Health care services and treatment adaptation for diabetes patients of Ethiopian origin immigrants in Israel

Dr. Nirit Aviran Barak [1] Mrs. Sheyla Nigri [1] Mrs. Limor Shimron Nachmias[1]

1. maccabi health service natanya

Introduction: During the last years there is an escalation in diabetes mellitus diagnosis in general population as well as in Ethiopian immigrant population, in Israel. A good cooperation between diabetes patients and medical staff is required to enable good disease control. Such cooperation was hard to achieve with Ethiopian immigrants in Maccabi clinic at Natanya, due to communication difficulties, cultural gap and in general a chronic disease perception by such patients. This program aimed to ease the communication and enable a better medical care, via the help of a mediator that can translate as well as bridge the culture gap.

Methods: The program identified 12 patients of Ethiopian origin with uncontrolled diabetes, 7 of them have actively participated in the program. An individual treatment plan was built for each patient by a multi disciplinary staff. An Ethiopian immigrant nurse was recruited, and functioned as a mediator between patients and diabetic clinic stuff as well as a translator. Patient's appointments to the diabetic clinic were scheduled consecutively, and synchronized with the Ethiopian nurse presence. At the second stage of the project appointments with these patients were set in their local Maccabi clinic rather than the diabetes clinic. The diabetic medical staff has traveled to this local clinic, in order to give the patients a better care and reduce the patients alienating.

Results: Satisfaction of all the patients in the program as well as the medical staff was enlarged significantly. Disease control and patients compliance were improved significantly as well.

Conclusions: Special medical staff training program as well as treatment plans should be adapted to the patient's culture, values and way of life. Assistance of local member of the community as part of the medical staff is a vital measure to guaranty program success.

POST-GRADUATE EDUCATION PROGRAM FOR DIETICIANS

Mrs. GILA FAYMAN [1'2'3] Mrs. MICHAL GILLON-KEREN [1'2'3] Mrs. IRIT PORAZ[2] Prof. MOSHE PHILIP [1] Prof. ITAMAR RAZ [3] Dr. ZIVA STAL [4] .

1. Institute for endocrinology and diabetes national center of childhood diabetes schnieder children's medical center
2. Nutrition and Diabetes Unit' Schneider Children's Medical Center of Isreal
3. The Nation Councils of Diabetes' Israel
4. Ministry of Health

Introduction: In the past decade, with the advent of new technologies and insulin preparations, the need for dieticians specializing in the field of diabetes became inherent. The Post-Graduate Education Program for Dieticians was created in order to address the professional needs of dieticians with the endorsement of the National Councils of Diabetes and the recognition of the Israeli Ministry of Health.

Methods: The program included clinical and epidemiological aspects of various types of diabetes and its complications, health promotion and prevention of diabetes, clinical guidelines and tools for decision making skills for the nutritional management of diabetes throughout life. Special emphasis was placed on the behavioral aspects of nutritional counseling. The dieticians practiced skills for improving coping strategies in order to enhance adherence to the treatment plan (i.e. motivational interviewing, cycle of change and narrative approach).

Results: One hundred and one dieticians from hospitals and clinics throughout the country participated in the first two education programs. All the participants completed the 24 weeks (168 academic hours) program with high attendance rates. Certification was given after completion of the requirements and written examination. The participants evaluated the course and rated it as excellent, stating that it improved their knowledge and gave them tools for analysis and problem solving.

Conclusions: This educational program addressed the need to train dieticians in the nutritional counseling of diabetes. Through knowledge and clinical practice the dieticians enhanced their counseling skills of the nutritional aspects of diabetes and thus promote therapeutic patient education.

The GC-MS urinary steroid metabolome correlated better with the real enzymatic activity status of a patient thought to have an isolated 17,20-lyase deficiency than molecular biology.

Dr. Carlos Knopf [1] Dr. Dov Tiosano [2] Prof. Ze'ev Hochberg[2]

1. Department of Clinical Biochemistry, Rambam Health Care Campus, Haifa, Israel
2. Pediatric Endocrinology, Rambam Health Care Campus, Haifa, Israel

Introduction: We studied an adolescent male with clinical and biochemical features of isolated 17,20-lyase deficiency, including micropenis, hypospadias, and gynecomastia, who is homozygous for CYP17 mutation E305G. The CYP17 gene encodes a unique enzyme that possess two enzymatic reactions, 17α-hydroxylase and 17,20-lyase activities. We have previously published (JBC 2003, 278:48563), the finding, in this patient, that the E305G mutation caused isolated 17,20 Lyase deficiency.

