Short Call Oral Abstracts
Saturday, September 26, 2009

Short Call Oral 1
Thyroid Hormone Metabolism and Regulation Saturday Oral 3:30 PM

ADDITIVE EFFECTS OF THE THYROID HORMONE ANALOG EPROTIROME ON DYSLIPIDEMIA IN EZETIMIBE-TREATED PATIENTS

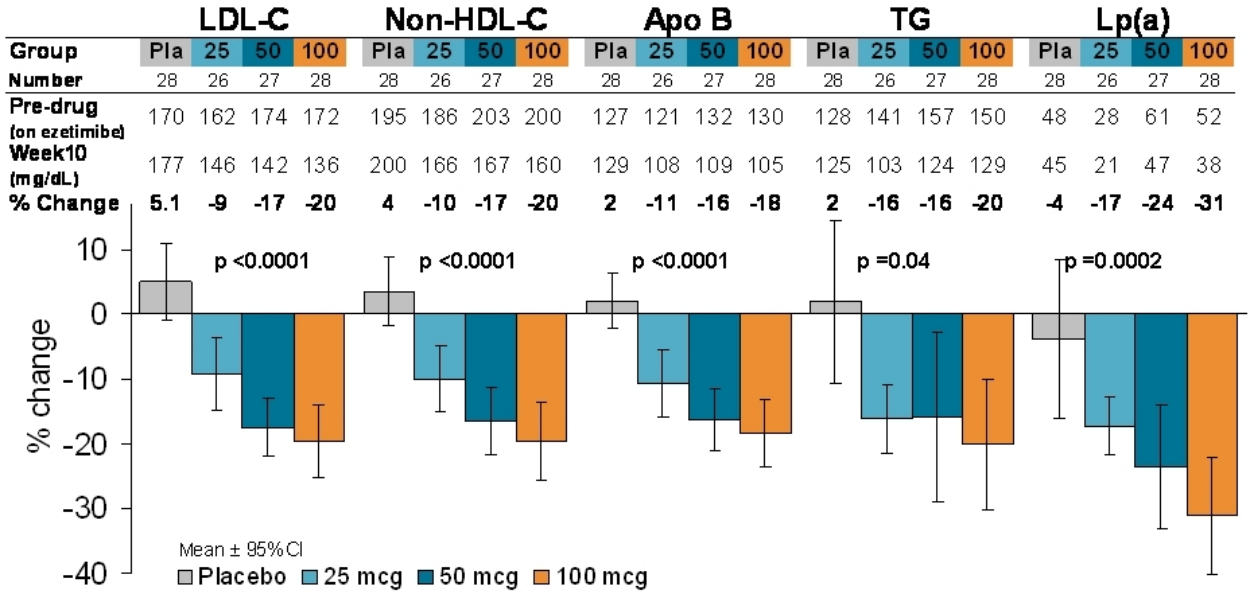
P.W. Ladenson[1], B. Angelin[2], E. Ridgway[3], I. Klein[4], J.D. Baxter[5], A.G. Olsson[6], B. Carlsson[7], J.D. Kristensen[7]
[1]Division of Endocrinology and Metabolism, Department of Medicine, The Johns Hopkins University School of Medicine, Baltimore, MD; [2]Department of Endocrinology, Metabolism & Diabetes, Karolinska Institute, Stockholm, Sweden; [3]Division of Endocrinology, Metabolism, and Diabetes, University of Colorado School of Medicine, Aurora, CO; [4]Department of Medicine, North Shore University Hospital and the Feinstein Institute for Medical Research, Manhasset, NY; [5]Center for Diabetes Research, Methodist Hospital Research Institute, Houston, TX; [6]Faculty of Health Sciences, Linköping University and Stockholm Heart Center, Stockholm, Sweden; [7]Preclinical & Clinical Development, Karo Bio, Stockholm, Sweden

Dyslipidemia, a well established risk factor for atherosclerotic cardiovascular disease risk, is incompletely reversed by currently available lipid lowering therapies in many patients. Because thyroid hormone lowers serum LDL cholesterol and has other positive actions on lipoprotein metabolism, thyromimetic drugs hold promise as lipid lowering agents if adverse effects can be avoided. Eprotirome is a hepatic-selective thyroid agonist previously shown to alter lipoprotein levels favorably at doses without apparent thyrotoxic effects. This report describes effects of eprotirome in patients already treated with the cholesterol absorption inhibitor ezetimibe.

A 10-week randomized, placebo-controlled, double-blind, multi-center trial assessed safety and efficacy of the thyromimetic compound eprotirome (KB2115) in lowering the serum LDL cholesterol in hypercholesterolemic patients already taking ezetimibe. Study patients (n=89) were randomized to receive eprotirome 25, 50, or 100 mcg per day or placebo while continuing ezetimibe. Secondary outcomes were changes in serum apolipoprotein B, triglyceride, and lipoprotein(a) concentrations. Safety monitoring included assessments of potential adverse thyromimetic effects on the heart (HR, BP, ECG), bone (S-CTX, bone-specific ALP, S-P1NP), and pituitary (TSH, T3, T4 and TBG).

Addition of eprotirome to ezetimibe treatment for 10 weeks resulted in placebo-adjusted reductions in serum LDL-cholesterol concentrations of -14%, -22%, and -25% with daily 25 mcg, 50 mcg and 100 mcg eprotirome, respectively. Similar reductions were seen in serum levels of apolipoprotein B (-13%, -18%, and -20%), triglycerides (-18%, -18%, and -22%), and lipoprotein(a) (-13%, -20%, and -27%). Eprotirome therapy was well tolerated without adverse cardiac or bone effects. No change in serum TSH or free triiodothyronine was detected although the thyroxine level was modestly decreased.

In this 10-week trial, the thyroid hormone analog eprotirome effectively lowered atherogenic lipoprotein fractions in ezetimibe-treated patients without evidence of adverse thyromimetic effects on the heart or other tissues. (ClinicalTrials.gov number, NCT NCT00677248)



Short Call Oral 2

Thyroid Cancer Saturday Oral 3:45 PM

ABSENCE OF AKT1 DELAYS THYROID CANCER DEVELOPMENT AND INHIBITS HISTOLOGIC DEDIFFERENTIATION IN THE TRβ$^{PV/PV}$ MOUSE

M. Saji[1], K. Narahara[1], S.K. McCarty[1], K. La Perle[2], Y. Koh[1], V. Vasko[3], C. Lu[4], S. Cheng[4], M.D. Ringel[1]

[1]Internal Medicine, The Ohio State University and Arthur G. James Comprehensive Cancer Center, Columbus, OH; [2]Veterinary Biosciences, The Ohio State University, Columbus, OH; [3]Pediatrics, Uniformed Services University of the Health Sciences, Bethesda, MD; [4]National Cancer Institute, National Institutes of Health, Bethesda, MD

Akt activation is common in progressive thyroid cancer. The three distinct Akt isoforms have unique and tissue-specific functions, for example, Akt1 promotes motility in thyroid cancer cells and fibroblasts but inhibits motility and metastases in breast cancer. Isoform-specific in vivo data are lacking in thyroid cancer and have potential therapeutic relevance. We previously reported Akt overactivity, co-localization of pAKT and Akt1, and PI3K-dependent cell motility in thyroid cancer tissue from homozygous thyroid hormone receptor β$^{PV/PV}$ knock-in (PV) mice which develop thyroid hormone resistance and progressive thyroid cancer.

To determine directly the role of Akt1 in PV mice, Akt1$^{-/-}$ and PV mice were crossed and the development, progression, and histology of thyroid cancer in TRβ$^{PV/PV}$/Akt1$^{-/-}$ (PV/Akt1-) and TRβ$^{PV/PV}$/Akt1$^{+/+}$ (PV/Akt1+) mice were compared. Mice were sacrificed at 3, 6, 9, and 12 months; necropsy was performed; serum TSH was measured beginning at 6 months.

Thyroid hyperplasia occurred in both groups; the thyroid size:body weight ratio was >2-fold greater in the PV/Akt1+ mice beginning at 6 months ($p<0.05$). In PV/Akt1+ mice, thyroid cancer was identified in 0%, 67%, 86%, and 100% at 3, 6, 9, and 12 months, respectively; 50% had pulmonary micrometastases at 12 months. By contrast, 0%, 0%, 17% and 86% of PV/Akt1- mice had thyroid cancer in at 3, 6, 9, and 12 months, respectively, and none had pulmonary metastases. The time to develop thyroid cancer was delayed in the PV/Akt1- mice ($p=0.021$) and only PV/Akt1+ mouse thyroid cancers displayed histological dedifferentiation. TSH levels in both groups were elevated vs. wild type and Akt1$^{-/-}$ controls ($p<0.01$), but levels were similar

between PV/Akt+ and PV/Akt- mice (p=NS) as was the degree of pituitary hyperplasia, suggesting the results are not caused by differences in TSH levels.
We have demonstrated for the first time that thyroid cancer development and histological dedifferentiation in PV mice are dependent on Akt1. These Akt1 effects occur with similarly high TSH levels and in the presence of Akt2 and 3. When combined with data from clinical samples, these results suggest a critical tumor promoting role for Akt1 in thyroid cancer.

Short Call Oral 3
Thyroid Hormone Action Saturday Oral 4:00 PM

EFFECTS OF LIVER-TARGETED PHOSPHONATE-CONTAINING THYROID RECEPTOR AGONISTS (TRA) ON LIPIDS AND THE THYROID HORMONE AXIS (THA)

B. Gumbiner, B. Ito, D. Bullough, A. Longcore, T. Stern, H. Foyt, M. Erion
Metabasis Therapeutics, Inc., La Jolla, CA

MB07811 and MB10866 are oral prodrugs of phosphonate-containing TRAs that are designed to target the liver. Both exhibit lipid lowering and an improved therapeutic index in pre-clinical models compared to non-liver targeted TRAs.
To assess the clinical safety and efficacy of MB07811, a randomized, double-blind, placebo (PBO)-controlled, rising multiple dose 14-day Phase 1 study was conducted in 56 subjects with fasting LDL≥100 mg/dL. The 2nd generation TRA, MB10866, was subsequently evaluated and compared to MB07811 in beagles.
In the 14-day study, baseline fasting LDL, triglycerides (TGs) and Lp(a) were ~126, 118 and 24 mg/dL, respectively. Dose-related decreases in each parameter were observed after 2 weeks of treatment (see Table); HDL was unchanged. Heart rate, rhythm, QTc (per ECG and Holter monitoring), plasma BNP and cardiac troponin I were unchanged in MB07811 and PBO subjects. Dose-related increases up to ~1.5xULN in liver transaminases occurred and returned to normal by 7 days post-treatment. Dose-related decreases in all thyroid function tests (TFTs) were observed (see Table), with partial reversal of TSH suppression during treatment, and with other TFTs reverting towards normal by 7 days post-treatment. Efforts to discover a TRA that retained the cardiac-sparing and lipid lowering properties of MB07811, but with reduced effects on the THA, led to the identification of MB10866. A comparison of MB10866 and MB07811 in beagles (0-10 mg/kg x 14 d) showed comparable dose-related decreases in total cholesterol of up to ~40-50% from baseline. However, while MB07811 resulted in dose-related reductions in plasma T4 levels, MB10866 had no effect on T4 at doses of 0.1-3 mg/kg, and only modestly decreased T4 at 10 mg/kg.
Treatment with MB07811 significantly reduces LDL, TGs and Lp(a) without apparent effects on HDL and cardiac parameters in man. MB07811 was safe and well-tolerated in this trial but was associated with THA perturbations. MB10866 has the potential for lipid lowering comparable to MB07811 but with reduced effects on the THA.

Fasting Plasma Lipids [% Δ baseline; LSM (SE)] and Key TFTs [mean (SD)]

Dose (mg)	LDL	TGs	Lp(a)	TSH (mU/L)	TT4 (ug/dL)	FT3 (pg/mL)
PBO	-15.5 (3.6)	26.2 (9.4)	-5.6 (18.2)	2.7 (2.1)	7.9 (1.5)	4.0 (0.5)
0.25	-5.1 (5.5)	16.6 (14.8)	-12.0 (11.7)	1.8 (0.8)	7.2 (0.7)	4.4 (1.0)
1	-24.7 (5.6)	35.8 (14.3)	-23.6 (12.2)	2.0 (0.9)	5.1 (0.8)	3.9 (0.2)
2.5	-16.2 (5.5)	-10.4 (14.5)	-30.1 (10.8)	1.3 (0.6)	6.1 (0.9)	4.1 (0.8)
5	-30.7 (5.6)	-8.6 (14.6)	-34.7 (6.6)	1.3 (0.8)	4.7 (0.7)	3.4 (0.7)

10	-42.6 (6.0)	-34.9 (15.9)	-60.0 (6.1)	0.9 (0.3)	4.3 (1.3)	3.0 (0.7)
20	-56.7 (5.5)	-36.0 (14.4)	-59.8 (9.7)	0.6 (0.7)	3.1 (0.7)	3.8 (0.8)
40	-52.1 (6.0)	-52.5 (16.1)	N/A	0.04 (0.03)	2.1 (0.6)	2.2 (0.3)

Short Call Oral 4

Autoimmunity Saturday Oral 4:15 PM

ACTIVATING AUTOANTIBODIES TO THE BETA1-ADRENERGIC AND M2 MUSCARINIC RECEPTORS FACILITATE ATRIAL FIBRILLATION IN PATIENTS WITH GRAVES' HYPERTHYROIDISM

X. Yu[1], S. Stavrakis[1], E.S. Patterson[1], R. Lazzara[1], M. Cunningham[2], S.A. Morshed[3], T.F. Davies[3], D.C. Kem[1]
[1]Internal Medicine, OUHSC, Heart Rhythm Inst and the OKC Veterans Affairs Medical Center, Oklahoma City, OK; [2]Department of Microbiology and Immunology, OUHSC, Oklahoma City, OK; [3]Thyroid Research Unit, Mount Sinai School of Medicine, James J. Peters Veterans Affairs Medical Center, New York, NY

Atrial Fibrillation (AF) may complicate hyperthyroidism especially in older subjects. Activating autoantibodies to β1-adrenergic (AAβ1AR) and M2 muscarinic receptors (AAM2R) have been described in some patients with atrial fibrillation. We hypothesized and are the first to identify the co-presence of such autoantibodies in autoimmune Graves' hyperthyroidism. We have studied their biological activity and potential role in facilitating atrial fibrillation in Graves' hyperthyroidism.

