Poster Abstracts Group C

Tc-99m MIBI-SPECTSCINTIGRAPHY IN THE PRESURGICAL ASSESSMENT OF SUSPICIOUS THYROID LESIONS

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Background: In recent years, few studies evaluated thyroid Tc-99m MIBI scan as a tool for work up of thyroid nodules suspicious for malignancy. The negative predictive value of this test in excluding malignant nodule from suspicious lesions appears to be very high (95%), but, despite that, it is not used routinely. The aim of this study was to evaluate an approach including MIBI-SPECT scan in the assessment of these lesions.

Methods: Patients with inconclusive follicular cytology and cold nodules at Tc-99m pertechnetate thyroid scan were included in the study during the period 2010-2011. Tc-99m MIBI SPECT scan was offered to patients who initially did not accept the surgery as a treatment option. Patients with Tc-99m MIBI cold lesions were offered surveillance, while patients with Tc-99m MIBIhot nodules were operated on.

Results: Six patients were included in the analysis. The results are summarized in the following table:

patient	age	size of lesion (mm)	MIBI result	pathology
1F	43	21*22	Hot	follicular adenoma & multifocal papillary microcarcinoma with follicular variant (3 and 4 mm)
2F	56	35*22	Hot	follicular adenoma and papillary microcarcinoma (2 mm)
3F	51	22*33	Hot	Hurthle cell follicular adenoma
4F	53	15*18	Hot	Sent for surgery
5F	34	27*30	Hot	Refuses surgery - observation
6M	72	26*21	Cold	2 years observation – no change

Conclusion: Based on a small sample size, hot Tc-99m MIBI scan was not a good predictor of thyroid malignancy. Larger studies are needed to evaluate the negative predictive value.

IS THERE A TRUE INCREASE IN THE PREVALENCE OF CONGENITAL HYPOTHYROIDISM? 30 YEARS OF NATIONWIDE SCREENING.

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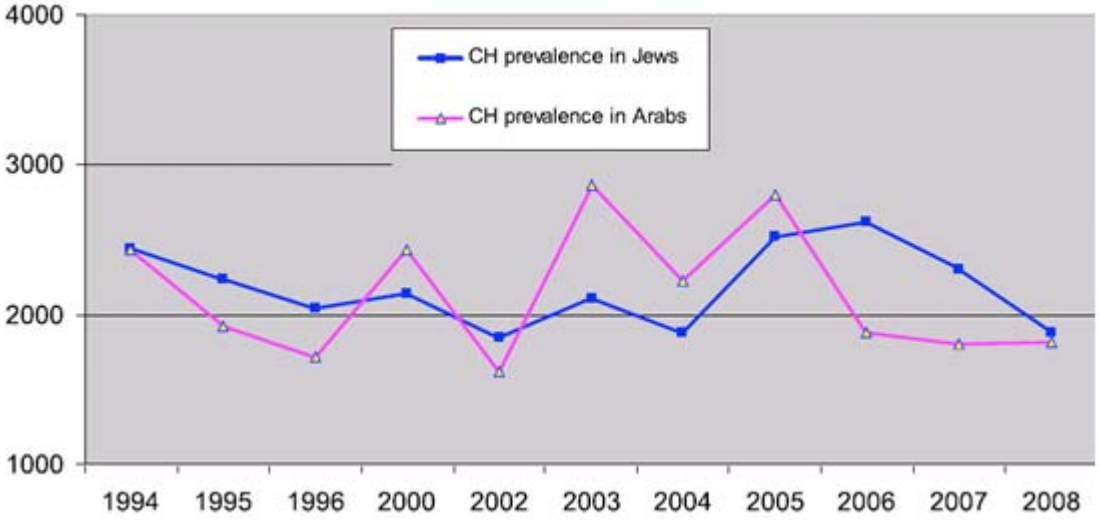
Background: A steady increase of Congenital Hypothyroidism (CH) among newborns has recently been reported in the USA. In Israel, a nationwide screening exists since 1978 covering 99% of the general population. The primary marker has been TT4 with a secondary TSH (above 40 mIU/L).

Objective: To study the prevalence of CH in the Israeli newborn populations (Jews and Arabs) and to find whether there is an overall change in the prevalence with time.

