Early metabolic effects of bariatric surgery in type II diabetic patients

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Introduction: The effect of bariatric surgery on glycemic control of diabetic patients has been extensively studied. Diabetes resolution after bariatric procedures is reported to be as high as 85%. The degree of hyperglycemia improved in most cases shortly after surgery. Yet, there is a relative paucity of data regarding the metabolic outcomes of bariatric operations in Israel. The aim of this study was to examine the early effects of surgery on weight loss as well as glycemic control parameters in one medical center in Israel..

Patients/ Methods: One hundred and seventy seven patients underwent bariatric procedures in our hospital during the last two years (2008-9). Of those, 37 (20.9%) were diabetic. Pre- and postoperative data was studied retrospectively. The parameters chosen were: weight, fasting glucose, HBA1C, dosage of anti diabetic drugs and lipid profile.

Results: Twenty eight patient's records were available for analysis. One patient died few days after surgery from massive Pulmonary emboli and another 8 patients were lost to follow up. The mean follow-up period was 9 months. Twenty two patients underwent sleeve gastrectomy (21 laparoscopic and one open), 4 underwent laparoscopic Roux-en-Y gastric bypass and 2 underwent gastric banding. Mean body mass index (BMI) before surgery was 41.9 (±4.9) and the mean weight was 116.6Kg (±15.6). Significant weight reduction was observed at 1, 3 and 6 months after surgery with mean weight reductions of 11.3, 19.3 and 27.1 kilograms respectively ($p<0.05$). Three months after surgery, subjects lost 42.2% (±13.5%) of their excess weight and after 6 months the excess weight loss reached 58.1% (±22.3%). Improvement in diabetic control was observed in the vast majority of patients (27 of 28) and diabetes remission in 9 patients (32.1%). Thirteen patients were treated with insulin before surgery. Of those, 5 stopped insulin treatment after surgery and the other 8 decreased their daily dose by more than half. After the operation, triglyceride level decreased from 207±129 mg/dl to 148±66 mg/dl, ($p=0.026$) with no influence on HDL or LDL levels. The subgroup of patients who experienced complete normalization of carbohydrate metabolic parameters (9 patients) had lower HbA1C before surgery (7.23 versus 8.79 $p=0.016$) and were less likely to have received insulin preoperatively (2 of 9 versus 11 of 18, $p=0.077$), compared to the non-cure group. The following parameters did not influence the chances of diabetes resolution: age, gender, pre–intervention BMI, rate or magnitude of weight loss or the type of surgery.

Conclusions: Our data suggest a lower rate of diabetes resolution than the rates previously reported. Improvement of diabetes control after bariatric surgery was observed in most of our patients (96.4%), which is consistent with previous data. Patients who were better controlled and possibly patients who were treated by oral anti diabetic agents had a higher rate of diabetes resolution. Surprisingly, our results did not support the correlation between the magnitude of weight loss and the chance of diabetes remission.

Cortisol, but not ACTH/CRH, increases circulating ghrelin in man

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Introduction: We have recently explored the involvement of ghrelin in the eating response to stress in humans and found that ghrelin levels increased in parallel to cortisol after a standardized psychological stress. To further elucidate this interaction, we examined the ghrelin response to pharmacological manipulation of the HPA axis.

Patients/ Methods: Following approval from the local Ethical Committee, six lean, healthy male volunteers were examined on two occasions. Blood samples were collected every 30 minutes for two sequential periods of two hours. Initially, a baseline period was followed by intravenous injection of ACTH 250 μg. Subsequently, metyrapone (2-3 g) was administered at midnight and in the following morning the initial 2-hour sampling was followed by intravenous injection of hydrocortisone 100 mg.