IgG purified from 38 patients with active or recently treated Graves' hyperthyroidism with AF (n=17) or sinus rhythm (n=21) and 10 healthy controls was tested for its biological effect on isolated canine Purkinje fiber contractility with and without atropine and nadolol to block muscarinic and βAR activity respectively. IgG electrophysiologic effects were studied using intracellular recordings from isolated canine pulmonary veins. Potential cross-reactivity of AAβ1AR and AAM2R with stimulating thyrotropin receptor (TSHR) antibodies was evaluated before and after adsorption to CHO cells expressing human TSHRs using flow cytometry and enzyme-linked immunosorbent assays.

The frequency of AAβ1AR and/or AAM2R differed significantly between patients with AF and sinus rhythm (AAβ1AR = 94% vs. 38%, $p<0.001$; AAM2R = 88% vs. 19%, $p<0.001$; and AAβ1AR+AAM2R = 82% vs. 10%, $p<0.001$). The co-presence of AAβ1AR and AAM2R was the strongest predictor of AF (odds ratio 33.61, 95% CI 1.17 - 964.11, $p=0.04$). IgG from autoantibody-positive patients induced hyperpolarization, decreased action potential duration, enhanced early afterdepolarization formation and facilitated triggered firing in pulmonary veins by local autonomic nerve stimulation. Immunoadsorption studies demonstrated that AAβ1AR and AAM2R were distinct from TSHR autoantibodies.

AAβ1AR and/or AAM2R were invariably present in patients with Graves' hyperthyroidism and atrial fibrillation. Their bio-activity would predictably facilitate development and/or maintenance of atrial fibrillation. Their presence may diminish the likelihood for spontaneous conversion of AF to a normal rhythm despite successful therapy for the hyperthyroidism.

Short Call Oral 5

Thyroid Cancer Saturday Oral 4:30 PM

INDUCTION OF ROBUST THYROID GENE EXPRESSION AND RADIOIODIDE UPTAKE IN THYROID CANCER CELLS BY TARGETING MAJOR SIGNALING PATHWAYS

P. Hou, E. Bojdani, M. Xing
Endocrinology and Metabolism, The Johns Hopkins University School of Medicine, Baltimore, MD

Radioiodine ablation treatment is commonly used for thyroid cancer, but a major challenge is the often loss of radioiodine avidity of the cancer. The underlying molecular mechanism is the aberrant silencing of iodide-handling genes, including sodium/iodide symporter (NIS), thyroid-stimulating hormone (TSH) receptor (TSHR), thyroperoxidase (TPO), thyroglobulin (Tg), and various transcription factors. There is currently no solution to this therapeutic obstacle in thyroid cancer.

We tested the therapeutic potential of targeting the aberrantly activated MAP kinase and PI3K/Akt/mTOR pathways and histone deacetylase to restore radioiodine avidity of thyroid cancer cells using the MEK inhibitor RDEA119, the mTOR inhibitor temsirolimus, the Akt inhibitor perifosine and the histone deacetylase inhibitor SAHA in a large panel of authenticated thyroid cancer cell lines. Quantitative real-time PCR, immunoblotting, immunofluorescent microscopy, radioiodide uptake assay, and a variety of standard molecular biology tools were used to analyze the expression and function of thyroid genes.

We were able to robustly restore the expression of a large number of thyroid genes, particularly NIS, TSHR, TPO and Tg, by treating cells with these inhibitors, with a particularly synergistic effect seen when in combination with SAHA. Robust expression of NIS in cell membrane, which plays the most important role in iodide uptake in thyroid cells, was confirmed by immunofluorescent microscopy. Effective radioiodide uptake by cells was correspondingly induced by suppressing the signaling pathways. Both thyroid gene expression and radioiodide uptake induced by targeting these pathways were robustly enhanced by thyroid-stimulating hormone.

Thyroid iodide-handling gene expression and radioiodine avidity can be robustly restored in various thyroid cancer cells by targeting multiple singling pathways. Given the established clinical applicability of the inhibitors tested here, it is attractive to propose clinical trials to further test their therapeutic potential in restoring radioiodine avidity of thyroid cancer for effective ablation treatment.

Short Call Poster 6
Autoimmunity Thursday Poster
FURTHER EVIDENCE OF A ROLE FOR X CHROMOSOME INACTIVATION CONTRIBUTING TO THE FEMALE PREPONDERANCE OF GRAVES' DISEASE
M.J. Simmonds, P.R. Newby, L.E. Jackson, C. Hargreaves, J.A. Franklyn, S.C. Gough
School of Clinical and Experimental Medicine, University of Birmingham, Edgbaston, Birmingham, United Kingdom

Graves' disease (GD) affects >2% of the population and occurs more frequently in females than in males, with females more likely to have a mother, as opposed to a father with GD. Several hypothesis have been put forward to explain the female preponderance including increased immune responsiveness, sex hormones, sex chromosome susceptibility loci and, more recently, skewed X inactivation (XCI). XCI occurs in females causing one of their X chromosomes to be randomly inactivated enabling dosage compensation with males who only have one copy of the X chromosome. Although each X chromosome should be inactivated with a parent of origin ratio of 50:50, skewed XCI can occur whereby >80% of a specific copy of the female X chromosome is inactivated (or extreme skewing with >90% inactivation). Several small GD datasets have detected association of skewed XCI with GD, suggesting a possible role for skewed XCI in GD onset in females.
The aim of this study was to use a microsatellite marker within the androgen receptor to determine levels of XCI in a large UK Caucasian GD cohort consisting of 417 female GD patients and 385 female control subjects.
Skewed XCI was found to be strongly associated with GD ($P=2.14x10^{-4}$, OR=2.17 [95% CI=1.43-3.30]), although no evidence of extreme skewing was detected (P=0.236). Correlation of clinical manifestations of GD with XCI levels showed goiter to be reduced in frequency in skewed GD females (81.7%) compared to non-skewed GD female patients (92.1%) (P=0.013, OR=0.38 [95% CI=0.18-0.83]).
Previous data, including our own, has shown goiter presence to be an independent predictor of disease severity and a surrogate marker for autoimmune activity. Further work is now required to elucidate the mechanism by which XCI skewing is triggering autoimmunity, parent of origin effect and to what extent XCI skewing explains the increased female preponderance in GD.

Short Call Poster 7
Autoimmunity Thursday Poster
PRIMARY HYPERPARATHYROIDISM AND SARCOIDOSIS IN A PATIENT WITH RECURRENT HYPERCALCEMIA
L. Chaychi, S. Chaidarun, A. Golding
Endocrinology and Metabolism, Dartmouth-Hitchcock Medical Center, Lebanon, NH

Hypercalcemia due to concurrent primary hyperparathyroidism and sarcoidosis.
Clinical history, physical examination, laboratory values, imaging and pathologic findings of a man who was on prednisone therapy for Erythema Nodosum (EN) and developed severe hypercalcemia, one month after parathyroidectomy.
A 67 y/o man presented to the endocrine clinic with serum calcium of 11.1 mg/dl and intact parathyroid hormone (iPTH) of 166 pg/ml(10-69).Serum creatinine was 1.9 mg/dL. 25-hydroxy-vitamin D (25 vit D)was 15pg/ml (>30) and 1,25 dihydroxy-vitamin (1,25 vit D)was 44 pg/dl (16-72). He was treated with 20 mg of

prednisone daily for one month for EN.Chest CT did not reveal any lymph node enlargement. A Tc 99m sestamibi scan demonstrated increased activity in the middle pole of the right thyroid lobe consistent with parathyroid adenoma. After parathyroidectomy, iPTH was 9.0 pg/ml and calcium was 9.0 mg/dl.Parathyroid adenoma was histologically confirmed.One month after surgery the patient was admitted with a calcium of 17 mg/dl and an undetectable iPTH and PTH-rP.The 25 vit D level was 16 pg/ml and 1,25 vit D level was 42 pg/dl. Prednisone was discontinued as his EN had resolved.Tc 99m sestamibi scan was obtained which revealed uptake in the right axilla, hilus, subcranial and bilateral cervical regions.ACE (Angiotensin Converting Enzyme) level was 70 (normal <60). A spiral chest CT and neck ultrasonography revealed mediastinal lymph nodes, bilateral axillary and cervical adenopathy.FNA biopsy of cervical lymph nodes demonstrated non-caseating granulomas and large giant cells consistent with sarcoidosis. The patient was started on 40 mg of prednisone and within one week his calcium was 8.5-9 mg/dl and PTH was 20pg/ml.The 25 vit D was 22 pg/ml and 1,25 vit D was 30 pg/ml.
PTH acts directly on the kidney and bone also increases the synthesis of 1,25 vit D via enhanced 1-alpha hydroxylase expression in the kidney. Sarcoidosis increases the 1,25 vit D due to over expression of 1-alpha hydroxylase in the macrophages of the granulomatous tissues.The cervical adenopathy causing hypercalcemia with positive Tc-99 sestamibi after parathyroidectomy is unique to this case.

Short Call Poster 8

Thyroid Diseases Thursday Poster

INDIRECT REFERENCE INTERVALS ESTIMATED FROM HOSPITALIZED POPULATION FOR THYROTROPIN (TSH) AND FREE THYROXINE (FT4)

T. Inal[1], M. Serteser[2], A. Coskun[3], A. Ozpinar[4], I. Unsal[5]
[1]Biochemistry, Acibadem University, School of Medicine, Istanbul, Turkey; [2]Biochemistry, Acibadem University, School of Medicine, Istanbul, Turkey; [3]Biochemistry, Acibadem University, School of Medicine, Istanbul, Turkey; [4]Biochemistry, Acibadem University, School of Medicine, Istanbul, Turkey; [5]Biochemistry, Acibadem University, School of Medicine, Istanbul, Turkey

It is very laborious and expensive for clinical laboratories to produce their own reference values according to the instructions of IFCC for hundreds of analytes available in routine practice. This obstacle forces the majority of laboratories to use reference intervals either reported in the literature or recommended by the manufacturers. An alternative to this unwanted situation is to establish indirect reference intervals from patients' results obtained during routine laboratory work.
All the results of TSH and free T4 that have been stored in our laboratory information system between the years of 2004 to 2008 are included to study. Patients below the age of twenty were excluded from the study. Only the first result for each patient was included. After the logarithmic transformation of the raw data the outliers were excluded. Non-parametric reference intervals were estimated statistically after the visual observation of the distribution by stem-and-leaf plots and histograms. Standard normal deviation test is performed to reveal the statistical significance of the difference between the sub-groups.
There were no statistically significant difference between serum TSH and free T4 concentrations of male and female subjects. Since no difference was found between the years, combined reference intervals were calculated. Indirect reference values with 90 % confidence intervals were 0,43-3,93 mU/L (90% CI was 0,425-0,435 and 3,887-3,974 for lower and upper limits, respectively) for TSH, and 11,98-21,33 pmol/l (90% CI was 11,669-12,299 for the lower, and 20,777-21,898 for the upper reference limits) for free T4. Our upper reference limits for TSH were slightly lower than the transferred and manufacturer's values (both are 4.2 mU/L), and we found narrower reference intervals for free T4 when compared with transferred reference interval.
Using laboratory patient data values is a relatively easy and cheap method of establishing laboratory

specific reference values if the skewness and kurtosis of the distribution are not too large. It is also convenient for age and sex specific reference intervals in children in whom collecting sufficient numbers of samples is relatively difficult than the adult group.

Reference and confidence intervals for TSH and free T4 calculated from patient data (indirect method), transferred data according to IFCC recommendations that we use currently in our laboratory (direct method), and manufacturer's recommended reference intervals.

Analyte		indirect method	indirect method	indirect method	direct method	Manufacturer's recommendations
	n	RI	Lrl CI (90%)	Url CI (90%)	RI	
TSH Male Female	55318 11779 43539	0,43-3,93 0,43-3,77 0,43-4,04	0,425-0,435 0,424-0,445 0,429-0,439	3,887-3,974 3,636-3,806 3,987-4,083	0,4 - 4,2	0,27 - 4,2
Ft4 male female	62713 13395 49318	11,98-21,33 12,66-22,23 11,91-20,98	11,669-12,299 11,940-13,423 11,573-12,257	20,777-21,898 20,966-23,571 20,386-21,591	10,3 - 23,2	12 - 22

Short Call Poster 9

Thyroid Diseases Thursday Poster

THE COST-EFFECTIVENESS OF ROUTINE WHITE BLOOD CELL COUNT MONITORING IN ANTITHYROID DRUG-INDUCED AGRANULOCYTOSIS

R. Dadu[1], M. Shimshi[2]

[1]Internal Medicine, Yale New Haven Health/Bridgeport Hospital, Bridgeport, CT; [2]Endocrinology/Internal Medicine, Yale New Haven Health/Bridgeport Hospital, Bridgeport, CT

Antithyroid drug (ATD)-induced agranulocytosis is uncommon (median prevalence 0.4%), but one of the most serious side effects of ATDs. In a recent systematic review of agranulocytosis induced by non-chemotherapy drugs, the median duration of treatment before the onset of acute agranulocytosis was 36 days for Propylthiouracil and 42 days for Methimazole. Tajiri et al suggested that routine white blood cell(WBC) count monitoring could be the most effective way of predicting and detecting agranulocytosis caused by ATDs. Some patients remain at least transiently asymptomatic, supporting a role for the routine close monitoring of WBC count.