Methods: For the years 1970-2008, data were collected from the Israeli Bureau of Statistics. The data was analyzed based on ethnicity (Jews and Arabs). In order to avoid the large number of false positive, CH was defined for this study as low TT4 and TSH above 80 mIU/L.

Results:



Conclusion: During the study period there was a twofold increase in the number of newborns screened. There is a yearly prevalence fluctuation but there was no increase in CH in the overall population and not in either the Arab or Jewish populations.

REDUCED SENSITIVITY TO THYROID HORMONE IN ISRAEL – MUTATIONS IN THYROID HORMON RECEPTOR TYPE- BGENE

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Background: Thyroid hormone (TH) action is mediated by 2 different receptors (THRA & THRB). Reduced end-organ responsiveness to thyroid hormone, known as the Resistance to Thyroid Hormone Syndrome (RTH) is, in most cases, attributed to mutations in the thyroid-hormone receptor-type-β (THRB) gene. Previous reports from Israel on RTH have identified two THRB mutations and one family with a mutation in another gene, MCT8.

Objective: To identify known or novel mutations in genes related with thyroid hormone function in Israeli patients suspected with RTH.

Methods: Between March-December 2011, a survey was made among endocrinologists in Jerusalem regarding patients in whom clinical follow-up and laboratory findings supported the diagnosis of RTH. Three probands, from 3 unrelated families were recruited. Clinical data, physical findings and medical histories were documented and informed consent obtained. Blood samples were collected, genomic DNA was extracted and all coding exons of THR-β gene were PCR amplified and Sanger sequenced.

Results: FT4, FT3 and TSH levels for the 3 probands were: 31, 9.3, 2.78; 75.9, 16.8, 2.43; and 40.4, 9, 3.26 respectively (reference ranges; 10-20 pmol/L; 3.1-6.8 pmol/L and 0.35-5.5 mU/L respectively. In probands from families 1 and 3, a heterozygote missense mutation was found in exon 10 (P453S). In proband 2 and one of her affected siblings, two heterozygote single-base-change variations were found, one in exon 9 (R338W), and the second a previously described intronic polymorphism rs13063628..

Conclusions: We identified two previously reported disease-associated mutations, P453S (probands 1 & 3) and R338W (proband 2) in 3 unrelated Israeli families.

VITAMIN D STATUS AND POST THYROIDECTOMY HYPOCALCAEMIA

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Total thyroidectomy is commonly performed for several indications, among them benign thyroid enlargement, hyperthyroidism or malignant thyroid disease. One of the most significant complications of thyroid surgery is hypocalcemia due to either inadvertent parathyroid gland removal most likely to result in permanent hypocalcaemia or, more prevalent, transient hypocalcaemia caused by trauma or disruption of blood supply to parathyroid glands.

Vitamin D deficiency is extremely common worldwide and in Israel. Vitamin D inadequacy causes secondary PTH elevation aimed at normalizing calcium homeostasis. Vitamin D deficient patient relies on high PTH for maintaining normal blood calcium level.

The question whether low vitamin D before surgery might adversely affect the post surgical calcium status is therefore, appropriate. Some existing data supports this hypothesis. This study aim was to check the relationship between preoperative vitamin D status and the risk for post thyroidectomy hypocalcaemia.

Methods: Medical records of patients who underwent total thyroidectomy in our institution between 2006 and 2010, were reviewed. Patients with Grave's disease were excluded. Data regarding pre-operative 25-OH-D, calcium, PTH level, post-operative nadir calcium, PTH and need for calcium or active vitamin D supplements after surgery, were recorded.

Results: Sixty patients' records were available for analysis. For 26 patients, preoperative 25-OH-D levels were available. Seven had total thyroidectomy due to PTC, two, due to MTC, and 17, due to thyroid enlargement. Vitamin D deficiency defined as 25-OH-D less than 20 ng/ml was found in 18 patients. Five had insufficiency (20-30 ng/ml). Only three patients had normal vitamin D level. The post operative calcium level in a group of 8 patients with severe deficiency (below 10 ng/ml) was significantly lower, than in the rest of the cohort (7.5 ± 0.8 vs $8.2 + 0.7$ mg/dl, $P=0.03$).

