDL, and LDL was elevated ($P < 0.001$), consistent with dependence of the LDL receptor on GH action. The indicator of insulin sensitivity, HOMA2%S, was more than twofold greater in GHRD (261 ± 133 vs 108 ± 87, $P<0.0001$) and the measure of insulin resistance, HOMA2-IR, 1/3 that of controls in GHRD (0.59 ± 0.51 vs 1.74 ± 1.84, $P<0.01$). High molecular weight adiponectin (HMWA) was greater in GHRD (7.59 ± 4.07 mg/L vs 4.29 ± 2.89, $P<0.001$) and leptin lower (7.3 ± 4.7 ng/mL vs 10.4 ± 5.2, $P<0.05$). Although GHRD subjects were ~65% of the weight of controls but consumed the same quantity of standard breakfast (~1000 cal, 114 g CHO, 47 g fat, 40 g protein), their mean glucose concentrations during the 300 minute study were significantly lower ($P<0.01$) with mean insulin levels 1/3 those of controls (11.4 ± 4.2 vs 33.1 ± 15.5, $P<0.01$). Glucose and insulin results of the 2 hour OGTT were similar. The area under the curve for triglyceride responses to the mixed meal during the 1st 150 minutes did not differ but was significantly less from to 180 to 300 minutes in the GHRD. We have demonstrated marked insulin sensitivity despite high percent body fat in GHRD, as well as absence of leptin resistance and elevated levels of HMWA inconsistent with typical obesity associations. Because GHRD eliminates direct metabolic effects of GH, the most straightforward explanation for the dissociation of obesity and insulin resistance in this group is the lack of the counterregulatory/diabetogenic effect of GH. Because it is likely that the obesity associated hyperinsulinism is acting as a mitogen (directly and via the type 1 IGF receptor and hybrids) to explain increased cancer risk with obesity, the reduced cancer mortality with GHRD is likely also a benefit of their insulin sensitivity.

Presentation Date: Sunday, June 22
Presentation Time: 11:30 a.m.-1:00 p.m.
Location: Room W471

SUN-0482: Hypothyroidism May Lead to Impaired Driving

People with significant hypothyroidism can experience impaired driving similar to those who are driving when intoxicated by alcohol, a new study finds. The results will be presented Sunday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

Hypothyroidism, insufficient thyroid hormone, is very common and has been known to cause impairment of many bodily functions, including brain function. Until now, studies have not sufficiently explored the extent of brain impairment and whether hypothyroid people are safe drivers, said the study's senior investigator, Kenneth Ain, MD, from the University of Kentucky and the Veterans Affairs Medical Center in Lexington, KY.

"We found that hypothyroid patients being tested on a driving simulator had a similar performance to that of drivers with a blood alcohol level above the legal limit in the U.S.," said co-author Charles Smith, MD, also of the University of Kentucky. "Physicians should warn their hypothyroid patients to avoid driving until they have been sufficiently treated with thyroid hormone."

In this study, thirty two patients with thyroid cancer, who were undergoing preparation for radioactive iodine scanning by stopping thyroid hormone, were evaluated with a battery of neurological and psychological tests, as well as testing on a driving simulator. They were studied when they were taking thyroid hormone, again when they were off of thyroid hormone, and then finally when they were back on thyroid hormone therapy.

Hypothyroid patients had depression and also showed declines in neurological function that resulted in increased automobile braking times; similar to the performance of drivers with a blood alcohol level of 0.082 g/100 mL. Taking thyroid hormone reversed all of these effects.

"Our results uncover a potential public and personal health hazard regarding impaired hypothyroid drivers," Ain said.

Funding for this study was provided by Genzyme, a Sanofi company.

# # #

SUN-0482: Quantified Cognitive, Motor and Driving Impairments in Hypothyroidism and Their Reversibility

Kenneth Ain. *VA Medical Center & University of Kentucy*

Kenneth Bruce Ain, MD[1], Charles D Smith, MD[2], Richard C Grondin, PhD[3], William B LeMaster[2], Barbara J Martin[2] and Brian T Gold, PhD[3], (1) Thyroid Cancer Research Lab & Thyroid Oncology Program, VA Medical Center & University of Kentucky, Lexington, KY, (2) Neurology, University of Kentucky, Lexington, KY, (3) Anatomy and Neurobiology, University of Kentucky, Lexington, KY

Cognitive and motor impairments have long been associated with hypothyroidism; however, the precise character of cognitive change remains controversial. Despite widespread anecdotal clinical recognition of impaired driving of hypothyroid patients, there is a paucity of data on motor impairment and vehicular safety that would validate precautions for hypothyroid patients. To evaluate neurological, psychological, and vehicular operation parameters altered by hypothyroidism, we performed sequential assessments in euthyroid, hypothyroid, and euthyroid hormone-replaced states in thyroid cancer patients who underwent thyroid hormone withdrawal for radioiodine scanning. Recruitment, informed consent (Univ. of Kentucky IRB), and initial phase of study evaluation were obtained while euthyroid. Inclusion criteria included: age 18-70 years, ≤ 2 years driving experience, valid driver's license, and normal corrected visual acuity. Exclusion criteria included: cognitive impairment or impairing psychoactive medications, interfering neurologic disorders (epilepsy, head injury with >5 minute loss of consciousness), or disabilities affecting assessment of driving and motor performance (e.g., stroke, spinal disease or Parkinson's disease). Target recruitment was reached at 32 subjects (drop-out replacement resulted in 40 recruited subjects). Assessments used: ThyDQoL and ThySRQ measures, Human Motor Assessment Panel, and a psychometric test battery (including: National Adult Reading Test, Boston Naming Test, Mini-Mental State Exam, Wechsler Adult Intelligence Test-Revised, Letter Fluency FAS, and Beck inventory). A driving simulator (STISIM Drive, M400, Hawthorne, CA) assessed vehicular skills. Experimental design used within-subject longitudinal "A-B-A" with each subject tested at 3 visits in the same sequence: euthyroid, hypothyroid, and euthyroid. We showed that, in hypothyroidism, fine motor performance of hands and reaction times in emergency braking tests were slowed, as well as subjective slowing reported on structured clinical scales. Depression was present, typified by vegetative and mood alterations, but lacking reported guilt and lowered self-esteem seen in other types of depression. Cognitive impairment was characterized by declines on speeded executive tests. In contrast, episodic memory performance improved over time regardless of thyroid hormone status. Braking times increased in hypothyroidism by 8.5%, equivalent to reports of effects from a blood alcohol level of 0.082 g/100 mL (above legal driving limit in USA). These data represent new empirical evidence supporting avoidance of complex activities requiring rapid responses, such as operating motor vehicles, in hypothyroidism. We did not observe reduced global mental function or a decline in episodic memory, distinguishing hypothyroidism from amnestic states.

Presentation Date: Sunday, June 22
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

OR23-5: High blood sugar causes brain changes that raise depression risk

Researchers have found a possible biological reason why people with diabetes are prone to depression. A new study shows that high blood glucose (sugar) levels in patients with Type 1 diabetes increase the levels of a brain neurotransmitter associated with depression, and alter the connections between regions of the brain that control emotions. The results will be presented Sunday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

"It was traditionally thought that patients with Type 1 or Type 2 diabetes have higher rates of depression than their nondiabetic peers because of the increased stress of managing a complex chronic disease," said study co-investigators Nicolas Bolo, PhD, from Beth Israel-Deaconess Medical Center, and Donald Simonson, MD, MPH, ScD from Brigham and Women's Hospital, both in Boston. "Our results suggest that high blood glucose levels may predispose patients with Type 1 diabetes to depression through biological mechanisms in the brain."

The researchers studied 19 adults who were not depressed: eight with Type 1 diabetes (three men and five women, with an average age of 26) and 11 healthy controls (six men and five women, whose average age was 29). They used a type of magnetic resonance imaging (MRI), called functional MRI, to measure brain activity, as well as magnetic resonance spectroscopy to measure the level of glutamate, a brain neurotransmitter linked to depression at high levels. Subjects underwent brain imaging when their blood sugar level was normal (90 to 110 milligrams per deciliter, or mg/dL) and after a continuous infusion of glucose, which moderately elevated their blood sugar (180 to 200 mg/dL).

Bolo explained how acutely raising the blood sugar level reduced the strength of the connections among regions of the brain involved in self-perception and emotions to a greater degree in diabetic patients than in healthy control subjects. The strength of these connections in the brain was reportedly also lower in diabetic patients with poor long-term glucose control, as shown by a high hemoglobin A1c level, compared with diabetic subjects in good control, who had a low hemoglobin A1c.

In addition, acutely raising the blood glucose level elevated the neurotransmitter glutamate, in an area of the brain responsible for controlling emotions, in patients with Type 1 diabetes but not in healthy individuals, the authors reported.

These changes in the brain increase the risk of developing depression, according to Simonson. Diabetic patients reported worse scores on a depression questionnaire than did the controls, but they were well below the range for major depression, he noted.

"Our findings may enable the development of more targeted approaches to treating depression in diabetes," Bolo stated.

This research received grant funding from the National Institutes of Health.

# # #

OR23-5: Hyperglycemia Disrupts Regional Brain Functional Connectivity and Increases Glutamate Neurotransmitter Levels in Type 1 Diabetes: A Link to the Development of Depression?

Nicolas Bolo. *Beth Israel Deaconess Medical Center*

Nicolas R Bolo, PhD[1], Brandon Hager, MA[1], Gail Musen, PhD[2], Alan M Jacobson, MD[3], Matcheri Keshavan, MD[1] and Donald C Simonson, MD, MPH, ScD[4], (1) Psychiatry, Beth Israel Deaconess Medical Center, Boston, MA, (2) Clinical, Behavioral and Outcomes Research, Joslin Diabetes Center, Boston, MA, (3) Research, Winthrop-University Hospital, Mineola, NY, (4) Division of Endocrinology, Brigham & Women's Hospital, Boston, MA

Type 1 diabetes mellitus (T1DM) is associated with a high prevalence of depression vs. age- and sex-matched controls. We examined whether hyperglycemia might be an etiologic factor for depression either 1) by disrupting resting state functional connectivity (FC) in the insula and posterior cingulate cortex (PCC), which are important in integrating interoceptive and exteroceptive stimuli, or 2) by increasing levels of brain glutamate, a neurotransmitter that is elevated in depression, in the anterior cingulate cortex (ACC, a region involved in emotional control). Eight non-depressed T1DM (3M / 5F; age = 26±1 yrs; HbA1c = 7.1±0.2%) and 11 healthy controls (CON; 6M / 5F; age = 29±3 yrs; HbA1c = 5.5±0.1%) were studied during a 60-min euglycemic (EU) basal period (T1DM: 111±8 mg/dl; CON: 93±2 mg/dl) followed by a 60-min +90 mg/dl hyperglycemic (HY) clamp (T1DM: 202±7 mg/dl; CON: 182±3 mg/dl). T1DM received basal insulin replacement at 0.25 mU/kg/min throughout. During steady-state EU and HY, FC was measured by resting-state functional magnetic resonance imaging using independent component analysis, and glutamate was measured in the ACC and a control region (occipital cortex) by proton magnetic resonance spectroscopy. Subjects also completed the Symptom Checklist-90R depression subscale (SCL-90R-dep) to evaluate depressive symptoms. FC of the right posterior insula and PCC with the salience network (comprising bilateral anterior cingulate, insula and amygdala) was significantly lower in T1DM than controls during HY ($p < 0.05$). In T1DM, HbA1c was negatively correlated with insula FC ($r2 = 0.43$, $p = 0.08$). Glutamate levels in the ACC increased more in T1DM vs. CON during the HY clamp (4.8±1.3 vs -0.7±2.2 mmol/l brain weight; $p = 0.07$), but did not change in the occipital lobe during HY in either group. SCL-90R-dep scores were higher in T1DM vs. CON (5.5±1.7 vs. 1.5±0.5, $p < 0.05$), but substantially below the range for clinical depression. Conclusions: Compared with healthy controls, T1DM subjects have 1) lower FC of the insula and PCC to the salience network during acute hyperglycemia, 2) an association of reduced FC with higher HbA1c, 3) a greater increase in ACC glutamate during acute hyperglycemia, and 4) higher depressive symptoms. These data suggest that acute and chronic exposure to hyperglycemia disrupt functional connectivity and increase levels of glutamate in brain areas relevant to mood and emotion, both of which may increase susceptibility to development of depression.

Presentation Date: Sunday, June 22
Presentation Time: 11:30 a.m.-1:00 p.m.
Location: Room W185

OR18-6: BPA exposure during fetal development raises risk of precancerous prostate lesions later in life

A new study has found for the first time that the endocrine-disrupting chemical bisphenol A (BPA) reprograms the developing prostate, making the gland more susceptible to precancerous lesions and other diseases later in a man's life. The results will be reported Sunday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

"By using two novel models of human prostate development involving embryonic stem cells, this study is the first to show that low doses of BPA can actually reprogram human fetal prostate tissue in a manner that raises the risk of prostate diseases as men age," said the study's presenting author, Esther Calderon-Gierszal, a PhD student at the University of Illinois at Chicago, Chicago, IL.

BPA is a chemical used to manufacture certain plastics and is often found in water bottles, food storage containers and other consumer products. BPA disrupts the normal functioning of the body's hormones by mimicking the hormone estrogen.

Past studies of adult prostate stem cells and animal models found that BPA exposure increased the risk of developing prostate cancer, so researchers at the University of Chicago at Illinois set out to examine the effect in human embryonic prostate cells. The study was the first to generate a human fetal prostate model grown in a dish in a laboratory. In addition, researchers developed a human-like model in a mouse to study the effects of BPA on the developing prostate.

When the human fetal prostate model grown in the laboratory was exposure to low doses of BPA, investigators reported that exposure altered fetal prostate formation and increased the number of stem cells in the adult prostate, which could lead to aberrant growth and disease with aging. This type of cell activity eventually could lead to the development of prostate cancer.

To observe the effects of BPA in prostate tissue grown in a host mouse, researchers combined human embryonic stem cells and rat cells called mesenchyme. The researchers then grafted the combined tissue on to the kidneys of mice where it developed into human-like prostate tissue. The experiment modeled human BPA exposure feeding the mice low-dose BPA which led to the development of lesions in the human prostate tissue, including a precancerous lesion known as prostate intraepithelial neoplasia, or PIN.

"Using human embryonic stem cells to generate prostate tissues, we were able to document the direct effect low-dose BPA exposure had in driving prostate pathology and disease," Calderon-Gierszal said.

# # #

OR18-6: Directed Differentiation of Human Embryonic Stem Cells (hESC) to Prostate: Novel Models That Verify Bisphenol A Effects on Human Prostate Development

Esther Calderon-Gierszal. *University of Illinois at Chicago*

Esther Calderon-Gierszal[1], Andre Kajdacsy-Balla, MD, PhD[2], Guannan Li[3], Ke Huang[3], Richard B van Breemen, PhD[3] and Gail S Prins, PhD[4], (1) Dept of Physiology & Biophysics, University of Illinois at Chicago, Chicago, IL, (2) Dept of Pathology, University of Illinois at Chicago, (3) Dept of Medicinal Chemistry & Pharmacognacy, University of Illinois at Chicago, (4) Dept of Urology, Univ of IL - Chicago, Chicago, IL

Evidence from rodent1 and adult human stem cell2 models suggests that early-life BPA exposure can reprogram the prostate and render it more susceptible to carcinogenesis with aging. To determine whether human embryonic prostate cells are similarly sensitive to BPA, the present studies derived two novel models of human prostate development using hESC (H9). First, we generated a pioneer in vitro model of directed differentiation of hESC into prostatic organoids using sequential exposure of hESC to stage-specific growth factors and steroids. Differentiation to prostatic structures was confirmed by immunofluorescence (IF) and RT-PCR for multiple prostate markers including PSA. Next, the hESC cells were exposed to vehicle, 1 or 10 nM BPA throughout culture. Budding and nonbudding structures were quantitated 4 days following transfer to Matrigel. While 1 nM BPA increased total and budding organoid numbers ($P<0.01$), 10 nM BPA reduced ($P<0.05$) structure numbers vs vehicle. Continued 3-D culture in BPA did not alter their differentiation to mature organoids at day 30 as assessed by IF and RT-PCR. However, BPA exposures at both doses resulted in focal clusters of resident stem cells within the organoids, a phenotype not observed in controls. RT-PCR for OCT4, NANOG and CD49f confirmed increased expression of stem cell genes in 10 nM BPA vs control ($P<0.05$). These results indicate that BPA directly targets hESC and disrupts human prostate morphogenesis. To determine whether hESC-derived prostatic tissues are susceptible to developmental BPA reprogramming and carcinogenesis in vivo, hESC colonies were mixed with embryonic rat prostatic mesenchyme and grafted to the renal capsule of nude mice. Mature prostatic-like tissues with human epithelium formed by 30 days; confirmed by multiple markers including PSA. Developmental BPA exposure was modeled by daily oral dosing of host mice (250µg/kg BW) for 14 days after grafting, producing free serum BPA levels of 0.49 ng/mL 20 min post-dosing. Estradiol (E)-driven carcinogenesis was initiated by E+T pellets at one month, to model rising E levels with aging. At 5 months, prostatic structures were evaluated for pathologic evidence of cancerous lesions. E+T treatment alone did not induce prostate cancer vs T alone (7% vs 0%, respectively) and this was not significantly enhanced by developmental BPA exposure (14%). Importantly, developmental BPA alone increased the incidence of total lesions (squamous metaplasia, hyperplasia and intraepithelial neoplasia) from 4% in controls to 25% ($P<0.037$) in the BPA exposed grafts. These results indicate that exposure to environmentally relevant levels of BPA during development is sufficient to drive prostate pathology in the mature human prostate epithelium. Taken together, the present studies suggest that the developing human fetal prostate gland may be reprogrammed by BPA making it more susceptible to diseases with aging.

Presentation Date: Sunday, June 22
Presentation Time: 11:30 a.m.-1:00 p.m.
Location: Room W475

OR18-1: Exposure to BPA substitute causes hyperactivity and brain changes in fish

A chemical found in many "BPA free" consumer products, known as bisphenol S (BPS), is just as potent as bisphenol A (BPA) in altering brain development and causing hyperactive behavior, an animal study finds. The results will be presented Sunday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

BPA has been linked to a wide range of hormone disorders, such as obesity, reproductive cancers and, recently, hyperactivity in children born to women exposed to high levels of this substance during the second trimester of pregnancy. Now, this research in fish found that exposure to BPS, a bisphenol compound, led to hyperactive offspring, just as BPA did.

"BPS, termed the safe alternative to BPA, may be equally as harmful to developing brains," said the study's senior investigator, Deborah Kurrasch, PhD, from Canada's University of Calgary. "Society must place increased pressure on decision makers to remove all bisphenol compounds from manufacturing processes."

The study investigated the effects of BPA and BPS on brain development in zebrafish. This fish is developmentally similar to humans, but the embryo grows externally, enabling researchers to see development of the offspring.

A PhD student in Kurrasch's lab, Cassandra Kinch, exposed zebrafish embryos during the period similar to the second trimester to the exact chemical concentration of BPA found in a local major water source, the Oldman River in Alberta, Canada. This concentration translated to a low dose of BPA for the embryos. By labeling some 5-day-old embryos with molecular markers, she monitored development of the hypothalamus, a powerful region of the brain that controls release of hormones in fish and humans. She counted the number of neurons, or nerve cells, in that brain region and compared it with the number of neurons from fish embryos without BPA exposure.

At the peak time of neuronal birth, the number of neurons in BPA-exposed fish rose 170 percent compared with unexposed fish, Kurrasch stated. In similar experiments using BPS, the number of neurons in exposed fish increased 240 percent. These results, she explained, suggest that BPA and BPS could lead to altered brain connections and might explain the hyperactivity they observed in another experiment. Specifically, the research team used movement tracking software to evaluate behavioral changes in young fish and found that fish exposed during brain development to either BPA or BPS were hyperactive, but unexposed fish were not.

Researchers have thought BPA causes harmful effects by mimicking the female hormone estrogen. However, the Kurrasch lab found another likely cause. They exposed another group of zebrafish to BPA plus various drugs that each block distinct hormone signals. Rather than influencing estrogen signaling pathways, as previously hypothesized, BPA appeared to stimulate neuronal birth by mimicking the male hormone testosterone, which then induced aromatase B, a brain-specific protein recently reported to control the birth of neurons and a key enzyme for estrogen synthesis (production), according to Kurrasch.

"These data provide a new avenue of research to investigate the recent rise in hormone disorders," she said.

This work received funding from the Natural Sciences and Engineering Research Council of Canada.

# # #

OR18-1: Bisphenol a Exposure Induces Precocious Neurogenesis and Hyperactivity By Increasing Local Estrogen Synthesis within the Brain

Cassandra Kinch. *University of Calgary*

Cassandra Dawn Kinch, BSc, Bio Sciences, Univ of Calgary, Calgary, AB, Kingsley Ibhazeheibo, PHD, Medical Genetics, University of Calgary, Carol Schuurmans, PHD, Biochemistry & Molecular Biology, University of Calgary, Hamid R Habibi, PHD, Univ of Calgary, Calgary, AB, Canada and Deborah Marie Kurrasch, PHD, University of Calgary, Calgary, AB, Canada

Children born to mothers with high urinary Bisphenol A (BPA) levels in the second trimester of gestation are hyperactive during childhood. However, the physiological insults incurred by prenatal exposure to endocrine disruptors such as BPA, remain poorly understood. Since neurogenesis (birth of neurons) is the main neurodevelopmental step occurring during the second trimester, we investigated whether prenatal BPA exposure could cause neurogenic perturbations within the hypothalamus, a small but powerful region of the brain responsible for controlling various neuroendocrine physiologies. Given that neural progenitors are responsive to estrogen, we reasoned that estrogenic BPA might influence the maintenance of the hypothalamic progenitor pool and affect timing of neuronal birth, perturbing establishment of key circuitry, and ultimately transducing into hyperactive behavior. By using the developmentally similar zebrafish as a model, we surpassed confounding effects observed in mammals such as degree of placental transfer and maternal metabolic dynamics. To evaluate the hypothalamic neurogenic profile, BPA-exposed fish were labeled with molecular markers for neuronal differentiation at key timepoints throughout the neurodevelopmental window. To assay BPA-induced behavioral changes we utilized movement tracking software to monitor locomotor patterns of exposed zebrafish. Significantly, exposure of embryonic zebrafish to a very low dose of BPA (0.0068uM) resulted in a 170% increase in hypothalamic neurogenesis with a concomitant hyperactive phenotype. Exposure to Bisphenol S (BPS), the main BPA analogue used in the production of BPA-free products, had similar neurogenic and locomotor effects. Surprisingly, these Bisphenol-induced effects were not mediated by the predicted estrogen receptor signaling pathways, but through a novel mechanism contingent on aromatase activity, the key enzyme for estrogen biosynthesis. Thus, by altering local estrogen synthesis, BPA/BPS may play a previously unappreciated role in inducing precocious cell cycle exit in hypothalamic progenitors. This study is the first to mechanistically link prenatal BPA/BPS exposure with changes in brain development (neurogenesis) and altered behavior. In addition, our results suggest that use of BPS, termed as the ‘safe alternative’ of BPA-free products, is equally harmful to developing brains and calls for continued societal push to eliminate all Bisphenol analogues from consumer goods production.
NSERC, CIHR (DMK); NSERC (HRH)

Presentation Date: Sunday, June 22
Presentation Time: 11:30 a.m.-1:00 p.m.
Location: Room W475

OR22-1: Denosumab treatment for postmenopausal osteoporosis increases bone density

Postmenopausal women with osteoporosis who take denosumab long-term have increased bone density, sustained low rate of fractures, and a favorable benefit/risk profile, a new multinational study finds. The results will be presented Sunday, June 22, at ICE/ENDO 2014, the joint meeting of the International Society of Endocrinology and the Endocrine Society in Chicago.

"This study provides reassurance to physicians and their patients that long-term treatment with denosumab for at least 8 years leads to significant increases in bone density and is safe for appropriately selected women with postmenopausal osteoporosis," said lead study author E. Michael Lewiecki, MD, clinical assistant professor of medicine at the University of New Mexico School of Medicine in Albuquerque. "It's important to note that the overall risk of side effects did not increase over time."