The MEDLINE database was searched for articles published from 1980 to date. We used the frequency of WBC count monitoring as described in previous studies(every 2 weeks),but we considered the duration of monitoring 40 day. The Medicare reimbursement cost for CBC(approximately 10$),for inpatient neutropenia(approximately 8,000$) as well as anagranulocytosis with complications(approximately 20,000$) was provided by a billing specialist.

The cost of routine WBC count monitoring is approximately 30,000$/1,000 patients. Four out of these patients will require hospitalization for agranulocytosis with complications which will cost approximately 80,000$. If they were detected in the stage of mild to moderate neutropenia using routine WBC count monitoring, the overall cost of hospitalization would have been less(32.000$), but they could have been "rescued" from developing a life-threatening condition.

Our observation suggests that routine WBC count monitoring every 2 weeks for the first 40 days after initiation of treatment associated with early discontinuation of ATDs as well as immediate therapy with G-CSF can prevent a life-threatening infection and is cost-effective. Screening could be cost-effective at a

disease prevalence as low as 0.2%, using weekly monitoring and for a longer period of time. The cost-effectiveness, the frequency and the duration as well as the clinical importance of routine WBC count monitoring in detecting ATD-induced agranulocytosis needs to be further assessed in future prospective studies in the present Health-Care System with the current reimbursement cost.

Short Call Poster 10
Thyroid Diseases Thursday Poster
ROBOTIC THYROID SURGERY - FEASIBILITY IN NORTH AMERICAN PATIENTS
R. Kuppersmith[1], M. Seybt[2], D. Terris[2], C. Holsinger[3]
[1]Texas Institute for Thyroid and Parathyroid Surgery, College Station, TX; [2]Deparment of Otolaryngology, Medical College of Georgia, August, GA; [3]Department of Head and Neck Surgery, MD Anderson Cancer Center, Houston, TX

Robot-assisted endoscopic thyroid surgery has been safely performed on a large series of patients in Korea. This approach offers the benefits of robotic surgery including improved visualization and improved instrument dexterity while eliminating cervical incisions. Until very recently, this procedure has not been performed on patients in North America. The daVinci Surgical System has recently received FDA approval for use in thyroid surgery.
Cadaver dissection and surgical procedures on live patients.
Twelve robot-assisted endoscopic thyroid surgeries were performed on fresh cadavers. Based on this experience and observation of surgery in Korea, the procedure was applied clinically, and a small series of 10 cases were successfully completed at three different sites. There were no recurrent laryngeal nerve injuries or instances of hypocalcemia.
Robot-assisted endoscopic thyroid surgery is technically feasible in North American patients. The variability in body habitus and lack of standard instrumentation for maintaining the surgical working space currently present challenges. While this technique is promising, there is a significant learning curve, indications still need to be clearly defined, and the cost-to-benefit ratio needs to be evaluated.

Short Call Poster 11
Thyroid Diseases Thursday Poster
THYROTOXICOSIS DUE TO MRSA ACUTE SUPPURATIVE THYRIODITIS
K.D. Brown[1], S.M. Mona[1,2]
[1]Internal Medicine/Endocrine, University of Maryland School of Medicine, Baltimore, MD; [2]Hypertension and Endocrine Unit, Veterans Administration Medical Center, Baltimore, MD

The thyroid is relatively resistant to infection due to its high iodine content, robust capsule, ample blood supply, and efficient lymphatic drainage. Acute suppurative thyroiditis is a rare cause of thyroid illness which typically presents with clinical euthyroidism, fever and neck pain. Differentiating between acute suppurative thyroiditis and other painful thyroid illnesses may be difficult. Here we present an unusual case of thyrotoxicosis from methicillin-resistant Staphylococcus aureus (MRSA) acute suppurative thyroiditis in a patient with intravenous drug abuse (IVDA).
A 48 year old man with hypertension, chronic renal failure, and active IVDA is admitted to a regional hospital with dysphagia and muscle pain. He later develops high fever, and is found to have MRSA positive blood cultures with abcesses in the thyroid and multiple muscle sites. He is started on appropriate antibiotics, but on Day #7 he has new onset rapid atrial fibrillation, with TSH 0.45, and elevated free T4 >7, and free T3 >33, and is started on methimazole, prednisone and propanolol.

He is transferred to our hospital on Day #12 after being intubated for hypoxia after a seizure, and most of his medications were subsequently held. Abcesses were confirmed in bilateral thyroid lobes, and Endocrine team was consulted for persistent thyrotoxicosis. We recommended restarting beta-blocker, but not anti-thyroid agents or corticosteroids, and patient underwent successful surgical drainage. He gradually improved, and ultrasound on Day #22 showed complete clearance of thyroid abcesses, and by Day #33 his free thyroid hormone levels returned to normal.
To our knowledge this is a unique case of a rare disorder, with atypical causative organism, unusual manner of infection, and frank thyrotoxicosis due to massive release of preformed hormone. This case is also uncommon due to the lack of predisposing thyroid disease or anatomical abnormalities. A high index of suspicion is key for a successful outcome in this potentially fatal illness. Definitive therapy requires complete drainage of thyroid abscess and appropriate anti-microbial therapy, with no role for anti-thyroid medications. This approach was ultimately curative in our patient.

Summary of Thyroid Labs

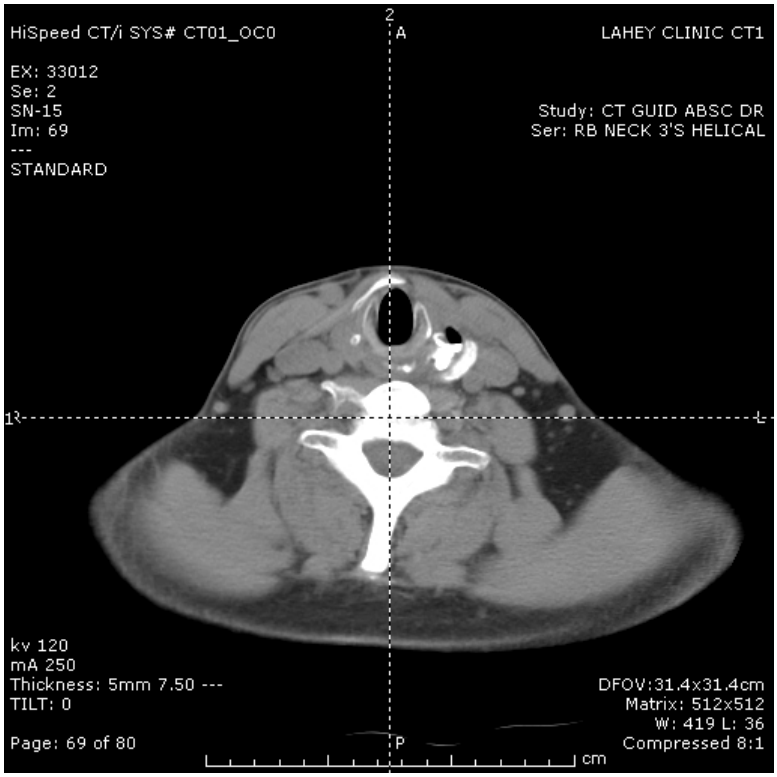
Admission Day	TSH (mcIU/mL)	Free T4 (ng/dL)	Free T3 (pg/mL)	Tg (0.5-55 ng/mL)	TPO ab (0-40 IU/mL)	Tg ab (0-34 IU/mL)
[a] # 7	0.45	>7.7	>32.55			
a # 12	0.18	>7.7	>32.55			
[b] # 14	0.65	4.9	9.0	47.7	<20	28
[b] # 22	0.20	3.5	7.7			
b # 33	0.14	1.3	3.6			

[a] Regional Hospital: reference range TSH (0.27-4.20), free T4 (0.9-1.7), free T3 (2.1-4.4) [b] University of Maryland Medical Center: reference range TSH (0.34-5.60), free T4 (0.6-1.9), free T3 (2.3-4.2) TSH, thyroid stiumulating hormone; T4, thyroxine; T3, Triiodothyronine; Tg, Thyroglobulin; TPO ab, anti-thyroperoxidase antibiody; Tg ab, anti-Thyroglobulin antibody

Short Call Poster 12
Thyroid Diseases Thursday Poster
A CASE OF SUPPURATIVE THYROIDITIS AND HASHIMOTO'S THYROIDITIS
T.D. Hislop-Chestnut, G. Cushing
Lahey Clinic, Burlington, MA

Suppurative thyroiditis is a rare disease of the thyroid gland usually caused by an infection. It is most commonly seen on the left side and it is frequently due to the presence of a fistulous communication between the piriform sinus and the perithyroid space. Patients usually present with normal thyroid function or rarely with transient thyrotoxicosis.
A 43-year old male was admitted to the hospital with neck pain, dysphagia and odynophagia. He had an upper respiratory tract infection for 10 days prior to his admission. He complained of chills. His past medical history was significant for obesity and a right inguinal hernia repair.
On examination he had a temperature of 99.4 degrees Fahrenheit and appeared moderately ill. Oropharynx was benign and there was trace erythema on the left side of the anterior neck with moderate tenderness on palpation. The left lobe of the thyroid was approximately one and a half times normal and tender, and the right was not palpable. Fiber-optic laryngoscopy was performed which revealed a left piriform sinus that was erythematous. A CT scan of the neck demonstrated a rim-enhancing tubular abscess extending

from the apex of the left piriform sinus to involve the entire left lobe of the thyroid, consistent with an infected left fourth branchial cyst. His admission labs were significant for an elevated TSH and positive thyroid peroxidase antibodies consistent with a diagnosis of Hashimoto's thyroiditis. He was started on ampicillin/sulbactam with improvement in his symptoms. Two days after admission a CT guided aspiration was attempted but unsuccessful due to the lesion spontaneously decompressing. Omnipaque was injected into the lesion and further imaging demonstrated contrast within the esophagus. Thyroid ultrasound was significant for bilateral nodules. The patient completed a 2 week course of antibiotics.
This case is unusual in that a middle aged male presented concomitantly with suppurative thyroiditis and Hashimoto's thyroiditis.



Post contrast image displaying contrast in the esophagus

Short Call Poster 13
Thyroid Imaging Thursday Poster
USING ULTRASONIC PRE-OPERATIVE THYROID LOBE VOLUME TO DETERMINE INCISION LENGTH FOR MINIMALLY INVASIVE THYROID SURGERY
A.P. Daly[1], J.L. Miller[2], D. Rosen[1], D. Cognetti[1], E. Pribitkin[1]
[1]Otolaryngology & Head and Neck Surgery, Thomas Jefferson University, Philadelphia, PA; [2]Division of Endocrinology, Thomas Jefferson University, Philadelphia, PA

Thyroid lobe volume determined by pre-operative ultrasound may enable surgeons to select candidates for a minimally invasive approach.
This study is a retrospective chart review of 72 patients that underwent minimally invasive non-endoscopic thyroid (MINET) surgery from January 2007 until the present. For this study ultrasonic pre-operative thyroid lobe volumes and operative incision lengths were collected and analyzed.

Groups consisted of thyroid lobectomy or total thyroidectomy. The median lobe volume was determined for thyroid lobectomy group and this value was used to further subdivide these patients. The first group (<28.32 mL) included 20 patients and the second group (>28.32 mL) also included 20 patients. The incision length for the first group ranged from 2.0 cm to 3.8 cm with a mean of 3.3 cm ± 0.65 cm. The incision length for the second group ranged from 3.5 cm to 5.0 cm with a mean of 3.7 cm ± 0.71 cm. This difference in incision size is significant (t test $p < 0.01$). The median total thyroid volume was also used to subdivide the total thyroidectomy patients. The first group (<49.24 mL) included 16 patients and the second group (>49.24 mL) included 15 patients. The incision length for the first group ranged from 2.5 cm to 4.0 cm with a mean of 3.4 cm ± 0.53 cm. The incision length for the second group ranged from 3.6 cm to 6.0 cm with a mean of 5.1 cm ± 0.99 cm. Again, the incision length correlated with the thyroid lobe volume on ultrasound (t test $p < 0.00001$).
Our study suggests that pre-operative ultrasonic thyroid lobe volume can be used to determine appropriate incision length for minimally invasive thyroid surgery.

Short Call Poster 14
Thyroid Imaging Thursday Poster

EVALUATION OF THYROID STRUCTURE AND BLOOD FLOW WITH DOPPLER ULTRASONOGRAPHY IN EUTHYROID SCHOOL-AGED CHILDREN IN CORRELATION WITH THEIR ANTHROPOMETRIC AND METABOLIC CHARACTERISTIC

P. Czarniak[1], A. Lewczuk[4], P. Szczesniak[1], Z. Esden-Tempska[4], E. Krol[2], T. Zdrojewski[3], K. Sworczak[4]
[1]Pediatric Nephrology, Medical University of Gdansk, Gdansk, Poland; [2]Nephrology, Transplantology and Internal Diseases, Medical University of Gdansk, Gdansk, Poland; [3]Hypertension and Diabetology, Medical University of Gdansk, Gdansk, Poland; [4]Endocrinology and Internal Diseases, Medical University of Gdansk, Gdansk, Poland

Ultrasonography (US) is a non-invasive, repetitive and cheap modality for the study of the thyroid gland. The objective of this study was to determine the relationship between thyroid structure and blood flow and chosen metabolic and anthropometric parameters in euthyroid school-aged children of Sopot, Poland.
452 healthy middle school children in Sopot, Poland have been given a full US thyroid examination including the assessment of thyroid volume, echogenicity, echostructure and blood flow using Doppler-US. At the same time some metabolic and anthropometric parameters have been determined (BUN, GFR, glucose, lipidogram, cystatin C, CRP, TSH, height, weight, BMI, waist, arm and hip circumference, thickness of skinfolds: biceps, triceps, sub-scapular, suprailliac, FFM, TBW, RR). This cohort has been divided into two groups- group A: children with at least one alteration found on thyroid US, B: children with no US alterations. The two groups were compared for differences in the metabolic and anthropometric parameters listed above.
86% of examined children showed no US alterations(group B). The most common alteration found in group A was altered echogenicity- 8.35%, increased thyroid blood flow- 6.19%, altered echostructure- 5.49% and increased thyroid volume- 5.87%. Children from group A had statistically higher levels of TSH then those from group B and the dispersion of TSH values increased with the number of US alterations found. Children from group B were statistically higher then those from group A and had smaller values of their triceps and subscapular skinfolds measurements. Children from group A had statistically smaller FFM and TBW then those from group B.
Euthyroid children with altered thyroid US differ from those without any US alterations in TSH levels, FFM, TBW, height and skinfold measurements. Further studies are needed to elucidate the mechanisms that undermine these observed differences.