Conclusions: Severe vitamin D deficiency predisposes for post-thyroidectomy hypocalcaemia. Vitamin D inadequacy correction prior to surgery might improve outcome in this regard. Interventional studies are needed.

EFFECT OF HIGH DOSES OF VITAMIN D ON ARTERIAL PROPERTIES, ADIPONECTIN, LEPTIN AND GLUCOSE HHOMEOSTASIS IN DIABETIC PATIENTS.

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Background: Since Vitamin D deficiency is linked to impaired insulin secretion and insulin sensitivity**,** vitamin D supplementation has the potential to alleviate the cardiovascular damage in diabetic patients. The present study was designed to evaluate long term impact of high doses of vitamin D on arterial properties, markers of insulin resistance, metabolic and inflammatory parameters in patients with type 2 diabetes mellitus.

Methods: In randomized, placebo-controlled study 47 patients with type 2 diabetes mellitus were assigned into two groups: Group 1 received oral daily supplementation with vitamin D at a dose of 1000 U/day. Group 2 received matching placebo capsules. Blood sampling for metabolic parameters, including fasting glucose, lipid profile, HbA1C, insulin, hs-CRP, 25 OH VitD, adiponectin and leptin was performed at baseline and at the end of the study. Insulin resistance was assessed by homeostasis model assessment (HOMA-IR). Central aortic augmentation index (AI) was evaluated using SphygmoCor (version 7.1, AtCor Medical, Sydney, Australia).

Results: The two groups were similar at baseline in terms of hemodynamic and arterial elasticity parameters. After 12months, AI decreased significantly during the treatment period ($p<0.0001$) in patients received vit D supplementation ($p<0.0001$) and did not change in placebo group. Glucose homeostasis parameters, leptin as well as leptin adiponectin ratio (LAR) did not change in both groups during the study. 25 OH Vit D level significantly increased ($p=0.022$) and circulating adiponectin marginally increased ($p=0.065$) during 12 month treatment period in active treatment and did not change in placebo group.

Conclusions: High doses of vitamin D supplementation in diabetic patients was associated with significant decrease in AI during one year treatment. This beneficial vascular effect wasn't associated with improvement in glucose homeostasis parameters.

SERUM 25-HYDROXYVITAMIN D LEVELS ARE ENHANCED FOLLOWING DEAD-SEA CLIMATOTHERAPY

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Background: The Dead Sea region in Israel is the deepest spot on earth, 422 meter beneath sea level. The atmosphere layer overhanging this region is larger than in any other place on earth, allowing a filtration effect on sunshine beams and leading to their moderate attenuation in the Ultraviolet B (UVB) spectrum. The question was raised whether exposure to this sunshine may increase serum Vitamin D levels of patients treated at the Dead Sea.

Objectives: To assess, in Norwegian patients suffering from joint disease and chronic pain syndromes, the magnitude of change in 25-Hydroxyvitamin D levels (25-OH-D) after Dead Sea Climatotherapy (DSC).

Methods: 117 Norwegian patients received regular DSC procedures during their 3 weeks visit, which includes sun exposure, Dead Sea bath and outdoor physical activities. The cumulative solar UVB exposure was calculated in Minimal Erythema Doses (MED). Blood sampling for measurements of 25-OH-D levels were performed upon arrival and on the last day of their stay. Data were evaluated by statistical analysis using paired t test.

Results: Daily sun exposure reached 60 to 90 minutes, delivering on average 38.3 ±12.8 MEDs. Mean serum 25 OH Vitamin D levels increased by 12.3 ±19.8 nM, (p-value <0.001). The mean relative change in Vitamin D level was 23.8%.

Conclusions: Even in the attenuated sunshine existing in the Dead Sea region, a daily sun exposure for 3 weeks induces significant increases in serum 25-OH-D levels by Caucasian patients suffering from musculoskeletal and joint diseases. Changes in 25-OH-D after sun exposure were found to be related to initial value of serum 25-OH-D, to age, and disease.

INFLUENCE OF NUMBER OF DELIVERIES AND TOTAL BREAST-FEEDING TIME ON MINERAL DENSITY IN PRE- AND PERIMENOPAUSAL WOMEN

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Introduction: Both pregnancy and lactation place significant stress on maternal calcium homeostasis. Although many reports have described changes in bone mineral density (BMD) in pregnant or lactating women, the recovery to baseline level and the relative roles of pregnancy and lactation in this process remain controversial.