Osteoporosis is a long-term disease that occurs when the creation of new bone doesn't keep up with the removal of old bone. The disorder primarily affects women past menopause, causing their bones to become weak and brittle, sometimes so much so that a fall or even a cough can cause a fracture. The treatments that reduce fracture risk by increasing bone density have important long-term effects.

This study showed that long-term treatment with denosumab was safe and resulted in continuing increases in bone density over the 8 years of treatment, with persistently low fracture rates.

To evaluate the long-term efficacy and safety of denosumab for up to 10 years, Dr. Lewiecki and his colleagues conducted the ongoing multinational FREEDOM clinical trial. In this study, the researchers present data from up to 8 years of continued denosumab treatment.

Among the almost 8,000 women originally enrolled in the FREEDOM trial, denosumab reduced their risk of vertebral fractures by 68%, reduced their risk of hip fractures by 40%, and reduced their risk of nonvertebral fractures by 20%, compared with placebo. The women taking the drug had no increase in their overall risk of cancer, infection, cardiovascular disease, delayed fracture healing, or hypocalcemia.

All the roughly 3,000 women in this long-term extension of the trial took denosumab for up to 8 years, and overall, they showed a continued increase in their mean bone mineral density, with a cumulative 8-year gain of 18.4% at the lumbar spine and 8.3% at the total hip, with few fractures and a good safety profile.

Amgen Inc. supported the study.

# # #

OR22-1: Effect of Denosumab Treatment in Postmenopausal Women with Osteoporosis: Eight-Year Results from the Freedom Extension, Phase 3 Clinical Trial

E. Michael Lewiecki. *New Mexico Clinical Research & Osteoporosis Center*

E Michael Lewiecki[1], Socrates Papapoulos[2], Kurt Lippuner[3], Christian Roux[4], Celia JF Lin[5], David L Kendler[6], Maria L Brandi[7], Edward Czerwinski[8], Edward Franek[9], Peter Lakatos[10], Salvatore Minisola[11], Jean-Yves Reginster[12], Soren Jensen[13], Nadia Daizadeh[5], Andrea Wang[5], Mary Gavin[5], Rachel B Wagman[5] and Henry G Bone[14], (1) New Mexico Clinical Research & Osteoporosis Center, Albuquerque, NM, (2) Leiden University Medical Center, Leiden, Netherlands, (3) Bern University Hospital, Bern, Switzerland, (4) Paris Descartes University, Paris, France, (5) Amgen Inc., Thousand Oaks, CA, (6) University of British Columbia, Vancouver, BC, Canada, (7) University of Florence, Florence, Italy, (8) Krakow Medical Center, Krakow, Poland, (9) Central Clinical Hospital MSWiA, Warsaw, Poland, (10) Semmelweis University, Budapest, Hungary, (11) Sapienza University, Rome, Italy, (12) University of Liège, Liège, Belgium, (13) CCBR, Ballerup, Denmark, (14) Michigan Bone and Mineral Clinic, Detroit, MI

Purpose: The FREEDOM trial open-label extension (1,2) is designed to evaluate the long-term efficacy and safety of denosumab (DMAb) for up to 10 years. Here we present data from the 5th year of the extension, representing up to 8 years of continued DMAb treatment.

Methods: All women in the extension received 60 mg of DMAb every 6 months and daily calcium and vitamin D. In this analysis, women in the long-term group received 3 years of DMAb in FREEDOM and 5 years of DMAb in the extension, totaling 8 years of DMAb treatment; women in the cross-over group received 3 years of placebo in FREEDOM and 5 years of DMAb in the extension, totaling 5 years of DMAb treatment.

Results: Of the women who entered the extension, 66% completed the 5th year. Bone turnover marker data showed that the reductions in serum C-terminal telopeptide of type 1 collagen and procollagen type 1 N-terminal propeptide were sustained through 8 years in the long-term group and were similarly reduced in the cross-over group. With 8 years of DMAb treatment in the long-term group, mean bone mineral density (BMD) continued to increase from the FREEDOM baseline for cumulative gains of 18.4% at the lumbar spine (LS) and 8.3% at the total hip (TH) (all $p < 0.0001$). With 5 years of DMAb treatment in the cross-over group, there were mean BMD increases from the extension baseline of 13.1% at the LS and 6.2% at the TH (all $p < 0.0001$). The incidence of new vertebral and nonvertebral fracture remained low throughout the extension, and hip fracture incidence was 0.2% and 0.1% for the long-term and cross-over groups, respectively, during year 8. The adverse event (AE) and serious AE profiles were consistent with data reported previously in the extension study.

Conclusions: Treatment with DMAb for up to 8 years was associated with persistent reduction of bone turnover, continued increases in BMD, and low fracture incidence. The benefit/risk profile for DMAb remains favorable.

Presentation Date: Sunday, June 22
Presentation Time: 11:30 a.m.-1:00 p.m.
Location: Room W181

LB-OR02-6: Empagliflozin lowers high blood pressure and blood sugar in diabetics

An investigational drug to treat Type 2 diabetes, empagliflozin, lowers blood pressure in patients with Type 2 diabetes and hypertension (high blood pressure), a new study finds. The results will be presented Sunday in a late-breaking abstract at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

This improvement in blood pressure reportedly was accompanied by a reduction in blood glucose (sugar) levels after 12 weeks of treatment with the drug, which is under development by Germany-based Boehringer Ingelheim Pharma.

"Tight blood pressure control in patients with hypertension and Type 2 diabetes is known to reduce the risk of death and complications related to diabetes," said a study co-investigator, Afshin Salsali, MD, executive director of the Diabetes and Metabolism therapeutic area for Boehringer Ingelheim Pharma, which funded the study. "Our results suggest the potential to reduce the risk of cardiovascular events with long-term treatment."

However, he emphasized that this hypothesis awaits confirmation in the long-term EMPA-REG OUTCOMETM trial (NCT01131676 on ClinicalTrials.gov), which is expected to complete in 2015.

The researchers tested two doses of empagliflozin, 10 milligrams (mg) and 25 mg, compared to a placebo, or "dummy" pill, in patients with Type 2 diabetes and high blood pressure, which ranged from 130 over 80 to 159 over 99 millimeters of mercury (mm Hg). Of the 824 patients, 276 received the lower dose of empagliflozin and another 276 received the higher dose; 272 patients received the placebo. All patients wore a blood pressure cuff that monitored their blood pressure at regular intervals for 24 hours before the start of the study and after 12 weeks of treatment. They also gave blood samples for checking their hemoglobin A1c, a measure of long-term blood sugar control.

Study data showed the differences between the average decreases with empagliflozin treatment and the average increases in results of patients treated with placebo. Empagliflozin at the 25-mg dose demonstrated the greatest 12-week reduction in both systolic blood pressure (the top number in a blood pressure reading) and diastolic blood pressure (bottom number). On average, blood pressure fell 4.2 mm Hg in comparison to placebo for systolic pressure and 1.7 mm Hg for diastolic in the group receiving 25 mg of empagliflozin. Patients who received the 10-mg dose had average decreases of 3.4 and 1.4 mm Hg compared to placebo in systolic and diastolic blood pressures, respectively.

From the start to the end of the study, the average hemoglobin A1c level dropped 0.62 percentage points with 10-mg empagliflozin and 0.65 percentage points with the 25-mg dose compared to placebo.

Salsali said empagliflozin improves blood sugar levels by reducing glucose re-absorption in the kidneys, leading to glucose elimination in the urine. He also said patients tolerated the drug well, with no increased rate of side effects in the empagliflozin groups compared to placebo. Most adverse events reported in all three groups were mild in intensity.

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LB-OR02-6: Empagliflozin Reduces Blood Pressure in Patients with Type 2 Diabetes and Hypertension: A Phase III, Randomized, Double-Blind, Placebo-Controlled Trial (EMPA-REG BPTM)

Ilkka Tikkanen. *Helsinki University Central Hospital*

Ilkka Tikkanen, MD[1], Kirsi Narko[2], Cordula Zeller[3], Alexandra Green[4], Afshin Salsali[5], Uli C Broedl[5] and Hans-Juergen Woerle[5], (1) Helsinki University Central Hospital, Helsinki, Finland, (2) Boehringer Ingelheim Finland Ky, Helsinki, Finland, (3) Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany, (4) inVentiv Health Clinical, Maidenhead, United Kingdom, (5) Boehringer Ingelheim Pharma GmbH & Co. KG, Ingelheim, Germany

Objective: To investigate the efficacy and safety of empagliflozin in patients with type 2 diabetes and hypertension (mean seated systolic blood pressure [SBP] 130–159 mmHg and diastolic BP [DBP] 80–99 mmHg).

Methods: In this study (NCT01370005), patients were randomized to empagliflozin 10 mg, empagliflozin 25 mg, or placebo once daily for 12 weeks. All patients who received at least one dose of study drug were included in the treated set for safety analyses (n=276, 276, and 272 for empagliflozin 10 mg, empagliflozin 25 mg, and placebo, respectively). Randomized patients who received at least one dose of study drug and had a baseline HbA1c value and a baseline mean 24-hour SBP value were included in efficacy analyses (n=276, 276, and 271 for the respective groups). Co-primary endpoints were changes from baseline in HbA1c and mean 24-hour SBP (ambulatory BP monitoring [ABPM]) at week 12. A key secondary endpoint was change from baseline in mean 24-hour DBP (ABPM) at week 12.

Results: Across the randomized groups, the mean age (SD) was 60.2 (9.0) years, and BMI was 32.6 (5.1) kg/m2. Mean (95% CI) differences vs placebo in changes from baseline in HbA1c were 0.62% (0.72%, 0.52%) and -0.65% (-0.75%, -0.55%) with empagliflozin 10 mg and 25 mg, respectively (both $p<0.001$), in mean 24-hour SBP were 3.44 mmHg (-4.78, -2.09) and -4.16 mmHg (-5.50, -2.83) with empagliflozin 10 mg and 25 mg, respectively (both $p<0.001$), and in mean 24-hour DBP were 1.36 mmHg (2.15, -0.56) and -1.72 mmHg (-2.51, -0.93) with empagliflozin 10 mg and 25 mg, respectively (both $p<0.01$). Adverse events were reported by 48.9%, 51.4%, and 52.6% of patients on empagliflozin 10 mg, 25 mg, and placebo, respectively. Events consistent with volume depletion were reported in 1 patient each on empagliflozin 10 mg and placebo.

Discussion: In patients with type 2 diabetes, hypertension is a common comorbidity and enhances the risk of cardiovascular complications, thus a treatment approach that includes control of BP and glycemia may reduce the risk of cardiovascular complications and mortality.

Conclusion: Empagliflozin significantly reduced BP and was well tolerated in patients with type 2 diabetes and hypertension.

Presentation Date: Sunday, June 22
Presentation Time: 11:30 a.m.-1:00 p.m.
Location: Room W471

OR18-3: Common BPA-like chemical, BPS, disrupts heart rhythms in females

Bisphenol S (BPS), a common substitute for bisphenol A (BPA) in consumer products, may have similar toxic effects on the heart as previously reported for BPA, a new study finds. The results will be presented Saturday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

In the years since research evidence first showed many potentially damaging health effects of the industrial chemical BPA, some manufacturers have switched to its chemical cousin, BPS, to make hard plastics and other products that they call BPA free, said the study's lead investigator, Hong-Sheng Wang, PhD, from the University of Cincinnati.

Although some BPA-free products contain no bisphenols, Wang said, "BPS is one of the substitutes used in BPA-free products. There is implied safety in BPA-free products. The thing is, the BPA analogs—and BPS is one of them—have not been tested for safety in humans."

BPA is an endocrine (hormone) disrupter that can interfere with the actions of native estrogen and other hormones, but it is not clear whether BPS also is disrupts hormones.

In what Wang called "one of the first assessments of BPS' effect in mammalian primary cells or organs," he and his co-workers tested an environmentally relevant dose of BPS in the hearts of approximately 50 rats. The 1-nanomolar dose was in the range of BPS found in human urine samples in a study by other authors.

In the current study, the investigators perfused, or flowed, BPS through the arteries of each animal's pumping heart, after stimulating the heart with the hormone catecholamine to mimic stress. For a control group, 30 rat hearts received only catecholamine and no BPS.

Exposure to BPS rapidly increased the heart rate of female rats and under the stress condition led to arrhythmias—heart rhythm abnormalities—far greater than in the control rats that did not receive BPS, Wang reported. Electocardiograms demonstrated that BPS caused extra heartbeats and a racing heartbeat, also known as ventricular tachycardia. In male rats, BPS reportedly did not have this rapid impact on the heart.

To determine the cause of the cardiac effects in female rats, the researchers studied cardiac muscle cells from some of the rats. Using studies at the cellular and protein levels, they found that BPS caused abnormal calcium handling, or cycling, which is a key cause of arrhythmias, according to Wang. This action is very similar to the underlying mechanism of BPA's toxic effects on the heart, which Wang and his colleagues showed in a previous study.

The investigators were able to abolish the BPS-induced heart rhythm abnormalities by blocking a type of estrogen receptor (beta) in the female rats. This result shows that "the BPA analog BPS is not necessarily free of endocrine-disrupting activity," Wang said.

"Our findings call into question the safety of BPA-free products containing BPS," he said. "BPS and other BPA analogs need to be evaluated before further use by humans."

Grants from the National Institutes of Health and the University of Cincinnati Center for Environmental Genetics helped fund this work.

# # #

OR18-3: Evaluation of the Rapid Effects of Bisphenol S (BPS) on the Heart: Impact on Arrhythmogenesis and Cardiac Calcium Handling

Hong-Sheng Wang. *University of Cincinnati*

Xiaoqian Gao, Jianyong Ma, Yamei Chen and Hong-Sheng Wang, PHD, Department of Pharmacology, University of Cincinnati, Cincinnati, OH

Bisphenol A (BPA) is an environmental endocrine disrupting chemical that has been widely used in the production of plastic consumer goods. Because of BPA's potential adverse impact on human health, another member of the bisphenol family, bisphenol S (BPS), is increasingly becoming an alternative to BPA in production of plastic bottles (often labeled "BPA-free") and thermal paper. Wide human exposure to BPS has been reported in various populations including in those in the US. However, the potential health impact of BPS exposure is poorly defined. The goal of the present study is to define the rapid actions and underlying mechanisms of BPS in the heart. The rapid effects of BPS on ex vivo whole heart and isolated ventricular myocytes from adult rats were examined. We found that environmentally relevant concentration of BPS (1 nM) acutely induced ventricular arrhythmias in female adult rat hearts in the presence of catecholamine stimulation. In isolated ventricular myocytes of female adult rats, BPS (1 nM) acutely increased arrhythmogenic triggered activities. The action of BPS on female ventricular myocyte had an "inverted-U" shaped dose-response curve. The cellular mechanisms underlying the cardiac actions of BPS were investigated. Acute BPS treatment significantly increased sarcoplasmic reticulum (SR) calcium leak, and beat-to beat calcium release and reuptake. The phosphorylations of ryanodine receptors and phospholamban, key calcium handling proteins in the heart, were markedly increased upon BPS exposure. The responses of female cardiac cells to BPS were abolished by blockade of estrogen receptor beta but not estrogen receptor alpha. In conclusion, BPS promoted cardiac arrhythmias in the female rat hearts under stress condition, and the action was mediated by altering myocytes calcium handling processes and activation of estrogen receptor beta. This is the first study of the impact of BPS on mammalian organ and primary cells; our results suggest that exposure to BPS, a substitute for the well-studied BPA, may have acute cardiac toxicity similar to that of BPA.

Presentation Date: Sunday, June 22
Presentation Time: 11:30 a.m.-1:00 p.m.
Location: Room W475

OR26-5: Most people with Type 1 diabetes do not use diabetes devices to get long-term data

Almost 70 percent of adults with Type 1 diabetes never use their blood glucose self-monitoring devices or insulin pumps to download historical data about their blood sugar levels and insulin doses—information that likely would help them manage their disease better. These new survey results, which will be presented Sunday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago, also show that only 12 percent of patients regularly review their past glucose and insulin pump data at home.

"This research highlights the fact that these devices used to manage Type 1 diabetes are not being used to their full potential," said Jenise Wong, MD, PhD, the study's principal investigator and an assistant adjunct professor of pediatrics at the University of California, San Francisco. "These devices can be useful not only for real-time disease self-management but also in helping to review past data to guide future treatment decision making."

Glucose monitoring devices include continuous glucose monitors, which automatically measure blood sugar levels every few minutes via a sensor inserted under the skin, and blood glucose meters, used with a fingerstick drop of blood. People with diabetes also use insulin pumps to deliver basal insulin and insulin boluses for high blood sugar levels or when they eat carbohydrates. These devices typically collect and store information such as the response of glucose levels to physical activity and food, as well as the individual's carbohydrate intake and insulin doses. Most insulin-dependent patients use the information displayed on the screen to make immediate decisions about insulin dosing, according to Wong.

She said many health care providers encourage their diabetic patients to download the information from their devices to their computers and look at the data collected for the past few days, weeks or months. "However, we know very little about how often people with Type 1 diabetes look at their past data on their own between visits with their providers," Wong said.

Through an online survey, Wong and her colleagues asked 155 adults with Type 1 diabetes how often they download the past data from their glucose monitoring devices. Seventy-seven survey participants were men, and 78 were women, and their average age was 34.5. Nearly all subjects used a glucose meter, and many used more than one device. A total of 106 individuals used an insulin pump, which either communicated with a glucose meter or allowed the user to manually enter glucose values from a glucose meter. Forty-three used continuous glucose monitors.

The researchers found that only 31 percent of survey respondents (48 of 154) reported ever downloading past data from their devices at home. Even fewer did so four or more times a year and actually read the information before giving it to their health care provider: 12 percent, or 18 of 154 participants. Users of continuous glucose monitors regularly downloaded and reviewed their data more often than users of the other devices: 28 percent versus 5 to 7 percent.

Older adults also were more likely to download their past data, Wong said. For every decade increase in age, there was 1.5 times the chance of the patient downloading and reviewing data from any device.

"Future studies are needed to understand why people with Type 1 diabetes rarely look at past data from their blood glucose monitoring devices," she said.

Few diabetes devices work with smart phones. Wong speculated that patients might find it too technically complicated to download and review the data, or they might not find the data helpful or may not understand how to use the past data to help them manage their diabetes in the future.

# # #

OR26-5: Few Adults with Type 1 Diabetes (T1D) Download and Retrospectively Review Their Diabetes Device Data

Jenise Wong. *University of California San Francisco*

Jenise Colleen Wong, MD PhD[1], Matthew Spindler, BA[1] and Aaron Barak Neinstein, MD[2], (1) Department of Pediatrics, Division of Endocrinology, University of California San Francisco, San Francisco, CA, (2) Department of Medicine, Division of Endocrinology and Metabolism, University of California San Francisco, San Francisco, CA

People with type 1 diabetes (T1D) use a number of devices that collect and store large amounts of data, including blood glucose levels, carbohydrate intake, and insulin doses, in order to help manage their diabetes. Patients typically use information from their devices when making real-time management decisions, and they or their health care providers can also retrospectively review and use this data to help adjust insulin regimens. It is unknown how frequently people with T1D retrospectively review data on their own between clinic visits. We conducted a cross-sectional survey of 98 adults with T1D (mean age 31.0 ± 14.7 years, 48% male, 66% non-Hispanic white, 68% on insulin pumps, 31% using continuous glucose monitoring, or CGM) to assess the frequency of using blood glucose monitor (BGM), insulin pump, and CGM data at home. We defined "Downloaders" as those who downloaded data ≥4 times in one year, and "Reviewers" as those Downloaders who looked at their data ≥50% of the times that they downloaded (as opposed to simply downloading and giving the data to a provider without self-review). Logistic regression was used to identify associated factors. Only 21%, 26%, and 43% of BGM, insulin pump, and CGM users, respectively, ever downloaded data from their devices at home. Even fewer met Downloader status (12% of BGM users, 15% of insulin pump users, and 37% of CGM users), and only 4% of BGM users, 3% of insulin pump users and 23% of CGM users were Downloaders who also met Reviewer status. After adjusting for sex, ethnicity, insurance status, and highest level of education, older age was associated with increased odds of being a BGM Downloader (OR=1.08; 95%CI 1.02, 1.14; p=0.005); for every 10-year increase in age, there was a 2.1 times increased odds (95%CI 1.3, 3.6) of being a BGM Downloader. No demographic factors were associated with insulin pump or CGM Downloader status or any Reviewer status. In conclusion, nearly 60-80% of adults with T1D never download data from their devices and <25% retrospectively review their data at home on a regular basis. As a group, subjects using CGM downloaded and reviewed their CGM data more frequently than did subjects using BGM or pumps. Because self-review of device data can be helpful to patients in managing TID, more effort should be made to increase awareness and education about these device features and to improve usability for patients.

Presentation Date: Sunday, June 22
Presentation Time: 11:30a.m.-1:00 p.m.
Location: Room W184

SUN-1005: Low number of taste buds linked to older age and higher fasting blood sugar

A study finds that the number of taste buds we have on our tongue decreases as we get older, and that the lower the number of taste buds, the more likely for fasting blood glucose (sugar) levels to be higher than normal. The results will be presented Sunday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

Because high fasting blood sugar level is a main characteristic of diabetes, the study findings suggest that the number of taste buds plays a role in glucose metabolism—how the body uses sugar—during aging, the authors proposed.

"The reduced number of taste buds with advancing age might be linked to the increased incidence of Type 2 diabetes among older adults," said the study's lead investigator, Chee Chia, MD, a medical officer at the National Institute of Aging (NIA) in Baltimore.

Diabetes affects more than 25 percent of Americans over age 65, according to the National Institute of Diabetes and Digestive and Kidney Diseases.

Chia explained why she and a co-worker at the NIA, Josephine Egan, MD, thought there might be a connection between taste buds and diabetes. Taste buds at the tip of the tongue, whose medical term is "fungiform papillae," contain sweet taste receptors, and past studies show that people with Type 2 diabetes have impaired sweet taste. Furthermore, animal studies suggest that taste buds produce hormones that are important for glucose metabolism and that, in rodents, taste buds decrease in number with age.

To learn whether humans also have an age-related decline in the density of taste buds, Chia and Egan analyzed data from 353 adults who participated in the NIA's Baltimore Longitudinal Study of Aging between 2011 and 2014. This ongoing observational study of normal aging in community-dwelling volunteers included counts of the density, or number, of taste buds at the tip of the tongue after staining the subject's tongue with blue food dye.

The researchers found that older age was associated with fewer taste buds, a finding also seen in a larger clinical study published last October (Beaver Dam Offspring Study).

In addition, Chia reported that the fewer taste buds that subjects had, the higher their fasting blood sugar levels were and the less they had of a beneficial fat cell hormone called adiponectin. Prior studies found that obesity and Type 2 diabetes are associated with lower adiponectin levels.

"To my knowledge, this is the first association found between the number of taste buds and fasting glucose," Chia said. "It's very possible they could be unrelated, so we plan to do the study over a longer time, to confirm our findings."

"It's also possible," she added, "that having fewer taste buds means fewer hormones are secreted that may control glucose metabolism."