Short Call Poster 15
Thyroid Imaging Thursday Poster

CLINICAL SIGNIFICANCE AND PATTERNS OF FOLLOW UP OF THYROID INCIDENTALOMAS FOUND ON PET SCANS IN CLEVELAND CLINIC

M. Skugor, R.M. Tedja, S.M. Srinivas, M. Reddy
Endocrinology, Cleveland Clinic, Cleveland, OH

Thyroid incidentalomas are occasionally reported after PET scans are done for another disease. They are defined as incidental radiologic finding of thyroid nodules. Clinical significance of these incidentalomas is not well understood resulting in minimal subsequent work up, if not, none at all. Available literature suggests the incidence of thyroid FDG accumulation ranges from 1.1 to 2.4%. About 14.7 to 71% of these underwent fine needle aspiration in different series. Of those, 28.6 to 50% were found to be malignant. The goal of our study was to determine the incidence of thyroid incidentalomas on PET scans in the Cleveland Clinic and to analyze the patterns of follow-up. We reviewed all PET scans performed over the period of two years (2007-2008).
There were 4,348 scans. Among those, we found 198 (4.5%) total instances of FDG accumulation in thyroid gland. Of those, 118 (2.7%) were diffuse uptake in the gland and 79 (1.8%) were focal uptake. The 13 patients (11.0%) with diffuse uptake were subsequently evaluated by ultrasound and no further intervention was deemed necessary. They were considered clinically insignificant. The 28 of 79 patients (35.4%) with focal uptake were evaluated after detection. Ultrasound examination of the gland was done in 13 patients (16.5%) and no further intervention was needed. Fine needle aspiration was done in 15 patients (19%). Of 15 patients who underwent the aspiration, 5 patients (33.3%) were found to have thyroid carcinoma and were treated appropriately. SUV ranged from 3.1 to 20.2. All nodules were greater than 1.0 cm in largest dimension by ultrasound.
Our data are in agreement with the literature and illustrate the need for better follow up of the incidental focal accumulation of FDG in the thyroid gland. We propose that every patient with focal uptake in the thyroid gland is examined by high resolution ultrasound and undergoes fine needle aspiration if the thyroid nodule is larger than 1.0 cm in largest dimension or exhibits features associated with higher risk of malignancy. If nodule is smaller, ultrasound followup in 6-12 months is advisable.

Short Call Poster 16 WITHDRAWN

Short Call Poster 17
Thyroid Nodules and Goiter Thursday Poster

HARMONIC SCALPEL VERSUS TRADITIONAL KNOT TYING - IS THERE A COST-SAVING OR TIME-SAVING ADVANTAGE?

W. Sacks, Y. Yang, G. Braunstein
Medicine, Cedars-Sinai Medical Center, Los Angeles, CA

Studies suggest that the harmonic scalpel (HS) is a safe alternative to conventional hand-tie or clip ligation for hemostasis for thyroid surgeries. Potential benefits include reduction in operative time, reduction in surgical complications, and improved hemostasis allowing for better views of surrounding structures. Disadvantages include increased cost and need for surgeon skill. Here we test the mean surgical times of using the HS and knot-tying method and assess whether specific variables influence the time of the surgery. Our objective is to evaluate whether use of HS in hemi and total thyroidectomies reduces surgical time such that it outweighs the additional cost. Variables such as thyroiditis, presence of thyroid cancer, lymph node dissection and specimen size are also assessed to determine whether they impact surgery time.
We retrospectively reviewed 99 patients undergoing hemi or total thyroidectomy from January 2007

through April 2009 by surgeons who used both HS and knot tying. Five surgeons performed a total of 46 hemithyroidectomies and 53 total thyroidectomies with average HS use ratio of 64% (34/53) and 72% (33/46), respectively. Data analyses used t-test, paired t-test and linear regression with significance level of 0.05.
When hemi- and total thyroidectomies were combined, there was no statistically significant difference in surgical time between use of HS and knot tying among each of the 5 surgeons who used both in their surgeries. Overall, use of HS versus knot tying did not reduce surgical time for hemithyroidectomy (132.5 vs 132.6 minutes; P=0.992) or for total thyroidectomy (187.5 vs 175.7 minutes; P=0.549). Multiple regression modeling for predicting surgical time for hemithyroidectomy demonstrates that size of gland (P=0.006) and experience of surgeon using HS (P=0.020) influenced surgical time. For total thyroidectomy, lymph node dissection (P=0.014) is the main variable predicting the mean surgical time.
There is no time saving advantage with use of HS, however there is additional cost incurred. Our results may differ from other studies due to low volume of total surgeries using HS.

Short Call Poster 18
Thyroid Hormone Action Thursday Poster

D3 EXPRESSION AND ACTIVATION ARE INCREASED IN ARDS WITH DECREASED TISSUE T3 IN HUMAN LUNGS

T.P. Rich[1,2], T.W. Bastian[4], T.J. Groppoli[1], M.A. Mulcahey[3], S.A. Huang[3], D.H. Ingbar[1], G.W. Anderson[4]
[1]Pulmonary, Critical Care, Allergy & Sleep Medicine, University of Minnesota-Mpls, Minneapolis, MN; [2]Pulmonary, Critical Care & Sleep Medicine, St Mary's Medical Center/Duluth Clinic, Duluth, MN; [3]Thyroid Program-Div of Endocrinology, Children's Hospital, Boston, MA; [4]College of Pharmacy, University of Minnesota-Duluth, Duluth, MN

The lung is a target tissue for thyroid hormone with multiple effects on type-II alveolar epithelial (AT2) cells including T3 stimulation of surfactant production, and Na+/K+ ATPase activity. T3 can be inactivated to T2 by iodothyronine deiodinase type-III (D3). D3 is at high concentrations in placenta, but otherwise at low levels in healthy adults. Inflammation may induce D3 expression, augmenting T3 inactivation and potentially causing a local hypothyroid state. In acute lung injury (acute respiratory distress syndrome, ARDS) there is alveolar inflammation and edema followed by AT2 cell proliferation along with damage to capillaries. Objective: Assess D3 expression and activity, and total tissue T3 levels in ARDS versus normal human lung tissue.
ARDS and normal human lung tissue were flash-frozen and fixed on autopsy within 12-hours of death. Careful histological screening confirmed ARDS tissue with characteristic diffuse alveolar damage versus controls with normal architecture. Assays performed on these tissues included: (1.) Immunocytochemistry to demonstrate and localize D3 protein expression; (2.) D3 enzymatic assays to measure lung deiodinase activity; and (3.) Radioimmunoassays to measure total lung T3 levels.
Lung tissue from patients with ARDS (N=3) compared normal lung tissue (N=3) demonstrated more intense and positive D3 staining in type II pneumocytes, capillary endothelium, and spindle cells in the interstitium. D3 enzyme activity was increased up to 10-fold in ARDS (N=4) versus normal lung tissue (N=1) (0.19-1.45 fmol/mg/min versus 0.15 fmol/mg/min). Total T3 levels were reduced by 63% in ARDS (N=6) lung tissue versus normal (N=3) lung tissue (0.56 ng/g versus 1.50 ng/g T3; p = 0.0005)
In ARDS, D3 is expressed in AT2 cells and with greater lung enzymatic activity in ARDS compared to normal human lung tissue. This is associated with decreased lung T3 concentrations, suggesting the possibility of a local hypothyroid state. We speculate that the D3-induced reduction of lung T3 levels may impede alveolar fluid clearance resulting in persistent hypoxia.

Short Call Poster 19

Thyroid Cancer Thursday Poster

VEGFR INHIBITORS IN PATIENTS WITH REFRACTORY ADVANCED THYROID CANCER

C.A. Perez[1], E. Vokes[2], M. Ratain[2], M. Maitland[2], K. Wroblewski[3], R. Williams[2], E.E. Cohen[2]

[1]Department of Medicine, Cleveland Clinic Florida, Weston, FL; [2]Department of Medicine, University of Chicago, Chicago, IL; [3]Department of Health Studies, University of Chicago, Chicago, IL

Iodine−refractory advanced thyroid carcinomas are highly vascular tumors with no standard treatment. Recent data suggest that thyroid cancers respond to antiangiogenic agents. We analyzed and compare the efficacy of 3 agents that target the VEGFR (sorafenib, sunitinib and axitinib) in patients with advanced thyroid cancer treated at our institution.

We analyzed the data of patients that participated in phase I and phase II trials treated with either sorafenib 400 mg BID, sunitinib 50 mg QD, or axitinib 5 mg BID. Response rate was evaluated per RECIST criteria and secondary end−points included overall survival (OS) and progression−free survival (PFS).

54 patients were included in the study, 34 male and 20 female, with a median age at study entry of 59 years. 11(20%) were treated with sorafenib, 26(48%) with sunitinib and 17(31%) with axitinib. Best response in 54 evaluable patients was PR 11%, SD 69%, PD 9%, and NE 11%, with no statistically significant difference in clinical benefit (CR+PR+SD) between the 3 treatment regimens (Fisher's exact test p−value = 0.305). Median survival was 35.0 months (90% CI, 18.4 to not reached) and median PFS was 11.0 months (90% CI, 9.6 to 13.8).There was no statistically significant difference in either OS or PFS across the three treatment regimens (log−rank test p=0.508 and p=0.125, respectively) or survival across histology groups (log−rank test p=0.414).

VEGFR inhibitors have significant anti−tumor activity in patients with advanced thyroid cancer and there appears to be similar efficacy in patients treated with sorafenib, sunitinib, or axitinib.

Short Call Poster Abstracts
Friday, September 25, 2009

Short Call Poster 20
Thyroid Cancer Friday Poster

P38α MAPK, MKP-2, AND MKP-3 MEDIATE THE CROSSTALK BETWEEN PI3K AND KRAS SIGNALING PATHWAYS IN A MOUSE MODEL OF FOLLICULAR THYROID CANCER

M. Dima, K. Baker, A. Di Cristofano
Developmental and Molecular Biology, Albert Einstein College of Medicine, Bronx, NY

Activating mutations of Ras family members and aberrant activation of the PI3K/AKT pathway are quite common in thyroid cancer originating from the follicular epithelium. We have recently shown in a relevant in vivo model that, contrary to many other cell types, Kras activation is not sufficient to induce oncogenic transformation of the thyroid follicular cells. However, PI3K activation is able to potently cooperate with Kras oncogenic mutation, thus inducing aggressive and metastatic thyroid follicular carcinomas.
To analyze in detail the molecular mechanisms responsible for this cooperation, we have used relevant genetically modified mouse strains as well as thyroid cancer cell lines derived from tumors developing in these models.
One key event mediated by PI3K in this cross-talk is the inhibition of Kras-initiated negative feedback signals, which shut down MAPK signaling and the induction of proliferation. PI3K signaling restores Kras-initiated MAPK activation, induction of proliferation, and oncogenic transformation. Our novel data reveal that activation of p38α MAPK, as well as up-regulation of MKP-2 and MKP-3 phosphatases, play a pivotal role in mediating the growth-suppressive negative feedback initiated by Kras oncogenic activation. Activation of p38α MAPK acts by inducing cell cycle arrest and the establishment of cellular senescence, while MKP-2 and -3 directly stunt ERK1/2 activation by direct dephosphorylation. Strikingly, we show that PI3K acts through Akt1 (but not Akt2) to potently suppress p38 phosphorylation and activation. Furthermore, PI3K activation results in the transcriptional repression of MKP-2 and MKP-3 promoters. PI3K activation contributes to unleashing to its full extent Kras oncogenic ability through at least two independent molecular mechanisms. These data further strengthen the rationale for the dual targeting of PI3K and MAPK pathways in thyroid cancer.

Short Call Poster 21
Thyroid Cancer Friday Poster

DEREGULATION OF MIRNA-200 FAMILY IN MEDULLARY THYROID CARCINOMA MODULATES THE EXPRESSION OF CADHERIN MEMBERS AND MEDIATES CELL-ADHESION AND TIGHT JUNCTIONS

L. Santarpia[1], G. Calin[2], G. Cote[1], L. Yei[1], A. El-naggar[3], R. Gagel[1]
[1]Endocrine Neoplasia, The University of Texas M.D. Anderson Cancer Center, Houston, TX; [2]Experimental Therapeutics, The University of Texas M.D. Anderson Cancer Center, Houston, TX; [3]Pathology, The University of Texas M.D. Anderson Cancer Center, Houston, TX

MicroRNAs (miRNAs) represent a class of small non-coding RNAs that control gene expression by targeting mRNAs and triggering either translation repression or RNA degradation. Objective of our study was to evaluate the involvement of miRNAs in human medullary thyroid carcinoma MTC), and to identify markers of metastatic cells and aggressive tumor behavior.
We investigated miRNA expression in matched primary and metastatic medullary thyroid carcinoma tumor samples using LNA microarrays. Abnormal expressed miRNAs were confirmed by quantitative real-time

reverse transcription-PCR (qRT-PCR) and by in situ hybridization on a large set of primary and metastatic MTC samples. Bioinformatic, gene ontology, gene enrichment targets, and pathway analysis were used with mRNA expression array data to reveal potential miRNA-targets. We used MTC TT and MZ cells as an in vitro model to validate the functions of identified miRNAs.
We found a signature of 16 miRNA significantly and differentially expressed between primary and metastatic tumors. Bioinformatics approaches revealed genes involved in cell-adhesion, tight junctions and integrins as the top most regulated. Accordingly, we found deregulation of miR-200 family regulating the expression of E-cadherin which inversely correlated with the expression of N-Cadherin and β-catenin. Interestingly, transfection of MTC cell lines with miR-200 showed concomitant reduction of cell-adhesion to culture surface and cell detachment, slightly enhancing cell migration but not their invasion capacity.
Our results are the first identifying a differential expression and a specific signature of miRNAs in metastatic MTC. We showed that the miR-200 family plays a role determining some of the metastatic cancer cell capabilities through a regulation of cadherin-members in MTC. This finding provides new insight into mechanisms of MTC progression. Combinations of miRNAs in the metastatic signature could be used to reveal new mechanisms of metastases and to detect and treat metastatic MTC cells preventing tumor recurrence and metastasis.