Methods: Expression studies in transfected HEK-293 cells and in yeast microsomes, expressing the mutant E305G, suggested intact 17-hydroxylase activity. This was at odds with subnormal ACTH stimulated cortisol in the patient, which suggested that the 17-hydroxylase activity was also affected in this mutation. Two years later we developed a gas chromatography-mass spectrometry (GC-MS) profiling of urinary steroid metabolites, which allowed us to study in vivo the global enzymatic activities and metabolic pathways of steroid hormones. Assessment of enzymatic activity was based on precursor/product ratios.

Results: Elevated metabolic ratios of corticosterone metabolites/C19-steroids (B-M/An+Et: 22.71, Control:0.32) reflected impaired global activity of the enzymatic system 17-hydroxylase/17,20-lyase. 17,20-lyase activity was markedly impaired, especially P5T/(A5-3ß,17ß): 362.5, Control:2.47. 17-hydroxylase activity was also impaired as indicated by the significantly elevated ratio corticosterone metabolites/cortisol metabolites (7.63, Control: 0.17)

Conclusions: In this patient, the GC-MS steroid metabolome expressed the real steroids enzymatic activity status more accurately than molecular biology, and lead to the conclusion that this mutation does not solely affect 17,20-lyase, as we previously reported, but also impairs 17-hydroxylase activity.

Characterization of three human adrenocortocal carcinoma cell cultures

Miss Inbar Levi [1] Mrs. Sulamit Karby [1] Dr. Alona Meir [2] Dr. Anat Jaffe [1]

1. Endocrinology and Diabetes Mellitus Unit, Hillel Yaffe Medical Center, Hadera, Israel
2. Department of Pathology, Hillel Yaffe Medical Center, Hadera, Israel

Introduction: Adrenocortical carcinomas (ACC) are rare and malignant tumors for which no effective medical treatment is currently available. There are two human ACC cell lines in the American type culture collection: SW13 - which does not secrete steroids, and the steroid producing H295 (and derivates) which retain the ability to respond to physiological stimulation. Thus, the addition of human research models is profoundly needed. The aim of this study is to characterize cell cultures from three different ACC female patients.

Patients: The patients: A, 29 years old with rapidly progressive Cushing's syndrome (CS), stage II ACC B, 68 years old with CS and virilization, stage IV ACC and C 47 years old with virilization, stage III ACC. The cells migrated onto the plates from tumor mini explants. Analysis was performed on cells grown in passages 4, 6 and 13 for A, B and C, respectively.

Results: On light microscopy the cells looked polygonal, with big nuclei, prominent nucleoli and many perinuclei cytoplasmatic granules. They had a positive Sudan red reaction. Immunohistochemical stain gave non-specific results, positive synaptophysin in-vivo became negative in-vitro. The functional profiles of the cells for A, B, C respectively are, Progesterone 0.32ng/ml, NA, NA, Cortisol 0.03±.00mcg/ml, 0.11mcg/ml, NA, DHEA-S: NA, <15 mcg/dl, <15 mcg/dl, Testosterone NA, 1.19±0.1ng/ml, 0.1±0.01ng/ml. Steroidogenic gene expression was tested using RT-PCR. Seven stereoidogenic genes were examined, StAR- Steroidogenic Acute Regulatory Protein, and HMGR- hydroxy-methylglutaryl-CoA reductase. The results were compared to gene expression in H295R cells. A, B and C show high expression of CYP11A - the first enzyme in steroidogenesis, StAR and HMGR. Nevertheless, a few differences in gene expression were found between the three different cells. C's cells expressed all the tested genes: CYP11A, 17β-HSD, CYP17, CYP11B2, CYP21, CYP12 and 3β-HSD2. A's cells expressed most of the genes, but showed very weak expression of CYP11B2, CYP19, and 3β-HSD2. B's cells expressed most of the genes, but showed weak expression of CYP19 and 3β-HSD2.

Conclusions: Our findings proved that the cells still express the majority of the genes that enable them to produce steroids. The gene expression intensity of A's and B's cells is lower than C's and H295R. The next step will be to examine the effect of medium additives and various types of stimulators on gene expression and steroid secretion.