Objective: To assess the influence of number of deliveries and total breast-feeding time on BMD values in a homogenous group of healthy premenopausal and early postmenopausal women followed at single tertiary medical center.

Patients and methods: The study group consisted of women aged 35-55 years who underwent routine screening for BMD from February to July 2011. Data on age at menarche and menopause, smoking, dairy product consumption, and weekly physical exercise were derived from the standard questionnaire completed by patients before BMD examination. In addition, the women were questioned about their deliveries and total duration of breast feeding. Height and weight were measured, with calculation of body mass index (BMI). Dual-energy X-ray absorptiometry (Lunar iDXA ME+200181, GE Healthcare, USA) was used to measure spinal (L2-L4), dual femoral neck, and total hip BMD. Associations between background characteristics and BMD values were analyzed statistically.

Results: Data were collected for 500 women of average age 47 years. Sixty percent were premenopausal. Mean number of deliveries was 2.5, and mean duration of breast feeding, 9.12 months. BMD values were negatively correlated with patient age and number of births and positively correlated with BMI. On logistic regression analysis, older age, lower BMI, and longer breast-feeding duration were significant predictors of low BMD.

Conclusions: Prolonged breast feeding may have a deleterious long-term effect on BMD and may contribute to increased risk of fracture later in life.

VITAMIN D LESS-CALCEMIC ANALOGJK 1624 F2-2 MODULATES MRNA EXPRESSION OF ERS AND 1OHASE IN HUMAN THYROID CANCER CELLS: IMPLICATION FOR THYROID CARCINOMA CELL GROWTH.

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Estrogen receptors (ERs) are expressed in various "non-reproductive" cancer cell types. Some cancer types express1α- hydroxylase 25- hydroxyvitamin D(1OHase) whose product, 1,25$(OH)_2D_3$ can inhibit cancer cell proliferation. Thyroid carcinoma cell growth is apparently promoted by estrogens, but whether or not this interaction is modified by vitamin D metabolites/analogs is presently unknown. Here we assessed the effect of a less calcemic vitamin D analog [JK 1624 F_2-2 (JFK)] in three human thyroid cancer cell lines: ARO (anaplastic carcinoma), NPA (papillary carcinoma) and MRO (follicular carcinoma).

First, all three cell lines expressed both ERαand ERβmRNA and 1OHaseas quantified by Real Time PCR. There was a general abundance of ERβ(over ERα expression, such that the ratio of ERβto ERα mRNA was >1000:1, 228:1 and 7.7:1 in ARO, MRO and NPA cells, respectively. JKF up regulated ERβexpression in ARO (by 110+15%) and in MRO (by 280+10%) but down regulated it in NPA cells (by40+15%). Second, all three human thyroid cancer cell lines were found to express1OHase. Further, the expression of 1OHasewas up regulated by JKF in MRO (350+25%) and NPA (35+8%) but down regulated in ARO (20+5%).

This is the first report to identify1OHasein human thyroid cancer cells. A functional role for this enzyme is suggested by the finding that the vitamin D analog can affect ER expression, which is involved in estrogen-induced cell growth in the same human thyroid cancer cell lines (JSBMB126:95, 2011).

FACTORS INFLUENCING PATIENTS' DECISION TO BE TREATED AFTER SUSTAINING AN OSTEOPOROTIC FRACTURE.

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Introduction: Fragility fractures from low trauma are common in the elderly. Patients with fragility fractures have a fivefold risk for further osteoporotic fractures. Most of these patients remain untreated after having an osteoporotic fracture.
In this work we tried to identify factors influencing patients' decision to start fracture prevention treatment.

Patients/methods: Fractures Prevention Program (FPP) was initiated in Rambam Health Care Campus in March 2009. All patients with fragility fractures were referred from the Department of Orthopedic Surgery to the Bone and Mineral Metabolism Unit for fracture prevention treatment.

