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Report of Scientific Activity

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Clinical and histopathological characteristics of differentiated thyroid cancer in two reference italian centers belonging to geographical areas exposed to different risk factors

Background and aim of the study

The incidence of the differentiated thyroid cancer (DTC) has been increasing in many countries over the last 30 years. This is almost exclusively due to an increase in the papillary thyroid carcinomas variant (PTC). Despite the most part of PTC consists in indolent micro/small carcinomas, the mortality rate has not decreased. Therefore, even if the increased incidence could be attributed to a better diagnostic accuracy, we cannot exclude environmental and lifestyle causative factors.

Aim of the study

The aim of our study was to retrospectively evaluate the clinical and histopathological characteristics of patients with DTC referred to two Italian centers, the University Hospital (AOU) "Maggiore della Carità" in Novara and the University Hospital (AOU), Federico II in Naples, in order to assess whether the different environmental factors to which the two territories are exposed, might affect thyroid tumorigenesis induction. According to ARPA (Regional Agency for Environmental Protection) data, the population of Novara is exposed to industrial chemicals (formaldehyde and benzene) while Naples area is exposed to minerals of volcanic origin (nitrates, vanadium, manganese and other heavy metals).

Patients and Methods

1081 patients with newly diagnosis of DTC referred to the two centers from January 2000 to December 2013 were included. Patients were subdivided into two groups, according to the centre of origin: group A (474 patients of Novara) and group B (607 patients of Naples).Patients data were collected through retrospective medical record review regarding patient demographics and clinical aspects (age, gender, body mass index, ioduria, type of surgery) and histological reports including information about tumoursize, extrathyroidal extension, multifocality, lymphonodal (LN) metastasis, and presence of peritumoral thyroiditis.
Environmental and occupational exposures were identified through a direct interview for each patient. Patients with history of neck irradiation, poorly differentiated, anaplastic, medullary thyroid carcinomas and secondary tumors or living for less than 5 years in the analysed areas were excluded. Smoking, hormonal and genetic factors were not investigated. Clinical outcomes, progressions and death were not analysed in this study.
Histological diagnoses were blindly determined by two independent pathologists, specialised in thyroid pathology, belonging to the two centers. Pathologic staging was redefined according to the Tumor, Lymph Node, and Metastasis classification system based on the 6th edition of the UICC/AJCC TNM classification. For all cases, tumour-associated thyroiditis was assessed. The histological criteria used to make this diagnosis included diffuse lymphoplasmacytic infiltration, germinal centers, and enlarged epithelial cells with large nuclei and eosinophilic cytoplasm (Hurthle cells), which are specific for Hashimoto's thyroiditis (HT) and also polynuclear macrophage-like

and fibroblastic-like population specific for non-specific lymphocytic thyroiditis, which might represent perineoplastic inflammation, when occurring immediately adjacent to a tumor.

Results

About 30.0% of patients belonging to the Group A were employed in the textile sector and about 25.0% in the engineering industry. The Group B population came from the areas around the volcano Vesuvius and Campi Flegrei (an active sunken volcanic area). No significant difference was found in gender, whereas the age at diagnosis was earlier in the group B (group A 53.1±15.16 years vs group B 41.9±14.25 years, $p<0.001$). In both groups, the most frequent histotype was PTC with a prevalence of follicular variant in group A (37.3% group A vs 19.9% group B, $p<0.0001$) and with a prevalence of classical variant in group B (36.9% group A vs 63.8% group B, $p<0.0001$). The diagnosis of microcarcinoma was more frequent in group A ($p<0.0001$) with a more aggressive behavior such as bilaterality ($p<0.0001$), multifocality ($p<0.0001$) and capsular invasion ($p<0.0001$) respect group B. In both groups, tumour-associated thyroiditis showed a significant progressive increase over the years, in both populations ($p<0.05$).

Conclusions

The more sensitive and widespread diagnostic procedures can only partially justify the progressive increase in DTC in Naples and Novara. Environmental factors such as occupational exposure in the population of Novara and contamination of volcanic minerals in the population of Naples could justify the differences found in our study. These preliminary data should stimulate the need for an Italian Cancer Registry of DTC in order to allow a correct epidemiological characterization, which could enable the identification of specific etiological factors and an improvement in the management of the disease.