Results: Mean total ghrelin levels during the 2-hour period after metyrapone administration was significantly lower than during the period following ACTH administration ($p=0.033$). After ACTH stimulation, there was a positive correlation between total ghrelin and cortisol AUC ($r=0.876$, $p = 0.021$). Mean acylated ghrelin levels were lower during the post metyrapone sampling than in the baseline period ($p=0.058$). Furthermore, acylated ghrelin levels significantly increased after acute hydrocortisone administration ($p = 0.032$) and was positively correlated with the decrease in ACTH ($R = 0.825$, $p = 0.043$) and the increase in cortisol ($r = 0.86$, $p=0.06$). There was a highly positive correlation between total and acylated ghrelin levels during all phases of the study ($r=0.96$, $p=0.002$).

Conclusions: In conclusion, increased cortisol levels secondary to ACTH stimulation or hydrocortisone administration is associated with increments in plasma ghrelin levels, whereas central stimulation of the HPA axis by blocking cortisol synthesis with metyrapone is associated with decreased plasma ghrelin levels. Collectively, this suggests that stress-induced elevations in ghrelin levels may be secondary to the rise in peripheral cortisol, independent of central elevation of ACTH and possibly CRH levels.

The coexistance of TSH receptor and thyroperoxidase mutations in the same kindred

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Introduction: Inherited hypothyroidism occurs in approximately 1 of 20,000 live births. We recently reported a high prevalence of mutations of the thyroperoxidase (TPO) and TSH receptor (TSHR) genes in consanguineous communities of Northern Israel. The aim of the present study was to determine the genetic background of an extended family with familial occurrence of congenital hypothyroidism (CH) and high rate of hyperthyrotropinemia.

Patients/ Methods: Thirty members belonging to extended kindred of an Arab-Muslim origin, two of whom with CH were enrolled. TSHR and TPO gene mutations were detected by sequencing.

Results: Three novel nucleotide substitutions in the extracellular region of the TSHR were identified in the same allele, two of which produced amino acid substitutions (Q90P and P264S). As one of the 2 subjects with CH had no TSHR gene mutation, other gene defects were sought. Two TPO gene mutations (G493S and R540X), which we previously described in the same population, were identified in different alleles. Thirteen individuals were heretozygous for the TSHR mutation, 9 of which were also heterozygous for one of the two TPO gene mutations. Of the 17 individuals heterozygous for one of the two TPO gene mutations, 4 had normal TSHR alleles. Of the 2 individuals with CH, one was homozygous for the TSHR gene mutation and one was compound heterozygous for the TPO mutations. Another homozygote for the TSHR mutation was born prior to the institution of neonatal screening. Genotype-phenotype correlation based on TSH concentration revealed no differences between heterozygotes for either TPO mutations (N=8) and WT (N=6). In contrast, heterozygotes for the TSHR mutation had significantly higher TSH compared to WT family members (7.1±0.3 vs. 2.3±0.5). TSH values in the two homozygotes for the TSHR mutation were 31 and 58 mU/L, and both had low FT4 levels.

Conclusions: Mutations of TPO and TSHR genes were found to coexist in the same consanguineous kindred. Patients homozygous for the TSHR gene mutation and compound heterozygous for the TPO gene mutation presented with hypothyroidism. The mild hyperthyrotropinemia of heterozygotes with the TSHR gene mutation was not aggravated by the coexistence of a TPO defect in only one allele.

Impact of pregnancy on outcome and prognosis of survivors of differentiated thyroid cancer

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Introduction: Differentiated thyroid cancer usually affects women of child-bearing age. During normal pregnancy, several factors may have a stimulatory effect on normal and nodular thyroid growth. The present study aimed to determine if pregnancy in thyroid-cancer survivors poses a risk of progression or recurrence of the disease