Short Call Poster 22
Thyroid Cancer Friday Poster

MADD, A NOVEL HUMAN PROTEIN, CAN CONFER RESISTANCE TO APOPTOSIS IN THYROID CANCER CELLS; AKT MEDIATED PHOSPHORYLATION REGULATES ITS PRO-SURVIVAL FUNCTION

B.S. Prabhakar[1], T. Pilli[1], S. Jayarama[1], M. Subramanian[1], L. Li[1], F. Pacini[2]
[1]Microbiology&Immunology, University of Illinois at Chicago, Chicago, IL; [2]Internal Medicine, Endocrinology&Metabolism and Biochemistry. Section of Endocrinology&Metabolism, University of Siena, Siena, Italy

The IG20 (Insulinoma-Glucagonoma), a novel human gene, is over-expressed in thyroid cancer tissues and cell lines relative to healthy controls, and it plays a critical pro-survival role by conferring resistance to TRAIL/TNFα-induced apoptosis. We have found that only the MADD splice variant of IG20 can confer protection. More recently, we discovered that MADD is a natural substrate for Akt phosphorylation and that only phosphorylated MADD (pMADD) can bind to death receptors 4 (DR4) and prevent TRAIL-induced FADD recruitment and caspase-8 activation.
We determined if MADD is required for, and its phosphorylation status can regulate, TRAIL-induced apoptosis of thyroid cancer cells.
Among the PTC-derived cell lines: BCPAP cells and TPC1 cells, and the FTC-derived WRO82-1 cells were highly sensitive to TRAIL-induced apoptosis even when TRAIL was used at a very low concentration. In contrast, PTC-derived cell line KTC1, the FTC-derived cell line FTC133 and the ATC-derived cell line FRO81-2 were only marginally susceptible even when a very high concentration of TRAIL was used. Furthermore, we found that MADD knockdown could not only render susceptible cells to become more sensitive, but also could convert resistant cells to become susceptible, to TRAIL-induced apoptosis. FRO81-2 cells were an exception in that they remained resistant and this was due to a lack of caspase-8 expression in these cells. Upon re-expression of caspase-8, these cells also became susceptible. Since pMADD can protect cells from undergoing TRAIL-induced apoptosis, we wondered whether TRAIL treatment could reduce Akt and MADD phosphorylation. Upon TRAIL treatment, in the TRAIL-sensitive BCPAP, TPC1 and WRO82-1 cells the levels of both pAKT and pMADD were significantly reduced, while they remained unchanged in the TRAIL-resistant KTC1, FTC133 and FRO81-2 cells.
The fact that in thyroid cancer activating mutation of Ras and PI3K, RET-PTC rearrangement and inactivating

mutations of PTEN can all lead to enhanced Akt activation and the pro-survival function of MADD is dependent upon its phosphorylation by Akt indicate that MADD is a critical pro-survival factor and could serve as a useful target for thyroid cancer therapy.

Short Call Poster 23
Thyroid Cancer Friday Poster

FOXP3+ REGULATORY T LYMPHOCYTES ARE ASSOCIATED WITH MORE AGGRESSIVE PAPILLARY THYROID CANCER

J.D. French[1], Z.J. Weber[2], D.L. Fretwell[1], M. Said[2], B.R. Haugen[1]
[1]Department of Medicine, Division of Endocrinology, Metabolism, and Diabetes, University of Colorado Denver, Aurora, CO; [2]School of Medicine, Pathology Department, University of Colorado Denver, Aurora, CO

10-30% of patients with papillary thyroid cancer develop recurrent disease and could benefit from innovative adjuvant therapies. Immune-based therapies are under investigation to treat many types of cancer. Although the immune response to PTC is poorly defined, previous studies suggest that lymphocytic infiltration of thyroid tumors correlates with decreased invasiveness, reduced recurrence, and improved survival.
Archived tumor samples from 100 PTC patients were analyzed for the presence of lymphocytes by H&E staining. Samples were grouped based on the absence of lymphocytes, the presence of lymphocytic thyroiditis, or the presence of tumor-associated lymphocytes in the absence of thyroiditis. In 10 patients with tumor-associated lymphocytes, CD20+, CD3+, CD8+, CD4+, and FoxP3+ subsets were identified and quantified using immunohistofluorescence. The presence of lymphocytes and the frequency of lymphocyte subsets were assessed for correlation with disease severity.
PTC patients with tumor-associated lymphocytes exhibited a higher incidence of lymph node (LN) metastasis and invasion compared to patients without lymphocytes or with concurrent thyroiditis. CD20+ B cells, CD4+ T cells, and CD8+ T cells were identified surrounding and within thyroid tumors. CD4+ T cells were prevalent, constituting 50-80% of the total tumor-associated T cells. FoxP3+ regulatory T cells (Tregs), a subset associated with poor prognosis in many cancers, accounted for 12-38% of the total CD4+ population. Treg frequency showed a strong correlation with LN metastases ($r = 0.90$, $p < 0.01$). All patients with high frequencies of Tregs (>20%) exhibited metastases in >50% of excised nodes. Furthermore, the CD8:Treg ratio correlated inversely with LN metastases ($r = -0.67$, $p = 0.039$), tumor size ($r = -0.82$, $p < 0.01$) and invasion ($r = -0.64$, $p = 0.049$).
Tumor-associated lymphocytes and lymphocytic thyroiditis should be distinguished when assessing significance in PTC. The frequency of lymphocyte subsets may provide a more accurate prediction of disease severity. Treg frequency and CD8:Treg ratio may be important predictive factors in PTC, and the suppressive effect Tregs must be considered in the design of future immune-based therapies.

Short Call Poster 24
Thyroid Cancer Friday Poster

MEDULLARY THYROID CARCINOMA CELL LINES CONTAIN A SELF-RENEWING CD133+ POPULATION THAT IS DEPENDENT ON RET ACTIVITY

W. Zhu, T. Hai, L. Ye, G. Cote
Endocrine Neoplasia, MD Anderson Cancer Center, Houston, TX

Medullary thyroid carcinoma (MTC) is a cancer of the parafollicular C cells commonly caused by an

inherited or acquired RET proto-oncogene (RET) mutation. Therapeutic resistance and recurrence of the disease imply the presence of cancer stem cells in MTC. In this study we sought to identify and characterize cancer stem cell-like cells in MTC.
The characterization of stem cell properties was performed using immunostaining, CD133 flow cytometry, sphere formation assay, rederivation assay, Western blotting, and quantitative RT-PCR of defined markers of neural stem cell progenitors. The role of RET activation was assessed through RNAi knockdown.
CD133 positivity was identified by immunostaining patient MTCs. Flow cytometry confirmed a subpopulation of CD133+ cells in two MTC cell lines. The CD133+ cells could be expanded by sphere formation assay, passaged multiple times, and expressed neural lineage markers TUBB3 and GFAP. The MZ-CRC-1 cell line, which harbors a M918T RET mutation, had greater CD133+ cell numbers and sphere forming ability than the TT cell line, which harbors the less active C634W mutation. Sphere formation was more dependent on RET activity, than EGF or FGF.
Our data support the existence of cancer stem-like cells in MTC, which exhibit the features of self-renewal and of multiple lineage differentiation that is dependent on RET receptor activity. These findings may provide new insights to develop more promising therapy for MTC.

Short Call Poster 25
Thyroid Cancer Friday Poster
PARVOVIRUS B19 INFECTION IN THYROID TUMORS
L.A. Adamson, M. Polcz, J.K. Grant, A.M. Zaytoun, J.A. Hobbs
Psychiatry, University of Florida, College of Medicine, Gainesville, FL

Thyroid cancer rates have been increasing over the past 30 years, with papillary thyroid carcinoma (PTC) accounting for the majority of those cases. Parvovirus B19 (B19) replication has recently been detected at a high rate in one study of PTC in comparison to normal and non-PTC tissues. To further substantiate B19 infection of thyroid tumors, we analyzed fetal, normal adult, and tumor tissue and thyroid cell lines for B19 nucleic acids and proteins.
Immunohistochemistry (IHC) was used to evaluate thyroid tissue for B19 using an antibody specific to B19 capsid proteins VP1/VP2. Nested PCR (nPCR) was utilized to study thyroid genomic DNA (gDNA). nPCR was also employed to study three cell lines used in thyroid cancer research for the presence of B19 DNA. The three cell lines analyzed include K1, a papillary carcinoma cell line; TT, a medullary thyroid carcinoma cell line; and SW579, a squamous cell carcinoma with some nuclear features of PTC.
IHC detected the presence of B19 capsid in 5 out of 6 adult tumor sections, with multiple areas of capsid protein staining found in each positive section. In contrast, only 1 area of staining was found out of 3 fetal tissue sections. In tumor samples, B19 capsid was most prevalent in the colloid space, but positive staining was also seen in follicular cells. nPCR analyses of gDNA isolated from frozen PTC tissues showed that 60% were positive for B19 DNA sequences compared to 0% in non-cancerous and fetal samples. nPCR analysis found the presence of B19 DNA in K1, TT, and SW579 DNA. Further studies in non-thyroid cell lines are underway in our laboratory.
B19 DNA and protein were detected in thyroid tissues, consistent with a previous report. Interestingly, there is increased NS1 compared to capsid DNA sequence detection in thyroid cell lines. B19 protein staining by IHC varied in size, possibly indicating replication within the thyroid tissue. The significance of B19 replication in thyroid cancer cells is unknown but could further indicate a possible role of B19 in thyroid tumorigenesis and/or that thyroid cancer cells provide an environment conducive to B19 viral replication.

Detection of B19 DNA Sequence in Thyroid Cancer Cell Lines

Cell Line	Cell Type	Cancer Type	NS1	VP1/VP2
SW579	Thyroid	Squamous Cell Carcinoma	2/2	3/6
TT	Thyroid	Medullary Carcinoma	4/4	4/8
K1	Thyroid	Papillary Carcinoma	3/3	1/3

Short Call Poster 26

Thyroid Cancer Friday Poster

PHASE 2 TRIAL OF PAZOPANIB IN RAPIDLY PROGRESSIVE, METASTATIC, MEDULLARY THYROID CANCER

K.C. Bible[1], R.C. Smallridge[1], W.J. Maples[1], J.R. Molina[1], M.E. Menefee[1], K. Sideras[1], V.J. Suman[1], J.K. Burton[1], C. Bieber[1], S. Ivy[2], C. Erlichman[1]

[1]Endocrine Malignancies Disease Oriented Group and Mayo Phase 2 Consortium, Mayo Clinic, Rochester, MN; [2]CTEP, National Cancer Institute, Bethesda, MD

Systemic therapies have historically proven ineffective in advanced medullary thyroid cancer (MTC). Expression of vascular endothelial growth factor (VEGF) is elevated in 50% of primary, and 75% of MTC metastases, suggesting involvement in MTC pathogenesis. Moreover, the high prevalence of activating mutations of the RET proto-oncogene suggests that RET may also represent an attractive therapeutic target in this cancer.

A three-outcome Phase II trial was conducted to assess the anti-tumor efficacy and toxicities of pazopanib (800 mg daily by mouth), an inhibitor of the tyrosine kinases VEGF, PDGF, C-KIT and RET, in patients with advanced, rapidly progressive, MTC. Up to 2 prior therapies were allowed, with measurable disease required. Design: at the 0.10 significance level, there would be a 90% chance of detecting a RECIST response rate of >20% given a true response rate of >5%; with the regimen considered promising if >4/28 confirmed responses observed. Interim analysis was scheduled after assessment of the first 14 enrolled patients, with at least 1 confirmed RECIST partial response (PR) required for continued accrual.

From February 2008 to May 2009, 14 patients (79% male, median: 51 years) were enrolled and evaluated, prompting scheduled interim analysis. Common sites of metastases were: nodes (65%), lungs (57%), and bone (57%). Measurement data are available for all patients, with the median number of cycles administered thus far 4 (range: 1-14+, total: 70). Overall, therapy has been well tolerated, but six patients (43%) had 1 to 2 dose reductions due to: grade 3 ALT/AST (1 pt.); grade 3 fatigue (2 pts.); grade 2 anxiety/depression (1 pt.); grade 2 diarrhea (1pt.); and radiation recall (1 pt.). Another patient discontinued treatment due to grade 4 depression. To date, there has been 1 confirmed RECIST partial response (7%); with 8 patients (57%) alive without disease progression, 2 patients (14%) alive with progressive disease, and 4 patients (29%) dead from disease.

Pazopanib appears to have both a favorable toxicity profile and sufficient clinical activity to prompt completion of trial enrollment. Supported by NCI CA15083 and CM62205.