A KINDRED WITH a RET CODON Y791F MUTATION PRESENTING WITH HIRSCHSPRUNG'S DISEASE

Dr. Merav Fraenkel[1] Mrs. Dganit Barak[1] Dr. Liat Appelpaum[2] Prof. David J Gross[1]

1. Endocrinology and Metabolism Service, Department of Medicine, Hadassah-Hebrew University Medical Center, Jerusalem, Israel.
2. Department of Radiology, Hadassah-Hebrew University Medical Center, Jerusalem, Israel.

Introduction: Activating mutations in the RET gene underlie hereditary medullary thyroid carcinoma (MTC), a prominent feature of MEN2, with a strong genotype/phenotype correlation. Inactivating mutations in the RET gene may be found in 35-75% of Hirschsprung's disease (HD). Co-occurrence of MTC and HD is rare, usually associated with mutations in exon 10. Recently, new missense mutations in exon 13, codons 790 & 791 have been described. Penetrance for MTC with Y791F is apparently low. This mutation has been previously described in one patient with HD and several patients with sporadic MTC, but there is no report of a Y791F patient or kindred with both diseases.

Patients/ Methods: We report a kindred identified after the diagnosis of a 3 months old baby with HD. RET proto-oncogene genotyping revealed a Y791F mutation. There was no family history suggestive of MTC or MEN2 Six other family members were found to be carriers of the same mutation (ages 0.5 to 75 years). None had palpable thyroid nodules. 6 of 7 mutation carriers had a neck US, one had a multinodular goiter and one had a 7 mm nodule with gross calcifications-FNA was not informative. Two other patients had several <1 cm nodules which did not require an FNA. Basal calcitonin levels were normal in all carriers. Calcium infusion tests were preformed in 5/7 mutation carriers: two had calcitonin levels consistent with C cell hyperplasia and 3 others had a normal response, 4/7 had urinary catecholamines performed with normal results.

Conclusions: In these kindred we have shown that despite the presence of RET Y791F mutation and advanced age in some of the carriers, none of the carriers displayed signs of MTC. This finding is compatible with other reports in the literature which point to a low penetrance of this mutation for the development of MTC, especially in families in which there is no MTC in the index patient as is the case in our kindred. Therefore, a conservative strategy with repeat neck US and Ca stimulation testing appears to be appropriate in these selected cases.

Treatment of disseminated sporadic MTC with Sorafenib, a novel tyrosine kinase inhibitor

Dr. Merav Fraenkel [1] Dr. Simona Grozinsky-Glasberg [3] Mrs. Dganit Barak[1] Dr. Liat Appelbaum [2] Prof. David J Gross [1]

1. Endocrinology and Metabolism Service, Department of Medicine, Hadassah-Hebrew University Medical Center, Jerusalem
2. Department of Radiology, Hadassah-Hebrew University Medical Center, Jerusalem
3. Endocrine Institute, Beilinson Hospital, Rabin Medical Center, Petach-Tikva, Israel

Introduction: Medullary thyroid carcinoma (MTC) is a rare tumor of the thyroid treated with extensive neck surgery. There is no available chemotherapy which is efficacious for this tumor once metastasized. Activating mutations in the RET gene underlie hereditary MTC and somatic RET mutations have been described in up to 40% of sporadic cases. Sorafenib is a tyrosine kinase inhibitor (TKI) which inhibits TK activity associated with RET, moreover, it has marked anti-VEGF activity. Promising preliminary results from clinical trials with several TKI's from this group prompted us to try Sorafenib in two patients with extensive metastatic MTC.

Patients/ Methods: Patient #1 is a 51 year-old male who was diagnosed with metastatic MTC 15 years ago for which he was operated several times. Two years ago he developed distant metastasis to the mediastinum, bones, lymph nodes, lungs and liver. External radiation was not beneficial. His clinical state deteriorated, with intractable diarrhea, cachexia and hypoxemia. PET CT showed extensive disease as mentioned above. Serum calcitonin and CEA levels were both elevated. After completion of 3 months of therapy with Sorafenib 400 mg bid, the patient's clinical status improved, serum calcitonin decreased by 80% with parallel radiographic improvement. The drug was generally well tolerated. Patient #2 is a 30 year-old woman diagnosed with metastatic MTC following 2 episodes of pulmonary embolism at the age of 26 and 29, and several years of troubling diarrhea. A chest CT showed diffuse miliary disease in the lungs and liver, together with bone metastases. Neck US showed a small thyroid nodule accompanied by cervical lymphadenopathy. Biopsy proved these to be MTC. Serum CEA and calcitonin were highly elevated (176 ng/ml and 250,000 pg/ml respectively). Due to the massively diffuse disease at presentation she was not operated, rather Sorafenib 400 mg bid was started. The patient experienced a severe diffuse skin reaction and the drug was temporarily discontinued while the patient received oral steroids. After the rash abated, Sorafenib was reintroduced in small doses and gradual increments until reaching full dose only 2 month ago. Possible additional side effects of Sorafenib were hypothyroidism and worsening of diarrhea. During therapy serum CEA and calcitonin levels went down by more than 50%. Follow up imaging is pending.

