by dormant primordial follicles (PMF) which are necessary to maintain female reproductive function. There is a continuous repression of PMF activation in early growing follicle through the balance between factors activating the initiation of follicular growth, mainly actors of the phosphatidylinositol-3-kinase (PI3K) signaling pathway, and inhibiting factors such as Anti-Müllerian Hormone (AMH). Any alteration of this equilibrium may induce early follicle depletion and subsequent infertility. Cyclophosphamide (Cy) one of the alkylating agents commonly used for treating breast cancer is able to trigger PMF activation further leading to premature ovarian insufficiency. Preventing chemotherapy-induced ovarian dysfunction might represent an option for preserving optimal chances of natural or medically assisted conceptions after healing.

We showed in a model of Cy-treated pubertal mice, that AMH administration was able to restrain PMF depletion by counting the total PMF number within mouse ovaries. Moreover, the PI3K signaling pathway was evaluated following Cy administration with and without AMH injection. We showed that AMH decreased the phosphorylation of FOXO3A, a transcription factor of PMF activation and induced its nuclear translocation. Altogether, the results support a protective role of AMH against Cy-induced follicular loss. To better understand AMH action in the ovary, we investigated the molecular mechanism to explain the protective effect of this hormone on the PMF pool. It has been reported that autophagy, a lysosomal degradative ubiquitous process implicated in cellular homeostasis, was involved in both ovarian follicular death and survival mostly by PI3K pathway (Gawriluk et al. Reproduction 2011 141, 759–765). We show in mice that Cy inhibits autophagy in the ovary while AMH induces autophagy. *In vivo* analysis of autophagic flux is currently in progress to dissect this process more finely. Interestingly, FOXO3A was shown to be related to autophagy activation. To investigate the role of FOXO3A in AMH-induced autophagy further, we analyzed mRNA and protein expression of autophagy-related genes controlled by FOXO3A, including BECLIN-1, ATG12, ULK1, BNIP3, GABARAP, and LC3B. These findings establish a close relationship between AMH and autophagy to protect PMF stockpile and to limit follicular depletion induced by Cy.

Adipose Tissue, Appetite, and Obesity
NEURAL MECHANISMS OF OBESITY

Growth Hormone-Releasing Hormone (GHRH) Antagonists Stimulate Feeding in Mice

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SAT-603

Growth hormone-releasing hormone (GHRH) is a hypothalamic neuropeptide which stimulates the synthesis and secretion of growth hormone (GH) in pituitary gland. GHRH was also found to modulate food intake in mammals. MIA-690 is a synthetic GHRH antagonist of the Miami (MIA) series with potent antitumor effects. To date, its role in hypothalamic feeding modulation has not been evaluated. In the present study, we aimed to investigate the effects of chronic MIA-690 administration on feeding behavior, locomotor activity and hypothalamic dopamine (DA), norepinephrine (NE), serotonin (5-hydroxytryptamine, 5-HT), orexigenic peptides [agouti-related peptide (AgRP) and neuropeptide Y (NPY)] and anorexigenic peptides [cocaine and amphetamine-regulated transcript (CART) and proopiomelanocortin (POMC)] activity.

Adult C57/BL6 mice were treated daily for 4 weeks by subcutaneous administration of (5 µg) MIA-690 or vehicle solution. Food intake and body weight were recorded every 4 days throughout the study. Immediately after the last injection, locomotor activity in the home cage was recorded, and thereafter animals were sacrificed. Visceral, subcutaneous and brown fat depots were quickly excised and weighed. Hypothalamus was also dissected for evaluating gene expression of AgRP, NPY, CART and POMC by real-time reverse transcription polymerase chain reaction. In addition, hypothalamic DA, NE and 5-HT levels were measured by high performance liquid chromatography (HPLC) coupled to electrochemical detection.

Our findings show that administration of MIA-690 increased food intake and body weight, without affecting locomotor activity. No difference was observed in visceral, subcutaneous and brown fat mass in animals treated with MIA-690 or vehicle. As for neuromodulatory effects, a significant increase of AgRP gene expression and NE levels, along with a reduction of 5-HT levels were found after MIA-690 treatment. On the other hand, we did not observe any alteration in NPY, POMC and CART gene expression, as well as DA levels, following MIA-690 administration.

In conclusion, chronic peripheral administration of MIA-690 could play an orexigenic role paralleled by increased body weight. The stimulation of feeding could be mediated, at least in part, by increased AgRP gene expression and NE levels and decreased 5-HT levels, in the hypothalamus.