Short Call Poster 27

Thyroid Cancer Friday Poster

MEASUREMENTS OF OUTCOME OF A PHASE II STUDY OF SORAFENIB FOR ADVANCED THYROID CANCER

M.S. Brose[1,2], A.B. Troxel[3,2], K. Puttaswamy[1], C. Ma[1], S.M. Keefe[5], A.A. Chalian[1,2], D.L. Fraker[7,2], S.J. Mandel[5,2], W.M. Lee[5,2], M.D. Feldman[6,2], L.A. Loevner[4,2], P.J. O'Dwyer[5,2]

[1]Otorhinolaryngology: Head and Neck Surgery, University of Pennsylvania, Philadelphia, PA; [2]Abramson Cancer Center, University of Pennsylvania, Philadelphia, PA; [3]Department of Biostatistics and Epidemiology,

University of Pennsylvania, Philadelphia, PA; [4]Radiology, University of Pennsylvania, Philadelphia, PA; [5]Medicine, University of Pennsylvania, Philadelphia, PA; [6]Pathology, University of Pennsylvania, Philadelphia, PA; [7]Surgery, University of Pennsylvania, Philadelphia, PA

From February 2006 to May 2009 we completed enrollment to an open-label phase II study of sorafenib in patients with metastatic, iodine-refractory thyroid carcinoma.
Patients were administered sorafenib 400 mg orally BID. Responses were monitored by PET and CT. Primary endpoints were response rate (RR) and progression free survival (PFS) by RECIST criteria and a secondary endpoint was overall survival (OS). BRAF and RAS mutation status was determined by DNA sequencing. Outcome data was evaluated using the Kaplan-Meier method and log-rank test. We have used quantitative immunohistochemistry (Q-IHC) to pERK, and pAKT and among others, on pre-treatment and on-treatment blocks to assess the biologic action of sorafenib on tumor cells.
We have completed enrollment of 55 patients; median time on study is 39 weeks and 27 pts (49%) are male. Of the 23 patients that are off study, 14 developed progressive disease, 7 withdrew for medical reasons that not due to progression, 5 withdrew due to toxicity and 2 withdrew due to non-compliance. Histological subtypes include 29 pts with papillary (PTC); 18 pts (33%) with follicular/Hürthle Cell (FTC) for a total of DTC of 47 (85%); 3 pts with medullary (5%), and 5 pts with poorly differentiated/anaplastic (9%). 53/55 patients are evaluable for response at this time. Median PFS was 63 weeks and overall survival was 140 weeks. PFS for patients with DTC was 84 wks and OS has not been reached. Genotyping of BRAF revealed a non-significant trend toward improved outcome. On-treatment tissue at progression demonstrates heterogeneity, with p-ERK and p-AKT suppressed in some areas, but highly expressed in others. Q-IHC shows a marked decrease in p-ERK staining in on-treatment samples. Response data on all 55 patients at 4 months post accrual of the last patient will be presented.
Sorafenib has significant clinical activity in patients with advanced thyroid cancer with an OS of 140 weeks and an overall PFS of 84 wks for patients with DTC and warrants further investigation in a dedicated Phase III study for DTC. Detailed Q-IHC data will allow us to better understand the mechanism of action of this agent.

Short Call Poster 28
Thyroid Cancer Friday Poster

CYSTIC LYMPH NODES IN THE LATERAL NECK ARE AN INDICATOR OF METASTATIC PAPILLARY THYROID CANCER

C. Landry[1], E.G. Grubbs[1], N.D. Perrier[1], N. Busaidy[2], B.S. Edeiken-Monroe[3]
[1]Surgical Oncology, The University of Texas MD Anderson Cancer Center, Houston, TX; [2]Endocrine Neoplasia and Hormonal Disorders, The University of Texas MD Anderson Cancer Center, Houston, TX; [3]Diagnostic Radiology, The University of Texas MD Anderson Cancer Center, Houston, TX

The presence of cystic lymph nodes found by ultrasound (US) in patients with papillary thyroid cancer (PTC) is concerning for metastasis. We sought to determine if radiographic findings portend to metastatic disease in patients with PTC, and if cystic lymph node metastasis can be recognized by preoperative US-guided fine needle aspiration (FNA).
We performed a retrospective review of patients with cystic lymph nodes in the lateral neck identified on preoperative US from 1996 to 2009. Factors examined included demographics, tumor stage, cytologic and final pathologic findings, serum thyroglobulin, and imaging characteristics including: location, size, presence of vascularity and calcifications. Time of cystic node identification in relationship to initial diagnosis was also recorded.
30 patients were found to have cystic lymph nodes of the lateral neck on cervical US. Among this group, 28

(93.3%) had a diagnosis of papillary thyroid cancer, 1 (3.3%) papillary serous carcinoma of the ovary, and 1 (3.3%) poorly differentiated thyroid cancer. Median age at the initial diagnosis of cancer was 41 years (range 16-64). 21 (70%) patients were women, and the median size of lymph node was 1.75 cm (range 0.7-4.8). 25(83%) patients had a solitary cystic lymph node, and the remainder had more than one cystic lymph node. Cystic lymph nodes were identified at the initial presentation in 11 (37%) patients, while 19 (63%) patients were found to have cystic lymph nodes after the initial operation. The cystic lymph nodes of 24 (80%) patients underwent FNA. The cytology was positive for metastatic disease in 18 out of 24 (75%) patients-all who had confirmation on final pathologic review. Final pathology after surgical resection of cystic lymph nodes with a negative FNA was consistent with metastatic disease in 4 out of 5 (80%) patients. In patients with papillary thyroid cancer, the presence of a cystic lymph node by ultrasonographic examination is highly suspicious for locally metastatic disease. Clinicians should strongly consider surgical lymph node resection of cystic lymph nodes regardless of the preoperative cytology results by FNA.

Short Call Poster 29

Thyroid Cancer Friday Poster

FATAL CARDIOTOXICITY AFTER 26-MONTH TYROSINE KINASE INHIBITORS (TKI) TREATMENT IN A REFRACTORY THYROID CANCER: INPUT OF 18-FDG PET-CT IMAGING

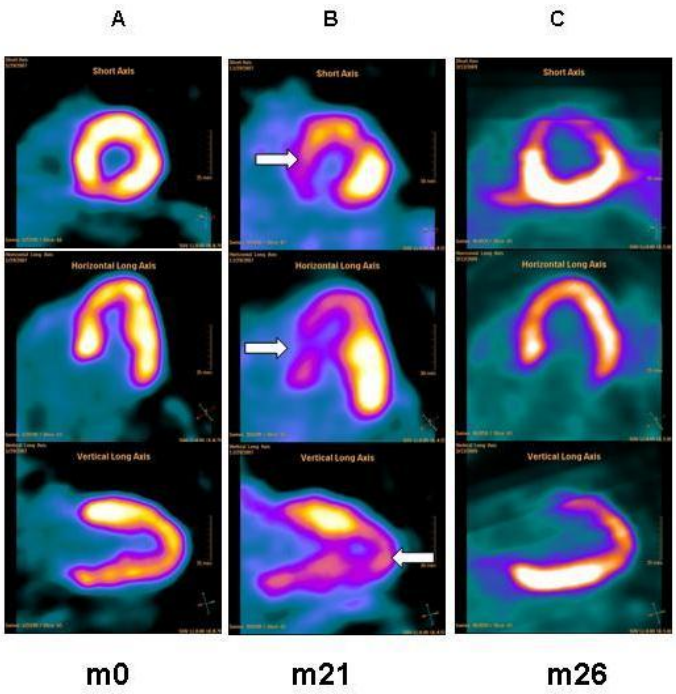
M. Toubert[1,3], I. Faugeron[1,3], G. Bousquet[2], G. Malouf[1], E. Hindié[1,3], D. Lussato[1], J. Misset[2], J. Moretti[1,3]
[1]Nuclear Medicine, Saint-Louis Hospital, Paris, France; [2]Oncology, Saint-Louis Hospital, Paris, France; [3]EAD: Imagerie moléculaire diagnostique et ciblage thérapeutique (B2T), Paris 7 University, Paris, France

Cancer treatment achieved a remarkable progress with the development of “targeted therapies”. Cardiotoxicity is mostly reversible, however with a 1-3% mortality incidence. Sorafenib (Nexavar, Bayer), targeting VEGF receptors and B-RAF, is one of those promising TKI proposed in the management of refractory thyroid cancer.

A 62-yr-old Polynesian man (with no cardiovascular risk factor) received sorafenib (800 mg/day) for a metastatic iodo-resistant papillary thyroid cancer with lung and cervical lymph node metastasis allowing a durable PR (RECIST). He simultaneously received imatinib, an anti PDGFR and stem-cell factor (c-Kit) TKI (400 mg/day) for concomitant chronic myeloid leukemia allowing complete molecular cytogenetic remission. Twenty-one months later (m21), he developed a clinical acute coronary syndrome related to a tritruncal stenotic coronary atheroma (coronary angiography) with left ventricular hypertrophy without kinetic changes (US). Medical treatment alone without angioplasty was introduced. However, at m26, whereas he was undergoing a 18-FDG PET-CT evaluation, he developed an acute thoracic pain and finally died despite immediate transfer in an intensive care unit.

This case report is remarkable regarding the cumulative impact on cardiac toxicity of long-term treatment with new targeted therapies, both in clinical and imaging management of such patients. Actually, 18-FDG PET-CT cardiac images (the only one acquired before acute heart failure) showed an important lack of viability in the apical and med-septal regions. Retrospective comparison with previous cardiac PET-CT images showed at m10 an unnoticed defect in the territory of the left anterior descending artery (whereas the patient was indolent) as compared to initial scan (m0). As myocardial 18-FDG uptake is physiological, cardiac PET-scan images are not currently checked in oncology. De novo defect in cardiac territories could be predictive of myocardial infarction in the absence of appropriate treatment.

We conclude that 18 FDG-PET/CT should be checked in the follow-up of TKI in new oncologic strategies not only on tumor sites, but also on heart viability, especially after long term treatment.



Short axis, vertical long axis and horizontal long axis images of cardiac F-18 FDG PET.

Short Call Poster 30
Thyroid Cancer Friday Poster

A CASE OF CONCURRENT PARATHYROID CARCINOMA AND PAPILLARY THYROID CANCER

L. Chaychi, K. Belbruno, A. Golding
Endocrinology and Metabolism, Dartmouth-Hitchcock Medical Center, Lebanon, NH

To present a case of simultaneous parathyroid carcinoma and papillary thyroid cancer.
Clinical history, physical examination, laboratory values, imaging and pathologic findings of a woman with two previously palpable thyroid nodules and mild hypercalcemia.
A 79-year-old presented to the endocrinology clinic for reevaluation of two thyroid nodules and possible parathyroid adenoma that was initially evaluated six years ago with intact PTH:89 pg/ml (10-69) and calcium:10.4 mg/dl. Her initial USG revealed: one nodule in the upper pole of the right thyroid lobe which measured 1.2x1.0x1.7 cm and a second nodule in the lower pole of the right thyroid lobe which measured 1.3 x 1.4x2.0 cm with well defined borders. The left lobe was unremarkable. No suspicious cervical lymph nodes or parathyroid adenoma were identified. FNA biopsy of the thyroid nodules was offered but the patient opted for observation with serial USGs. She was referred to us with calcium: 11.4 mg/dl. The USG demonstrated two right thyroid lobe nodules. The upper pole nodule measured 2.5 cm in length and 1.3 cm in AP dimension. The lower pole nodule measured 1.8 x 1.6 cm width. These nodules had demonstrated some interval growth over the preceding two years. The left thyroid lobe contained a 4.9 cm x 1.1 cm x 1.2 cm solid mass which was hypoechoic with poorly circumscribed margins. A Tc-99 sestamibi demonstrated uptake at the lower pole of the right thyroid fossa and throughout the left thyroid fossa suggestive of parathyroid hyperplasia. FNA biopsy revealed papillary thyroid cancer in both thyroid nodules. The patient underwent total thyroidectomy and left sided parathyroidectomy. Both thyroid nodules stained strongly for thyroglobulin and TTF-1. The left lobe mass demonstrated an infiltrative margin and trabecular pattern with fibrous septations consistent with parathyroid carcinoma which stained very strongly for parathyroid hormone.

Synchronous parathyroid and thyroid carcinomas are extremely rare. We present a case of simultaneous papillary thyroid carcinoma and parathyroid carcinoma in which mild primary hyperparathyroidism developed and had remained stable for six years.

Short Call Poster 31
Thyroid Cancer Friday Poster
MULTIFOCAL PARATHYROID CARCINOMA: A RARE ENTITY?
N. Bhatt, B.J. Jimmy
Otolaryngology-Head and Surgery, Medical College of Georgia, Augusta, GA

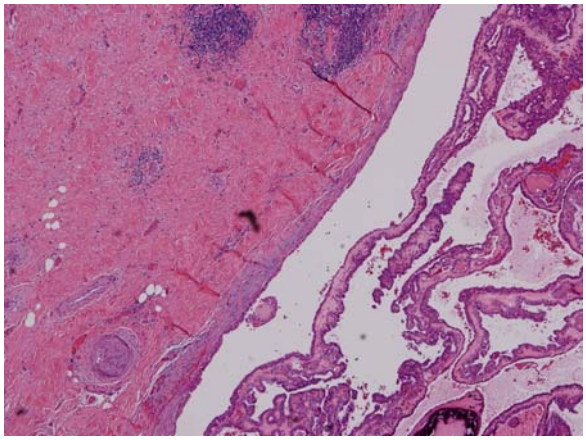
Multifocal parathyroid carcinoma is an exceptionally rare entity with only two published cases (one of which was previously published by the senior author) in the world literature. In this study, the authors wish to present a case of multifocal parathyroid carcinoma to further elucidate the proper evaluation and diagnosis of this elusive and frequently diagnosed condition.
One patient with multifocal parathyroid carcinomas was diagnosed and treated at a tertiary care institution. The patient's presentation, diagnosis and subsequent management are highlighted in this study, in addition to a survey of the literature.
The aforementioned patient presented with vague symptoms and profound hypercalcemia. An exhaustive medical workup demonstrated a markedly elevated parathyroid hormone level of 1491 pg/ml and a non-localizing Sestamibi scan. The patient underwent underwent surgical exploration of the neck revealing enlargement, grey discoloration and adherence of both the right and left inferior parathyroid glands. Intraoperative frozen section was suspicious for carcinoma in both glands. From the senior author's prior experience with this condition, an intraoperative decision was made to proceed with completion thyroidectomy, anterior neck dissection and total parathyroidectomy. Permanent histological examination showed three distinct parathyroid carcinomas with capsular and lymphovascular invasion with no nodal disease. The patient was been treated post-operatively with levothyroxine, calcium, and vitamin D with no evidence of recurrence or metastasis 17 months post-operatively.
Multifocal parathyroid carcinoma is a rare phenomenon and with this study, we hope that this may stimulate discussion and to ensure this diagnosis is considered in the appropriate setting

Short Call Poster 32
Thyroid Cancer Friday Poster
PAPILLARY CARCINOMA IN A THYROGLOSSAL DUCT CYST: A CASE REPORT AND APPROACH TO MANAGEMENT
P.E. Simon, S. Shintani Smith, A. Karagianis, N. Berg, J. Dutra
Otolaryngology, Northwestern Memorial Hospital, Chicago, IL

Thyroglossal duct cysts, the most common form of congenital midline neck masses, are reported in 7% of the adult population. Carcinomas are found by pathologic analysis of approximately 1% of thyroglossal duct cysts. Debate persists regarding management of the thyroid for patients with thyroglossal duct cyst malignancies. We report a case of a thyroglossal duct papillary carcinoma diagnosed in a 35 year old female with a midline neck mass, and review the literature addressing the surgical management of this uncommon disease.
A review of the literature was performed, with emphasis on management of the thyroid and cervical lymph nodes. Our patient presented with a midline neck mass suggestive of a thyroglossal duct cyst. CT demonstrated a 2.5x 2.2 x2.1cm mass with cystic and solid components and extension into the strap

muscles. Ultrasound guided FNA of the mass revealed papillary carcinoma. Thyroid function tests were normal. The patient underwent a Sistrunk procedure, total thyroidectomy, and lateral neck node sampling. Our patient's pathology revealed a thyroglossal duct cyst measuring 2.8 x 2.2cm with papillary thyroid carcinoma within the cyst. Surgical margins of the mass, resected hyoid bone, and thyroid gland were negative for malignancy. Five lymph nodes were negative for carcinoma.