# # #

SUN-1005: Fungiform Papillae Density Is Associated with Age and Markers of Glucose Metabolism in the Baltimore Longitudinal Study of Aging

Chee Wei Chia. *National Institute on Aging/National Institutes of Health*

Chee Wei Chia, MD, Translational Gerontology Branch, NIA/NIH, Baltimore, MD and Josephine Mary Egan, MD, Laboratory of Clinical Investigation, National Institute on Aging/National Institutes of Health, Baltimore, MD

Diabetes affects more than a quarter of persons older than 65 years, with progressively higher prevalence in older men and women. Interestingly, patients with type 2 diabetes and their first-degree relatives have impaired sweet taste, suggesting that impaired taste may play a role in the pathogenesis of diabetes. This hypothesis is consistent with recent findings from animal studies suggesting that tongue fungiform papillae, which contain sweet taste receptors, produce hormones such as GLP-1 and glucagon which are important for glucose metabolism and modulate taste sensitivity. In addition, taste bud size, taste cell number, taste precursor cell number, and taste modulating factors have been shown to decrease with age in rodents. Therefore, we hypothesized that fungiform papillae density declines with aging and is associated with metabolic dysregulation in humans. In a cross-sectional analysis, 353 (male = 170, 48%) participants from the Baltimore Longitudinal Study of Aging had data on fungiform papillae density, fasting plasma glucose (FPG), fasting insulin and adiponectin levels. Fungiform papillae density measurement was obtained using two clear hole reinforcements (diameter of 7mm) placed between median sulcus and apex of the tongue. The fungiform papillae present within the two 7mm holes were counted and normalized to the area of the hole. The participants have the following characteristics: age 70.2 ± 0.7 years, BMI 27.2 ± 0.3 kg/m2, FPG levels 98.5 ± 0.7 mg/dL, adiponectin levels 23.4 ± 0.9 µg/mL, fasting insulin levels 7.6 (IQR 4.2-12.8, µU/mL), and fungiform papillae density 22.0 ± 0.6 N/cm2. Multiple linear regression analysis adjusted for sex and BMI revealed a strong negative, independent association between fungiform papillae density and age ($\beta = -0.28$, $P < 0.001$), and between fungiform papillae density and FPG ($\beta = -0.11$, $P = 0.042$). A positive association was found between fungiform papillae density and adiponectin levels ($\beta = 0.12$, $P = 0.029$), but no association with fasting insulin was noted. These results support the hypothesis that fungiform papillae density may play a role in glucose metabolism during the aging process. These findings suggest that taste receptors on fungiform papillae influence dietary habits, and decline in these receptors with aging may ultimately lead to obesity and alter carbohydrate metabolism. This hypothesis should be tested in longitudinal studies.

Presentation Date: Sunday, June 22
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

SUN-0413: Nutritional Sports Supplements Sold in Australia Test Positive for Banned Androgens

Some nutritional sports supplements marketed to athletes — claiming to help them build lean muscle, reduce body fat and enhance endurance — are secretly fortified with androgens, which are banned from use in sports, a new study from Australia finds. The results will be presented in a poster Sunday, June 22, at ICE/ENDO 2014, the joint meeting of the International Society of Endocrinology and the Endocrine Society in Chicago.

"The point is that 'you can't judge a book by its cover.' The nutritional supplement label may not disclose all ingredients, and sometimes these additions are not declared on the product label. Athletes risk testing positive for a banned substance and the general public risks being inadvertently exposed to androgens, which have recognized health risks," said principal investigator Alison Heather, PhD, professor in the Department of Physiology of the School of Medical Sciences at the University of Otago in Dunedin, New Zealand.

"The presence of androgens in the supplements is concerning, given that the products do not declare their addition. We need to investigate further just what the androgens in these supplements are so we can better understand the implications for health and sports doping," she said.

The worldwide dietary supplement market is worth an estimated $142.1 billion and by 2017 is expected to reach $204.8 billion, and most androgen-containing supplements state their contents on the label. Yet, the scientific literature contains reports of unlabeled androgen-containing supplements, and lacking good manufacturing practice and regulation, companies can covertly add androgens to their nutritional supplements to better satisfy their advertised claims.

To investigate the availability of unlisted androgens in over-the-counter nutritional sports supplements, Professor Heather and her co-authors purchased 74 nutritional supplements randomly from Sydney-based stores, including protein powders, amino acids, creatines, fat metabolizers, "testosterone-boosters," carbohydrates and stimulant/nitric oxide "pre-workout"-based supplements.

Of the 74 samples they tested by bioassay, 6 were androgen-positive but did not list them on the label, and 1 was positive but listed an androgen on the label.

Professor Heather cautioned that, although only 10% of their supplements tested positive for androgens, the nutritional sports supplement industry is not very transparent about revealing all the ingredients in their products. She recommended more stringent legislation to enable the public to be fully aware of what they are putting into their bodies.

The Anti-Doping Research Panel (ADRP, Australia) and the University of Technology, Sydney partly funded the study.

# # #

SUN-0413: Steroidal Extracts from Nutritional Sports Supplements Sold in Australia Test Positive for Androgenic Activity

Elliot Cooper. *University of Technology (Sydney, Australia)*

Elliot R Cooper[1], Xiaohong Li[1], Kristine McGrath[1] and Alison Heather[2], (1) School of Medical and Molecular Biosciences, University of Technology, Sydney, Australia, (2) Department of Physiology, School of Medical Sciences, University of Otago, Dunedin, New Zealand

Nutritional sports supplements are often marketed to athletes claiming to help build lean muscle tissue, reduce body fat, and enhance endurance. The world-wide dietary supplement market is estimated to be worth $142.1 billion USD and is expected to reach $204.8 billion USD by 2017. The lack of good manufacturing practice and regulation in the production and sale of nutritional supplements has led to the covert fortifying of these supplements with anabolic steroids to better achieve the claimed benefits. It has been discovered that in some instances these additions are not declared on the product label. Therefore, the aim of the study was to screen a range of nutritional sports supplements from the Australian market for the presence of androgens using an in vitro yeast cell-based bioassay. Seventy four nutritional supplements were randomly purchased from Sydney-based stores that included protein powders, amino acids, creatines, fat metabolisers, 'testosterone-boosters', carbohydrates, and stimulant/nitric oxide 'pre-workout'-based supplements. Steroid extracts were obtained using solid-phase extraction with a C18 column. The steroid extracts were then tested for androgenic activity using a yeast-based bioassay whereby Saccharomyces cerevisiae cells were co-transformed with a human androgen receptor (AR) expression vector and a β-galactosidase reporter vector under the control of tandem androgen response elements. Two supplements had relative potencies (RP) (defined as 'extract receptor activity/receptor activity of testosterone (T)') greater than T, 2.64 ± 0.33 (p-value 0.0197) and 7.20 ± 0.24 (p-value 0.0008), respectively. A third supplement had a RP less than, but not significantly different than, T (0.79 ± 0.067, p-value 0.0504). Four supplements activated AR, however with lower RP values than T (supp. 4 RP = 0.21 ± 0.03, p-value 0.0066; supp. 5 RP = 0.43 ± 0.09, p-value 0.0162; supp. 6 RP = 0.27 ± 0.02, p-value 0.0053; and supp. 7 RP = 0.36 ± 0.04, p-value 0.0025). In summary, steroid extracts from 7 sports nutritional supplements from the Australian market had AR bioactivity, however, only 1 of these supplements declared the addition of an androgen.

Presentation Date: Sunday, June 22
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

SUN-0910: Fatty liver is linked to maternal use of the SSRI antidepressant fluoxetine

Adult offspring of mothers who used fluoxetine, a common antidepressant, during pregnancy were more likely to develop a fatty liver, a new animal study has found. The results will be reported Sunday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

"When mothers take antidepressants during pregnancy, they may be predisposing their children to metabolic disturbances, including obesity and fatty liver in adulthood," said, the study's senior investigator, Alison Holloway, PhD, associate professor, McMaster University, Hamilton, Ontario.

Fluoxetine (marketed as Prozac®) is in a class of antidepressants called selective serotonin reuptake inhibitors, or SSRIs. Although adults taking antidepressants have an increased risk of obesity and Type 2 diabetes, Holloway said it is unclear whether a woman's use of an SSRI during pregnancy increases the risk of metabolic problems in her children.

To learn the answer to this question, researchers at several Canadian institutions collaborated on this study, which received funding from the Canadian Institutes of Health Research. The investigators studied the consequences of fetal exposure to fluoxetine in rats, which Holloway called a good model for liver and metabolic disorders in humans.

Presenting author Nicole De Long, a PhD student at McMaster, gave 15 female rats the antidepressant (at a daily dosage of 10 milligrams per kilogram of body weight) mixed in plain gelatin for two weeks before mating, during pregnancy and during lactation until weaning their young. As controls, another 15 female rats received the gelatin without the drug for the same period.

When the offspring were 26 weeks old—an age considered young adulthood—the researchers assessed the rats' livers for presence of fatty liver disease, also called nonalcoholic steatohepatitis, as well as for levels of liver lipids (fats) and markers of inflammation.

Compared with offspring of control rats, the offspring of fluoxetine-treated rats more often had signs of mild to moderate fatty liver disease, the authors reported. These rats also had higher levels of triglycerides and cholesterol in the liver.

Both male and female offspring of fluoxetine-exposed mothers also showed increased inflammation in the liver. This inflammation and increased accumulation of fat in the liver is associated with metabolic abnormalities, including obesity and Type 2 diabetes.

"We think it is possible that prenatal exposure to SSRI antidepressants may contribute to obesity and Type 2 diabetes in the children," Holloway commented.

This study provides the first evidence that children exposed to SSRIs in the womb may have increased risk of fatty liver disease," she said. "Exposed children may need monitoring and lifestyle interventions targeting obesity and diabetes prevention."

About 10 to 15 percent of pregnant women take antidepressants, past research shows.

# # #

SUN-0910: Perinatal Exposure to the Selective Serotonin Reuptake Inhibitor Fluoxetine Results in Hepatic Lipid Accumulation and Inflammation

Nicole De Long. *McMaster University*

Nicole E De Long, BSc[1], Eric Barry[1], Christopher Pinelli, DVM[2], Geoffrey Wood, DVM, DVSc, PhD[2], Daniel B Hardy, PHD[3], Katherine Mary Morrison, MD, FRCP[4], Valerie H Taylor, MD, PhD[5], Hertzel C Gerstein, MD, MSc, FRCPC[6] and Alison C Holloway, PhD[1], (1) Department of Obstetrics and Gynecology, McMaster University, Hamilton, ON, Canada, (2) Department of Pathobiology, University of Guelph, Guelph, ON, Canada, (3) Ob/Gyn and Physiol & Pharmacol, The Univ of Western Ontario, London, ON, Canada, (4) Department of Pediatrics, McMaster University, Hamilton, ON, Canada, (5) Department of Psychiatry, University of Toronto, Toronto, ON, Canada, (6) McMaster University, Director, Division of Endocrinol, Hamilton, ON, Canada

Introduction: According to current estimates, 10-15% of women take antidepressant medications during pregnancy. The side effects of this class of medication during pregnancy have been extensively studied, but most studies examine teratogenic outcomes, not metabolic changes. A recent clinical study however has reported that the use of selective serotonin reuptake inhibitor (SSRIs) antidepressants during pregnancy is associated with an increased risk of postnatal obesity. In humans, obesity is often associated with fatty liver, dyslipidemia and inflammation. However the effects of perinatal exposure to SSRIs on markers of fatty liver and inflammation have not been examined.

Objective: In this study, we examined the effect of fetal exposure to fluoxetine (Prozac®), a SSRI antidepressant, on hepatic lipid accumulation and markers of inflammation.

Methods: Female nulliparous Wistar rats were given vehicle (N=15) or fluoxetine hydrochloride (FLX 10 mg/kg/d; N=15) orally for 2 weeks prior to mating until weaning. We assessed liver histology, hepatic lipids and markers of inflammation in the offspring at 26 weeks of age.

Results: There was a significant increase in the number of offspring with mild to moderate NASH in FLX-exposed offspring relative to controls ($p=0.04$). The female offspring of FLX-treated dams had significantly higher levels of hepatic triglycerides and cholesterol ($p<0.01$); similar results were seen for male offspring although the cholesterol levels did not reach statistical significance ($p=0.057$). There was also evidence of increased inflammation of the liver in FLX-exposed offspring; males had significant elevations in relative mRNA expression of TNFα (CON: 0.4 ± 0.22; FLU: 1.8 ± 0.58; $p=0.02$), IL-6 (CON: 0.2 ± 0.13; FLU 1.7 ± 0.52; $p=0.003$) and MCP1 (CON: 0.2 ± 0.13; FLU: 1.3 ± 0.45; $p=0.008$) whereas female offspring had higher expression of TNFα (CON: 0.8 ± 0.48; FLU: 2.5 ± 0.8; $p=0.045$), and increased macrophage infiltration (CD68; CON: 1.0 ± 0.09; FLU: 1.5 ± 0.06; $p=0.01$).

Conclusion: These data demonstrate that in this model fetal and neonatal exposure to FLX results in evidence of fatty liver and inflammation in both male and female offspring. Since fatty liver and hepatic inflammation are associated with a number of metabolic abnormalities, these results raise concerns regarding the long term metabolic sequelae of fetal exposure to SSRIs.

Presentation Date: Sunday, June 22
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

SUN-0345: BPA stimulates growth of an advanced subtype of human breast cancer cells called inflammatory breast cancer

Environmental exposure to the industrial chemical bisphenol A (BPA) lowers the effectiveness of a targeted anti-cancer drug for inflammatory breast cancer, according to a new study that was performed in human cancer cells. The results, which will be presented Sunday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago, also show that BPA causes breast cancer cells to grow faster.

“Routine exposures to common environmental chemicals like BPA appear to contribute to breast cancer cell progression and to diminish drug treatment efficacy, particularly in inflammatory breast cancer,” said principal investigator Gayathri Devi, PhD, associate professor, Department of Surgery, Duke University Medical Center, Durham, N.C.

Inflammatory breast cancer is a rare, aggressive form of breast cancer with one of the worst survival outcomes due to high rate of treatment failure.

“Not everyone with inflammatory breast cancer responds to treatment, and environmental factors are one of many factors thought to explain why,” Devi said.

Other studies have pointed to increased cancer risk with exposure to BPA, a hormone-disrupting chemical found in many consumer products, including hard plastics. However, Dr. Devi said, “This to the best of our knowledge is the first study to show BPA’s effects in altering effectiveness of a targeted drug treatment approved for use in breast cancer patients including those with inflammatory breast cancer.”

This study is a collaboration between Duke University, the Environmental Protection Agency, NC (EPA) and the Biomanufacturing Research Institute and Technology Enterprise (BRITE) at North Carolina Central University. The EPA’s library of chemicals called Toxicity Forecaster or ToxCast, a panel of approximately 300 environmental compounds was used in a newly developed automated screening technology for assessing cancer cell behavior parameters. These "high-content, high throughput screening” assays expose living cells to various doses of chemicals and allow for studying of changes in cell growth and survival.

Devi and colleagues subjected cancer cells isolated from the tumors of patients with inflammatory breast cancer to BPA and other common environmental contaminants in the ToxCast library. They tested a wide range of BPA doses and periods of exposure time including the range observed in human blood samples and from environmental exposures in past, published studies. The researchers then analyzed the cellular changes in culture and compared them with cancerous cells not exposed to BPA.

Although BPA is known to mimic estrogen, it also affected inflammatory breast cancer, which are frequently estrogen receptor-negative, meaning they do not respond to estrogen. BPA exposure caused breast cancer cells to grow faster than untreated cancer cells regardless of whether the cancer was estrogen receptor-positive or -negative, the investigators found.

In addition, this study reported that BPA lowered the effectiveness of an approved cancer-fighting drug, lapatinib, used in breast cancer therapy. Other FDA approved anti-cancer drugs are currently being tested by this team. Devi said the results may have immediate implications in cancer treatment. “Cancer patients must understand there’s a component in their daily lives that could influence their treatment outcome. These studies provide the foundation for additional research to develop tools that can be used to identify patients who may be at greater risk of developing treatment resistance. Further, the findings could also lead to biomarkers that identify patients who have heavy exposure to chemicals that could diminish the effectiveness of their cancer therapy.” Dr. Devi stated. Scott Sauer, a research fellow in the Devi Laboratory in Duke’s Department of Surgery, will present the research.

# # #

SUN-0345: Bisphenol A Interacts with Gper, Activates EGFR and ERK Signaling and Antagonizes Efficacy of Epidermal Growth Factor Receptor Tyrosine Kinase Inhibitors in Breast Cancer Cells

Gayathri Devi. *Duke University*

Scott Jeffrey Sauer, PhD, Dept of Surgery, Duke Univ Med Ctr, Durham, NC, John B Davis, Duke University, H Kim Lyerly, MD, Surgery, Duke University Medical Center, Imran Shah, PhD, Computational Toxicology Research Program, Environmental Protection Agency, Kevin P Williams, PhD, BRITE, North Carolina Central University and Gayathri R Devi, PHD, Duke University Med Ctr, Durham, NC

Bisphenol A (BPA), a known endocrine disrupting agent and ubiquitously found plasticizer has recently been identified to interact with G-protein-coupled receptor 30 (GPR30/GPER), an alternate estrogen receptor (ER). GPER overexpression has been observed in breast cancer with particularly high levels in an aggressive and commonly hormone-independent subtype, inflammatory breast cancer (IBC). In the current study, screening the EPA Tox Cast I library of environmental chemicals using a high-throughput cell proliferation assay identified BPA to be one of the top toxicants that increased proliferation in IBC cells, irrespective of ER status. This is supported by recent evidence that BPA can induce proliferative effects in ER-negative breast cancer cells via GPER. Further, GPER has the ability to activate downstream ERK signaling via cross-talk with the epidermal growth factor receptor (EGFR) pathway. Therefore, we sought to determine BPA's effect on the anticancer efficacy of EGFR tyrosine kinase inhibitors (TKIs) used clinically for the treatment of breast cancer. Using normal and breast cancer cells with differential expression of ERa, GPER and EGFR, proliferation was measured using an MTT assay to assess the effect of BPA alone and in combination with EGFR TKIs lapatinib and gefitinib. Clonogenic, anchorage-independent growth, Annexin-V/7-AAD flow cytometry and signaling assays were also used to assess the functional effect of BPA on lapatinib action. Our results reveal that breast cancer cells with either EGFR-activation or ER-positivity were highly responsive to BPA-mediated proliferative effects. BPA increased pEGFR and pERK levels along with expression of antioxidants (SOD1/2, GSTP1) in EGFR-activated breast cancer cells. Further, we observed that lapatinib in addition to inhibiting pEGFR levels decreased GPER expression. BPA attenuated the cancer cell growth inhibitory effect of EGFR-TKIs and abrogated the lapatinib-mediated inhibition of pEGFR, GPER and downstream pNFkB signaling. In conclusion, understanding BPA's effect on drug resistance is a new paradigm that has immediate implications in treatment regimens.

Presentation Date: Sunday, June 22
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

SUN-0897: Hydrogel capsule, Gelesis100, reduces weight in overweight and obese subjects

A new "smart pill" called Gelesis100 safely leads to greater weight loss in overweight and obese individuals compared with those who receive an active comparator/placebo capsule, while all subjects have similar diet and exercise instructions, an international multicenter study finds. The three-month results of the First Loss Of Weight (FLOW) study will be presented Sunday June 22, 2014 at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

Gelesis100 (formerly Attiva) is an orally administered capsulated device designed to cause weight loss by inducing satiety and reducing caloric intake, according to its manufacturer, Boston-headquartered Gelesis, which funded the FLOW study. In 128 nondiabetic subjects, weight loss was most pronounced in those who had impaired levels of fasting blood glucose (sugar), also known as prediabetes, said Hassan Heshmati, MD, chief medical officer for Gelesis and a study co-investigator.

"Given the excellent safety profile observed in the FLOW study, Gelesis100 has the potential to fulfill the unmet need for a safe and effective weight loss agent. This is particularly impactful for individuals with mildly elevated blood sugar (prediabetic subjects), for whom weight loss is particularly important because they are at increased risk for diabetes," Heshmati said.

This proof-of-concept study tested two doses of Gelesis100, a superabsorbent hydrogel, when taken twice a day with water before a meal. Forty-three subjects were randomly assigned to receive 2.25 grams (g) of Gelesis100 before lunch and dinner, another 42 subjects received 3.75 g of Gelesis100 and a third group of 43 subjects received a placebo capsule containing cellulose, a fiber which is used as a bulking agent. All subjects were instructed to eat 600 fewer calories a day. Neither the subjects nor the investigators knew which treatment they received during the 12 weeks of the study.

Among 125 subjects who weighed in at the start of the study and at least once after treatment, the average reductions in body weight by group at the end of treatment were as follows: 6.1 percent for 2.25 g of Gelesis100, 4.5 percent for 3.75 g of Gelesis100 and 4.1 percent for placebo. For subjects receiving the 2.25-g dose of Gelesis100, those with initial high fasting blood sugar (greater than the median level of 93 milligrams per deciliter, or mg/dL) had greater weight loss than did the others, losing 8.2 percent of their body weight on average, Heshmati reported.

The greatest weight loss reportedly occurred in prediabetic subjects whose starting fasting blood sugar level was 100 to 125.9 mg/dL. They lost an average of 10.9 percent of their body weight.

Heshmati said he thinks the higher dose of Gelesis100 resulted in less weight loss because of lower tolerability leading to lower compliance with the study requirements. The most common side effects reported were bloating, flatulence, abdominal pain and diarrhea, which he said occurred less often with the smaller dose and were tolerable at that dose. No apparent serious problems occurred in either Gelesis100 group.

Gelesis100 capsules contain thousands of tiny hydrogel particles that expand in the stomach and mix with digested foods, said Gelesis' founder and chief executive officer, Yishai Zohar. He said this increases the volume and elasticity of the stomach and small intestine contents, inducing satiety and reducing caloric intake. The particles are composed of two components which are used as food ingredients, but when cross-linked together form a unique structure that increases in volume. Gelesis100 does not create one big mass, rather thousands of small individual gel beads which have exactly the same elasticity (rigidity) as digested foods, but without any calories.

The first in a new class of weight management and obesity therapies, Gelesis100 will be regulated as a medical device if approved by the Food and Drug Administration, Zohar said.

# # #

SUN-0897: Oral Administration of Gelesis100, a Novel Hydrogel, Significantly Decreases Body Weight in Overweight and Obese Subjects

Hassan Heshmati. *Gelesis*

Arne Astrup, MD[1], Mette Kristensen, PhD[1], Lucio Gnessi, MD, PhD[2], Mikiko Watanabe, MD, PhD[2], Stepan Svacina, MD[3], Martin Matoulek, MD, PhD[3], Pavol Hlubik, MD[4], Hana Stritecka, PhD[5], Franco Contaldo, MD, PhD[6], Fabrizio Pasanisi, MD, PhD[6], Hassan M Heshmati, MD[7], Yishai Zohar[7], Eyal S Ron, PhD[7], Alessandro Sannino, PhD[8], Christian Demitri, PhD[8] and Cosimo Saponaro[8], (1) University of Copenhagen, Frederiksberg C, Denmark, (2) Policlinico Umberto I, Rome, Italy, (3) General Hospital in Prague, Prague, Czech Republic, (4) Nutrition Disorder Center, Hradec Kralove, Czech Republic, (5) Faculty of Military Health Sciences, Hradec Kralove, Czech Republic, (6) Federico II University Hospital, Naples, Italy, (7) Gelesis, Boston, MA, (8) Gelesis, Lecce, Italy

The effect on body weight of chronic oral administration of Gelesis100, a novel hydrogel, was assessed in 128 non-diabetic overweight and obese subjects randomized to two Gelesis100 arms (2.25 g twice daily, n = 43 and 3.75 g twice daily, n = 42) and a placebo arm (n = 43). Treatment was administered in capsules with 500 mL of water before lunch and dinner, in a double-blind, parallel-group fashion, over 12 weeks, in subjects on hypocaloric diet (-600 kcal/day). Statistical analysis used analysis of covariance model with baseline weight, gender, and body mass index (BMI) as covariates, comparing Gelesis100 arms to placebo arm. One hundred twenty-five subjects had at least one post-baseline body weight assessment (intention-to-treat "ITT" population). The ITT population included 40 males and 85 females, with a mean age ± standard deviation (SD) of 44 ± 12 years and a mean BMI ± SD of 31.7 ± 2.4. One hundred ten subjects completed the treatment. Dropout rates were 5%, 24%, and 21%, with Gelesis100 2.25 g, Gelesis100 3.75 g, and placebo, respectively. One hundred twenty-six subjects provided safety data. In the ITT population, the mean ± SD body weight percent changes from baseline to the end of treatment were -6.1 ± 5.1%, -4.5 ± 4.5%, and -4.1 ± 4.4%, with Gelesis100 2.25 g, Gelesis100 3.75 g, and placebo, respectively. Weight loss was statistically significant with Gelesis100 2.25 g ($P = 0.026$). Lower tolerability and compliance may explain the observed efficacy result with Gelesis100 3.75 g. The extent of weight loss was more pronounced in subjects on Gelesis100 2.25 g with high fasting glucose (> median, 5.15 mmol/L) at baseline (-8.2 ± 5.3%; $P = 0.006$), especially in those with impaired fasting glucose at baseline (-10.9 ± 4.3%; $P = 0.019$). There was a significant negative correlation between fasting glucose at baseline and change in body weight in Gelesis100 2.25 g arm ($r = -0.50$; $P < 0.001$) contrasting with a lack of correlation in placebo arm ($r = -0.06$; $P = 0.708$). The most common adverse events (AEs) were bloating, flatulence, abdominal pain, and diarrhea, with lower prevalence in Gelesis100 2.25 g arm compared to placebo and Gelesis100 3.75 g arms. Serious AEs were observed in 3 subjects on placebo (gallstone and abdominal pain). In conclusion, chronic administration of Gelesis100 (2.25 g twice daily) to overweight and obese subjects significantly decreases the body weight, especially in subjects with impaired fasting glucose at baseline. The treatment is safe and well tolerated. Gelesis100 can be considered as a promising new therapy for obesity and a tool for weight management. If confirmed in subsequent studies, Gelesis100 has also the potential to induce dramatic weight loss in overweight and obese subjects with type 2 diabetes.