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Endotrial SIE: an Italian Survey on diagnosis and clinical management of primary hypothyroidism (EDIPO): an ongoing study.

Background

Primary hypothyroidism is a common disease. Several guidelines on its diagnosis and management are available and monotherapy with oral levothyroxine (L-T4) is the standard treatment. The estimated adherence to L-T4 therapy is 68.4% in the United States. Difficulty to reach euthyroidism could be explained by factors affecting the L-T4 absorption or by a poor adherence to therapy in 40% and 60% of patients, respectively. However no methods to evaluate adherence to L-T4 therapy are available. Morisky-Green Medical Adherence Scale-8 items (MMAS-8) represents the

most used questionnaire to evaluate medical therapy adherence. MMAS-8is simple, fast and economical and evaluates the principal limits to adherence to a specific therapy. MMSA-8 was created in 2008 for antihypertensive therapy and was subsequently validated in several languages and for other diseases, but not for hypothyroidism.

Aim of the study

1) to evaluate adherence of the Italian endocrinologists to the principal guidelines for the management of patients with a first diagnosis of primary hypothyroidism;
2) to validate the MMAS-8 questionnaire for the therapy of hypothyroidism. Secondary endpoints will be the identification of most prescribed drugs, dosages and L-T4 formulations and the evaluation of adherence according to different L-T4 formulations.

Subject and methods

It will be a prospective, multicentre and observational study, involving 13 Italian Endocrinological Centres. We will enrol all new hypothyroid patients affering to the participating Centres in 6 months. Exclusion criteria will be: age <18 years, surgery for thyroid cancer, central hypothyroidism, pregnancy and patients on L-T4 therapy. Each clinician will record anamnesis, examinations,therapy and follow-up for all patients enrolled. Special attention will be given to factors that could interfere with the management of hypothyroid patients (e.g. cardiovascular diseases, known interferences with L-T4 absorption, etc.). In case of a follow-up visit the same data will be recorded and the MMAS-8questionnaire will be filled inby patients on l-T4 therapy. All data will be included in an electronic database. Data will be analyse by the coordinating centre, Unit of Modena. So far about 250 patients were enrolled for this study.

Expected result

We estimate to analyse a cohort of 1000 patients. We expect to be able to evaluate the adherence to the principal guidelines on the management of hypothyroidism and possibly to identify differences among the participant centres in Italy. This study could be the first step to validate the MMAS-8 questionnaire for hypothyroidism, allowing a better comprehension of the causes of L-T4 therapy low adherence. This study could lead to future actions aiming at improving L-T4 adherence, validating a new important tool in chronic treatment evaluation, suggesting future adjustment in clinical practice in the hypothyroidism management.

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Relation between the Body Mass Index, adipokines levels and clinical-pathological features of thyroid cancer

Background

Obesity is a worldwide major health issue with an increasing prevalence.

Increasing incidence of differentiated thyroid cancer (DTC) has been observed in both women and men across all tumour sizes. Epidemiological studies have shown that obesity is associated with an increased risk of thyroid cancer;moreover, a systematic review of prospective observational studies showed a positive association between Body Mass Index (BMI) categories at diagnosis and the risk of developing DTC in both sexes and young adults,and, more recently, a cross-sectional study demonstrated that BMI is a significant predictor of DTC in women but not in men.

However, the exact nature of the relationship, especially with respect to the behaviour of the cancer, remains uncertain.

The increased serum level of TSH, frequently observed in obese patients, might play a role, as TSH is a growth factor for thyroid cells and a predictor of malignancy in thyroid nodules. Moreover, a

potential role for insulin, insulin-like growth factor (IGF), growth hormone (GH) secretagogues and adipokines was also postulated. In fact, the insulin–cancer hypothesis postulates that hyper-insulinemia, a common finding in obesity, would decrease the concentrations of IGF binding protein (BP)-1 and IGFBP-2, which, in turn, would increase the bioavailable free IGF-Ithat may play a role in the tumour formation and progression due to its mitogenic and anti-apoptotic effects.
Further potential links between obesity and DTC, might be ghrelin, the GH-secretagogue receptor (GHS-R), and obestatin, which are expressed in cancer tissues. A study in patients with papillary thyroid cancer found that the malignancy was associated with low circulating level of ghrelin, a condition which is typically observed in obese individuals.
In conclusion, the question of whether the epidemics of obesity might be responsible for the increased incidence rate of DTC is still an open matter of debate.