Conclusions: Based on these very limited preliminary and short responses, it seems that Sorafenib has a promising role in the treatment of metastatic MTC. Limitations to therapy are the high cost and long term treatment, as long there is a response. Results from large scale clinical trials with other TKI's are pending, and will provide further data as to the role of this class of drugs in the treatment of MTC

Neurological Manifestations of Thyroid Dysfunction

Prof. Menachem Shapiro [1] Dr. Rosane Ness Abramof [1] Dr. Gabriela Salomon[1] Dr. Mark Niven [2] **Dr. Dan Nabriski** [1]

1. Unit of Endocrinology , Diabetes and Metabolism Meir Medical Center
2. Unit of Endocrinology , Laniado Medical Center .

Introduction: Thyroid dysfunction may appear with a multitude of clinical features. Among these are neurological presentations which may be a predominant feature of the disease. We present our collective , retrospective , experience with these manifestations to emphasize their presence. A history and physical examination are needed to detect and appreciate these findings.

Patients/ Methods: This review covers over 500 patients with overt clinical hyperthyroidism and hypothyroidism with confirmatory laboratory data using routine commercial kits. Subclinical disorders are not included because of the rarity of these presentations in such setups.

Results: Hyperthyroidism: thyrotoxic myopathy (proximal muscle weakness) with normal CPK was detected by the presence of Gower' s sign in over 60% of patients. EMG's were not performed. Hyperreflexia and tremor was very common among the entire group. . In individual patients proximal weakness was the overriding feature of hyperthyroidism delaying a proper diagnosis. 5 patients had myasthenia gravis. Hypokalemic periodic paralysis was present in 2 patients. One case each was found with a single manifestation: thyrotoxic chorea, myokyemia, thyrotoxic storm with coma, epilepsy. . Ophthalmic myopathy was commonly present with severe thyroid exopthalmopathy. Stoke associated with thyrotoxic – induced atrial fibrillation was present but rare. Hypothyroidism: myopathy presenting as elevated CPK, LDH and SGOT was very common. Overt clinical myopathy was infrequent. Abnormal Gower's sign was present often . Severe disabling generalized cramps were present in a few patients. Carpel tunnel syndrome was not unusual. Slowed mentation was common in overt hypothyroidism, Severe cognitive impairment was striking in only a few patients. Myxedema coma was seen periodically. "Myxedema madness" was present in 2 patients. The "hung up " Achilles reflex was typical and associated with myoedema.

Conclusions: Neurological involvement in hyper and hypothyroidism is very common and its appreciation depends on careful clinical evaluation in addition to a set of laboratory results.

Overt hypothyroidism in hospitalized patients: presenting symptoms and outcome

Dr. Pnina Rotman-Pikielny [1,3] Dr. Oksana Borodin [2,3] Dr. Yair Levy [1,3]

1. Departments of Medicine E, Meir Medical Center, Kfar-Saba
2. Department of Geriatrics, Meir Medical Center, Kfar-Saba
3. Tel-Aviv University, Tel-Aviv

Introduction: Hypothyroidism is often diagnosed and treated in an outpatient-setting. Most common, symptoms include weakness, cold intolerance, and lack of energy. Yet, sometimes hypothyroidism is seen in the hospital-setting. The prevalent symptoms in hospitalized patients diagnosed with overt hypothyroidism have not been fully characterized. OBJECTIVE: To determine the clinical characteristics of hospitalized patients with overt hypothyroidism during hospitalization.