Presentation Date: Sunday, June 22
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

SUN-0076: Low testosterone raises risk of age-related functional disability

Elderly men with low levels of testosterone or other sex hormones have twice the likelihood of having declining physical function over two years' time compared with their peers who have the highest hormone levels, a new study from Australia finds. The results will be presented Saturday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

"We also found that increasing muscle weakness—possibly due to decreasing testosterone concentration in the blood—could explain most of this relationship," said Benjumin Hsu, MPH, the study's principal investigator and a PhD candidate at the University of Sydney.

Although testosterone levels and the ability to perform self-care activities both decrease with age, it is unclear whether one or the other is a cause or an effect of aging, or if they are both due to a common third cause, Hsu said.

The aim of this study was to determine the relationship between an age-related decline in androgens, or male hormones, and increasing physical disability in older men.

As part of the Concord Health and Ageing Project (CHAMP) in Sydney, the research included 1,318 men ages 70 and older who had health assessments when they entered the study from 2005 to 2007, and again two years later. The CHAMP study is funded by the National Health and Medical Research Council, the Sydney Medical School Foundation and the Ageing and Alzheimer's Institute, all in Australia.

As a measure of their capacity to function independently, the men reported their ability to perform activities of daily living, such as walking, eating, getting dressed and personal hygiene. They also had blood tests that measured levels of important hormones, including their male hormones—testosterone and dihydrotestosterone—and two types of the female hormone estrogen (estradiol and estrone) that are present in men in lower amounts than in women. Also tested were measures of muscle strength: grip strength and the strength of their quadriceps muscles in the thigh.

In their analysis, the investigators took into account known risk factors for physical decline, such as older age, smoking and obesity. Despite this, they found that the lower the level of testosterone or either of the estrogens, the higher the chance that the men had worse functional abilities at the two-year follow-up evaluation.

"Low testosterone, estradiol and estrone concentrations may be important contributors to, or biologic markers for, physical decline in older men, which impairs their independent living," Hsu said.

However, the relationship between lower reproductive hormones and functional decline did not remain statistically significant when either of the measures of muscle strength was added to the analysis, he noted.

"This study suggests that low testosterone in older men could lead to a decline in muscle strength, which might explain their increased risk of functional disability," Hsu said.

# # #

SUN-0076: Longitudinal Relationships of Circulating Reproductive Hormone Levels and Functional Disability in Community-Dwelling Older Men: The Concord Health and Ageing in Men Project

Benjumin Hsu. *University of Sydney*

Benjumin Hsu, MPH[1], Robert G Cumming, MBBS MPH PhD[1], Fiona M Blyth, MBBS MPH PhD[2], Vasi Naganathan, MBBS MMed PhD[2] and David J Handelsman, MB BS, FRACP, PhD[3], (1) School of Public Health, University of Sydney, Sydney, Australia, (2) Centre for Education and Research on Ageing, University of Sydney, Sydney, Australia, (3) ANZAC Research Institute, University of Sydney, Sydney NSW, Australia

Objectives: To identify relationships between circulating reproductive hormones and decline in of functional ability over two-years of follow-up in older men; and to examine whether muscle strength explains any of the observed relationships.

Methods: 1318 men aged 70 years and older from the Concord Health and Ageing in Men Project (CHAMP) were assessed at both baseline (2005-2007) and 2-year follow-up (2007-2009). At baseline, testosterone (T), dihydrotestosterone (DHT), estradiol (E2), and estrone (E1) were measured by liquid chromatography-tandem mass spectrometry (LC-MS/MS), and SHBG, LH, and FSH by immunoassay. The calculated free testosterone (cFT) was computed using an empirical formula derived from the measured TT and SHBG. Functional disability was assessed by self-report using a basic Activities of Daily Living (ADL) scale (Katz) at both time points. Functional decline was determined by change in ADL stages, defined by specific threshold definitions ranging from no difficulty in Stage 0 to complete difficulty in Stage IV. Grip and quadriceps strength were measured using dynamometers.

Results: All reproductive hormones were significantly associated with functional decline in univariate analyses. However, only T, E2, E1, and cFT remained significantly associated after adjusting for age, BMI, smoking status, and number of comobidities. In the multivariable analyses, compared to men in the highest T quartile, men in the lowest T quartile had an increased risk of functional decline (OR: 1.96, 95%CI: 1.01-3.82). The associations with E2, E1, and cFT were similar to T. When muscle strengths were added into the multivariable model, the associations between T, E2, E1, and cFT and functional decline were no longer statistically significant.

Conclusion: Low circulating T, E2 and E1 in older men were associated prospectively with functional decline over two years and this relationship is mediated by decreased muscle strength.

Presentation Date: Sunday, June 22
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

SUN-1029: Gestational diabetes is associated with declining cognitive function

Women who develop diabetes during pregnancy, called gestational diabetes, perform worse on cognitive function tests than do women with a normal pregnancy, according to a new study from Turkey. The results are to be presented Sunday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

Type 2 diabetes has been linked to accelerated cognitive, or brain-related, decline and an increased risk of dementia in elderly individuals. However, exactly when the memory problems can begin during diabetes is unclear, said the study's lead investigator, Ela Keskin, MD, of Istanbul University Cerrahpasa Medical Faculty.

"This is the first study that has associated a decline in cognitive function with gestational diabetes mellitus, which is an early diabetic state that raises the risk of Type 2 diabetes later on," Keskin said. "Based on our results, cognitive dysfunction in diabetes may begin early in the disease."

"Maybe with early interventions and therapies, the cognitive impairment in diabetes can be delayed," she said. "People at risk of Type 2 diabetes, especially women who had gestational diabetes, should be closely monitored by their doctor, and they need to control their weight and other risk factors for diabetes."

Keskin and her co-workers compared 44 women with gestational diabetes and 56 women with a healthy pregnancy who were similar in age, geographic location and educational level. According to Keskin, none of the subjects took medications other than insulin, including cholesterol-lowering statins, which have led to reports of confusion and forgetfulness in some users. Both groups reportedly had similar scores on a questionnaire regarding depression.

The women with gestational diabetes were slightly older than the other group, with an average age of 31 versus nearly 30 years, according to the abstract. At the start of pregnancy, they also had a higher body mass index (BMI), a measure of body fat based on height and weight. As expected, these women had much higher blood glucose, or sugar, levels.

Compared with the nondiabetic women, those who had gestational diabetes performed worse on several tests of cognitive function performed at the same week of pregnancy, the investigators reported. On a 30-point test that evaluates for mild cognitive impairment, called the Montreal Cognitive Assessment, the diabetic women had an average score three points lower: 21 points versus 24 points in women with a healthy pregnancy.

Women with gestational diabetes also had worse speed of mental activity and attention, as measured by the Symbol Digit Modalities Test, a test that measures the time to pair abstract symbols with specific numbers in 90 seconds. Their average score was about five points lower, indicating worse performance. In addition, they scored worse on the Spatial Recall Test 10/36, a visual memory test. Subjects see a checkerboard with 10 dots for 10 seconds and must replicate the pattern on a blank checkerboard, both immediately and 25 minutes later. For delayed recall, women with gestational diabetes scored worse: 4.5, on average, versus 5.4 in the nondiabetic group.

The researchers found that the higher the BMI and blood sugar levels, the lower the cognitive function. "Our results show an association of cognitive function with metabolic status," Keskin said.

# # #

SUN-1029: Cognitive Dysfunction and Gestational Diabetes Mellitus

Fatma Ela Keskin. *Istanbul Universtiy*

Fatma Ela Keskin[1], Mucahit Ozyazar[2], Esra Suheda Hatipoglu[1], Ayse Selcen Bay[3], Ayse Deniz Elmalı[4], Basak Yilmaz[4], Abdullah Tuten[5], Ayhan Bingol[6], Ugur Uygunoglu[4] and Gokhan Erkol[4], (1) Endocrinology and Metabolism, Istanbul University, Cerrahpasa Medicine Faculty, Istanbul, Turkey, (2) Endocrinology and Metabolism, Istanbul Univetsity, Cerrahpasa Medicine Faculty, Istanbul, Turkey, (3) Internal Medicine, Istanbul University, Istanbul, Turkey, (4) Neurology, Istanbul University, Istanbul, Turkey, (5) gynecology and obstetrics, Istanbul University, Istanbul, Turkey, (6) Istanbul University, Istanbul, Turkey

Objective: To evaluate the association between cognitive functions, depression and metabolic status in cases with gestational diabetes mellitus.

Method: In this crossectional study 44 patients with gestational diabetes mellitus (GDP) and 56 subjects with a normal pregnancy (NP), matched for age, origin and education were included. Status of depression was evaluated with Beck's depression scale (BDS). Cognitive functions were evaluated with Montreal cognitive assessment (MOCA) and brief repetible battery of neurophysiological tests (BRB-N). Additionally fasting blood glucose (FBG), postprandial blood glucose (PBG), HbA1c, insulin, total cholesterol (T-chol), HDL, LDL, triglyceride (TG) levels of both groups were obtained. Two groups were compared based on their BDI, MOCA and BRB-N scores and metabolic parameters.

Results: The mean age of GDP and NP was 31.4 ± 3.7 and 29.8 ±4.6 years, respectively (p=0.06). The mean FBG and PBG were significantly higher in GDP (FBG in GDP: 99.1±23.5 mg/dl and in NP: 75.1±11.4 mg/dl, p<0.001). PBG in GDP was 165.4±39.3 mg/dl and in NP was 114.8±24.7 mg/dl (p<0.001). BMI in GDP and NP was 27.6 ± 5.8 and 25.4± 5.6 kg/m2(p=0.03). Domain score for symbol digit modalities (SDM) in GDP and NP was 33.4±11.2 and 38.5±10.1, respectively (p=0.02). Additionally GDP had lower domain scores for spatial recall (SR) and long term SR (SR in GDP: 14±4 and in NP: 16.3±5.2, p=0.02, long term SR in GDP: 4.5±1.9 and in NP: 5.4±2.3, p=0.04). Also score for MOCA was significantly lower in GDP (20.8±5.3) compared to the score in NP (23.7±3.9) (p=0.03). SDM score was negatively correlated with BDI (r=-0.2, p=0.03) and PBG (r=-0.2, p= 0.02). There was also a negative correlation between the domain score for SR and PBG (r=-0.2, p=0.04). Also the score for long term SR decreased as BMI (r=-0.2, p=0.04) and FBG (r=-0.2, p=0.03) increased. Score for BDI were similar between the 2 groups (p=0.3).

Conclusion: In this study cases with gestational diabetes mellitus performed worse in symbol digit modalities and spatial recall of BRB-N in addition to MOCA compared to controls. The decline in cognitive functions were related with their BMI and blood glucose levels, showing association of cognitive functions with metabolic status. Our findings may be a clue for early onset of impairment in cognitive functions in case of disrupted glucose homeostasis, particularly in cases with new onset diabetes during pregnancy.

Presentation Date: Sunday, June 22
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

SUN-0887: Cold exposure stimulates beneficial brown fat growth

Long-term mild cold exposure can stimulate brown fat growth and activity in humans and benefit their glucose and energy metabolism, a new study finds. The results will be presented in a poster Sunday, June 22 at ICE/ENDO 2014, the joint meeting of the International Society of Endocrinology and the Endocrine Society in Chicago.

Brown fat, also known as brown adipose tissue (BAT), is a special kind of fat that burns energy and glucose to generate heat. It keeps small animals and babies warm, and animals with abundant brown fat are protected from diabetes and obesity. How brown fat is regulated in humans and how it relates to metabolism, though, remains unclear.

"Our research points to a simple and practical brown fat activating and growing strategy in humans through temperature exposure modulation. We show that long-term minimal manipulation of overnight ambient temperature — well within the range found in climate-controlled buildings — was able to modulate brown fat activity in humans. Mild cold exposure stimulated brown fat activity while mild warm exposure suppressed it. Brown fat increase was accompanied by improvement in insulin sensitivity and energy burning rate after food," said Paul Lee, MD, PhD, research fellow at the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH).

In their Impact of Chronic Cold Exposure in Humans (ICEMAN) study, Dr. Lee and his colleagues explored the impact of controlled temperature acclimatization on BAT and energy balance by following 5 men between 19 and 23 years of age over a 4-month period. The volunteers engaged in their usual daytime activities but slept in a private room in which the air temperature varied monthly between 66°F (19°C) and 81°F (27°C). Personal temperature detectors monitored each volunteer's exposed temperature continuously over the entire 4 months.

At the end of each month, the researchers measured the men's BAT and energy metabolism and found that mild cold (19°C) increased the men's brown fat amount and activity while mild warm (27°C) suppressed it.

"The improvement in insulin sensitivity accompanying brown fat gain may benefit people with impaired glucose metabolism. On the other hand, the reduction in mild cold exposure in contemporary society from widespread central heating may impair brown fat function and may be a hidden contributor to obesity and metabolic disorders," he said.

The authors suggest that recruiting and suppressing BAT by manipulating temperature may be a promising therapeutic strategy in obesity and diabetes treatment.

The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) of the National Institutes of Health (NIH) funded the study. Paul Lee was supported by an Australian National Health Medical Research Council (NHMRC) Early Career Fellowship, the Diabetes Australia Fellowship and Bushell Travelling Fellowship, and the School of Medicine, University of Queensland.

# # #

SUN-0887: Impact of Chronic Cold Exposure in Humans (ICEMAN) Study: Evidence for Brown Adipose Tissue Plasticity Modulating Glucose Metabolism in Humans

Paul Lee. *NIDDK, NIH*

Paul Lee, M.D., Ph.D1, Sheila Smith, RN1, Joyce D Linderman, RN1, Amber B Courville, Ph.D2, Robert J Brychta, Ph.D1, William Dieckmann3, Charlotte D Werner, B.Sc.1, Kong Chen, Ph.D1 and Francesco S. Celi, M.D., M.H.Sc.4, (1)Diabetes Endocrinology Obesity Branch, NIDDK, NIH, Bethesda, MD, (2)Clinical Center, NIH, Bethesda, MD, (3)PET Department, NIH, Bethesda, MD, (4)Division of Endocrinology and Metabolism, Virginia Commonwealth University, Richmond, VA

In addition to heat production during cold exposure, growing evidence suggests brown adipose tissue (BAT) may contribute to healthy metabolism in humans (1). Even a mild reduction in environmental temperature is sufficient to activate BAT (2) and induce hormonal changes (3). However, the long-term consequences of temperature acclimatization on BAT, and whether it impacts on whole body energy/substrate metabolism in humans, are unclear.

In this study, we examined the impact of controlled temperature acclimatization on BAT and energy homeostasis in five men (21±2 years old, BMI: 22±1 kg/m2, body fat: 21±2%) over a 4-month period. Volunteers engaged in usual daytime activities but slept in a temperature-adjusted private room: 24°C (month 1) → 19°C (month 2) → 24°C (month 3) → 27°C (month 4). Personal temperature detectors monitored individual exposed temperature continuously for the entire 4-month period. At the end of each testing month, BAT was quantified by Positron Emission Tomography (PET)-CT scanning and energy metabolism by whole room indirect calorimetry, mixed meal test, blood hormonal/substrate profiling and adipose/muscle biopsies ex vivo analyses.

During the 4-month period, mean BAT volume and overall fat metabolic activity increased upon cold acclimatization (19°C) by 42±18% ($p<0.05$) and 10±11% ($p<0.05$), respectively; decreased after the thermoneutral month (24°C) to nearly baseline level, and completely muted at the end of one-month warm exposure (27°C). Room ($p<0.05$) and individually exposed temperatures ($p<0.01$), but not outdoor temperatures, correlated with BAT changes during study period. BAT-acclimatization was accompanied by diet-induced thermogenesis and post-prandial glucose metabolism enhancement, evident only after cold exposure. Mechanistically, BAT acclimatization was associated with reciprocal changes of circulating adiponectin and leptin levels, mirrored by corresponding transcriptosomal changes in adipose tissue ex vivo.

In summary, sequential monthly acclimatization modulated BAT reversibly, boosting and suppressing its abundance and activity in mild cold and warm conditions, respectively, independent of seasonal fluctuations. The inducibility and suppressibility of human BAT paralleling whole body metabolic changes suggests regulatory links between BAT thermal plasticity and glucose metabolism in humans. We propose BAT enhancement as a promising therapeutic strategy to improve glycemia in humans..

Presentation Date: Sunday, June 22
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

SUN-0900: Dietary and lifestyle changes made early in pregnancy benefit obese women

Obese pregnant women who adhere to an intensive nutritional and exercise program starting in the first trimester gain less weight in pregnancy and have fewer pregnancy complications compared with peers who receive standard prenatal care, a new study from China finds. The results will be presented Sunday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

"Obese pregnant women should start an intensive intervention involving dietary and lifestyle modifications as early as possible in pregnancy," said lead investigator Guanghui Li, MD, PhD, associate professor, Department of Obstetrics, Capital Medical University, Beijing.

Obesity is a risk factor for pregnancy complications, such as gestational diabetes and pre-eclampsia, which is high blood pressure and protein in the urine. It also increases the risk of having an infant who is large for gestational age (birth weight greater than the 90th percentile adjusted for gestational age) or who has macrosomia, a birth weight exceeding 8 pounds, 13 ounces (4,000 grams). A high-birth-weight baby raises the risk of needing a cesarean section.

The study enrolled obese Chinese women who were six to 12 weeks pregnant (first trimester) and randomly assigned them to receive either standard care (72 women) or the intensive program (141 women), both of which included visits to the obstetrician. Standard care consisted of one group session with a dietitian, who discussed proper nutrition, physical activity and recommended pregnancy weight gain. The other group participated in one group session followed by individual counseling tailored for each subject regarding regular exercise and eating a balanced diet between 1,500 and 2,000 calories a day. Subjects were asked to record what they ate, their physical activity and their weekly weight gain, and this information was used to modify the plan for each individual.

Of the 141 women in the program, 68 adhered to the recommendations and 73 did not, which Li said indicated how difficult it is for obese women to modify their lifestyles. "Health care providers should pay more attention to make practical and effective intervention strategies for obese pregnant women to enhance their compliance with the recommendations," she said.

According to Li, women who complied with the recommendations had significant benefits compared with the other study participants. Throughout pregnancy, they gained an average of 24 pounds (10.83 kilograms, or kg). Both the nonadherent group and standard-care group gained just over 31 pounds (14.13 and 14.10 kg), on average. Weight gain was less in the adherent group before and after an oral glucose tolerance test performed between 24 and 28 weeks of pregnancy to check for gestational diabetes.

In addition, no one in the adherent group developed mild pre-eclampsia, versus 2.7 percent of the nonadherent group and 6.9 percent of the standard-care group, study data showed. The intervention did not harm fetal growth or lead to any maternal or fetal complications, Li stated. In fact, she said it reduced the chance of having an abnormally large baby. The reported macrosomia rate was 7.4 percent in the adherent group versus 27.4 percent in the nonadherent group and 25 percent in the standard-care group. Rates for large-for-gestational age infants were 10.3 percent in the adherent group versus 32.9 percent and 25 percent for the other groups.

This project received special funding from the Beijing Health Bureau and the Ministry of Health, People's Republic of China.

# # #

SUN-0900: Effects of Dietary and Lifestyle Intervention in Obese Pregnant Women on Gestational Weight Gain and Pregnancy Outcomes

Guanghui Li. *Capital Medical University*

Guanghui Li, PhD, MD[1], Li Zhang, MD[2], Lijun Kong, MD, PhD[1], Ling Fan, MD[1], Weiyuan Zhang, MD, PhD[3] and James C Rose, PHD[4], (1) Department of Obstetrics, Beijing Obstetrics and Gynecology Hospital,Capital Medical University, Beijing, China, (2) Department of Obstetrics, Beijing Obstetrcis and Gynecology Hospital,Capital Medical University, Beijing, China, (3) Department of Obstetrics, Beijing Obstetrics and Gynecology Hospital,Capital Medical University, (4) Wake Forest School of Med, Winston Salem, NC

Background: Maternal obesity is associated with higher risks of adverse maternal and fetal complications, but the effect of dietary and lifestyle interventions for obese pregnant women on gestational weight gain(GWG) and pregnancy outcomes is unclear.

Objective: This study examined whether an intensive dietary and lifestyle intervention in the early pregnancy performed in obese pregnant women could effectively decrease GWG,and prevent relevant adverse pregnancy outcomes.

Methods: 258 obese pregnant Chinese women were enrolled in the randomized controlled trial at 6 to 12 weeks of gestation. Participants were randomly assigned to the standard care (n=72) or the intervention groups(n=141). The intervention focused on restricting energy intake combined with behavioral lifestyle modification through participation in group sessions and individual counseling. Obese pregnant women in the intervention group were advised to record in a dietary diary, physical activity and weekly weight gain. They met the obstetrician at least 5 times face to face including 3 or more times before OGTT was performed at 24-28weeksof gestation. The primary outcomes were gestational weight gain and the incidence of GDM, pregnancy hypertensive disorders,large-for-gestational-age (LGA) infants, macrosomia and the rate of caesarian section.

Results: Adherent participants(n=68) had a significantly decreased total GWG compared with the non-adherent and the control groups(10.83Kg in the adherence group,14.13Kg in the non-adherence group,14.10Kg in the standard care group,p=0.001). The GWG before OGTT was preformed was less in the adherence group(4.79Kg) than in the non-adherent group(6.9kg) and the standard care group(6.7kg) p=0.005. Mild pre-eclampsia was reduced in the adherence group(0.0%), compared to the non-adherence group(2.7%), and the standard group(6.9%),p=0.031.The incidence of macrosomia was decreased in the adherence group. (7.4% in the adherence group, 27.4% in the non-adherence group,25.0% in the standard care group,p=0.006).A significant lower incidence of LGA infants was also detected in the in the adherence group.(10.3% in the adherence group, 32.9% in the nonadherence, 25.0% in the standard care group,p=0.006).No significant difference was observed in other maternal and fetal complications.

Conclusions: The study showed that the intensive dietary and lifestyle intervention performed from the first trimester in obese women could significantly decrease total GWG, and reduce the risk of developing mild preeclampsia, macrosomia, and LGA infants. The intervention did not result in adverse effects on fetal growth and maternal and fetal complications.

Presentation Date: Sunday, June 22
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

SUN-0896: Exercising first, dieting later protects patients with metabolic syndrome from muscle loss

Younger and older women tend to lose lean muscle mass, along with fat, unless they engage in physical activity before they attempt weight loss, a new study from Israel finds. The results will be presented Sunday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

"To preserve muscle in metabolic syndrome, irrespective of age, exercise should precede the initiation of weight loss and not be started at the same time as diet," said lead study author Yonit Marcus, MD, PhD, endocrinologist at the Institute of Endocrinology, Metabolism and Hypertension of Tel Aviv Medical Center in Tal Aviv, Israel.

The recommended treatment for metabolic syndrome (MetS) patients is a combination of proper diet and exercise, yet most attempted weight loss periods end with later weight regain. Muscle loss often occurs during diet, so repeated weight loss attempts may lead to increasing loss of muscle mass, frailty and disability.

"The metabolic syndrome and obesity have become the pandemic of the 21st century," Dr. Marcus said, "and the only measures taken to counter this problem are exercise and diet. Exercise and diet are commonly started at the same time, but this should be reconsidered."

For this study, Dr. Marcus and colleagues recruited 38 patients with MetS, aged 19 through 71 years. All patients completed a 1-year intervention program involving frequent interactions with physicians, a dietician and a physiologist. Overall, 9 men and 8 women were above the median age of 53 years, and 12 men and 6 women were below the median age. At the beginning and the end of the year, dual-energy x-ray absorptiometry (DEXA) bone scans were performed to determine body composition.