Results: 1331 patients, age 50-107 (74.5±12.7), 365 (28%) men, 966 (72%) women.
954 had hip fractures, 79 vertebral, 298 other fractures. 234 (14.6%).had previous fragility fractures. Prior to hospitalization 227 (17%) have received a fracture prevention treatment: 223 (23%) women, 4 (1%) men.
Currently 205 (15.4%) are treated, 187 (19.4%) women, 18(4.9%) men, $p<0.001$.
124 (54.6%) of patients [123(55%) women]who received anti-osteoporotic treatment in the past are currently treated, versus 80 (7.3%) [63 (8.5%) women] of previously untreated, $p<0.001$.
Of patient with previous fractures 49 (20.9%) currently receive treatment, without previous fractures -14.1% (153 of 1084), $p=0.012$. In women 25.8% with previous fractures vs 17.6% without receive the treatment currently, $p=0.01$.
Age, co-morbidities, number of concomitant medications did not influenced patient/ decision

Conclusion: Despite high prevalence of osteoporosis in the elderly, most patients remained untreated after fragility fractures. Factors positively influencing patients' decision to start fracture prevention treatment are female gender, previous fractures, previous fracture prevention treatment

PLANT-DERIVED MICRONUTRIENTS INHIBIT IGF-I ACTIVITY IN BREAST CANCER CELLS BUT ENHANCE IT IN BONE CELLS.

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Insulin-like growth factors (IGFs) are involved in tumor formation and progression. Blood IGF-I levels years before malignancy diagnosis correlate positively with the risk for breast and prostate cancer. In contrast, IGF-I is an important positive regulator of bone homeostasis throughout life. Carotenoids and polyphenols which are abundant in a fruit and vegetable-rich diet were found to improve markers of bone health and to inhibit breast cancer proliferation. Although previous work suggest that such phytonutrients inhibit IGF-I activity in cancer cells their effect on the growth factor activity in bone was not studied yet. Lycopene, the major tomato carotenoid, inhibits IGF-I activity in breast cancer cells by reducing the IGF-I-induced tyrosine phosphorylation of insulin receptor substrates. In previous work from our as well as from other labs it has been shown that some cellular effects of lycopene are mediated by its oxidized derivatives. These apo-carotenal derivatives can be formed by chemical or enzymatic oxidation.

Our aim in the current study was to determine whether carotenoids, their derivatives and polyphenols inhibit IGF-I activity in breast cancer cells but do not inhibit this activity in bone derived osteoblast-like cell.

For this aim, we examined the effect of lycopene and its oxidized derivative on IGF-I stimulated proliferation of human (MG-63) and mouse (MC3T3-E1) osteoblast like cells and MCF-7 breast cancer cells. We used a synthetic lycopene derivative, diapocarotene-6,14′-dial (6,14') which is one of the most active di-apocarotenals. As expected, lycopene and 6,14' inhibited IGF-I-stimulated proliferation in breast cancer cells. In contrast, in the bone derived cells these phytonutrients did not inhibit and even enhanced cell proliferation. Similar results were obtained with the polyphenol curcumin. We found that the effects of these compound on IGF signaling, as measured by IGF-I stimulation of Akt phosphorylation, was similar to the effect on cell growth, namely, inhibition of the phosphorylation in cancer cells and enhancement in bone-derived cells.

In conclusion, we suggest that phytonutrients contribute to cancer prevention by inhibition of IGF-I activity and they enhance bone health by increasing the activity of the growth factor in bone cells.

CLINICAL EVALUATION OF A NEW SPECIFIC 1-84 PTH ASSAY ON AUTOMATED PLATFORM

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Background: 2nd generation "Intact" PTH assays currently available, measure 1-84 PTH and additional fragments. Recently a third generation kit developed which detects only active 1-84 PTH molecule, based on an immuno-radiometric sandwich assay.

Methods: Evaluation took place in an HMO central lab. 240 plasma samples collected. 161 randomly out patients and 78 hospitalized nephrologic patients. Patients' samples, controls and NEQAS samples tested by CLIA Method: DiaSorin LIAISON®1-84 PTH assay, DiaSorin LIAISON®N-TACT®PTH II, SIEMENS Centaur iPTH and DiaSorin IRMA N-tact®PTH SP ("Gold Standard"). Results were compared with laboratory parameters and patients clinical status.