Thyroid
THYROID NEOPLASIA AND CANCER

Pre-Operative Calcitonin Value as a Predictive Factor of Cancer Related Death in Sporadic Medullary Thyroid Carcinoma

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OR21-01

Introduction: Medullary thyroid carcinoma (MTC) is a rare tumor, it originates from the C cells producing calcitonin (CT) and can occur as sporadic or associated to germline RET mutation. The initial treatment is represented by total thyroidectomy associated with central

compartment lymph nodes dissection and possible extension to the laterocervical compartment. CT is the main marker of follow-up of MTC, conversely its pre-operative role as diagnostic and prognostic factor is still debated. The aim of the present study was to evaluate several predictive factors of cancer related death in a large series of sporadic MTCs. **Patients and Methods:** We evaluated 537 consecutive patients surgically treated for sporadic MTC, from 2000 to 2019, and followed at the Operative Unit of Endocrinology 1 of the University of Pisa. We evaluated epidemiological, clinical and pathological data and pre and post-operative CT values, and their correlation with cancer related death. **Results:** At the end of the follow-up (average 75 months), 300/537 (55.9%) pts were cured, 100/537 (18.6%) pts showed biochemical disease, 88/537 (16.4%) pts showed metastatic disease and 49/537 (9.1 %) pts died for the disease. The factors significantly correlated with the cancer related death to the univariate analysis were the male gender, dimension of the primary tumor> 4 cm, the presence of lymph node metastasis to histology (N1) and/or distant metastasis (M1) at the time of diagnosis, multifocality, minimal extrathyroidal extension (mETE), initial staging, pre-operative CT values> 500 pg/ml and post-operative> 20 pg/ml. At multivariate analysis, statistical significance persisted only for pre- and post-operative CT and for the staging. **Conclusions:** 1) In our study we observed a significant improvement in the outcome and survival in the medium-long term of sporadic CMT patients, compared to the previous studies. 2) A more advanced staging at the time of diagnosis has been confirmed as a negative prognostic factor and it is evident that an early diagnosis is an essential requirement for improving cancer related death. 3) This is the first study that showed, in a large monocentric series of sporadic MTCs, as pre-operative CT represents a prognostic factor associated with cancer related death, as well as the value of post-operative CT.

Thyroid
BENIGN THYROID DISEASE AND HEALTH DISPARITIES IN THYROID II

Graves' Disease Displayed as a Risk Factor of Vertebral Fracture Even in Premenopausal Women

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SUN-412

Abstract:
Background
Hyperthyroidism is a known risk factor for osteoporosis and fractures especially in older men and postmenopausal women. However, it remains unclear whether younger patients with Graves' diseases are at a higher risk of fracture compared to healthy individuals.
Objective
This study aimed to clarify whether premenopausal women with Graves' disease represents a risk factor for vertebral fracture (VF).
Patients and Methods
We enrolled 30 premenopausal women (mean age, 32 ± 10 years) who were diagnosed with Graves' disease at our institution between April 2007 and December 2017. We also enrolled 40 healthy control women who visited our hospital. The control subjects were confirmed to have no endocrine disease or any condition that might affect bone metabolism. None of the study subjects had taken drugs known to influence bone and calcium metabolism such as vitamin D, bisphosphonates, or glucocorticoids. Also, none has taken an oral contraceptive. Serum and urinary biological parameters, alkaline phosphatase (ALP), glycosylated hemoglobin (HbA1c), creatinine, serum calcium, total cholesterol, intact parathyroid hormone, free triiodothyronine (Free T3), free thyroxin (Free T4), thyroid-stimulating hormone (TSH) and urinary type I collagen cross-linked N-telopeptides (NTX; a bone resorption marker) were compared between the groups. Bone mineral density (BMD) of the lumbar spine and femoral neck was determined using dual-energy X-ray absorptiometry and vertebral fractures were diagnosed from lateral X-rays of the thoracic and lumbar spine. The chi-square and unpaired t-tests for two groups comparison were utilized to determine the statistical significance ($P < 0.05$). Multiple logistic regression analyses were proceeded after adjustments for variables.
Results
Patients with Graves' disease displayed the higher ALP, eGFR, Ca, free T3, free T4 and urinary NTX levels, and lower body mass index (BMI), Alb, total cholesterol and intact PTH compared to controls.
The prevalence of VFs was significantly higher in patients with Graves' disease (20.0%) than in controls (2.5%, <0.05). Such association remained significant even after adjustment for age, BMI, ALP, eGFR and free T3, but except for BMD. Among premenopausal patients with Graves' disease, the values of several parameters, such as BMI, ALP, HbA1c, serum Ca, intact PTH and BMD and the prevalence of thyroid related antibodies did not differ significantly between those with and without VF; subjects with VF were older and exhibited lower free T3, free T4 and urinary NTX levels compared to subjects without VF. The mean value of lumbar BMD T score in subjects with VF among premenopausal patients with graves' disease was -1.0, indicating osteopenia.
Conclusions
VF risk could be elevated even in the premenopausal women with Graves' disease, although the BMD risk levels is not equivalent to that of osteoporosis.

Pediatric Endocrinology
PEDIATRIC GROWTH AND ADRENAL DISORDERS

Positive Effect of an Early Start of Growth Hormone Therapy on Auxology and Metabolic Parameters in Children with Prader Willi Syndrome

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SAT-092

Introduction:Prader-Willi-Syndrom (PWS) is a rare multisystem genetic disorder characterized by hypothalamic-pituitary dysfunction. Various characteristic