Management of the thyroid gland and cervical nodes, in the setting of papillary carcinoma of a thyroglossal duct cyst, has remained controversial. Review of the literature suggests that for small tumors incidentally discovered during thyroglossal duct cyst removal, Sistrunk procedure may be adequate. Other studies suggest a high incidence of concomitant thyroid malignancy. We support an aggressive approach to the treatment of thyroglossal duct papillary carcinomas with a Sistrunk procedure and total thyroidectomy, followed by postoperative radioactive iodine ablation to allow for surveillance by thyroglobulin monitoring. Our approach is based on the biological behaviors of papillary carcinomas in case reports in thyroglossal duct cysts and in the thyroid gland, the utility of postoperative serial thyroglobulin levels in surveillance, and the low risks associated with total thyroidectomy.



Histologic sections demonstrate the wall of the thyroglossal duct cyst is lined by simple bland epithelium, ranging from columnar to squamous and demonstrates foci of secondary chronic inflammation. The cyst contains a mass with papillary architecture and nuclear features characteristic for papillary carcinoma.

Short Call Poster 33

Cell Biology Saturday Poster

ESTABLISHING A COMPREHENSIVE LIBRARY OF TRANSCRIPTS ENRICHED IN THE EARLY THYROID PRIMORDIUM

H. Fagman[2], E. Amendola[2], P. De Luca[2,3], P. Zoppoli[2], M. Ceccarelli[2,4], M. De Felice[2,1], R. Di Lauro[3,2]
[1]Biol. Patol. Cell. Molec., University Federico II, Napoli, Italy; [2]IRGS, Biogem scarl, Ariano Irpino (Av), Italy; [3]Stazione Zoologica, Stazione Zoologica A. Dohrn, Napoli, Italy; [4]Sci.Biol. Ambien., Universita' del Sannio, Benevento, Italy

Congenital hypothyroidism (CH) is commonly due to structural defects of the thyroid. Understanding the regulation of early thyroid morphogenesis is thus important to elucidate the pathogenesis of CH. Targeted inactivation of the transcription factors Nkx2-1, Pax8, Foxe1 and Hhex has demonstrated their cell-autonomous functions in thyroid development. However, very few germ-line mutations have been detected in these genes in human patients suggesting the importance of additional genes. The overall aim of this work has been to identify these by an unbiased search for transcripts enriched in the early thyroid primordium.
Mouse thyroid primordia at the bud stage (E10.5) were isolated by laser capture microdissection. Three biological replicates of ~10 ng RNA were acquired by pooling several primordia. In parallel, RNA from whole embryos (E10.5) was obtained. RNA integrity was confirmed and after two rounds of IVT-based linear amplification and labelling, samples were hybridized to Affymetrix microarrays. Bioinformatic analysis tools identified several transcripts as significantly enriched in the thyroid bud as compared to expression in the whole embryo.Such an enrichment is expressed as Fold Change (FC), a value that indicates how many folds each transcript is more abundant in the RNA of thyroid bud vs the RNA of the whole embryo.
Among the transcripts thus identified, genes already known to be highly expressed in the thyroid bud, such as Hhex and Pax8, were found. Approximately 2000 transcripts displayed a FC >1.5 and 350 of these a FC >5. High and restricted expression of several of these in the E10.5 thyroid bud was confirmed experimentally by in situ hybridization on mouse embryos. This preliminary analysis indicates that the list has a high degree of validity.
Taken together, by this approach we have identified a large number of transcripts enriched in the embryonic thyroid bud with currently unknown functions in its development. This list will be an important resource in further efforts to elucidate the genetic networks that govern thyroid morphogenesis and might underlie CH. This work was supported by the European Community, Integrated Project CRESCENDO grant LSHM-CT-2005-018652.

Short Call Poster 34

Thyroid and Development Saturday Poster

METABOLIC AND ANTHROPOMETRIC CHARACTERISTIC OF CHILDREN WITH TSH IN THE HIGH END OF THE REFERENCE RANGE (2.5- 4.49 UU/ML). AN ARGUMENT FOR LOWERING THE UPPER REFERENCE LIMIT OF TSH

A. Lewczuk[1], P. Czarniak[2], P. Szczesniak[2], Z. Esden-Tempska[1], M. Krawczyk[3], E. Krol[4], T. Zdrojewski[3], K. Sworczak[1]
[1]Endocrinology and Internal Diseases, Medical University of Gdansk, Gdansk, Poland; [2]Pediatric Nephrology, Medical University of Gdansk, Gdansk, Poland; [3]Hypertension and Diabetology, Medical University of

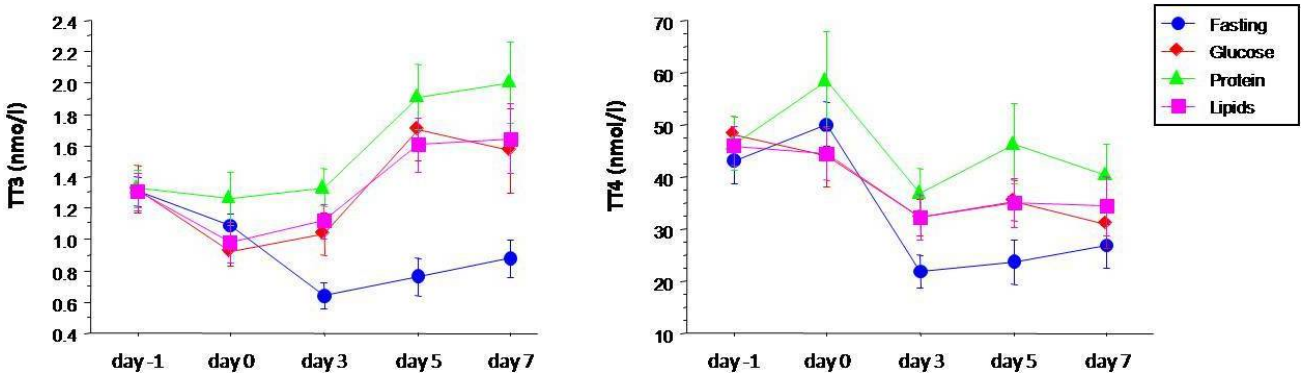
Gdansk, Gdansk, Poland; [4]Nephrology, Transplantology and Internal Diseases, Medical University of Gdansk, Gdansk, Poland

The upper limit of the reference range for serum TSH is still a topic of some debate. The objective of this study was to compare the metabolic and anthropometric parameters and thyroid ultrasound imaging pattern of children with TSH in the lower (0.34- 2.5 uU/ml) and upper (2.5-4.49 uU/ml) reference range. Laboratory (glucose, lipidogram, cystatin C, CRP, microalbuminuria, TSH) anthropometric (height, weight, BMI, waist, arm and hip circumference, thickness of skinfolds: biceps, triceps, sub-scapular, suprailliac), metabolic (BMR , percentage of body fat and FFM) clinical (RR, HR) and ultrasonographic parameters (thyroid volume, echogenicity, echostructure, thyroid blood flow) have been determined in 477 healthy school children in Sopot, Poland. The cohort has been divided into groups: A- children with TSH level 0.34-<2.5 (uU/ml) and B- children with TSH 2.5-4.95 (uU/ml) and compared according to the upper listed parameters.
Children with TSH in the upper reference limit (group B) presented statistically higher levels of total cholesterol, LDL, TAG, cystatin C and CRP and also had statistically higher values of average measured diastolic blood pressure whereas no differences have been found within the values of the systolic blood pressure or heart rate. The thyroid ultrasound of children in group B showed statistically more differences in echogenicity, echostructure and thyroid blood flow and no differences in thyroid volume. No differences between groups A and B have been observed within the anthropometric measurements or the metabolic parameters.
The children with TSH within the upper limit of the reference range proved to have more parameters considered as risk factors of cardiovascular diseases, more alterations on thyroid ultrasound imaging and elevated inflammatory markers. Our findings contribute to the discussion on whether the upper TSH reference limit should be redefined.

Short Call Poster 35
Thyroid Hormone Metabolism and Regulation Saturday Poster
IMPACT OF NUTRITION ON CIRCULATING THYROID HORMONE PARAMETERS DURING CRITICAL ILLNESS
L. Mebis[1], S. Derde[1], E. Ververs[1], V.M. Darras[2], G. Van den Berghe[1]
[1]Intensive Care Medicine, K.U.Leuven, Leuven, Belgium; [2]Laboratory of Comparative Endocrinology, K.U.Leuven, Leuven, Belgium

Fasting as well as critical illness evoke a “low T3 syndrome”, with most characteristically, reduced 3,5,3’-tri-iodothyronine (T3) levels and in severe cases low thyroxine (T4) levels as well. Since critical illness is often accompanied by nutrient deprivation, we hypothesized that the low T3 syndrome of critical illness may, at least partially, be evoked by reduced food intake.
We investigated the impact of parenteral nutrition on circulating iodothyronine levels in a rabbit model of prolonged critical illness. Critically ill rabbits were randomly allocated to a fasting group (4.4 kcal/kg/day) or to one of three groups, each receiving parenteral nutrition containing a total of 92 kcal/kg/day but with different substrate composition to also assess the impact of different substrates on thyroid hormone levels. Group 1 received 84% of the calories as glucose, 5% as protein and 11% as lipids; group 2 received 65% as glucose, 24% as protein and 11% as lipids and group 3 received 64% as glucose, 5% as protein and 31% as lipids. We measured circulating total T3 (TT3) and total T4 (TT4) on d-1 (= baseline), d0 (=day of injury), d3, d5 and d7. Results were compared with a healthy control group.
Critically ill rabbits that were fasted for 7 days after onset of illness revealed a 40% decrease of TT3 and a 45% decrease of TT4 levels, detectable from d3 onwards. When critically ill rabbits received parenteral nutrition, the decrease in TT3 was prevented, independent of the substrate composition of parenteral

feeding. At d7, circulating TT3 levels in fed rabbits were comparable to those in healthy rabbits. A drop in TT4 levels on d3 could not be prevented by parenteral nutrition. However, only the rabbits receiving protein-rich parenteral nutrition revealed TT4 levels on d7 comparable to those in healthy rabbits.
in this rabbit model of prolonged critical illness, low T3 levels, but not low T4 levels, could be prevented by parenteral nutrition independent of substrate composition. Only protein-rich parenteral nutrition was able to also increase circulating T4 levels later in the course of illness. Hence, the low T3 syndrome of critical illness was partially explained by concomitant nutrient deprivation.



Short Call Poster 36
Thyroid Hormone Metabolism and Regulation Saturday Poster
PHARMACOKINETICS OF 3-IODOTHYRONAMINE IN MICE
B. Hettinger[1], T. Geraci[3], K.G. Schuff[1], T. Scanlan[2]
[1]Endocrinology, Oregon Health and Sciences University, Portland, OR; [2]Physiology and Pharmacology, Oregon Health and Science University, Portland, OR; [3]School of Medicine, Oregon Health and Science University, Portland, OR

Thyronamines are putative products of decarboxylation and deiodination of thyroxine. In 2004, Scanlan et al. characterized 3-iodothyronamine (T1AM) and found it to be an endogenous compound with rapid metabolic effects. With a potential role of T1AM in metabolism and hibernation, we are interested in evaluating the chronic effects of T1AM administration. T1AM is structurally similar to dopamine, epinephrine and norepinephrine. Therefore, we designed the following studies to determine if T1AM has similar pharmacokinetic properties to these other biogenic amines.
C57Bl6 mice were injected with T1AM i.v. or orally at doses based on previous experiments evaluating the acute pharmacologic function of T1AM. Sera were collected at various time points and T1AM levels were determined by liquid chromatography-tandem mass spectroscopy (LC/MS/MS) using deuterated T1AM as an internal standard.
The serum half-life (t1/2) of T1AM after i.v. administration was 5.45 hours, the total body clearance (CL) was 4.075 ml/min, and the volume of distribution was 6.21 L/kg. This is in contrast to pharmacokinetic values for other biogenic amines, specifically epinephrine with a CL of 12471.8 ml/min and a volume of distribution of 0.045 L/kg. Another biogenic amine, serotonin, has been estimated to have a half-life of 1-2 minutes. Following oral administration, the bioavailability of T1AM was found to be 16.8% which is in contrast to other biogenic amines with essentially no oral bioavailability.
The values for epinephrine and serotonin are representative of compounds that have low distribution to tissues, and are rapidly eliminated. Our data suggest that T1AM, in contrast to other biogenic amines, is

distributed widely to tissues and substantially less susceptible to elimination. These unusual pharmacokinetic properties are important for understanding the unique pharmacology of T1AM, and may be important in its physiological actions.