Patients: The patients were hospitalized in Meir Medical Center, a secondary referral hospital from January 1997 through December 2007, and discharged with hypothyroidism as a main diagnosis. A retrospective chart review was undertaken to determine the clinical characteristics of patients with overt hypothyroidism during hospitalization. All the patients had elevated thyrotropin level and low free thyroxine level. Patients that were diagnosed with sub-clinical thyroid disease (elevated thyrotropin level and normal free thyroxine level) were excluded.

Results: Twenty nine admissions of 23 patients (16F/7M, age 61.5±21.8 years) with a main diagnosis of hypothyroidism during hospitalization were identified. Only 11% of the patients were nursing-home residents. Hypothyroidism was diagnosed prior to the admission in 55% of the patients. Weakness was a major complaint in 89% of the patients, and was the main reason for admission in 58.6%. Constipation was reported in 68% of the patients. Anemia (Hemoglobin <12g/dL) and macrocytosis were present in 60 and 46.6% of the patients, respectively. Sodium level was >135U/L in 86.7% and creatinine phosphokinase was elevated in 89% of the patients. Thyrotropin level was elevated at 74.3±53.5mU/L (normal 0.23-4), while free thyroxine was level 0.43±0.29ng/dL (normal 0.8-2). Ninety three percent of the patients were discharged from the hospital after 4.7±5.5 days.

Conclusions: Most of the patients with overt hypothyroidism during hospitalization were known to have hypothyroidism prior to the admission. The clinical manifestations included weakness, constipation and anemia. Other typical "hypothyroid" symptoms like cold intolerance and hoarseness were overlooked in this population. High index of suspicion is needed to detect hypothyroidism in the hospital-setting. Routine follow-up on thyroid function tests in patients with a known thyroid disease is warranted.

Color Flow Doppler Sonography in patients with subclinical thyroid dysfunction

Dr. Avraham Ishay [1,4] Dr. Yael Pollack [2] Dr. Leonid Chervinsky[2] Mrs. Idit Lavi [3] Prof. Rafael Luboshitzky [1,4]

1. Endocrine Institute, Haemek Medical Center, Afula,
2. Department of Radiology, Haemek Medical Center, Afula.
3. Department of Community Medicine and Epidemiology, Carmel Medical Center, Haifa.
4. The B.Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa.

Introduction: Subclinical thyroid dysfunction (SCTD) is a common clinical problem defined by normal free thyroxine (FT4) and free triiodothyronine (FT3) concentrations in the presence of abnormal thyrotropin (TSH) levels. Color flow Doppler sonography (CFDS) is a non-invasive technique that allows direct visualization of the thyroid vasculature and measurement of intrathyroid blood flow. Hypervascularity and increased blood flow velocities have been observed in patients with overt thyroid dysfunction. As CFDS may provide an indirect measure of thyroid function, we assessed the value of CFDS in patients with SCTD.

Patients/ Methods: We investigated 27 patients with subclinical hypothyroidism (Shypo), 15 patients with subclinical hyperthyroidism (Shyper) [6 with autonomous adenoma, 9 with Graves's disease or nodular goiter] and 20 normal subjects. Subclinical thyroid dysfunction (SCTD) was defined as normal serum free thyroxine (FT4) and free triiodothyronine (FT3) in the presence of high (Shypo), or low-suppressed (Shyper) serum TSH levels. All participants underwent conventional sonography and CFDS. CFDS patterns were scored from 0 to III according to color Doppler display. Mean peak systolic velocities (PSV) and resistive index (RI) were obtained from multiple extranodular thyroid parenchyma samplings and inferior thyroid arteries measurements for each lobe.

Results: Patients with Shypo had significantly higher intrathyroid (IT) mean PSV values (19.9±5.6 cm/s vs. 15.7±4.4, p=0.008). A greater proportion of Shypo patients had marked CFDS patterns (type II/III), when compared with controls (77.8% vs.15%, p<0.001). Shyper patients had significantly higher mean PSV values at inferior thyroid artery (ITA) level (29.7±10.7cm/s vs. 21.9±6.8, p=0.014) with greater percentage having more prominent vascular pattern when compared with controls (53.3% vs. 15%, p<0.0001). There was a positive correlation between prominent CFDS pattern and IT-PSV in the Shyper (r=0.57, p=0.026) and Shypo groups (r=0.48, p=0.01). Across all subjects, a significant association was found between positivity for thyroid autoantibody and intense CFDS patterns (median =3.0, p=0.0001 and p=0.02, for TPOAb and TGAb, respectively). No correlation was found between TSH or thyroid hormones levels and CFDS pattern or velocities.