The DEXA scans showed that women and men younger than 53 years lost 11% and 10% of their body weight, respectively, while those over 53 years lost only about 6% of their body weight. Younger women and men lost about 17% of their fat mass but older women and men lost only 10% and 15%, respectively. Younger men lost less of their muscle mass than women (1% vs 5%), and both older men and women lost 3% of their muscle mass.

Strikingly, the authors wrote, all patients who gained or lost less than 2.9% of muscle mass were exclusively those who engaged in physical activity prior to beginning the program and continued throughout the year.

The study was supported by the Sami Sagol Foundation.

# # #

SUN-0896: Exercise First, Diet Later: Exercise Prior to Diet Protects Subjects with the Metabolic Syndrome from Muscle Loss, Independent of Age/Gender

Yonit Marcus. *Tel Aviv Medical Center*

Yonit Marcus, MD, PhD[1], Jessica Sack, MD[2], Elad Segev, PhD[3], Brurya Tal, PhD[4], Galina Shenkerman, MD[5], Rona Limor, PhD[6], Karen Michele Tordjman, MD[2], Gabi Shefer, PhD[4] and Naftali Stern, MD[2], (1) Institute of Endocrinology,Metabolisim and Hypertention, Tel Aviv Medical Center, Tal Aviv, Israel, (2) Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Medical Center, Tel Aviv, Israel, (3) Department of Science, Holon Institute of Technlogy, Holon, Israel, (4) Institute of Endocrinology Metabolism and Hypertension, Tel Aviv Medical Center, Tel Aviv, Israel, (5) Institute of Endorinology Metabolism and Hypertension, Tel Aviv Medical Center, Tel Aviv, Israel, (6) Institute of Endocrinology, Metabolism and Hypertension, Tel Aviv Sourasky Medical Center, Tel Aviv, Israel

Background: Recommended treatment for metabolic syndrome (MetS) patients is a combination of proper diet with exercise. Most attempted weight loss periods terminate in subsequent weight regaining. Muscle loss during diet occurs often, thus repeated weight loss attempts could lead to increasing sarcopenia, frailty and disability. Here we assessed the effect of a 1-year multidisciplinary intensive intervention program on body composition and metabolic outcome.

Methods: Thirty-eight patients that completed 1 year of intervention involving frequent interaction with physicians, a dietician and physiologist. Patients' ages were 19-71 years, median age ~53. Nine men and 8 women were above and 12 men and 6 women below median age. Body composition was determined based on DEXA scans done at the beginning and the end of 1-year intervention.

Results: Women and men younger than 53 years lost 11 and 10% of their body weight, respectively, while older than 53-year-old subjects lost only about 6% of their body weight. Younger women and men lost about 17% of their fat mass but only 10 and 15%, respectively, at older age. As for lean mass loss, younger men lost less than women (1% vs. 5%), where both older men and women lost 3% of their lean mass. Strikingly all subjects that gained or lost less than 2.9% lean (median value of % lean loss) were exclusively those engaged in physical activity prior to intervention, and continued throughout this year (χ^2, $p<0.001$).

Conclusions: During intensive weight-loss supervised by a multidisciplinary team according to current "best practice" guidelines: a) young and older men can lose weight without obligatory lean mass loss; b) young and older women tend to lose lean mass (muscle), along with fat loss, unless they engaged in physical activity prior to the attempted weight loss. We submit that to preserve muscle in MetS, irrespective of age, exercise should precede the initiation of weight loss and not be started coincident with diet.

Presentation Date: Sunday, June 22
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

SUN-0366: Exposure to fungicide, tolyfluanid, disrupts energy metabolism

Mice exposed to the fungicide tolyfluanid (TF) showed metabolic changes similar to those that signify the development of prediabetes. The results, which will be presented Sunday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

Rates of occurrence of metabolic diseases such as obesity and diabetes are continuing to increase worldwide. Although poor diet and lack of physical activity are primary causes of the majority of metabolic disease, environmental factors have increasingly been implicated as important contributing causes that may increase the risks of developing metabolic diseases brought on by lifestyle.

“Recently, attention of scientists has been attracted to endocrine-disrupting chemicals (EDCs), compounds that are suspected of promoting the development of various metabolic disorders via their capacity to impact hormonal and metabolic signaling pathways,” said lead author Shane Regnier, a doctoral candidate at the University of Chicago’s Committee for Molecular Metabolism & Nutrition. “Our study showed one potential EDC, an agricultural fungicide called tolylfluanid (TF), lead to metabolic changes in mice including accumulation of body fat, disruption of glucose metabolism, and reduction of insulin sensitivity.”

Adult male mice that consumed a diet containing TF for 12 weeks showed the types of changes in key indicator proteins in their blood serum that signify development of prediabetic conditions. In a separate study, mice were exposed to TF only during fetal development and as newborns. When examined at the time of weaning, the young mice displayed reduced body weight, a symptom that has been associated with an increased risk of metabolic disease later in life. These mice were followed to adulthood, and, although experiencing no further contact with TF, mice that had been exposed only before and immediately after birth nevertheless displayed impaired glucose tolerance as adults.

The results of these two studies suggest that exposure to TF may promote the development of metabolic disease in humans. While TF levels have been measured in some food crops, in agricultural runoff, and in ground water, TF levels have not been measured in humans. The authors of the study suggest that the results of their two mouse experiments indicate that efforts should be made to characterize exposure of humans to TF to determine whether similar metabolic impacts are seen in humans and that continued use of TF should be carefully considered.

Although approximately 150,000 unique chemicals are registered with the European Chemicals Agency, most are tested only for acute toxicity and carcinogenic capacity. “We are only beginning to understand the role that human-made chemicals play in causing human disease,” said Regnier. “The potential for chronic, low-dose exposure to impact and elicit human disease has only begun to be investigated,” he added.

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SUN-0366: Effects of the Endocrine Disruptor Tolylfluanid on Global Energy Metabolism

Shane Regnier. *The University of Chicago*

Shane Michael Regnier[1], Xiaojie Zhang[2], Essam El-Hashani[2], Andrew Kirkley[3], Ayanna Williams, MS[4], Wakanene Kamau[2], Celeste Thomas, MD[5] and Robert M Sargis, MD, PHD[5], (1) Committee on Molecular Metabolism & Nutrition, The University of Chicago, Chicago, IL, (2) The University of Chicago, Chicago, IL, (3) Committee on Molecular Pathogenesis and Molecular Medicine, The University of Chicago, Chicago, IL, (4) Kennedy-King College, Chicago, IL, (5) Department of Medicine, Section of Endocrinology, The University of Chicago, Chicago, IL

The last several decades have witnessed a dramatic deterioration in global metabolic health with the burgeoning worldwide epidemics of obesity and diabetes. While recent changes in diet and physical activity are central drivers of metabolic disease, increasing attention has turned to contributing factors that may potentiate the effects of lifestyle changes; this includes exposure to endocrine disrupting chemicals (EDCs), exogenous chemicals with the capacity to modulate endogenous hormonal and metabolic signaling pathways. Tolylfluanid (TF) is a phenylsulfamide fungicide widely used on agricultural crops outside of the United States as well as a booster biocide in marine paints. Prior work has implicated TF as an environmental glucocorticoid, with the capacity to promote adipocyte differentiation in the 3T3-L1 cell line, and to induce insulin resistance in human and murine adipose tissue through a specific downregulation in insulin receptor substrate-1 (IRS-1). While these effects suggest a potential role for TF in promoting diabetes, whether cellular effects are recapitulated after in vivo exposure is not known. Furthermore, while adipose tissue plays a central role in metabolism, the ultimate metabolic phenotype is governed by crosstalk between a network of metabolic tissues. To investigate the hypothesis that TF disrupts metabolic homeostasis in vivo, male C57BL/6 mice were exposed to a diet fortified with TF at 100 ppm for 12 weeks. Compared to control-fed animals, TF-treated mice had a 23% increase in adiposity that was most pronounced in the perigonadal fat pad. This augmentation in adiposity was confirmed by DEXA scan where the effect was observed by eight weeks of exposure. Metabolic cage analysis also revealed a reduction in the diurnal variation in energy usage suggesting some loss of metabolic flexibility. Interestingly, the effects of TF on adipocyte physiology recapitulated findings obtained ex vivo. Specifically, dietary supplementation with TF resulted in a significant 30% reduction in adipocyte IRS-1 levels; in addition, adiponectin gene expression was significantly reduced by 31%. In a related study, C57BL/6 dams were exposed to TF-supplemented diet throughout pregnancy and lactation, and the perinatally exposed pups were then followed to adulthood. Both male and female pups exhibited reduced body weight at weaning (13% and 11%, respectively), with males exhibiting impaired glucose tolerance in adulthood as measured by intraperitoneal glucose tolerance tests. These findings suggest that exposure to TF throughout the life span has the capacity to disrupt energy homeostasis in a manner that could contribute to metabolic derangements, including obesity and diabetes. Moreover, the current data supports efforts to characterize human exposure to TF and its potential metabolic consequences.

Presentation Date: Sunday, June 22
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

SUN-0080: Testosterone replacement may help mobility limited older men improve and maintain aerobic capacity

Testosterone replacement therapy may help older men who have limited mobility and low testosterone improve their aerobic capacity and lessen its decline with age, new research finds. The results will be presented in a poster Sunday, June 22, at ICE/ENDO 2014, the joint meeting of the International Society of Endocrinology and the Endocrine Society in Chicago.

"These findings are potentially relevant to older men who have experienced the age-related decline in endurance capacity that may be due in part to low testosterone. If proven safe over the long-term, restoring testosterone to normal levels may improve an important measure of physical performance and enhance their quality of life," said lead study author Thomas W. Storer, PhD, Director of the Exercise Physiology Laboratory at Brigham and Women's Hospital of Harvard Medical School in Boston, Massachusetts.

Aerobic fitness declines as people grow older. In previous research, the authors showed that testosterone therapy might improve endurance capacity in aging men, but the effects of testosterone on aerobic performance in mobility limited older men have not been evaluated.

"We believe this is the first report of enhanced endurance performance as a result of testosterone therapy in men who have difficulty performing some physical tasks but are otherwise healthy.

At least in the short term, testosterone therapy may lessen the rate of decline of an important marker of physical fitness in older men with low testosterone. This may lead to reduced fatigue and improved quality of life," he said.

To investigate whether testosterone supplementation improves measures of aerobic function — the peak oxygen uptake and the gas exchange lactate threshold — Dr. Storer and his colleagues analayzed data from subjects in a larger randomized controlled study of men over age 65 who had low testosterone levels and difficulty performing the usual physical activities of daily living. For 6 months, 28 men in one group received 10 milligrams of testosterone gel and 36 men in a second group received a placebo gel. All subjects completed a cycle exercise test to measure their peak aerobic fitness before and after the 6 month study.

The men taking testosterone displayed a slight improvement in aerobic fitness while those taking placebo showed a slight decline. This small increase in aerobic capacity in the testosterone group eliminated the expected decrease that men generally experience with natural aging.

Among the men taking testosterone, the age-related decline in the peak oxygen uptake was 3.4 times less than expected, while the rate of decline among the men taking placebo accelerated to nearly twice the expected rate. The decrease in gas exchange lactate threshold was significantly smaller in the testosterone group than in the placebo group. Longer term studies are needed to evaluate safety and durability of effect.

The National Institutes on Aging, Boston Claude D. Pepper Older Americans Independence Center, and the Boston University Clinical and Translational Science Institute funded this study.

# # #

SUN-0080: Testosterone Replacement Improves Aerobic Function in Mobility Limited Older Men with Low Testosterone

Thomas Storer. *Brigham and Women's Hospital*

Thomas W Storer, Ph.D[1], Joseph Mosholder, MS[1], Ayan Elmi, MHA[1], Renee Miciek, MS[2], Thomas G Travison, PhD[1], Shehzad Basaria, MD[1] and Shalender Bhasin, MD[1], (1) Men's Health, Aging, and Metabolism, Brigham and Women's Hospital-Harvard Medical School, Boston, MA, (2) Harvard School of Public Health, Boston, MA

Background: Testosterone (T) replacement unequivocally increases skeletal muscle mass and strength but previous trials have not shown consistent improvements in physical function. We have shown that T stimulates mitochondrial biogenesis, increases red cell mass, 2,3 BPG, and tissue capillarity, all of which would be expected to increase tissue O2 delivery and aerobic performance. However, the effects of testosterone on aerobic performance in older men have not been evaluated. To determine whether T supplementation improves measures of aerobic function [peak oxygen uptake (VO2peak) and the gas exchange lactate threshold (LTGE)], men aged ≥65yrs with mobility limitation (ML) and low total or free T levels were randomized to receive 10 mg of T (n=28) or placebo gel (n=36) daily for 6-mo (these participants comprise a subset of men participating in the Testosterone in Older Men with Mobility Limitation (TOM) Trial). We also determined the effects of T therapy on the age-related decline in VO2peak, which in the sedentary male population is expected to be approximately 0.4 mL/kg/min/year.†

Methods: Subjects performed symptom limited cycle exercise using a 10-15 watt ramp protocol and breath-by-breath measures of oxygen uptake to determine VO2peak and LTGE. VO2peak was selected from the last 15 sec of exercise and the V-slope method was used to detect LTGE. Changes in VO2peak within and between groups were compared using paired and unpaired t-tests, respectively. The change between groups for VO2peak vs. its expected change over treatment was examined with an unpaired t-test.

Results: Baseline VO2peak and LTGE [mean (SD)] as well as their 6-mo changes [mean (SE)] are displayed in the table. VO2peak and LTGE improved slightly in the T arm while decreases were seen in the P group. The decrease in LTGE was significantly smaller for the T compared to P group. The 6-mo increase in VO2peak in the T arm represented 3.4 fold attenuation of the expected age-related decline, whereas men in the P group experienced accelerated decline at nearly twice the expected rate.

Conclusion: Testosterone therapy in mobility-limited older men was associated with improved VO2peak and attenuated its age-related decline. Long-term intervention studies are needed to determine the durability of this effect and whether T affects fatigue.

	Testosterone		Placebo		Difference	
	Baseline	Change	Baseline	Change	in change	P
VO2peak(mL/kg/min)	20.5 (4.2)	0.68 (0.50)	19.2 (2.9)	-0.36 (0.43)	1.04 (0.66)	0.12
LTGE(mL/kg/min)	13.7 (2.5)	0.0 (0.41)	14.0 (3.2)	-1.61 (0.49)	-1.49 (0.66)	0.03

Presentation Date: Sunday, June 22
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

Presentations

Monday, June 23, 2014

ENDOCRINE SOCIETY

OR34-4: African American women more resistant to anti-inflammatory effect of aspirin than white women

African American women respond differently to the anti-inflammatory effect of aspirin than do white American women, new research finds. The results will be presented Monday, June 23 at ICE/ENDO 2014, the joint meeting of the International Society of Endocrinology and the Endocrine Society in Chicago.

"African American women appear to be more resistant than white American women to the anti-inflammatory benefits of aspirin in reducing cardiovascular disease and its risk factors," said lead study author Nora Alghothani, MD, MPH, endocrinology fellow in the Division of Endocrinology, Diabetes, & Metabolism at The Ohio State University in Columbus.

Even though African American women have higher high-density lipoprotein (HDL, the "good" cholesterol) and lower triglyceride levels, they also have increased insulin resistance, oxidative stress burden, proinflammatory markers, HDL dysfunctionality — and significantly higher mortality. Aspirin therapy has been recommended to reduce subclinical atherosclerosis and cardiovascular disease outcomes, including stroke.

In their pilot study of 21 African American and 21 white American nondiabetic postmenopausal women with subclinical atherosclerosis, Dr. Alghothani and her colleagues randomly assigned half the women in each group to receive 325 mg of enteric-coated aspirin and half of them to receive an identical placebo, every day for 6 months.

The researchers looked at the subclinical pro-inflammatory markers hsCRP and IL-6 to compare the anti-inflammatory response to aspirin therapy between the AAW and WAW groups.

After 6 months, while hsCRP increased in both AAW and WAW placebo groups, and remained essentially unchanged in the aspirin-treated AAW group, it decreased by 25% in the aspirin-treated WAW group. While IL-6 increased in both placebo groups and in the aspirin-treated AAW group, it decreased by 48% in the aspirin-treated WAW group.

The African American women appeared to be more resistant to the anti-inflammatory properties of aspirin.

"Aspirin therapy has long been recommended to help reduce poor cardiovascular disease outcomes. Its benefits, however, may be different among African Americans compared with white Americans. This research shows an overall blunted response to the anti-inflammatory properties of aspirin among African Americans, and it suggests that a higher dose may be required in African Americans to achieve better cardiovascular disease prevention and lessen disparities among the different ethnic groups," Dr. Alghothani advised.

An award from the National Center for Research Resources funded by the National Institutes of Health funded the study.

# # #

OR34-4: African American Nondiabetic, Postmenopausal Women (AAW) Are More Resistant to Anti-Inflammatory Effect of Aspirin Therapy Than White Women (WAW)

Nora Alghothani. *The Ohio State University*

Nora Alghothani, MD, MPH, Division of Endocrinology, Diabetes, & Metabolism, The Ohio State University, Columbus, OH, Trudy Gaillard, RN, PhD, Division of Endocrinology, Diabetes, & Metabolism, The Ohio State University, Lianbo Yu, PhD, The Ohio State University and Kwame Osei, MD, Division of Endocrinology, Diabetes, & Metabolism, The Ohio State University, Columbus, OH

Ethnic disparities in CVD outcomes exist among AAW & WAW women. The significantly higher mortality in AAW occurs despite higher HDL-C & lower TG. AAW manifest increased insulin resistance, oxidative stress burden, & proinflammatory markers as well as HDL dysfunctionality (1). ASA therapy has been recommended to reduce subclinical atherosclerosis & CVD outcomes such as stroke. Although its anti-platelet effects are well established, additional anti-inflammatory benefits of ASA in the prevention of CVD & its risk factors in AAW is unknown. Thus, it remains uncertain whether AAW equally benefit from ASA.

To explore the anti-inflammatory response to ASA therapy in AAW compared to WAW, we examined the subclinical proinflammatory markers hsCRP & IL-6. We conducted a placebo-controlled, double blind randomized study for 6 mos duration of 42 nondiabetic postmenopausal AAW & WAW (mean age 57.2 ± 3.6 years) with subclinical atherosclerosis by CIMT (mean in AAW 0.6911 ± 0.0509 vs. WAW 0.6113 ± 0.0525 mm). Subjects received either daily enteric coated ASA 325 mg or identical placebo. Fasting blood samples & anthropometric parameters were obtained at baseline & 6 mos later. AAW (n=21) were more obese than WAW (BMI 32.8 ± 6.5 vs. 27.8 ± 5.0 kg/m2, P = 0.007). We found no significant differences between AAW & WAW in fasting glucose, insulin, C-peptide, HOMA-IR, LDL-C, HDL-C, apoB, or blood pressure at baseline & 6 mos. At baseline, AAW had lower TG (62.2 ± 23.4 vs. 88.3 ± 46.5 mg/dL, P = 0.02) & higher apoA1 (185.2 ± 29.7 vs. 159.7 ± 46 mg/dL, P = 0.03). Compared to WAW, AAW also had higher baseline hsCRP (3.96 ± 3.7 vs. 2.2 ± 2.5 mg/L, P = 0.07), but no significant difference in IL-6 (0.77 ± 0.411 vs. 2.05 ± 4.20 pg/mL, P = 0.171). Although when using ANOVA models to assess treatment & race effect as well as their interaction, no statistically significant difference was concluded, AAW did appear to have an overall blunted response to the antinflammatory properties of ASA when compared to WAW. While hsCRP increased from baseline to 6 mos in placebo AAW (n=10, 3.34 ± 2.42 vs. 8.36 ± 12.83 mg/L) & placebo WAW (n=10, 2.19 ± 2.82 vs. 2.69 ± 3.24 mg/L), it remained essentially unchanged in ASA treated AAW (n=11, 4.53 ± 4.69 vs. 4.62 ± 3.84 mg/L). In contrast, hsCRP decreased by 25% in ASA treated WAW (n=11, 2.13 ± 2.41 vs. 1.60 ± 2.44 mg/L). IL-6 increased in both placebo groups at 6 mos (in AAW was 0.58 ± 0.28 vs. 2.97 ± 3.41 pg/mL & in WAW 0.99 ± 1.02 vs. 2.31 ± 2.47 pg/mL). We found IL-6 also increased in ASA treated AAW (0.93 ± 0.45 vs. 2.56 ± 0.95 pg/mL). On the other hand, ASA reduced IL-6 by 48% in WAW (2.69 ± 5.43 vs. 1.39 ± 0.51 pg/mL).

In summary, our pilot study demonstrated that AAW appear to be more resistant than WAW to anti-inflammatory properties of ASA. We conclude that there are ethnic differences in response to ASA mediated anti-inflammatory benefits, & speculate that perhaps a higher dose of ASA may be required in AAW to achieve better CVD outcomes & lessen disparities.

Presentation Date: Monday, June 23
Presentation Time: 11:30 a.m.-1:00 p.m.
Location: Room W184

OR40-2: Roux-en-Y gastric bypass surgery may reduce heart disease risk for obese patients with type 2 diabetes

Obese patients with Type 2 diabetes who don't have excessive surgical risk may find that Roux-en-Y gastric bypass (RYGB) surgery can help them reduce their risk of heart disease, a new clinical trial shows. The results will be presented Monday, June 23, at ICE/ENDO 2014, the joint meeting of the International Society of Endocrinology and the Endocrine Society in Chicago.

"There is emerging evidence highlighting the potential health benefits of bariatric surgery in managing obese patients with Type 2 diabetes. In the past, lifestyle advice and medications provided the mainstay of treatment for this group of patients, but despite the substantial improvements in pharmacotherapy for adults with Type 2 diabetes, many patients still do not achieve targeted health goals," said lead author Su Ann Ding, MBBS, a research fellow at Joslin Diabetes Center in Boston, Massachusetts.

"Roux-en-Y gastric bypass surgery is an acceptable therapeutic option for risk reduction in heart disease in obese patients with Type 2 diabetes in whom surgical risk is not excessive," she said.

To compare the benefits of RYGB surgery with lifestyle and medication modification in these patients, the researchers conducted the randomized prospective SLIMM-T2D clinical trial in Boston.

They recruited 38 obese patients between 21 and 65 years of age who had at least one year of established Type 2 diabetes, a body mass index between 30 and 42 kg/m2, a strong desire for substantial weight loss and a commitment to life-long medical and nutritional follow up. The study participants did not have active cardiovascular or other diseases that would prevent them from exercising safely or undergoing a bariatric surgical procedure and had not smoked for over two months.

The researchers randomly assigned all patients to either have Roux-en-Y gastric bypass surgery at Brigham and Women's Hospital, or to take part in a medical diabetes and weight management program at the Joslin Diabetes Center.

Patients in the medical treatment group enrolled in Joslin's comprehensive Weight Achievement and Intensive Treatment (Why WAIT) program, and worked with an endocrinologist, a registered dietician, an exercise physiologist, a mental health provider, and a certified diabetes nurse educator. For the first 12 weeks, they took part in two-hour weekly group sessions and they followed this with monthly individual counseling.

Patients in both groups lost significant weight and kept it off for 2 years, but the surgical group lost more. The Roux-en-Y group lost roughly 57 pounds on average (25% of their initial body weight) compared with the lifestyle and medication modification group's 13 pounds (6% of their initial body weight). The surgical group also showed better improvements in blood sugar control, blood pressure and cholesterol levels, all of which helped them reduce their risk of developing coronary heart disease.

National Institute of Diabetes and Digestive and Kidney Diseases, a branch of the National Institute of Health principally supported the trial. Covidien; Lifescan, a Division of Johnson & Johnson; Nestlé Nutrition, Inc.; Novo Nordisk; and Mercodia provided additional support.