Aim of the study

The aim of our prospective study is to evaluate the correlation between the BMI and clinico-pathological features of thyroid cancer patients.
Moreover we aim to investigate the relation between the patients and tumours characteristics, serum levels of ghrelin, obestatin, insulin, IGF-BPs and obestatin and ghrelin expression in neoplastic tissues.

Patients and Methods

We are enrolling 80 consecutive patients from 2 centres (Maggiore dellaCarità Hospital-Novara and Molinette Hospital–Turin) with newly cytological diagnosis of THYR3-THYR4-THYR5, waiting for surgery.
Of each patient we are collecting anthropometric data (gender, age, weight, height, BMI, waist circumference, hip circumference) before surgery.
We are evaluating the histological examination of all cases. Patients with histological diagnosis of differentiated thyroid cancer will be included.
Of each patient we are taking blood samples to evaluate TSH, fT3, fT4, Thyroglobulin, Anti-Thyroglobulin Antibodies (TgAb), Anti-Thyroperoxidase Antibodies (TPOAb), calcitonin before surgery and during follow up after treatment.
Moreover we are taking blood samples to evaluate ghrelin, obestatin, insulin, IGF-BPs, before surgery, one month after, 6 months after and 12 months after treatment.
Tissues of all patients enrolled will be used to evaluate ghrelin and obestatin expression, with immunohistochemistry, immunofluorescence and RNA isolation with quantitative real-time PCR.
Patients will be divided into 3 groups, according to their BMI:

- group A: BMI < 25;
- group B BMI > or = 25 and < 30;
- group C BMI > or = 30.

Each group will be divided into 2 subgroups, according to age:

- group 1 < 45 years;
- group 2 > or = 45 years.

Finally we will perform statistical analysis and comparison between the different subgroups.

Until now 30 patients have been enrolled.

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DEPARTMENT OF GENERAL MEDICINE, SAN GIUSEPPE HOSPITAL, ISTITUTO AUXOLOGICO ITALIANO, PIANCAVALLO - Projects

Thyroid function and obesity

Background

During the last few decades, the prevalence of obesity has increased worldwide. This condition is associated with a higher risk of all-cause mortality especially cardiovascular disease, diabetes, dyslipidemia and cancer. Thus, obesity is a potential cause of premature mortality among middle-aged adults. Moreover it is associated with many endocrine dysfunctions, including thyroid disorders. In the last years, an increased interest on the relationship between thyroid function and obesity occurred. In particular thyroid hormones are involved in the regulation of basal metabolism and thermogenesis, playing an important role in lipid and glucose metabolism, fat oxidation and food intake. Although thyroid function is usually normal in obese patients, several studies have demonstrated that thyrotropin (TSH) and body mass index (BMI) are positively related, in particular TSH levels are slightly increased (usually below 10 IU/l) in obese patients compared to normal weight people.Furthermore, also a positive correlation between weight gain during 5 years and a progressive increase of serum TSH has been demonstrated. Nevertheless, several studies have excluded clinically considerable hypothyroidism in obese patients with moderately elevated TSH levels. Different studies have suggested several causes of increased TSH, in particular subclinical hypothyroidism caused by iodine deficiency or autoimmune thyroiditis, derangement in the hypothalamic-pituitary axis, thyroid hormone resistance and adaptation process to increase energy expenditure. Reinehr et al and Rotondi et al demonstrated that only a minority of obese subjects with increased TSH levels suffered from autoimmune thyroiditis, while the majority had a moderately increased TSH values without any thyroid disease. Besides several studies argued that the increase in TSH levels was not attributed to iodine deficiency or autoimmune diseases. Moreover, a dysfunction of the hypothalamic-pituitary axis resulting in an abnormal secretion of TSH, could be a cause of elevated TSH levels. In fact the adipocyte derived hormone leptin has been demonstrated to alter the hypothalamic-pituitary secretion.Furthermore, the increased TSH levels could be due to hormone resistance. As a matter of fact in obesity T3 receptors are decreased as well as the negative feedback between TSH and the peripheral thyroid hormones, leading to increased levels of TSH and T3. On the contrary the increase of both TSH and T3 may be an adaptation process to increase REE and energy expenditure. The evidence of TSH levels normalization after weight loss could confirm this theory.The moderate increase of TSH values is not related with a reduction of fT4 and T4 since fT4 and T4 levels are similar in normal weight and obese patients excluding significant hypothyroidism even if TSH is slightly increased in obesity.
In summary, it is important for clinicians to know the alterations of thyroid hormones in obesity, in order to avoid inappropriate treatments with thyroxin since these alterations in thyroid hormones are probably a consequence of obesity.