Short Call Poster 37

Thyroid Hormone Metabolism and Regulation Saturday Poster

THYRONAMINES: TANDEM MASS SPECTROMETRY QUANTIFICATION IN BIOLOGICAL FLUIDS

O.P. Soldin, J. Gu, S.J. Soldin
Medicine, Georgetown University, Bethesda, MD

A novel analytical method applying liquid chromatography tandem mass spectrometry (LC/MS/MS) was developed for the simultaneous identification and quantification of thyroid hormones and thyronamines in biological samples (profiles).
An API-5000 MS/MS equipped with TurboIonSpray source and Shimadzu HPLC system was employed using isotope dilution with internal standard for each analyte. 200uL of human plasma/serum were deproteinized by adding 300uL of acetonitrile containing internal standards. 350 µL of supernatant were diluted with 1000µL of distilled de-ionized water and a 1000µL aliquot was injected onto a Supelco LC-18-DB (3.3cm x 3.0mm, 3µm ID) chromatographic column, where it underwent cleaning with 2% (v/v) methanol in 0.1% formic acid at a flow rate of 1.0 mL/min. After a 3 min wash, analytes were eluted with a water/methanol gradient (flow rate of 0.6 mL/min).Quantification by multiple reaction-monitoring (MRM) analysis was performed in the positive mode. Stock solutions were prepared to a concentration of 1 mg/mL each. 40% ammonium hydroxide (v/v) in methanol was used as a solvent except that methanol was used for dissolving 3,3'-Diiodo-L-thyronine (3,3'-T2) and its internal standard 3,3'-T2-13C6. Standards for the calibration curve in the range of 0.1-2 ng/mL for 3-Iodothyronnamine (3-T1AM), 0.1-2 ng/mL for 3,3'-T2, 0.3-5 ng/mL for T3 and 10-200 ng/mL for T4 were prepared by adding spiking solutions to 4% human γ-globulin (volume of spiking solution < 2% of final volume). In-house quality control solutions at three concentration levels (low, medium, high) were prepared in the same way to evaluate within-day and between-day precision as well as the accuracy of the method. A diluted solution containing 0.5 ng/mL 3-T1AM- d4, 0.5 ng/mL 3,3'-T2-13C6, 1.5 ng/mL T3-13C6, and 20 ng/mL T4-d5 in acetonitrile was used as working internal standard solution.
We developed a novel method for the simultaneous identification and quantification of TH and thyronamines in biological concentrations.
Our method can measure down to around 2 pg/mL for both T2 and 3T1AM, orders of magnitude more sensitive than the current published methods.

MRM conditions in positive ion mode

Compound	MRM transition	Declustering potential	Entrance potential	Collision energy	Collision cell exit potential
3-T1AM	356.1/212.0	86	10	29	12
3-T1AM- d4	360.1/216.1	86	10	27	8
3,3'-T2	525.9/480.0	141	10	29	10
3,3'-T2-13C6	531.9/485.9	116	10	29	22
T3	651.8/605.8	171	10	29	26
T3-13C6	657.8/611.7	16	10	33	26

T4	777.7/731.5	231	10	35	30
T4- d5	782.7/736.5	61	10	35	30

Short Call Poster 38

Thyroid Hormone Metabolism and Regulation Saturday Poster

A STABLE ISOTOPE STUDY: SINGLE DOSE PHARMACOKINETICS OF LEVOTHYROXINE IN PREGNANCY

O.P. Soldin[2], S.J. Soldin[1], D. Mattison[5], A.A. Vinks[6], H.M. Landy[3], I. Yunis[4]

[1]Pharmacology and Bioanalytical Core Laboratory, Georgetown University, Bethesda, MD; [2]Medicine, Oncology, Physiology and Biophysics, Georgetown University, Washignton, DC; [3]Obstetrics and Gynecology, Georgetown University Hospital, Bethesda, MD; [4]Center for Drug Evaluation and Research (CDER), US Food and Drug Administration, Silver Spring, MD; [5]National Institutes for Child Health and Development, National Institutes of Health, Bethesda, MD; [6]Pharmacology, Cincinnati Children's, Cincinnati, OH

Sufficient thyroxine is critical in pregnancy for fetal neurodevelopment. We developed a novel liquid chromatographic tandem mass spectrometric (LC/MS/MS) method to measure carbon-13 labeled levothyroxine (13C-LT4) enabling us to conduct single dose pharmacokinetics (PK) of levothyroxine (LT4). The use of 13CLT4 prevents interference by endogenous thyroid hormones and affords the measurement of LT4 PK profile which would not be otherwise possible by measuring concentrations of unlabelled drug at steady state over a single 24 hour dosing interval. We set out to determine whether LT4 pharmacokinetics are altered during pregnancy in women receiving LT4 replacement, when compared with non-pregnant women.

We conducted single dose LT4 pharmacokinetic studies of eight pregnant women (gestation weeks 12-36) and 7 non-pregnant women using carbon 13-labeled levothyroxine. Drug concentrations were compared to same dose PK longitudinally once during pregnancy and again at least three months after delivery. Levothyroxine pharmacokinetics was best described by a 2-compartment model with zero order absorption and lag-time. There were no significant differences in Tmax and Cmax between the pregnant and non-pregnant women studied. In pregnant women 13C-LT4 was absorbed over 7.8h±2.0h (mean±SD) with Tmax at 7.4 h (±1.0h) in non-pregnant and Cmax reaching 1.20 (±0.49) ng/mL. Mean oral clearance (CL/F) was 6.7±6.4L/h in pregnant women, and 11.8±5.5L/h in non-pregnants ($p<0.03$), resulting in a mean serum half-life of 32.1h in pregnant and 24.1h in non-pregnants ($p<0.039$). Drug exposure measured by the area-under-the-curve (AUC) was 20.9ng*h/mL during pregnancy and significantly lower (mean 10.0ng*h/mL) in non-pregnants ($p<0.03$). AUC∞ was 23.0ng*h/mL during pregnancy and significantly lower (14.8ng*h/mL) in non-pregnants ($p<0.03$).

Reported are unique studies of single dose levothyroxine pharmacokinetics in pregnancy. Non-pregnant pharmacokinetic parameters are not consistent with LT4 pharmacokinetic estimates projected in the published literature. Future work will focus on larger sample size and the mechanism responsible for the changes in PK, and whether these changes should necessitate dose schedule changes in pregnancy.

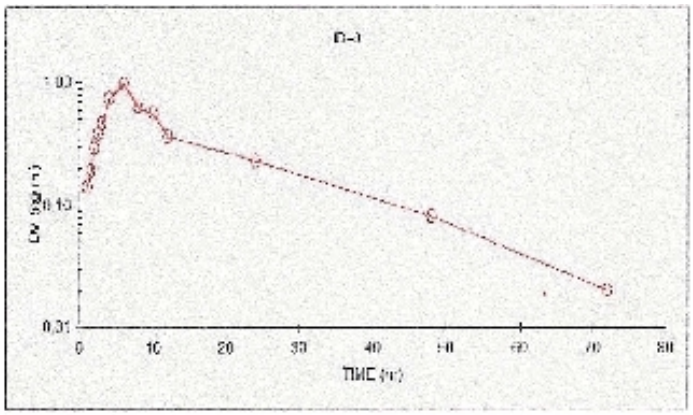


Fig. 1: PK profile of a non-pregnant woman

Short Call Poster 39

Thyroid Hormone Metabolism and Regulation Saturday Poster

L-THYROXINE ABSORPTION IS NOT AFFECTED BY ROUX-IN-Y BARIATRIC SURGERY IN MORBID OBESE PATIENTS

I.G. Rubio[1], A.L. Galrao[1], M.A. Santo[2], A.C. Zanini[1], G. Medeiros-Neto[1]

[1]Clinical Medicine, University of São Paulo Medical School, São Paulo, Brazil; [2]Gastroenterology, University of São Paulo Medical School, São Paulo, Brazil

Intestinal absorption of L-thyroxine (LT4) tablets depends on its dissolution in the gastric acid secretion. Impaired duodenal absorption due to low LT4 dissolution in the gastric cavity has been observed in patients with atrophic or chronic gastritis. Similarly bariatric interventions (such as Roux-in-Y) will reduce the gastric hydrochloric acid secretion. We evaluated the absorption of L-T4 tablets in morbid obese patients before and after bariatric surgery.

Thirty morbid obese patients were divided in two groups, NS group: 15 patients that were waiting for bariatric surgery (BMI=43.1±4 Kg/m2) and S group: 15 patients after Roux-in-Y surgery (BMI= 37.3±4 Kg/m2). After two basal samples were collected 600ug of LT4 p.o. was given to all patients. Blood samples were collected after 30, 60, 120, 180, 240, 300, and 1440 minutes (24h) after the LT4 dose. Serum Free T4 (FT4), Total T4 (TT4) and TSH were measured at each time. The increase of TT4, FT4 and TSH (ΔTT4, ΔFT4, ΔTSH) was calculated subtracting the basal value. LT4 absorption (%) was estimated by multiplying the maximal ΔTT4 by the volume of distribution (VD=0.442 X BMI).

The pharmacokinetics parameters, mean LT4 absorption, area under the curve (AUC), peak mean value and time of the peak were similar in both groups. ΔTT4,ΔFT4, the AUC-ΔTT4 and AUC-ΔFT4 were significantly higher in S Group as compared with the NS group (P=<0.05). The serum TSH levels were significant higher in NS Group (p=0.016) and the ΔTSH and the AUC-ΔTSH were similar in both groups.

These results suggests that after bariatric surgery the new gut configuration with the jejunum just below the stomach pouch may compensate the possible gastric acid reduction, achieving L-thyroxine absorption similar to that observed in the morbid obese patients with an intact stomach.

Short Call Poster 40

Thyroid Hormone Metabolism and Regulation Saturday Poster

SERUM FIBROBLAST GROWTH FACTOR 21 (FGF21) LEVELS ARE SIGNIFICANTLY ASSOCIATED WITH FREE THYROXIN (FT4) IN PATIENTS WITH METABOLIC SYNDROME

D. Cuevas-Ramos, P. Almeda-Valdés, J. Garduno, F.J. Gómez-Pérez, C.A. Aguilar-Salinas
Endocrinology and Metabolism, INCMNSZ, Mexico City, Mexico

FGF21 have been linked with beneficial effects on glucose and lipid metabolism in animals. Recently, it has been found elevated in humans with metabolic syndrome (MetS) and a negative correlation (r=-0.54, p=0.02) with free triiodothyronine was identified in healthy control women. The study aimed to explore the association between FGF21, and other adipokines, with TSH and FT4.

This was a cross-sectional study. A clinical and biochemical evaluation was done to detect the metabolic syndrome, defined by the ATPIII criteria, in a never-treated cohort. A total of 53 individuals with (n=20) and without (n=33) metabolic syndrome were included.

There were no significant differences in TSH (mU/L) and FT4 (pmol/L) levels between groups. Serum FGF21 levels were significantly higher (p=0.01) in subjects with the MetS [339.5ng/l (248.0-492.7)] in comparison with patients without the syndrome [276.4ng/l (169.0-404.4)]. In the group with MetS, a significant and positive correlation (r=0.46, p=0.04) between FGF21 and FT4 was identified (Figure 1). Similarly, a negative association between FGF21 and TSH was observed, however, it was not significant and showed only a trend (r=-0.36, p=0.07). The association between FGF21 and FT4 was further increased (r=0.92, p=0.02) in men with MetS. Interestingly, a negative association was identified in men with MetS (r=-0.81, p=0.05) between FT4 and total adiponectin, and it was positive (r=0.74, p=0.02) when MetS was absent. Nevertheless, these associations were not identified in women.

These preliminary results suggest an association between FGF21 and thyroid function in patients with the metabolic syndrome.

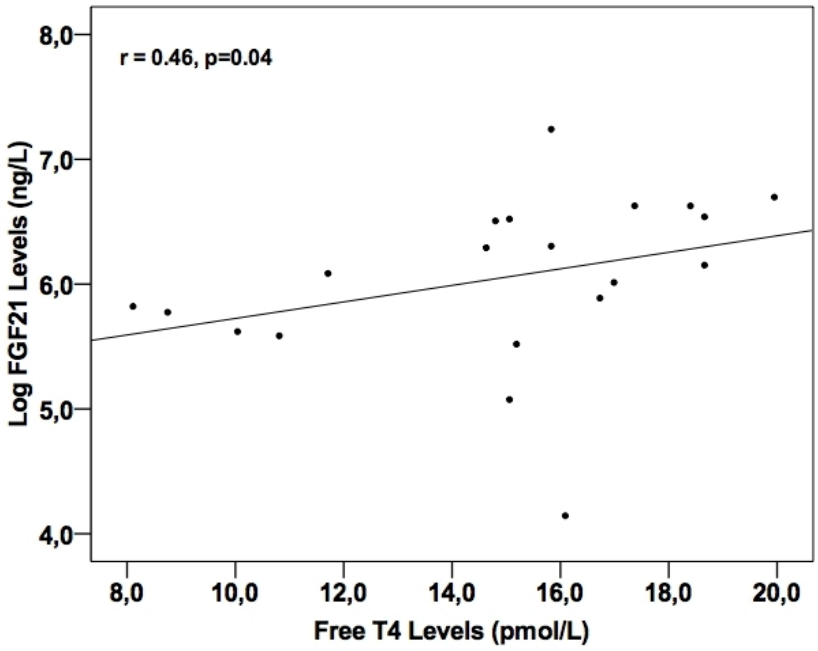


Figure 1. Association between serum FGF21 and free T4 levels in patients with metabolic syndrome (n=20).