# # #

OR40-2: Comparative Effectiveness for Cardiometabolic Outcomes of Roux-En-Y Gastric Bypass with Intensive Diabetes and Weight Management in Obese Type 2 Diabetes

Su Ann Ding. *Joslin Diabetes Center*

Su Ann Ding, MD[1], Donald C Simonson, MD, MPH, ScD[2], Florencia Halperin, MD[2], Marlene Wewalka, MD[1], Kathleen Foster, RN[1], Katherine Kelly[1], Jennifer Panosian[1], Ann Goebel-Fabbri, PhD[1], Osama Hamdy, MD[1], Kerri Clancy, RN[3], David Lautz, MD[3], Ashley Vernon, MD[4] and Allison B Goldfine, MD[1], (1) Joslin Diabetes Center, Boston, MA, (2) Division of Endocrinology, Brigham & Women's Hospital, Boston, MA, (3) Emerson Hospital, (4) Department of Surgery, Brigham and Women's Hospital, Boston, MA

To compare effectiveness for cardiometabolic outcomes of bariatric surgery to intensive medical weight management, we randomized 38 obese T2D (15M/23F; weight 104±16 kg; BMI 36.3±3.4 kg/m^2; age 52±6 years; HbA1c 8.5±1.3%; 61% on insulin) to laparoscopic Roux-en-Y gastric bypass (RYGB; n=19) or intensive medical diabetes and weight management (IMWM; n=19) with follow up for up to 18-24 months. At 12 months, there was greater reduction in weight (-28±2 vs -7±2 kg; RYGB vs IMWM, P<0.0001) and fat mass by bioelectrical impedance (-23±1 vs -6±2 kg, P<0.0001) post-RYGB; and at 18-24 months, weight loss (-29±2 vs -5±2 kg, P<0.0001) and loss of fat mass (-23±2 vs -2±2 kg, P<0.0001) were sustained post-RYGB. HbA1c reduction was greater post-RYGB (-2.0±0.4 vs 0.0±0.4, P<0.001) at 12 months and maintained at 18-24 months (-1.7±0.4 vs -0.2±0.3, P<0.01). Reductions in systolic blood pressure (BP) (-12±3 vs -1±3, P<0.05) and triglycerides (-47±9 vs -5±9, P<0.001) and increase in HDL (10±2 vs 0±2, P<0.001) were greater post-RYGB at 12 months. At 18-24 months improvement in systolic BP (-10±5 vs 7±3, P<0.01) and HDL (15±4 vs 2±2, P<0.05) were maintained, and reduction in diastolic BP (-9±3 vs 1±2, P<0.05) emerged only post-RYGB. Changes in UKPDS cardiometabolic risk scores from baseline of 10.3±8.2% for coronary heart disease (-2.8±1.2 vs 0.3±1.0%, P<0.05), 6.7±6.4% for fatal coronary heart disease (-2.1±1.0 vs 0.7±0.7%, P<0.05), 4.0±3.3% for stroke (0.23±0.25 vs 1.04±0.25%, P<0.05) and 0.54±0.49% for fatal stroke (-0.04±0.06 vs 0.19±0.05%, P<0.01) were all more favorable at 18-24 months following RYGB than IMWM. In summary, RYGB produces greater weight loss, sustained improvements in HbA1c, and greater improvements in BP and lipids at 18-24 months compared to medical management. UKPDS risk scores are more favorable post-RYGB for coronary heart disease and fatal coronary heart disease, and in lesser magnitude for stroke and fatal stroke at 12 months, and persist over 18-24 months, which parallel the improvement of cardiometabolic risk factors and HbA1c. Over intermediate duration of follow-up, these findings support that RYGB is an acceptable therapeutic option for cardiovascular risk reduction in obese patients with diabetes in whom surgical risk is not excessive.

Presentation Date: Monday, June 23
Presentation Time: 11:30 a.m.-1:00 p.m.
Location: Room W185

OR40-1: Physical fitness level affects kidney function in Type 2 diabetes

Adults with Type 2 diabetes who improve their physical fitness lower their chances of getting chronic kidney disease (CKD), and if they already have kidney damage, they can improve their kidney function. These findings come from a new study being presented Monday at the joint meeting in Chicago of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014.

Health care providers have long known that exercise has a beneficial impact on overall health and wellness in both the general public and people with Type 2 diabetes. This study, though, demonstrated the benefit of improved physical fitness on a common complication of diabetes—CKD—which in some people can lead to kidney failure and death.

"It is essential for individuals with Type 2 diabetes to improve their physical fitness because it can improve kidney deterioration and reduce mortality," said the study's lead investigator, Shruti Gandhi, MD, an endocrinologist at Washington DC Veterans Affairs (VA) Medical Center.

The study had two parts. In the first part, the researchers looked at data for 2,007 patients (primarily men) with Type 2 diabetes who had normal kidney function when they completed an exercise stress test at the VA hospital in Washington, D.C. They had an average age of 61.Their fitness level, or peak exercise capacity, was scored using the number of metabolic equivalents (METs) they achieved during the test, which increases with exercise intensity. Patients who achieved less than 5.5 METs were classified as least fit; 5.5 to 7.5 METS, as low fit; 7.6 to 9.5 METS, as moderately fit; and more than 9.5 METs, as highly fit.

During the follow-up period, which averaged seven years, 572 patients developed CKD or died of any cause. Because there were not enough data for separate analysis, the researchers combined cases of CKD and deaths, Gandhi explained.

Their data analysis showed that the combined death rate and progression to CKD was much lower with an increased level of fitness. Compared with the least fit patients, the highly fit patients had a 68 percent lower combined CKD-death rate, and the moderately fit had a 51 percent lower rate of progression to CKD and death. Even the low-fit group had a 41 percent lower rate than that of the least fit, according to Gandhi.

In the second part of the study, the researchers assessed the effect of a 12-week supervised exercise program on kidney function in 67 patients with Type 2 diabetes. The program combined aerobic exercise and resistance for at least 30 minutes twice a week. Patients could exercise at home on their own, and approximately 50 percent exercised on one more day, Gandhi said. Before and after the program, the patients had a test of their kidney function, the estimated glomerular filtration rate, or eGFR.

After completing the exercise program, 15 individuals whose initial eGFR indicated stage 3 CKD, or moderate kidney damage, improved their exercise capacity from an average of 7.2 METS to nearly 8.6 METS, Gandhi reported. Their eGFR level decreased after the program, with 53 percent of patients improving their CKD to stage 2, indicating mildly reduced kidney function.

Gandhi said 60 to 90 minutes of exercise weekly "is not a burdensome amount. Our study, while small, provides hope to patients with progressive kidney disease that there is something they can do to improve their kidney function and perhaps prevent or delay the need for dialysis."

# # #

OR40-1: Fitness Impact on Renal Function and Chronic Kidney Disease in Type 2 Diabetics

Shruti Gandhi. *VA Medical Center*

Shruti Mahendra Gandhi, MD, Department of Endocrinology, VA Medical Center, Washington DC and George Washington University School of Medicine and Health Sciences, Peter Kokkinos, PhD, FAHA, FACSM, Department of Cardiology, VA Medical Center, Washington, D.C., Lauren Korshak, MS, VA Medical Center, Washington, D.C., Joseph Powell, PA-C, Endocrinology, VA Medical Center, Washington, D.C. and Eric S Nylen, MD, Department of Endocrinology, VA Medical Center, Washington, D.C.

Introduction: Diabetes is the most common cause of end-stage kidney disease. Fitness status and increased physical activity are essential for diabetic health. Their impact, however, on CKD outcomes and renal function have not been extensively investigated.

Objectives: The primary objective was to assess the exercise capacity-progression to CKD- mortality association. A secondary objective was to assess the effect of a 12-week exercise program on eGFR.

Methods: We identified 2,007 type 2 diabetics (mean age: 61±10.3 years) with normal kidney function who completed an exercise stress test at the VA Medical Center, Washington, DC. Cox proportional hazard model with spline function of MET was used to define the MET level associated without increased risk of progression to CKD (HR=1.0). This MET level (7.5 METs) was used to form four fitness categories based on intervals of 2 METs above and below this threshold: Least-Fit (<5.5 METs); Low-Fit (5.5-7.5 METs) Moderate-Fit (7.6-9.5 METs) and High-Fit (>9.5 METs). Cox proportional hazard analysis, adjusted for age, BMI, cardiac risk factors, sleep apnea, alcohol dependence and cardiac medications, was used to assess the risk of progression to CKD or death. The Least-Fit category was used as the referent.

We also assessed the effects of exercise on renal function in 67 type 2 diabetics. All completed a 12-week aerobic/resistance supervised exercise program. Peak exercise capacity (METs) metabolic panel and blood pressure were evaluated at baseline and after the completion of the program. Patients were classified into 2 groups based on baseline eGFR >60 mL/min/1.73m2 (n=52) and eGFR 30-60 mL/min/1.73m2 (n=15). The effect of exercise was compared within groups using a paired samples t-test.

Results: In the CKD outcomes cohort (mean f/u=7.3 ±5.1 years), the combined events (CKD/death) were 572 (39 deaths/1000 person-years). The mortality risk and rate of progression to CKD were progressively lower with increased fitness. More specifically, the rate was lower by 41% (HR=0.59; CI: 0.49-0.72; p<0.001) for Low-Fit; 51% (HR=0.49; CI: 0.372-0.633; p<0.001) for the Moderate-Fit and 68% (HR=0.32; CI: 0.172-0.6; p<0.001) for High-Fit individuals.

No significant change in eGFR was noted for the group with eGFR>60 mL/min/1.73m2 despite significant improvement in METs (p<0.001), HbA1c (p=0.009) and plasma glucose level (p=0.032). However, patients with eGFR 30-60 mL/min/1.73m2 had significant improvement in both exercise capacity (7.22±1.85 METs vs 8.56±2.3 METs, p=0.042) and eGFR (53.0±4.2 vs 61.5±9.9; p=0.002) at baseline and post intervention, respectively.

Conclusions: Exercise capacity amongst diabetics was inversely associated with the rate of progression to CKD and mortality. In addition, renal function improved in CKD Stage 3 diabetics following the exercise program with 53% patients improving to CKD Stage 2.

Presentation Date: Monday, June 23
Presentation Time: 11:30 a.m.-1:00 p.m.
Location: Room W185

OR40-5: Blood sugar improves with first gastrointestinal microbiome modulator, NM504

In adults with prediabetes, a new drug that alters microbial populations and their environment in the gastrointestinal (GI) tract improves glucose tolerance—the body's response to consuming carbohydrates—after four weeks of treatment and without a change in diet. These results, from a pilot study, will be presented Monday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

The not-yet-named therapeutic, NM504, is the first in a new class of therapies known as GI microbiome modulators. The GI microbiome—the mix of microbial and associated physical and chemical factors in the digestive system—may play a critical part in regulating the body's metabolism, some researchers believe. There is recent scientific evidence that microbial imbalance, or dysbiosis, in the gut contributes to the development of Type 2 diabetes.

"We believe that modern Western diets contribute to development of Type 2 diabetes, in part because they change the habitat of the microorganisms that reside in the gut. This shifts the microbial populations that live there in ways that affect metabolic health," said Mark Heiman, PhD, the study's principal investigator. Heiman is chief scientific officer for MicroBiome Therapeutics, the Colorado-based biotechnology company that is developing NM504 and sponsored the study.

NM504 is designed to shift the GI bacteria and other microorganisms—called microbiota—and their environment in specific ways to achieve improved health outcomes, according to Heiman. He said the drug contains concentrated bioactive food ingredients: inulin, a fiber; beta-glucan and polyphenolic antioxidant compounds.

Heiman and colleagues conducted a study in 28 adults with prediabetes, a frequent precursor to Type 2 diabetes. Fourteen subjects were randomly assigned to receive NM504 twice a day, and the other 14 were assigned to receive placebo, or "dummy" material. Neither the subjects nor the investigators were aware of the drug assignments. Before any treatment and again at four weeks of treatment, all subjects had an oral glucose challenge. In this test, they drank a concentrated glucose (sugary) drink and then had their blood sugar levels tested at various times and compared with pretest levels.

Blood sugar levels at 120 and 180 minutes after the glucose challenge were significantly lower in subjects who took NM504 than those who received the placebo, Heiman reported. Also during this test, NM504 increased insulin sensitivity, the body's ability to successfully clear glucose from the bloodstream.

Compared with placebo, NM504 treatment also decreased the desire to eat, which Heiman said Microbiome Therapeutics' researchers had hoped the therapeutic would do. He said the subjects tolerated NM504 well, with only a mild increase in flatulence, or gas.

"This work indicates a new therapeutic target—the GI microbiome—that has the potential to revolutionize the treatment of metabolic diseases such as Type 2 diabetes," Heiman commented.

MicroBiome Therapeutics reports that the company plans to develop NM504 and/or a closely related therapeutic as a prescription medicine to treat prediabetes and diabetes.

# # #

OR40-5: Improved Oral Glucose Tolerance in Prediabetics and Type 2 Diabetics (T2D) in a Pilot Clinical Trial Testing a Novel Gastrointestinal (GI) Microbiome Modulator

Mark Heiman. *MicroBiome Therapeutics*

Mark Louis Heiman, PHD, MicroBiome Therapeutics, Indianapolis, IN, Jeffrey H Burton, Pennington Biomedical Research Center, Baton Rouge, LA, Elena Deych, Medicine, Washington Univ, St. Louis, St. Louis, MO, William D Shannon, BioRankings, LLC, St. Louis, MO and Frank Lyons Greenway III, MD, Dept Clin Trials, Pennington Biomed Res Ctr, Baton Rouge, LA

People living in wealthy cultures are inflicted with metabolic diseases, in part, because of over eating processed food. Human physiology has limited ability to adapt to these modern dietary habits. In contrast, the ecosystem of the intestines; containing bacteria, fungi, undigested- and partially digested- foods, quickly adapts. For example, shifts in the GI microbiome are documented for T2D when compared to the microbiome of healthy individuals (1,2). The first microbiome modulator designed to treat dysbiosis in T2D is NM504. A trial was done to test if NM504 improves the oral glucose tolerance of prediabetics and untreated T2D by modulating the GI microbiome. Thirty subjects were enrolled in the double-blind, randomized, placebo-controlled trial for 28 days (14 subjects completed each arm). NM504 was administered twice a day prior to either breakfast or lunch and prior to dinner. The microbiome modulator was well tolerated and improved ($p < 0.05$, n=14) the serum glucose levels during an oral glucose tolerance test at both 120 - and 180 - min when compared to those values in subjects assigned to the placebo (n=14). Insulin levels were similar between the 2 groups during the oral glucose tolerance testing. The improved glucose tolerance was associated with decreased circulating levels of ALK phosphatase (p=0.06, n=14), hsCRP (p=0.012, n=14), and total cholesterol (p=0.01, n=14). NM504 treatment also decreased the desire to eat (p=0.03, n=14), increased stool IgA levels (p=0.03, n=14), and decreased stool pH (p=0.03, n=14). We think that NM504 attenuates absorption of glucose and bile salts. Other possible mechanisms of action in the lower gut include maintenance of the mucosal barrier, increased luminal exposure to antioxidants, increased viscosity within the lumen. Individual changes in microbiota abundance and short chain fatty acid production were evident but were not different when grouped by treatment. A tendency for increased GLP-I levels and decreased ocatanoyl ghrelin levels in response to a meal tolerance test during week 3 was also observed. In conclusion, NM504 is the first therapeutic to directly modulate the GI microbiome in prediabetics and in T2D to improve oral glucose tolerance with decreased markers of inflammation and blood lipids. Moreover, this improved metabolic state occurred without change in dietary habits. Follow-up studies will include more subjects and longer trials.

Presentation Date: Monday, June 23
Presentation Time: 11:30 a.m.-1:00 p.m.
Location: Room W185

OR40-4: Sleeve gastrectomy surgery improves diabetes control better than medical care

Adults with Type 2 diabetes achieve better blood glucose (sugar) control two years after undergoing laparoscopic sleeve gastrectomy than do patients who receive standard medical diabetes care without this weight loss surgery, a new study finds. The results will be presented Monday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

In addition, 76 percent of surgery patients were able to reduce their use of diabetes medications, compared with only 26 percent of patients in the nonsurgical group, study authors reported.

“Individuals with obesity now have another treatment option that can help reduce weight and manage diabetes,” said the study’s principal investigator, Pietra Greenberg, MD, an endocrinologist at James J. Peters Veterans Affairs (VA) Medical Center in Bronx, N.Y.

Sleeve gastrectomy, a newer minimally invasive technique for making the stomach smaller, is gaining popularity, and several studies have found it is effective for weight loss. However, Greenberg said few prior studies of diabetes outcomes in diabetic patients who underwent this surgical procedure compared results with those of nonsurgically treated patients who have the disease.

She and fellow researchers compared the medical records from 2010 to 2014 of 53 veterans with Type 2 diabetes: 30 patients who underwent sleeve gastrectomy and 23 who received medical diabetes care but did not receive any weight loss surgery (controls). Study participants—nearly all of whom were men—ranged in age from 29 to 80 years, and had diabetes for an average of 10 years..

Nonsurgical control subjects did not lose weight on average over a two-year follow-up period and therefore had no change in average body mass index, or BMI, Greenberg said. In the sleeve gastrectomy group, BMI decreased from 41 kg/m2 (morbidly obese) to 34 kg/m2 two years after surgery.

Hemoglobin A1c, a measure of blood sugar control over the past few months, also was significantly different between the two groups. It fell from an average of 7.25 percent before sleeve gastrectomy (but after lifestyle changes, such as diet and exercise) to 5.98 percent.. Among controls, the average Hemoglobin A1C at two years was not significantly changed.

As is common when people with Type 2 diabetes lose a great deal of weight, most (76 percent) of the patients after sleeve gastrectomy took fewer diabetes medications, such as insulin, she said.

“This research highlights the benefits of a surgical approach such as sleeve gastrectomy to help improve diabetes outcomes, especially compared to more conservative medical management,” Greenberg commented.

She noted, however, that the improvement in diabetes measures in the surgical group reached a plateau at the end of two years. “Surgery may not be a permanent solution to improving diabetes control. However the procedure does have immediate benefits that appear to set the patient on a path to a healthier future.

Sheetal Malhotra, MD, MS, internal medicine resident at James J. Peters VA Medical Center, will present this research.

# # #

OR40-4: Sleeve Gastrectomy Outcomes in Veterans with Type II Diabetes

Sheetal Malhotra. *JJ Peters VA Medical Center*

Sheetal Malhotra, MD, MS[1], Namita Gupta, MD[2], Sneha Galiveeti, MD[1], Bojana Milekic, MD[1] and Pietra Dale Greenberg, MD[3], (1) Internal Medicine, JJ Peters VA Medical Center, Bronx, NY, (2) Endocrinology, University of Nebraska Medical Center, Omaha, NE, (3) Dept of Endo/Med, James J Peters VA Med Ctr, Bronx, NY

The link between obesity and type 2 diabetes is clearly established with weight loss resulting in improvement in insulin sensitivity and glycemic control. Laparoscopic sleeve gastrectomy involves the removal of the greater curvature of the stomach, and is now a common low-morbidity surgical technique for weight loss. Previous cohort studies have shown improvement in obesity in patients undergoing sleeve gastrectomy. However, there have been no studies comparing long term diabetes outcomes in patients undergoing surgical intervention as compared to controls who are on nonsurgical diabetes care.

Research question: To compare long term diabetes outcomes in patients undergoing sleeve gastrectomy as compared to controls who undergo nonsurgical diabetes care.

Methods: We reviewed medical records of veterans between 18 and 80 years of age with type 2 diabetes undergoing sleeve gastrectomy at a VA medical center in a major metropolitan area. Primary study outcomes included measures of diabetes control including HbA1C and BMI. Secondary outcomes such as total and LDL cholesterol, hospitalizations and mortality were also assessed. Data from surgery patients were compared to data from diabetic controls that did not undergo surgery using descriptive analyses, t-tests , and repeated measures ANOVA.

Results: Data from charts of 30 surgery patients and 23 controls were analyzed from 2010 to 2013. Most of the subjects enrolled were males (96%) with an average age of 57 years (range 29-80 years). The median BMI at baseline was 41 (range 36-60) kg/m2 and median Hba1c was 7.3. There was a significant improvement in BMI and Hba1c in surgery patients over one year follow up; improvements were sustained through the end of two years after surgery. Mean BMI decreased from 41 to 34 over two years ($P<0.001$) and mean Hba1c decreased from 7.25 to 5.98 ($P<0.001$). Similar outcomes were not seen in controls during the study period. Differences in these outcomes between surgery patients and controls were significant over short term and long term follow up ($P<0.001$). No changes were seen in total cholesterol or LDL cholesterol for surgery patients. However, it was noted that the changes in outcomes plateau after the first year of surgery.

Discussion: It is interesting to note that sleeve gastrectomy may offer better diabetes control and improved outcomes compared to patients who follow medical care only. However, the improvement in outcomes in surgery patients may not be a permanent solution for diabetes outcomes.

Conclusion: Sleeve gastrectomy is effective in improving diabetes outcomes in veterans as compared to those receiving nonsurgical diabetes care.

Presentation Date: Monday, June 23
Presentation Time: 11:30 a.m.-1:00 p.m.
Location: Room W185

OR40-3: Gastric bypass surgery improves diabetic patients' quality of life better than diet and exercise

An intensive weight loss program involving lifestyle modifications improves obese diabetic patients' physical and mental health as well as gastric bypass surgery does over two years, but the weight loss surgery leads to a greater reduction in adverse effects of obesity on quality of life. These results, from a new study in patients with Type 2 diabetes, will be presented Monday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

Gastric bypass also led to patients having a somewhat greater reduction in problems associated with managing their diabetes, according to the study's lead investigator, Donald Simonson, MD, MPH, ScD, from Brigham and Women's Hospital, Boston.

"Patients with obesity and Type 2 diabetes should consider these long-term results when making decisions about their weight loss treatment," Simonson said.

The researchers evaluated the effects of weight loss on 38 patients' self-reported health status for both physical and mental health, as well as the impact of their weight on their quality of life and on problem areas in managing their Type 2 diabetes.

Fifteen men and 23 women participated in the Surgery or Lifestyle with Intensive Medical Management in the Treatment of Type 2 Diabetes (SLIMM-T2D) trial. Of the 38 patients, 19 were randomly assigned to undergo gastric bypass surgery at Brigham and Women's Hospital, and 19 patients, to a medical diabetes and weight management program, called Why WAIT (Weight Achievement and Intensive Treatment), at the Joslin Diabetes Center in Boston. The program consisted of exercise, diet with meal replacements, 12 initial weekly group sessions and nine additional months of individual counseling. Follow-up evaluation ranged from 18 to 24 months.

Before treatment, patients reported high scores on the questionnaire Impact of Weight on Quality of Life, which included physical function, self-esteem, sex life, public distress and work. Up to two years after treatment, patients who underwent gastric bypass surgery had nearly twice the improvement (reduction) in the adverse effects of weight on their quality of life, which Simonson said strongly correlated with the greater amount of weight they lost.

Two years after treatment, the surgical patients lost an average of 64.4 pounds versus 11 pounds in the Why WAIT group, he noted.

At 18 to 24 months after treatment, patients in the surgical group also reported a 60 percent greater reduction in problems with managing their diabetes, as found by an eight-point better score on the Problem Areas in Diabetes scale than the medical group. Problems surveyed included emotional distress, eating behaviors, and difficulty with diabetes self-management.

Although the Why WAIT program improved self-reported physical and mental health more than gastric bypass did at three months, improvements were generally similar in the two groups after one and two years of follow-up and were in the moderate range, Simonson reported.

Primary support for the study came from the National Institute of Diabetes and Digestive and Kidney Diseases. Partial funding, medications or materials were supplied by Covidien, Nestlé Nutrition, Novo Nordisk, LifeScan and Mercodia.