Patients/ Methods: A retrospective evaluation of consecutive women who were followed at a single Endocrine Institute for differentiated epithelial thyroid cancer and who had at least one pregnancy and delivery after receiving treatment for thyroid cancer between 1992 and 2009. The patients' medical records were reviewed for data including age at diagnosis, pathological cancer staging, number of operations, number and doses of radioactive iodine treatments the patient underwent, interval from diagnosis to pregnancy, thyroglobulin (Tg) levels and neck ultrasound findings before and after pregnancy, and thyroid stimulating hormone (TSH) levels during pregnancy. Tg levels and neck ultrasound findings were compared before and after pregnancy. Disease progression in pregnancy was defined as a significant increase in Tg level, a new imaging finding or enlargement of a known pre-pregnancy mass suggestive for thyroid cancer metastasis within a year after delivery. The demographic and disease-related characteristics and levels of TSH measured in pregnancy were correlated with disease progression during pregnancy using Pearson correlation analysis.

Results: Sixty-three women met the study criteria. The mean time to the first delivery after completion of initial thyroid-cancer treatment was 5.16±3.76 years, the mean duration of follow-up after delivery was 4.66±3.75 years. Forty women had one and 23 women had more than one delivery, for a total of 90 births. Biochemical and/or imaging evidence of thyroid cancer progression during the first pregnancy after treatment was documented in 9 patients (14.2%). Three of them also showed disease progression during a second pregnancy. Another 3 patients showed no disease progression during the first pregnancy but did so during the second. TSH was measured 4.87±2.24 times during pregnancy and mean TSH level was 2.53±4.03 mIU/ml. There was no correlation of most of the indices evaluated with disease progression during pregnancy. A strong positive correlation with cancer progression during pregnancy was noted for persistence of thyroid cancer before pregnancy and total I-131 dose administered.

Conclusions: Pregnancy does not cause thyroid cancer progression or recurrence in thyroid-cancer survivors who have no structural or biochemical evidence of disease persistence before pregnancy. However, in the presence of such evidence, disease progression may occur during pregnancy, yet not necessarily as a consequence of pregnancy. A non-suppressed TSH level during pregnancy does not stimulate disease progression in thyroid-cancer survivors and may be an acceptable therapeutic goal, especially in those with a history of miscarriages or preterm deliveries.

Radioiodine therapy for graves' disease is associated with increased rate of the metabolic syndrome

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Introduction: Although the treatment of Graves' thyrotoxicosis with radioactive iodine is generally perceived as clinically efficient, cost effective and safe, most radioiodine-treated patients become hypothyroid rapidly after radioiodine treatment and need life-long thyroxine replacement. Further, observational studies show that radioiodine therapy is linked to increased mortality due to cardio- and cerebrovascular disease. Here we evaluated the cardiometabolic outcome of radioiodine-treated (RI) vs. medically treated (Med) subjects with Grave's disease as assessed after ≥ 3 years of follow up.

Patients/ Methods: All subjects were actively recruited to undergo complete physical examination and blood testing which included glucose, HBA1C, CRP, liver, kidney and thyroid function. Non-diabetic patients also underwent 75 gram oral glucose tolerance test. Arterial stiffness was evaluated using applanation tonometry and pulse wave analysis by different standard devices which assess distinct measures of arterial stiffness: pulse wave velocity (PWV), augmentation index, and large/small artery compliance (C1 and C2). Additionally, all subjects were referred for ambulatory blood pressure monitoring.

Results: Sixty five RI-treated and 33 Med-treated patients with Graves' disease were included in the study. Mean age (53±12 vs. 48±13.6, p=NS), gender (M-28% vs. 21%, p=NS), duration of the disease (5.2 vs. 5.3 yrs, p=NS), and thyroid function tests (TSH: 2±1.4 vs. 1.6±1.1, p=NS) were similar in the RI and Med groups, respectively. Post-RI-therapy patients had higher BMI, waist circumference, systolic blood pressure, PWV, hs-CRP levels, higher prevalence of the metabolic syndrome and lower C2 than antithyroid drug-treated patients. After adjustment to age and gender RI- treated patients had higher BMI (27.4±5.7 vs. 24.3±3.6, p=0.03), hs-CRP levels (4.14±5.3 vs. 1.62±1.44, p=0.047), and higher prevalence of the metabolic syndrome (52.3 vs.15.6%, p=0.003).