Conclusions: In the present study we have demonstrated significant increased thyroid blood flow velocities and vascularity in patients with SCTD. This technique can be an easy and useful adjunctive tool for initial evaluation of patients with subtle thyroid dysfunction.

Growth Characteristics and Final Height in Female Adolescents Diagnosed with Anorexia Nervosa

Dr. Dalit Modan-Moses [1,4,5] Dr. Yariv Dorom [2] Dr. Amit Yaroslavsky[3,4,5] Ms. Brigitte Kochavi [3,4] Ms. Anat Toledano [3,4] Ms. Sharon Iron-Segev [3,4] Dr. Daniel Stein [3,4]

1. Pediatric Endocrinology and Diabetes Unit, The Edmond and Lily Safra Children's Hospital
2. the Nes Ziona Mental Health Center, Nes Ziona
3. Pediatric Psychosomatic Department, The Edmond and Lily Safra Children's Hospital
4. The Chaim Sheba Medical Center, Tel-Hashomer
5. the Sackler School of Medicine, Tel Aviv University, Tel Aviv.

Introduction: Growth retardation is an established complication of anorexia nervosa (AN). However, findings concerning final height of AN patients are inconsistent. The aim of this study was to assess these phenomena in female adolescent inpatients diagnosed with AN.

Patients: 72 female adolescents hospitalized because of AN, aged 15.5±1.6 years, were prospectively studied, from admission until they achieved their final height.

Results: Patients' height standard deviation scores (SDS) at admission (-0.22±0.9) and discharge (-0.21±0.9), as well as final-height SDS (-0.24±0.8) were significantly lower than expected in normal adolescents, whereas the pre-morbid height-SDS (0.18±0.88, available for a subgroup of 34 patients), was not significantly different from the expected in normal adolescents. Patients admitted with a bone age of <15 years, i.e. still having growth potential at the time of admission, showed some degree of catch-up growth during follow-up, but did not reach their full height potential. A multiple logistic regression analysis was performed in which the covariates included age at hospitalization, duration of hospitalization, bone age delay, body mass index-SDS on admission and discharge, and number of hospitalizations. Age on admission was the only predictor of the degree of catch-up growth ($p<0.001$): younger age at admission was associated with less catch-up growth.

Conclusions: Our findings suggest that whereas the premorbid height of female adolescent AN patients is normal, linear growth retardation is a prominent feature of their illness. Weight restoration is associated with catch-up growth, but complete catch-up is often not achieved.

Anti-Mullerian hormone level in the follicular fluid is a predictive factor of the fertilization potential of the oocyte aspirated from this follicle

Dr. Alon Kedem[1] Dr. Gil yerushalmi [2] Dr. Ettei Maman Dr. Masha Brengauz Dr. Irina Lojkin, Dr. Rina Hemi, Dr. Hana Kaneti[2] Prof. Jehoshua Dor, Dr.Ariel Hourvitz

1. In Vitro Fertilization Unit, Department of Obstetric and Gynecology, Sheba Medical Center.
2. Institute of Endocrinology, Sheba Medical Center, Tel-Hashomer

Introduction: Anti-Mullerian hormone (AMH) has recently been shown to be one of the most important markers of ovarian reserve. It is highly associated with ovarian follicular development and disordered folliculogenesis such as polycystic ovary syndrome. However, the correlation between follicular fluid (FF) AMH concentration and the reproductive potential of an individual follicle is still unclear. Aim: This study examined the possible correlation between follicular fluid (FF) AMH concentrations and the outcome of the ensuing oocytes obtained during in vitro fertilization.

Methods: We conducted a prospective study. Eighteen infertile women, 21-40 years of age undergoing IVF treatment in our unit were enrolled in the study. Written informed consent was obtained from all patients. FF from 60 large follicles (16-24mm) were individually aspirated during oocyte pickup. FF AMH levels were determined using ELISA (DSL) method. Seventeen hours after the ICSI procedure or regular insemination, fertilization was assessed using an established pronuclei (PN) scoring system.

Results: An oocyte was found in 41 follicles (68.3%) out of the 60 follicles aspirated. Twenty eight oocytes (68.3%) were fertilized. The concentrations of FF AMH were significantly lower in the group of fertilized oocyte (1.63 ng/ml) as compared to non fertilized oocyte (4.50 ng/ml), $p<0.005$. There was no significant correlation between FF AMH levels in oocyte containing follicles compared to empty follicles.