# # #

OR40-3: Changes in Patient-Reported Outcomes up to Two Years after Roux-En-Y Gastric Bypass Vs. Intensive Medical Weight Management in Obese Patients with Type 2 Diabetes Mellitus

Donald Simonson. *Brigham & Women's Hospital*

Donald C Simonson, MD, MPH, ScD[1], Su Ann Ding, MD[2], Florencia Halperin, MD[1], Marlene Wewalka, MD[2], Kathleen Foster, RN[2], Katherine Kelly[2], Jennifer Panosian[2], Ann Goebel-Fabbri, PhD[2], Osama Hamdy, MD[2], Kerri Clancy, RN[3], David Lautz, MD[3], Ashley Vernon, MD[4] and Allison B Goldfine, MD[2], (1) Division of Endocrinology, Brigham & Women's Hospital, Boston, MA, (2) Joslin Diabetes Center, Boston, MA, (3) Emerson Hospital, (4) Department of Surgery, Brigham and Women's Hospital, Boston, MA

Weight loss improves patient-reported outcomes (PRO) in obese type 2 diabetes (T2D) patients; however, differences between surgical and medical weight management, and the durability of their effects, are not well established. We randomized 38 obese T2D (15M/23F; weight 104±16 kg; BMI 36.3±3.4 kg/m²; age 52±6 yrs; HbA1c 8.5±1.3%; 61% on insulin) to laparoscopic Roux-en-Y gastric bypass (RYGB; n=19) or intensive medical weight management (IMWM; n=19) with follow-up for 18-24 mos. At baseline, subjects had moderately reduced SF-36 physical health (PH) (65±17) and mental health (MH) (64±14), high Impact of Weight on Quality of Life (IWQOL) (75±23), and high Problem Areas in Diabetes (PAID) (54±15) health status scores. At 10% weight loss or 3 mos (if 10% loss was not achieved), RYGB resulted in greater weight loss (-11±1 vs. -7±1 kg; P<0.001), but a similar decline in HbA1c (-1.7±0.2 vs. -1.6±0.2%) vs. IMWM. SF-36 PH (12±3 vs. -2±3; P<0.01) and MH (15±3 vs. 1±3; P<0.001) improved more in IMWM vs. RYGB. Improvements in IWQOL and PAID were similar between groups. At 12 mos, RYGB had much greater weight loss (-28±2 vs. -7±2 kg; P<0.0001) and lowering of HbA1c (-2.0±0.4 vs. 0.0±0.4%; P<0.001) vs. IMWM, both of which persisted at 18-24 mos (-29±2 vs. -5±2 kg, P<0.0001; -1.7±0.4 vs. -0.2±0.3%, P<0.01, respectively). IWQOL improved more in RYGB (-32±4 vs. -17±4; P<0.01), and correlated with greater weight loss at 12 mos (r = 0.70, P<0.001) and 18-24 mos (r = 0.67, P<0.001). Change in PAID score did not differ between groups at 12 mos (-20±2 vs. -15±2), but RYGB trended toward greater improvement at 18-24 mos (-20±3 vs. -12±3, P=0.06) consistent with sustained lowering of HbA1c. In contrast, improvements in SF-36 PH (4±4 vs. 7±4) and MH (5±4 vs. 11±4) did not differ between RYGB and IMWM at 12 mos, and did not substantively change further at 18-24 mos. Thus, in obese T2D, 1) RYGB produces greater weight loss, sustained improvements in HbA1c, and improvement in the impact of weight on quality of life up to 24 mos compared to medical management, 2) both treatments reduce problems associated with diabetes management, although the long-term effect is somewhat greater after RYGB, and 3) IMWM improves general physical and mental health more than RYGB up to 3 months, but both groups had similar moderate improvements in the longer term. These outcomes should be considered in therapeutic decisions for weight loss strategies in obese T2D.

Presentation Date: Monday, June 23
Presentation Time: 11:30 a.m.-1:00 p.m.
Location: Room W185

MON-0329: Mystery solved of source of anti-cancer effects in pregnancy hormone

University of Montreal scientists have identified a small molecule found in pregnant women's urine that apparently blocks the growth of several types of cancers, including AIDS-related Kaposi's sarcoma, which currently has no cure. Their study results will be presented Monday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

These findings resurrect a nearly 20-year controversy over whether human chorionic gonadotropin (hCG), a hormone produced in high amounts during pregnancy, or its core fragments, or something else yields anti HIV and cancer-fighting activity against Kaposi's sarcoma tumors. Some researchers in the mid-1990s reported that "clinical-grade" hCG—crude or partially purified preparations of hCG extracted from pregnant women's urine—shrunk these AIDS tumors, but they later retracted their original claim that hCG itself was the active component responsible for activity against Kaposi's sarcoma.

"The real compound has been elusive," said principal investigator Tony Antakly, PhD, a biochemist at the University of Montreal, who said it has taken his small group of researchers more than 12 years to find the answer.

Early on, and shortly before this retraction, Antakly's group tested highly purified or recombinant hCG in Kaposi's sarcoma cells and found no anti-cancer effects. They concluded that the cancer-fighting compound, closely associated with the pregnancy hormone, must be removed when hCG is purified. Both clinical-grade and recombinant hCG are approved by the U.S. Food and Drug Administration as prescription medications for the treatment of select cases of female infertility and as hormone treatment for men.

The researchers narrowed their search to small molecular weight factors present in clinical-grade hCG that they called hCG-like inhibitory products, or HIP. To find the active molecule or part of a molecule, they used a biochemical approach involving systematically splitting the molecule (fractionation), repeatedly performing biological assays and chemical characterization.

Their results indicate that a small metabolite—the product of transformation of a larger molecule carried throughout blood and urine—into a potent bioactive metabolite that affects living tissue.

"We don't know if it changes only when needed," Antakly said. "Perhaps in cancer, it changes to fight the disease."

This HIP metabolite, they discovered, rides "piggyback" on the larger hCG molecule, which chaperones it to target cells. When hCG is extensively purified, the metabolite loses its ride and disappears, Antakly stated.

However, when he and his colleagues exposed human Kaposi's sarcoma cells in tissue cultures to hCG after purification from pregnant women's urine, he said the active HIP metabolite "wiped out the cancer cells completely."

Antakly said they do not yet know whether a synthetic replica of the HIP metabolite, which they are developing, is safe and effective to use at high doses in patients with cancer. However, in preliminary tests in cancer patients, they have shown that the "natural" HIP (purified from clinical-grade hCG) is safe and has anti-cancer activity.

# # #

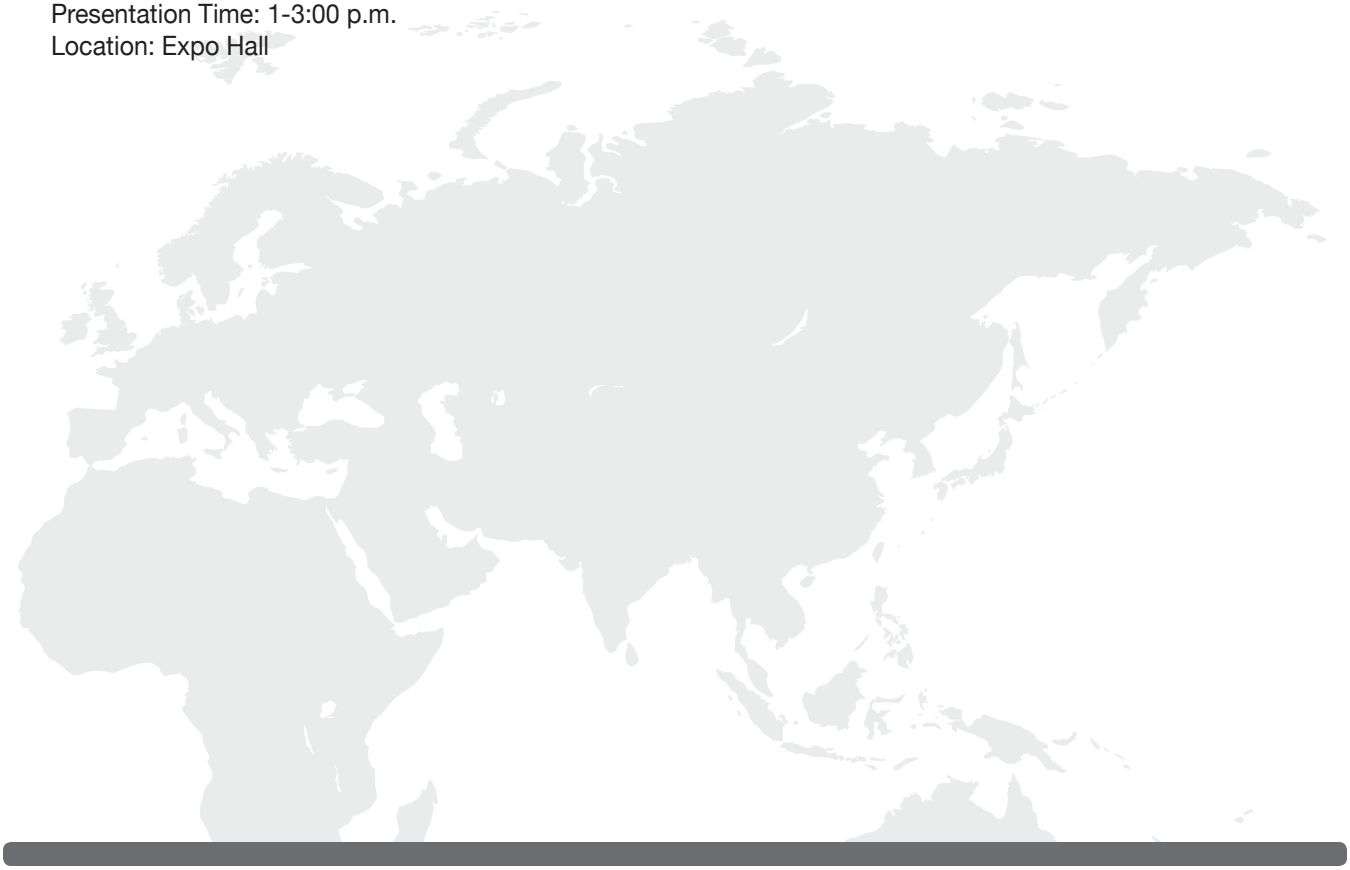
MON-0329: Small Molecules from Human Urine Bound to HCG Display Potent Anti-Cancer Activity

Tony Antakly. *University of Montreal*

Tony Antakly, PHD, Dept of Biochemistry, Univ of Montreal, Montreal, QC, Canada, Emil Toma, MD, Univ Medical Center, U Montreal, Montreal, QC, Canada and Jose Menezes, Ph.D., Microbiology Immunology, Univ of Montreal, Montreal, QC, Canada

The urine contains known compounds that play important roles in key physiological functions and it may contain as yet undiscovered molecules with potential therapeutic properties. In previous studies, we have isolated small molecular weight factors called HIP from human urine which potently block the growth of several types of cancers including AIDS-Kaposi's sarcoma (Nature Biotechnol 15, 1228). Subsequently, we and others have attempted to purify HIP to homogeneity. To date, the chemical identity as well as the exact signaling mechanisms have remained elusive. In order to efficiently characterize this molecule, we undertook a systematic approach to decipher the molecular components of HIP. Chromatographic purification and high-resolution fractionation showed that the active moiety comprises more than one molecular species, two of which are required for full biological activity. Using proteomics, metabolomics and nuclear magnetic resonance spectroscopy (NMR), we have now identified these components and tested their anti-cancer activity using a bioassay platform. Characterization was done by proteomics (QTOF-2, LC mass spectrometer (LC)-QTOF liquid chromatography) and NMR (950 MHz). Results indicate that the active moiety of HIP is a small metabolite. This small molecule binds to a hydrophilic "pocket" of a small peptide. The situation of HIP is not unique, since recently accumulating data indicate that small molecular weight molecules, which otherwise do not possess functional activity, can be turned into potent bioactive molecules once metabolized or following their binding with other molecules. This study allowed us to synthesize HIP in an attempt to use it as a therapeutic anti-cancer product. To this end, our recent preliminary HIP human clinical trial data suggest the active agent is well tolerated and effective.

Presentation Date: Monday, June 23
Presentation Time: 1-3:00 p.m.
Location: Expo Hall



MON-0996: Poor awareness of the proper injection techniques adversely affects glucose control

Diabetic patients who don't know proper injection techniques may administer insulin incorrectly, leading to poor glycemic control and adverse outcomes, a new study from Iraq finds. The results will be presented in a poster Monday, June 23 at ICE/ENDO 2014, the joint meeting of the International Society of Endocrinology and the Endocrine Society in Chicago.

"Lack of simple education about proper injection techniques could be blamed for many complications and adverse outcomes. I thought about conducting this study after managing two teenage patients who suffered diabetic ketoacidosis, a life-threatening acute emergency. The condition occurred due to the lump formed because they were unaware of the proper injection techniques," said study author Hassan A-R Ibrahim, MBChB, MSc, diabetes specialist at the Layla Qasim Diabetes Center in Erbil, Kurdistan, Iraq.

Insulin therapy injection technique among insulin-treated diabetic patients has been poorly studied, Dr. Ibrahim said. So, to investigate the impact of injection technique on diabetes control, he administered a 12-item, oral structured Injection Technique Knowledge (ITK) Questionnaire to 216 clinic patients that assessed their understanding of injection techniques and ability to administer their injections successfully.

Overall, the mean score was 47.5%, and only 31% of the patients answered more than half the questions correctly. Half the patients with poor test scores had poor glycemic control compared with 28% of the participants with acceptable scores.

"I was surprised by the results of the study and at the same time disappointed. I did not expect that such a great number of patients would not be aware of the proper use of insulin. This was mainly due to inadequate education and resources for the patients using insulin," Dr. Ibrahim said.

Dr. Ibrahim found no significant association between the test score and the patients' residency, gender, age or duration of diabetes, although more highly educated patients, including patients who had received previous education on injection technique, had higher scores. He did find associations between the test score and the type of diabetes, insulin regimen, insulin devices, glycemic control, prior training on the correct injection technique and previous lump formation at the site of injection.

Dr. Ibrahim advises that educating patients is crucial. He recommends that an educator should be available in the clinic to teach all new patients having their first injection the correct techniques and that no patient should be sent home unless the doctors are sure that they have the knowledge they need. Patients need to learn the correct insulin dosing for vials and syringes, knowledge about the preferred sites of injection, how to prevent the formation of lumps at the injection sites, and the negative consequences on blood sugar control.

"We have an educator but she cannot cope with the large number of the patients visiting the center. Some patients are not given enough time to learn. Therefore, more educators should be allocated and annual reassessment is recommended," he advised.

# # #

MON-0996: Poor Awareness of the Right Injection Techniques Deteriorates Glycemic Control Among Insulin Treated Diabetic Patients

Hassan Ibrahim. *Diabetes Center (Erbil, Iraq)*

Hassan A-R Ibrahim, MBChB, MSc, Erbil (Layla Qasim) Diabetes Center, Erbil, Iraq

Background: Insufficient knowledge of injection technique contributes to errors in insulin use that may cause poor control and adverse patient outcomes. Knowledge of injection technique of insulin therapy among the insulin-treated diabetic patients has been poorly studied.

Objective: To assess the knowledge of injection technique principles and to evaluate its association with sociodemographic and clinical characteristics of insulin treated diabetic patients. To investigate the impact of injection technique on diabetes control.

Methods: A 12-item, structured Injection Technique Knowledge (ITK) Questionnaire was used for data collection. The questionnaire was developed depending on Forum of Injection Technique recommendations (1). The participants (n=216) were categorised as having poor or acceptable scores if total percentage scores were ≤50 or >50, respectively.

Results: The mean percentage of ITK score was 47.5 ±19.5%, and only 31% (n=67) of the participants had acceptable score. There was no significant association between place of residency, gender or age of the patients or duration of having diabetes and the ITK score. However, participants with higher level of education had significantly higher scores than those with lower levels ($P < 0.005$). Chi square test of associations also showed significant association between ITK scores category and type of diabetes, insulin regimen, insulin devices, glycemic control, prior training on the correct injection technique and previous lump formation at the site of injection.The results of logistic regression analysis showed that high school education (OR=4.56, 95% CI, P=0.027), prior training on the correct injection technique (OR=10.14, P=<0.001) and no previous lump formation at the site of injections (OR=3.9, P=<0.01) were predictors of acceptable scores on ITK. 51% of participants with poor ITK scores had poor glycemic control (HbA1c >9%) compared to 28.4% of the participants with acceptable ITK scores (P=0.005).

Conclusion: This study showed that the majority of insulin-treated diabetic patients had knowledge deficit of the right injection practice. Delivering education about injection techniques among diabetics can result in better glycaemic control and outcome among insulin treated patients.

Presentation Date: Monday, June 23
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

MON-0365: Hormone-disrupting activity of fracking chemicals worse than initially found

Many chemicals used in hydraulic fracturing, or fracking, can disrupt not only the human body's reproductive hormones but also the glucocorticoid and thyroid hormone receptors, which are necessary to maintain good health, a new study finds. The results will be presented Monday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

"Among the chemicals that the fracking industry has reported using most often, all 24 that we have tested block the activity of one or more important hormone receptors," said the study's presenting author, Christopher Kassotis, a PhD student at the University of Missouri, Columbia. "The high levels of hormone disruption by endocrine-disrupting chemicals (EDCs) that we measured, have been associated with many poor health outcomes, such as infertility, cancer and birth defects."

Hydraulic fracturing is the process of injecting numerous chemicals and millions of gallons of water deep underground under high pressure to fracture hard rock and release trapped natural gas and oil. Kassotis said spills of wastewater could contaminate surface and ground water.

In earlier research, this group found that water samples collected from sites with documented fracking spills in Garfield County, Colorado, had moderate to high levels of EDC activity that mimicked or blocked the effects of the female hormones (estrogens) and the male hormones (androgens) in human cells. However, water in areas away from these gas-drilling sites showed little EDC activity on these two reproductive hormones.

The new study extended the analysis to learn whether high-use fracking chemicals changed other key hormone receptors besides the estrogen and androgen receptors. (Receptors are proteins in cells that the hormone binds to in order to perform its function.) Specifically, the researchers also looked at the receptor for a female reproductive hormone, progesterone, as well as those for glucocorticoid—a hormone important to the immune system, which also plays a role in reproduction and fertility—and for thyroid hormone. The latter hormone helps control metabolism, normal brain development and other functions needed for good health.

Among 24 common fracking chemicals that Kassotis and his colleagues repeatedly tested for EDC activity in human cells, 20 blocked the estrogen receptor, preventing estrogen from binding to the receptor and being able to have its natural biological response, he reported. In addition, 17 chemicals inhibited the androgen receptor, 10 hindered the progesterone receptor, 10 blocked the glucocorticoid receptor and 7 inhibited the thyroid hormone receptor.

Kassotis cautioned that they have not measured these chemicals in local water samples, and it is likely that the high chemical concentrations tested would not show up in drinking water near drilling. However, he said mixtures of these chemicals act together to make their hormone-disrupting effects worse than any one chemical alone, and tested drinking water normally contains mixtures of EDCs.

"We don't know what the adverse health consequences might be in humans and animals exposed to these chemicals," Kassotis said, "but infants and children would be most vulnerable because they are smaller, and infants lack the ability to break down these chemicals."

This study received funding from the Passport Foundation Science Innovation Fund, the University of Missouri, and from the Environmental Protection Agency, through a STAR predoctoral fellowship awarded to Kassotis.

# # #

MON-0365: Endocrine Disrupting Activity of Hydraulic Fracturing Chemicals and in Vivo Adverse Health Outcomes

Christopher Kassotis. *University of Missouri*

Christopher D Kassotis, Dept of Bio Sci, Univ of Missouri, Columbia, MO, Chung-Ho Lin, PhD, Dept of Agroforestry Bioremediation, Forestry, University of Missouri, Columbia, MO, Donald Tillitt, PhD, Biochemistry & Physiology Branch, United States Geological Survey, Columbia, MO and Susan Carol Nagel, PhD, Dept of OB/GYN, Univ of MO-Columbia, Columbia, MO

There has been a rapid rise in the use of hydraulic fracturing to produce natural gas and oil. Over 750 chemicals are used in this process and many are known toxicants, carcinogens, and/or endocrine disrupting chemicals (EDCs). Spills of wastewater associated with this process are common and can contaminate surface and ground water. We have previously found an association between hydraulic fracturing spills and endocrine disrupting activity in surface and ground water. Water samples collected from sites with documented natural gas drilling contamination exhibited the highest levels of activity, samples collected from the Colorado River had intermediate levels of activity, and reference sites in areas away from natural gas drilling exhibited the lowest levels.

We previously found that eleven of twelve chemicals used in hydraulic fracturing exhibited significant anti-estrogenic activity and nine exhibited significant anti-androgenic activity. Based on this small subset of chemicals and the vast number of chemicals used, we hypothesized that a wider analysis of chemicals would reveal other hormonally active chemicals. Initial work focused exclusively on the estrogen and androgen receptor, while this study extends the analysis to include agonist and antagonist activities of the estrogen, androgen, progesterone, glucocorticoid, and thyroid receptors for 24 individual chemicals used in the fracturing process. To date, we have identified 19, 16, 7, 7, and 5 chemicals that exhibit antagonist activities for the estrogen, androgen, progesterone, glucocorticoid, and thyroid receptors, respectively.

Previous work has reported additivity of EDCs with the same mechanism of action. With hundreds of chemicals used, it is essential to begin to assess in vitro and in vivo effects of complex mixtures of the EDCs used throughout the natural gas drilling process. Chemical mixtures will be made at equimolar concentrations for 1) all 24 EDCs analyzed, 2) 9 EDCs that we have analytically measured in hydraulic fracturing wastewater, and at equipotent concentrations for 3) chemicals interacting with each of the five receptors individually. These mixtures will all be tested in an in vitro system, and the smaller mixture of analytically identified EDCs will also be tested in an in vivo model. Briefly, timing of puberty and other estrogen, androgen, and thyroid-related endpoints will be assessed in mice following peripubertal exposure to four concentrations of the mixture, provided via drinking water. Overall, we have shown that many chemicals used in hydraulic fracturing are EDCs. Completion of the in vivo studies will substantially increase our knowledge associated with exposure to complex mixtures of EDCs used in hydraulic fracturing and increase our understanding of the potential health risks.

Presentation Date: Monday, June 23
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

MON-0005: High testosterone may predict more shallow sleep in overweight or obese men

In overweight and obese men, higher testosterone levels are associated with poorer sleep quality, according to a new study whose results will be presented Monday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

"This finding could have clinical relevance in the context of the recent increase in testosterone prescriptions in middle-aged men, as poor sleep quality has been linked to increased risk of diabetes and hypertension," said Eve Van Cauter, PhD, the study's senior investigator. She is director of the University of Chicago Sleep, Metabolism and Health Center, where the study took place.

With three of four U.S. men now overweight or obese, the researchers wanted to determine which factors influence sleep quality in this population. Overweight and older age can contribute to obstructive sleep apnea (OSA), a condition in which breathing repeatedly stops and starts during sleep and which disrupts sleep.

The research team performed a polysomnogram, or overnight sleep study, in 44 men ages 20 to 50 years who were overweight or obese. All subjects were otherwise healthy and were nonsmokers. Their selection for the study did not consider whether they had symptoms or a history of sleep apnea, according to Van Cauter. However, the sleep study showed that 29 (66 percent) of the men did have OSA, which she said was moderately severe in most cases.

In addition to apnea episodes, the sleep study evaluated the brain's slow-wave activity during non-rapid eye movement sleep, which is a marker of sleep depth. Low slow-wave activity indicates shallow sleep, which causes a person to wake up easily and feel unrested after a night of sleep.

The morning after the sleep study, the men gave blood samples for measurement of their total testosterone level.

To explore the factors associated with slow-wave activity, the researchers performed statistical analyses (using multivariate regression) that first included only subjects' demographic characteristics. Older age and African-American race predicted low slow-wave activity, or shallow sleep, the data showed. Body mass index, a measure of height and weight, had no significant effect on slow-wave activity.

Later analyses demonstrated that higher total testosterone level strongly correlated with more shallow sleep. This association, Van Cauter said, was independent from the presence of other factors known to decrease sleep quality, such as age, race/ethnicity and OSA severity.

Because doctors are increasingly prescribing testosterone replacement therapy for middle-aged and older men with low testosterone levels, Van Cauter said, "Further studies are needed to clarify the impact of testosterone replacement on sleep quality, especially sleep depth."

Study funding sources were the National Institutes of Health, the ResMed Foundation and a grant from the Brussels Institute for Research and Innovation.