Results: Correlation between LIAISON®1-84 PTH and LIAISON®N-TACT PTH II showed R= 0.9164, slope=0.9076. Correlation between LIAISON®1-84 PTH and Centaur iPTH showed R= 0.98, slope=2.7622. Correlation between LIAISON®1-84 PTH and IRMA N-tact®PTH SP showed R= 0.97, slope=1.0893.The following LIAISON®1-84 PTH parameters obtained: Samples and controls within run precision showed 2.58%-5.34% CV. Samples and controls between run precision showed 4.03%-4.65% CV. Functional sensitivity matched manufacturer claim at 4 pg/mL. Recovery between 77%-101%. Clinical agreement between LIAISON®1-84 PTH and IRMA N-tact®PTH SP on nephrologic patients was 97.5%. 3 discrepant patients were clinical matched with LIAISON®1-84 PTH results. From the healthy out patients tested samples 54% were found high with SIEMENS Centaur iPTH and 16% were high with LIAISON®1-84 PTH. The same behavior observed with NEQAS data. PTH levels were influenced similarly by low CA levels.

Conclusions: High diagnostic correlation was observed between IRMA N-tact®PTH SP and LIAISON®1-84 PTH together with high clinical correlation of patients' status. It is concluded that the LIAISON®1-84 PTH can be used as a reliable and accurate kit for setting up a clinical and high throughput laboratory.

CHOLESTEROL INDUCES CANCER CELL PROLIFERATION AND METABOLISM

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Obesity is one of the major risk factors to develop cancer in the western world. Obesity can be result in hyperglycemia and hyperinsulinemia which leads to type 2 diabetes mellitus (T2DM), and hypercholesterolemia which might lead to coronary diseases and cancer development and progression.

Here we demonstrate that addition of cholesterol to MC-38 Colon adenocarcinoma as well as to MVT-1 Mammary Tumor results in higher proliferation rate then un-treated cells. Moreover, by using gene-array and western blot analysis, we saw that cholesterol stimulates several metabolic pathways such as the Phosphatidylinositol 3-kinases (PI3K) and AP-1 transcription factor super-family such as C-Jun and Jun-B. Interestingly, inhibition of the PI3K pathway results in decreased transcription of C-Jun and Jun-B as well as the Chemokine (C-X-C motif) ligand 1 (CXCL1).

These results lead us to the conclusion that cholesterol via different signaling pathways maybe involved in cell proliferation, and determining the exact process will help in understanding its effect on cancer proliferation.

NORMAL URINARY FREE CORTISOL AS PITFALL IN DIAGNOSIS OF CUSHING DISEASE IN CHILDREN: ALTERNATIVE WORKUP OPTIONS

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Introduction: Cushing disease is a rare cause of weight gain and growth deceleration in children, diagnosed by elavated urinary free cortisol (UFC).

Aim: To describe Cushing disease with normal UFC and suggest alternative workup options.

Patients: Patient 1 – Nine years old boy with altered behavior, obesity and blunted growth. On physical examination truncal obesity and hyperpigmentation. UFC normal in 3 different laboratories. Overnight 1 mg dexamethasone suppression test abnormal. 2 days 2 mg dexamethasone suppression test abnormal followed by CRH test abnormal. Midnight cortisol level elevated. 24 hours cortisol profile showed no diurenal variation. Normal pituitary MRI twice and suspected microadenoma in a third MRI. During operation an microadenoma found on the opposite side to the one found on the MRI was removed but the pathology report was negative. After hours from surgery cortisol level dropped and steroid therapy was began. During half a year he lost10 kgand grew7 cm.

Patient 2 – Thirteen years old girl with obesity and blunted growth. She lost11 kgon diet before admission. On physical examination mild obesity and hyperpigmentation. UFC elevated. MRI showed pituitary maroadrnoma which was removed. 2 years later UFC and 1 mg dexamethasone suppression test were normal. 2 days 2 mg dexamethasone suppression test abnormal followed by CRH test abnormal. Pituitary MRI showed suspected microadenoma. During operation an microadenoma was found in the cavernous sinus and was removed. The pathology report was positive.

Conclusions: NormalUFC do not exclude the diagnosis of Cushing disease nor do normal MRI or normal pathology report. If clinical findings support the diagnosis alternative diagnostic options including overnight 1 mg dexamethasone suppression test , 2 days 2 mg dexamethasone suppression test followed by CRH test ,midnight cortisol level and 24 hours cortisol profile should be considered.