Conclusions: Oocyte from follicles with lower AMH concentration have lower chances to fertilized. Thus, AMH could be a prediction marker for fertilization.

A pre-formed signaling complex mediates GnRH-activated ERK-phosphorylation of paxillin and FAK at focal adhesions in LbT2 gonadotrope cells.

Mrs. Liat Rahamim [1] Dr. Masha Dobkin-Bekman [1] Dr. Michal Naidich[1] **Mr. Boris Shterntal** [1] Mrs. Fiorenza Przedecki [1] Mr. Tal Almog [1] Dr. Stefan Lim [2] Prof. Philippa Melamed [3] Mrs. Ping Liu [4] Prof. Thorsten Wohland [4] Prof. Rony Seger [5] Prof. Zvi Naor [1]

1. Department of Biochemistry, George S. Wise Faculty of Life Sciences, Tel Aviv University, Israel
2. School for Integrative Sciences and Engineering, Life Sciences, National University of Singapore
3. Faculty of Biology, Technion - Israel Istitute of Technology, Israel
4. Department of Chemistry, National University of Singapore, Singapore
5. Department of Biological Regulation, The Weizmann Institute of Science, Israel .

Introduction: Most receptor tyrosine kinases (RTKs) and G-protein coupled receptors (GPCRs) operate via a limited number of MAPK cascades, but still exert diverse functions and therefore signal specificity remains an enigma. Also, most GPCR ligands utilize families of receptors for mediation of diverse biological actions, however the mammalian type I GnRH receptor (GnRHR) seems to be the sole receptor mediating GnRH-induced gonadotropin synthesis and release. Signaling complexes associated with GPCRs may thus provide the means for signal specificity.

Results: Here we describe a signaling complex associated with the GnRHR, which is a unique GPCR lacking a C-terminal tail. Unlike other GPCRs, this signaling complex is pre-formed and exposure of LbT2 gonadotropes to GnRH induces its dynamic rearrangement. The signaling complex includes c-Src, PKC delta, epsilon and alpha, Ras, MEK1/2, ERK1/2, tubulin, FAK, paxillin, vinculin, caveolin-1, KSR-1 and the GnRHR. Exposure to GnRH (5 min) causes MEK1/2, ERK1/2, tubulin, vinculin and the GnRHR to detach from c-Src, but they re-associate within 30 min. On the other hand, FAK, paxillin, the PKCs and caveolin-1 stay bound to c-Src, while KSR-1 appears in the complex only 30 min after GnRH stimulation. GnRH was found to activate ERK1/2 in the complex in a c-Src-dependent manner and the activated ERK1/2 subsequently phosphorylates FAK and paxillin. In parallel, caveolin-1, FAK, vinculin and paxillin are phosphorylated on Tyr residues apparently by GnRH-activated c-Src.

Conclusions: RTKs and GPCRs translocate ERK1/2 to the nucleus to phosphorylate and activate transcription factors. We therefore propose that the role of the multi-protein signaling complex is to sequester a cytosolic pool of activated ERK1/2 to phosphorylate FAK and paxillin at focal adhesions.

Thyroid nodules: the correlation between US features and the cytopathological/histopathological results

Dr. Olga Lanshkov [2] Dr. Evgeny Moshkovich* [1] Dr. Rosanne Ness-Abramof[1] Dr. Miryam Werner [3] **Dr. Dan Nabriski [1]**

1. Unit of Endocrinology Diabetes and Metabolism Meir Medical Center Kfar-Sava
2. Department of Internal Medicine C Meir Medical Center Kfar Sava
3. Unit of Ultrasound Imaging Meir Medical Center Kfar Sava.

Introduction: Thyroid nodules are a common finding in the general population and they can be palpated in 5% of the population. Imaging test can detect a higher proportion of these nodules, not identified by palpation only, with a prevalence of more that 70%. Due to an increase in the availability of imaging tests, particularly ultrasound, a higher proportion of these nodules are diagnosed. In spite the high prevalence of thyroid nodules, the prevalence of thyroid cancer is relatively low, and less than 5% of thyroid nodules are malignant. Fine needle aspiration biopsy (FNA-B) is an accurate test to diagnose malignancy, but due to the high prevalence of nodules, and since many patients have multinodular goiters, ultrasonographic characteristics have been defined to improve the specificity of the FNA-B. Ultrasonographic features that are suspicious of malignancy include hypoechogenicity, fine calcifications, irregular borders and increased vascularity.