# # #

MON-0005: High Testosterone Levels Predict More Shallow Sleep in Overweight and Obese Men, Independently of Obstructive Sleep Apnea

Eve Van Cauter. *University of Chicago*

Eve Van Cauter, PhD[1], Lisa L Morselli, MD, PhD[1], Karla A Temple, PhD, RD[2], Florian Chapotot, PhD[1], Rachel Leproult, PhD[1], David A Ehrmann, MD[2], and Babak Mokhlesi, MD[3], (1) Sleep, Metabolism and Health Center, University of Chicago, Chicago, IL, (2) Section of Endocrinology, Diabetes & Metabolism, University of Chicago, Chicago, IL, (3) Section of Pulmonary and Critical Care Medicine, University of Chicago, Chicago, IL

Slow-wave activity (SWA) is a marker of sleep depth and a stable within-subject characteristic that has been implicated in the control of glucose homeostasis and blood pressure. Studies exploring the predictors of the large inter-individual differences in SWA have been performed mainly in lean individuals. As 75% of men are now overweight or obese in the United States, the aim of this study was to identify predictors of SWA in overweight and obese men.

Forty-four overweight and obese men aged 20-50 years (mean±SE: 35±1 years) were recruited from the community and underwent an overnight in-laboratory polysomnogram. SWA was computed as the average absolute spectral EEG power in the frequency band 0.75-4.5 Hz during non rapid eye movement (NREM) sleep, in the first 6 hours of sleep. Obstructive sleep apnea (OSA) was defined by an apnea-hypopnea index (AHI) ≥5. Total plasma testosterone was measured on the morning following the polysomnogram. Multivariate regression models were run to explore the predictors of SWA.

Obstructive sleep apnea was present in 66% of the men, and the median AHI was 16 (interquartile range 9-26) events/hour. In a model including only demographic characteristics, NREM SWA was negatively predicted by African-American race (β=-0.25, $p<0.0001$) and age (β=-0.03, $p=0.004$), but not BMI. When total testosterone was added, it improved the percentage of variance accounted for by the model and was independently and strongly associated with SWA (β=-0.75, $p=0.005$). In order to maintain statistical power, BMI was dropped from the last model, which examined the simultaneous contribution of AHI and total testosterone levels. In this model, the negative association of total testosterone (β=-0.56, $p=0.02$) and race (β=-0.26, $p<0.0001$) with NREM SWA persisted, whereas AHI (β=-0.11, $p=0.08$) and age (β=-0.02, $p=0.08$) only weakly predicted SWA.

In conclusion, in overweight and obese men under 50 years old, NREM SWA is negatively predicted by total circulating testosterone levels, in addition to race, age and AHI. These results have potential clinical implications as exogenous testosterone is being increasingly prescribed to middle-aged men.

Presentation Date: Monday, June 23
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

MON-0154: Growth hormone treatment for children may exacerbate feelings of depression

Short, otherwise healthy children who are treated with growth hormone (GH) may become taller, but they may also become more depressed and withdrawn over time, compared to children the same age and height who are not treated with GH, a new study finds. The results will be presented in a poster Monday, June 23 at ICE/ENDO 2014, the joint meeting of the International Society of Endocrinology and the Endocrine Society in Chicago.

"Daily injections, frequent clinic visits and repeated discussions about height might exacerbate instead of improve psychosocial concerns in children with idiopathic short stature (ISS) who are otherwise healthy, and give them no cognitive improvements," said lead author Emily C. Walvoord, MD, associate professor of clinical pediatrics at the Indiana University School of Medicine in Indianapolis.

While the link between using GH to increase height and improved psychological adaptation is being debated, early data suggest that the subtle cognitive problems seen in adults with growth hormone deficiency (GHD) might also occur in children with GHD and might improve with treatment.

Dr. Walvoord and her colleagues evaluated the cognitive and behavioral status of children with GHD and ISS after they received either GH therapy or observation alone, and their preliminary results presented here challenge the idea that improvements in height also result in improvements in psychological functioning. Their findings also raise the concern that GH treatment of these otherwise healthy children might even worsen their emotional symptoms.

In their study, 41 children with GHD and ISS between the ages of 6 and 16 years of age, 11 on average, took a series of tests that examined their cognitive functioning, and their parents completed questionnaires that assessed their child's emotional and behavioral functioning.

The children were then assigned to either the group that was treated with growth hormone or the untreated control group, and after 9 to 12 months, the children in both groups were retested.

So far, 41 children have had initial testing and 28 have had follow up testing. Among these children, the researchers have found no differences in cognitive functioning between GHD and the ISS children from their first test to their retest.

However, compared with the untreated ISS children, whose depression and withdrawal according to their parents' questionnaire responses have lessened over that period, the depression and withdrawal symptoms in the treated GHD and ISS children have worsened.

"This novel study of the cognitive and emotional effects of GH therapy in children with GHD and ISS compared to untreated short children raises concerns that, despite improvements in height, these children may not achieve psychosocial benefits," Dr. Walvoord said.

Eli Lilly and Company funded the study.

# # #

MON-0154: Psychological Changes in Children Following Growth Hormone Treatment

Emily Walvoord. *Indiana University School of Medicine*

Emily C Walvoord, MD, Pediatrics, Section of Endocrinology, Indiana University School of Medicine, Indianapolis, IN, Ariana H Greene, Pediatrics, Indiana University School of Medicine, Indianapolis, IN, Jennifer M Katzenstein, PhD, Neurology, Indiana University School of Medicine, Indianapolis, IN and Brenna C McDonald, PsyD, Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN

Substantial debate persists around the idea that using growth hormone (GH) to increase height will correlate with improved psychological adaptation. Additionally, early data suggest that the subtle cognitive problems seen in adults with GH deficiency (GHD) might also occur in children with GHD and improve with treatment. We evaluated cognitive and behavioral status following GH therapy or observation alone in children with GHD and idiopathic short stature (ISS).

Methods: Subjects were 6-16 years old with heights ≤ 3rd percentile for age. GHD was defined as a peak GH level <5 ng/mL. All subjects underwent a targeted neuropsychological test battery at baseline and following 9-12 months of GH therapy. Parents completed the Behavior Assessment System for Children-Second Edition (BASC-2) to assess emotional and behavioral functioning. ANOVA, dependent and independent samples t-tests and chi square tests were used for between and within-group comparisons, as appropriate to the results outlined (SPSS20). GHD subjects treated with GH (N=19) were compared to ISS subjects who were treated (ISS-T, N=9) and not-treated with GH (ISS-NT, N=13). At baseline, GHD subjects were compared to all ISS subjects. Longitudinal analyses compared all three groups (GHD, ISS-T, ISS-NT), and treated vs. untreated subjects (GHD+ISS-T vs. ISS-NT).

Results: Forty-one children (25 boys) had baseline testing; 28 children have completed follow-up testing (19 boys). Mean age at baseline was 11.0 years, (SD = 2.4), with no between-group differences in age, sex, or height SDS. GH-treated children showed a significant improvement in height SDS over time. No clinically meaningful cognitive differences were found between GHD and ISS children at baseline, or between any groups longitudinally. At baseline, no differences were apparent between GHD and ISS subjects on BASC-2 scales. However, longitudinal analyses showed that treated subjects were rated to have worsening depression and withdrawal symptoms over time, while untreated subjects showed lessening of symptoms. Both groups were rated as less anxious at follow-up. When the three groups were compared separately, improvement in anxiety scores was seen for all groups. Both treated groups showed worsening of withdrawal symptoms over time, while the ISS-NT group showed less withdrawal symptoms.

Discussion: GHD and ISS children treated with GH had worsening emotional symptoms over time when compared to children of the same age and height who were not treated with GH. Medical intervention with daily injections, frequent clinic visits and repeated discussions about height might exacerbate instead of improve psychosocial concerns for short, otherwise healthy children. This novel longitudinal study of both the cognitive and emotional effects of GH therapy in GHD and ISS children raises concerns that psychosocial benefits may not be achieved despite improvements in height.

Presentation Date: Monday, June 23
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

MON-0194: Bone loss persists two years after weight loss surgery

A new study shows that for at least two years after bariatric surgery, patients continue to lose bone, even after their weight stabilizes. The results—in patients undergoing gastric bypass, the most common type of weight loss surgery—will be presented Monday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

"The long-term consequences of this substantial bone loss are unclear, but it might put them at increased risk of fracture, or breaking a bone," said Elaine Yu, MD, MSc, the study's principal investigator and an endocrinologist at Massachusetts General Hospital, Boston. "Therefore, bone health may need to be monitored in patients undergoing bariatric surgery."

Yu's team previously reported that patients who have gastric bypass lose bone mineral density—an indicator of bone fragility—within the first year after the surgery. Because the rate of bone loss was high, the researchers continued to monitor them in this study, funded by the National Institutes of Health.

The standard imaging method for bone mineral density, dual-energy x-ray absorptiometry, or DXA, can sometimes give inaccurate results in obese individuals. Therefore, the researchers also measured bone density using a method that is often more accurate, a three-dimensional type of computed tomography (CT) called quantitative CT. They compared bone density at the lower spine and the hip in 50 very obese adults: 30 who had bariatric surgery and 20 who lost weight through nonsurgical ways but were similar to surgical patients in baseline age, sex and body mass index. After surgery, nearly all patients received calcium and high-dose vitamin D supplementation, Yu said.

Two years later, bone density was 5 to 7 percent lower at the spine and 7 to 10 percent lower at the hip in the surgical group compared with the nonsurgical control group, as shown by both DXA and quantitative CT, Yu reported. In addition, she said the surgical patients had substantial and persistent increases in markers of bone resorption, the process of breaking down old bone that may play a role in bone loss.

The bone loss in the surgical patients, Yu said, occurred despite the fact that they were not losing any more weight in the 2nd year after surgery and had stable blood levels of calcium and vitamin D. "Therefore, the cause of the bone loss is probably not related to weight loss itself," she said.

Fortunately, none of the gastric bypass patients has required osteoporosis treatment, according to Yu. However, she said, "The question is, when is the bone loss going to stop? Over time this could be a problem in terms of fracture."

Although obese adults tend to have higher bone densities than nonobese people, they reportedly have similar rates of fracture at the wrist and a higher fracture rate at the lower leg. Yu recommended that bariatric surgery patients who have risk factors for osteoporosis receive bone density tests.

Despite the possible risk to bone health after gastric bypass, Yu said, "This surgery is the most effective treatment for severe obesity and offers phenomenal health benefits."

The researchers plan to investigate possible causes of the bone loss observed. Yu speculated that major changes in gastrointestinal and fat hormones, which occur almost immediately after bariatric surgery, could affect bone.

# # #

MON-0194: Bariatric Surgery Patients Have Continued Bone Loss for 2 Years after Surgery Despite Weight Stabilization

Elaine Yu. *Massachusetts General Hospital*

Elaine W. Yu, MD, MSc[1], Mary L Bouxsein, PhD[1], Elizabeth Monis, BA[1], Adam Roy, BA[1], W. Scott Butsch, MD, MSc[2] and Joel Stephen Finkelstein, MD, MS[1], (1) Endocrine Unit, Massachusetts General Hospital, Boston, MA, (2) Weight Center, GI Unit, Massachusetts General Hospital, Boston, MA

Background: Substantial bone loss occurs after bariatric surgery, but the full extent and duration are unknown. We previously reported bone loss in the 1st year after Roux-en-Y gastric bypass (RYGB) as measured by quantitative computed tomography (QCT) and dual-energy x-ray absorptiometry (DXA).(1) Because skeletal changes had not yet reached a steady state, we continued to monitor subjects for a 2ndyear.

Methods: We evaluated 50 adults with severe obesity in a prospective 2-year study (30 undergoing RYGB surgery + 20 non-surgical controls). Bone mineral density (BMD) was measured at the lumbar spine and proximal femur by QCT and DXA at 0, 1 and 2 years. We measured serum calcium, 25(OH)-vit D, parathyroid hormone (PTH), amino-terminal propeptide of type I collagen (P1NP) and C-telopeptide (CTX) levels at these same time points. P-values are for comparisons between RYGB and controls.

Results: Baseline age, weight, and BMD were similar in the RYGB and control groups. Weight loss plateaued 1 year after RYGB but remained greater than controls at 2 years (-30 ± 2% vs. -5 ± 4%, $p<0.0001$). BMD did not change in the controls over 2 years. In previous analyses, spine BMD from baseline to year 1 after RYGB declined 3.4% by QCT and 3.3% by DXA. In current analyses, spine BMD from year 1 to 2 after RYGB continued to fall by QCT (-1.7 ± 0.8%, $p=0.045$) and DXA (-2.2 ± 0.6%, $p=0.009$). We also previously noted the 1st year after RYGB led to an insignificant loss in QCT total hip BMD and decline of 8.9% in DXA total hip BMD. We now report that total hip BMD from year 1 to 2 after RYGB declined markedly by QCT (-4.2 ± 1.0%, $p=0.001$), with a similar trend observed by DXA (-2.6% ± 0.7%, $p=0.061$). QCT trabecular total hip BMD also declined in the 2nd year after RYGB (-3.4 ± 1.1%, $p=0.018$). In total, by 2 years after RYGB, spine BMD was 5 and 7% lower and total hip BMD was 7 and 10% lower than controls by QCT and DXA, respectively ($p<0.001$ for all). Bone turnover markers peaked at 6 months after surgery but remained markedly elevated above baseline 2 years after RYGB (CTX 149 ± 20%, P1NP 65 ± 13%, $p<0.001$ for both). Calcium and 25(OH)-vit D were unchanged in both groups. There were small increases in PTH in the 2ndyear after RYGB that were not different from controls. Changes in BMD, assessed by QCT or DXA, were not associated with weight loss or changes in PTH.

Conclusions: Bone loss persists in the 2nd year after RYGB, as evidenced by declining QCT and DXA BMD at the spine and hip, and persistently elevated bone turnover markers. Bone loss occurs despite stability of weight, calcium and PTH during the 2nd year after RYGB. The mechanisms underlying bone loss after RYGB remain to be elucidated.

Presentation Date: Monday, June 23
Presentation Time: 1-3:00 p.m.
Location: Expo Hall

Presentations

Tuesday, June 24, 2014

ENDOCRINE SOCIETY

OR48-2: Quick, easy, inexpensive cortisol testing should soon be available on all smartphones

Researchers have developed a device that uses any smartphone to measure the cortisol concentration in saliva. The device will be presented Tuesday, June 24, at ICE/ENDO 2014, the joint meeting of the International Society of Endocrinology and the Endocrine Society in Chicago.

"We have developed a method for measuring cortisol in saliva using a smartphone and a disposable test strip. This innovation enables anyone with a smartphone to measure their salivary cortisol level quickly, accurately, and affordably," said lead study author Joel R. L. Ehrenkranz, MD, director of diabetes and endocrinology of the Department of Medicine at Intermountain Healthcare in Murray, Utah.

Cortisol is a hormone made by the adrenal glands that's essential for the body's response to stress, and measuring cortisol can help diagnose adrenal diseases and monitor stress levels. Current testing for salivary cortisol levels involves collecting a saliva sample and sending it to a clinical lab for analysis.

"A lab charges about $25 to $50 for a quantitative salivary cortisol test and has a turnaround time of days to a week. This test, taken in a medical office or at home, will cost less than $5 and take less than 10 minutes," Dr. Ehrenkranz said. "The device is a reader that includes a case, a light pipe, and a lens and costs about a dollar to make. There is no battery power and it's unbreakable, passive and reusable."

Doctors worldwide can use the smartphone test to help them diagnose adrenal insufficiency and hypercortisolism and monitor physiologic variations in cortisol concentration; and individuals can monitor their own cortisol levels whenever they like.

The software is "operating-system-agnostic," he explained, meaning that the device can be used on all platforms, including iOS, Android, Windows, and BlackBerry, and it has a universal form factor that works with all smartphones.

The person being tested inserts a straw-like saliva collector under the tongue. The collector wicks the saliva by capillary action to an immunoassay strip housed in a cassette and the cassette is inserted into the reader. The smartphone uses its camera and flash to take a picture of the saliva-coated strip and an algorithm converts the image's pixel density to a cortisol value.

Marketing this test as a cortisol assay would make it a class 2 medical device, Dr. Ehrenkranz explained. He and his research team are now collecting clinical data for the FDA submission, and hope to attain approval in 2015.

This study was privately funded.

# # #

OR48-2: Point-of-Care Salivary Cortisol Immunoassay Using a Smartphone

Joel Ehrenkranz. *Intermountain Healthcare*

Joel R L Ehrenkranz, MD, Dept. of Medicine, Intermountain Healthcare, Murray, UT, Randall Polson, Ph.D., Dept. of Physics and Astronomy, University of Utah, Salt Lake City, UT and Theodure Espiritu, School of Architecture and Planning, University of Utah, Salt Lake City, UT

Measuring salivary cortisol by laboratory immunoassay or mass spectroscopy requires instrumentation and technical personnel and is unable to deliver timely results. We have developed a smartphone-based quantitative salivary cortisol immunoassay that provides results in 5 minutes and can be performed at the point of care.

Disposable cortisol immunoassay strips consisted of nitrocellulose membranes to which cortisol-BSA conjugate (test line) and goat anti-mouse IgG antibody (control line) were attached. A glass fiber element containing colloidal gold labeled murine anti-cortisol antibodies and a saliva collection pad were inserted at the proximal end of the nitrocellulose membrane and a wicking sump placed at the membrane's distal end. These tests, read by a spectrophotometer, were able to detect cortisol in PBS in 0.1 mcg/ml increments between 0.1-30 mcg/ml. Samples of artificial saliva containing cortisol in concentrations between 0.012 and 3.0 mcg/dl were deposited on the strip's saliva collection pad. The assay strip was then inserted into a reader that aligned a collimating lens and light diffuser with a smartphone's camera and flash and the strip was imaged 5 minutes after specimen addition. Because gold nanoparticles with a diameter of 70-100 nm have a plasmon surface resonance peak around 600 nm, a smartphone flash can illuminate and camera image the color generated by colloidal gold labeled anti-cortisol antibodies. A smartphone image analysis app identified the control and test lines on the assay strip and quantified the pixel density of the green color channel of the test line image. An algorithm derived by fitting an exponential curve to a graph of observed versus reference salivary cortisol values converted the pixel density of the green color channel of the test line image to a cortisol value. The R value of this curve was 0.996 for salivary cortisol in the range of 0.012-3.0 mcg/dl.

This smartphone-based immunochromatographic quantitative salivary cortisol technology can measure cortisol with a detection limit and dynamic range sufficient to diagnose adrenal insufficiency, hypercortisolism, and monitor physiologic variations in cortisol concentration. Measuring salivary cortisol at the point-of-care in 5 minutes using an inexpensive immunochromatographic assay, reader, and smartphone may obviate the need to presumptively treat patients for adrenal insufficiency and makes cortisol assays available to regions of the world which currently lack access to this diagnostic test.

Presentation Date: Tuesday, June 24
Presentation Time: 9:30-11:00 a.m.
Location: Room W470

OR51-4: New transdermal SARM drug for muscle-wasting without negatively impacting liver function and HDL levels

Muscle wasting that occurs as a result of cancer negatively impacts the well-being and recovery prospects of millions of patients, particularly the rapidly-growing elderly populations in Western societies. Drugs called selective androgen receptor modulators (SARMs) offer hope for these patients, and a new SARM for transdermal administration is promising excellent efficacy without harming liver function and HDL levels. Results and conclusions will be presented Tuesday at the joint meeting of the International Society of Endocrinology and the Endocrine Society: ICE/ENDO 2014 in Chicago.

SARMs are able to stimulate the growth of muscle with effects similar to those seen by use of traditional anabolic steroids but without the undesirable side effects of those established muscle-building drugs, in particular, the adverse effects on prostate health that can occur from their use.

There are several SARMs currently in human clinical trials, with successful animal studies having already been conducted with these compounds. However, all of these drug candidates have been developed for oral administration. Because of potential adverse effects on liver function and on depression of HDL levels (the "good" cholesterol), the orally-administered drugs suffer limitations to their full therapeutic potential to grow muscle and strengthen bone.

A similar situation for oral delivery exists in the administration of male hormone therapy. Here, the adverse impacts on liver health and HDL levels can be overcome by the use of skin patches or gel that release a drug directly into the body through the skin, i.e., transdermal application. Recognizing the similarity, scientists at the pharmaceutical company Novartis therefore developed a SARM specifically for transdermal administration. In describing their drug candidate, AUSRM-057, Senior Investigator Dr. Hans-Joerg Keller of the Novartis Institutes for BioMedical Research, Basel, Switzerland said, "AUSRM-057 is the first SARM with excellent skin permeation properties which may exploit the full therapeutic potential of SARMs."

In this preclinical drug discovery project, Novartis researchers used classical techniques of drug development, first identifying a compound with good potential as a muscle-building drug in cell culture. Skin permeation tests, also conducted in cell culture, predicted that their drug candidate would show good penetration of skin in transdermal delivery. The drug did work as predicted in building muscle when tested in rats and did not show the masculinizing effects of SARMs that can harm the prostate gland. The authors are optimistic regarding the prospects of this drug candidate to become the first in its class to utilize not only the advantages SARMs have displayed for muscle growth without negative impacts on prostate health, but, by avoiding the digestive system, to also avoid adverse effects on liver function and HDL levels.

The research to develop AUSRM-057 was funded entirely by Novartis, although the project has been stopped for now due to what the authors termed "portfolio prioritization".

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OR51-4: Ausrm-057 a Novel Selective Androgen Receptor Modulator (SARM) for Transdermal Administration

Hansjoerg Keller. *Novartis Institutes for BioMedical Research*

Authors: Thomas Ullrich[1], Sanjita Sasmal[2], Chetan Pandit[2], Sven Weiler[1], Sujatha Rajagopalan[2], Dhanya Shashikumar[2], Shekar Chelur[2], Chikwendu Ibebunjo[3], Paulo G Santos[4], Bharat Lagu[3], Mark Perrone[3], Mark Bock[3] and Hansjoerg Keller[1], (1) Novartis Institutes for BioMedical Research (NIBR), Basel, Switzerland, (2) Aurigene Discovery Technologies Ltd., Bangalore, India, (3) NIBR, Cambridge, MA, (4) Novartis Pharma, Basel, Switzerland

Drug discovery efforts have identified selective androgen receptor modulators (SARMs) that, similar to steroidal androgens, exert strong anabolic effects on skeletal muscle and bone, but with minimal androgenic effects in tissues such as prostate. To date, only oral SARMs have been developed whose efficacies in the clinic are critically limited by adverse events including induction of liver enzymes such as alanine aminotransferase (ALT) and lowering of high density lipoprotein (HDL). To overcome these drawbacks we developed SARMs for transdermal administration as mostly used in testosterone (T) therapy. A 3-alkoxy-pyrrolo[1,2-b]pyrazoline compound termed AUSRM-057 was identified that bound to human androgen receptor (AR) with a Ki of 0.45 nM with great selectivity over other nuclear receptors such as progesterone, glucocorticoid and estrogen receptor alpha. AUSRM-057 potently activated AR in a C2C12 muscle cell reporter gene assay with an EC50 of 0.5 nM and induced hypertrophy in human myotubes with a comparable EC50 of 0.2 nM. AUSRM-057 showed good aqueous solubility of 1.3 g/L at pH7.4 and in silico predictions as well as a skin parallel artificial membrane permeability assay (PAMPA) indicated good skin penetration. Indeed, when measuring human skin permeation in vitro an excellent flux of 2.8 µg/cm2/h was determined without any permeation enhancers. In a short single subcutaneous (s.c.) injection 24h biomarker in vivo assay in castrated rats, it reduced more potently the atrophy marker gene MAFbx and induced more potently the hypertrophy marker gene IGF1 in levator ani (LA) muscle than T. Furthermore, it only partially induced the prostate marker gene probasin compared to T. In a two week Hershberger assay using castrated rats AUSRM-057 showed dose-dependent effects fully restoring LA weight at 0.3 mg/kg/day s.c. with high selectivity over prostate stimulation. Next, AUSRM-057 was assessed in young growing pubertal rats where two week treatment selectively stimulated LA over prostate at 1 mg/kg/day. Finally, AUSRM-057 restored LA muscle weight and significantly increased triceps brachii and quadriceps muscle weights compared to vehicle treated animals without significant stimulation of prostate weight in voluntary running adult castrated mice following 2 week s.c. administration of 1 mg/kg/day. In conclusion, we have identified a novel highly potent SARM AUSRM-057 that exerts selective anabolic action on skeletal muscle tissues over androgenic prostate tissues and easily penetrates human skin. Thus, AUSRM-057 holds promise as a novel transdermal SARM for the treatment of various muscle wasting disorders avoiding important limitations of oral SARMs.

Presentation Date: Tuesday, June 24
Presentation Time: 9:30 a.m.-11:00 a.m.
Location: Room W475

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