Conclusions: Radioiodine treated patients with Grave's disease gain more weight and have higher rate of the metabolic syndrome compared with medically treated subjects with this condition. The difference is seen despite normal and indistinguishable thyroid hormone levels with thyroxin treatment. We suggest that in the choice between these two major therapeutic modalities, physicians and patients should be aware of this emerging difference in outcome. Additionally, RI-treated patients should be carefully followed in an attempt to reduce the risk of weight gain and the metabolic syndrome.

Prognostic value of post thyroidectomy thyroglobulin levels in patients with differentiated thyroid cancer

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Introduction: Thyroglobulin (Tg) is an excellent biological marker for recognition of persistent or recurrent thyroid cancer. Most studies have looked at the diagnostic value of Tg but not at the prognostic value over time. Furthermore, very few studies evaluated the prognostic value of Tg levels at the early point after total thyroidectomy and before iodine ablative treatment.

Patients/ Methods: Our center has a registry of patients with well differentiated thyroid carcinoma who were followed at our institute since 1973. In the present study, data on the clinical, laboratory and outcome characteristics of 420 patients with post operative and preablation Tg values (baseline thyroglobulin) after total thyroidectomy were collected from the registry.

Results: Patients were classified into 4 groups according to baseline Tg levels (0-2, 2-10, 10-100, >100 ng/ml). Higher Tg levels were associated with a shift to male gender, larger tumor size (P=0.01, P=0.02 respectively) and more extensive disease (P<0.0001). In addition, higher Tg levels were related to persistence of disease and disease presence at last follow up (P<0.0001). The 10 ng/ml cut-off level identified patients with persistent disease with a sensitivity and specificity of 73%, PPV 43% and NPV 89%. In multivariate analysis the following variables were predictive of persistent disease: baseline Tg levels, male gender, lymph node involvement, distant metastases, higher invasiveness and larger tumor size. Yet, the predictive power of baseline Tg levels was relatively weak (OR 1.002, 95% CI 1.00-1.04).

Conclusions: Post-operative Tg level is a weak prognostic marker, however it can be used with other disease characteristics in decision making regarding treatment and follow-up of well differentiated thyroid carcinoma patients.

Papillary Microcarcinoma of the Thyroid

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Introduction: No increased mortality has been reported in patients with thyroid microcarcinoma (PMC), however neck recurrences and distant metastases have been described. The study aim was to compare patients' outcomes after total thyroidectomy versus hemithyroidectomy for treatment of PMC.

Patients/ Methods: Two hundred ninety-three patients from two major medical centers in Israel were included. The mean follow-up period was 7.2±6.8 years.

Results: Total thyroidectomy (TT) was performed in 214 patients and hemithyroidectomy (HT) in 79 patients. Mean tumor size was 6.3±3 mm. Lymph node metastases and extraglandular extension were more frequent in the TT group than in the HT group, 24.8% vs 1.3 ($p<0.001$) and 11.7 vs 3.8 ($p=0.042$), respectively. Permanent complications were also more frequent in the TT group than the HT group (14.0% vs 5.1%) ($P=0.034$). The cumulative incidence of recurrence at the end of follow-up was 11.6% in the TT group and 14.3% in the HT group (p=NS). Considering low risk patients only (monofocal tumors, no lymph-node involvement, n=74 in the TT group vs n=66 in the HT group) neck recurrence was found in 9% of patients in the HT group but none in the TT group. In the HT group all locoregional recurrences were diagnosed using ultrasonography, compared to 50% in the TT group. The incidence of recurrence was higher in patients with multifocal tumors and lymph-node involvement in both groups.

Conclusions: Hemithyroidectomy is associated with a lower rate of complications compared with total thyroidectomy, however higher rate of locoregional recurrences should be expected.