Patients/ Methods: A retrospective analysis was performed. One hundred and forty five charts of patients that had ultrasonographic guided FNA-B (US-FNAB) of thyroid nodules between the years of 2004 and 2005 at the ultrasound unit at Meir Hospital, Kfar Saba. Data extracted for charts included demography and ultrasonographic features of the nodule including: size, echogenicity (hypoechoic, isoechoic or hyperechoic), calcifications (fine or gross), borders (regular or irregular), presence of halo and cystic changes. The results of the cytopathlogy were defined as benign, malignant, suspicious of malignancy of non diagnostic.

Results: The prevalence of malignancy in thyroid nodules was higher in nodules that were hypoechoic, had fine calcifications and irregular borders. The presence of a halo was more prevalent in benign nodules while cystic nodules were not more suspicious of malignancy compared to solid nodules.

Conclusions: Malignant thyroid nodules have a higher prevalence of hypogenicity, fine calcificications and irregular borders. Cystic changes within the nodule (mixed nodules) or the presence of an halo does not increase the likelihood of malignancy. Ultrasonographic features of the thyroid nodule can help to identify more suspicious thyroid nodules for malignancy and increase the specificity of FNA-B and not merely be used to detect nodules and follow their size.

Successive degradation of StAR by soluble and membrane-bound mitochondrial proteases: protecting steroidogenic mitochondria under "protein Stress" scenario

Assaf Bahat and Joseph Orly

Department of Biological Chemistry, The Alexander Silberman Institute of Life Sciences, The Hebrew University of Jerusalem

Introduction: Steroidogenic Acute Regulatory protein (StAR) is a nuclear encoded vital mitochondrial protein that is essential for synthesis of steroid hormones in the adrenal cortex and gonads. In these tissues, StAR mediates translocation of cholesterol into the inner mitochondrial membranes, where it is converted to the first steroid, pregnenolone. The hypothesized mechanism of StAR action assumes that the role of StAR is probably executed prior to StAR import, when the protein is paused at the surface of the outer mitochondrial membrane. Import, therefore, is presently perceived as a turning-off mechanism of StAR activity and leads to a rapid and excessive accumulation of non-functional StAR in the mitochondrial matrix. This study shows that StAR is a rare authentic example of a mitochondrial protein that is rapidly degraded by a cascade of ATP-dependent mitochondrial proteases, in order to protect the organelle under an unprecedented scenario of protein stress readily threatening its functional integrity.

Methods: 1) For assessing the degradation rates of StAR by different mitochondrial proteases, we screened the proteases by performing pulse-chase experiments in HEK293 cells over-expressing StAR following siRNA mediated knockdown of the mitochondrial proteases; efficiency of siRNA was tested by qRT-PCR and Western analyses. 2) "protein-stress" conditions were generated in two different ways; in vitro, we over-expressed StAR for 16h, 24h and 48h in HEK293 cells; in vivo, we generated physiologically relevant StAR expression during hormone induced follicular development in ovaries of rats treated with PMSG for 10h, 48h, or 50h PMSG + 8h hCG.
Results: StAR degradation within the mitochondria is at least bi-phasic. First, Lon protease degrades StAR upon its entry into the matrix. Then, StAR readily adheres onto the surface of the inner membranes where a homo-oligomeric form of the AFG3L2 protease/chaperone is responsible for StAR elimination. "Protein-Stress" caused by over-expression of StAR in HEK293 cells resulted in upregulation of AFG3L2 and Lon mRNAs levels. Hormonal induction of StAR in rats results in upregulation of AFG3L2 mRNA level in the ovary.

Discussion: AFG3L2 together with paraplegin (SPG7) function as proteases and chaperons involved in protein quality control and mitochondrial morphology; also, loss-of-function mutations in the latter cause terminal neurodegenerative disorders such as hereditary spastic paraplegia. Our results suggest that rapid turnover of mitochondrial StAR is conducted by a succession of proteases/chaperones that function in a typical steroidogenic cell as an emergency crew in charge of maintaining the functions of the mitochondria undisturbed under "protein stress" and reactive oxygen stress circumstances.