Aim of the study

We aimed to evaluate the relationship between anthropometric measures, biochemical parameters and serum thyroid hormones (TSH, fT4) concentrations in euthyroid obese subjects in order to characterized the physiological changes related to obesity.

Subject and methods

We retrospectivelyenrolled 5000 obese subjects (BMI > 30 Kg/m^2) referred to General Medicine of San Giuseppe Hospital, Piancavallo from 1999 and 2014. Patients data were collected through retrospective medical record including gender, age, smoke, biochemical analysis (TSH, fT4, leukocytes, VES, PCR, fibrinogen, glucose, insuline, urea, creatinine, urate, total bilirubin, AST, ALT, GGT, total protein, alkaline phosphatase, cholesterol, triglycerides, electrolytes), anthropometric data (weight, height, body mass index, waist and hip cirumference, WHR), body composition parameters and calorimetric data. Patients with known thyroid disorders and/or under the use of levothyroxine or other medication that causes alteration in thyroid function were excluded.

Statistical analysis are ongoing.

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Betatrophin and Irisin axis in the endocrine system – MAIN PROJECT

Background

The recently described myokine and adipokine, irisin is cleaved from fibronectin type III domain containing protein 5 (FNDC5) and has been proposed to be secreted upon exercise to promote the browning of beige fat cells in white adipose tissue that results in enhanced thermogenesis and increased energy expenditure.
Initial studies suggested a potential role of irisin as treatment option for obesity and associated diseases such as type 2 diabetes mellitus (T2D) and stimulated further research. However, the results of subsequent studies investigating the regulation of irisin by different type of exercise are partly conflicting and effects were only shown in highly selective patient population so far. Moreover, other parameters like body weight or fat free mass were shown to influence irisin adding more complexity to the mechanisms regulating this hormone. In vitro and animal studies suggested the induction of brown fat like-phenotype by FNDC5/irisin: overexpression of FNDC5 gene in animal model of obesity resulted in a marked upregulation of UCP 1 and several mitochondrial genes, an increase in oxygen consumption and an amelioration of glucose tolerance and reduction of insulinemia.
Betatrophin, also known as TD26/RIFL/lipasin/ANGPTL8/C19orf80, is a novel protein predominantly expressed in human liver. To date, several betatrophin orthologs have been identified in mammals. Increasing evidence has revealed an association between betatrophin expression and serum lipid profiles, particularly in patients with obesity or diabetes. Stimulators of betatrophin, such as insulin, thyroid hormone, irisin and caloric intake, are usually relevant to energy expenditure or thermogenesis. In murine models, serum triglyceride levels as well as pancreatic cell proliferation are potently enhanced by betatrophin. Intriguingly, conflicting phenomena have also been reported that betatrophin suppresses hepatic triglyceride levels, suggesting that betatrophin function is mediated by complex regulatory processes. However, its precise physiological role remains unclear at present.
Both hormones are connected by a new pathway clearly involved in insulin resistance. In particular exercise raises ROS levels activating p38MAPK, whereas PGC-1α is regulated by activation of p38MAPK. PGC-1α, through an increase in expression of FNDC5, secretes irisin, which acts on white adipose cells to stimulate UCP1 expression. This promotes the expression of betatrophin and β-cell regeneration and decreases insulin resistance. In addition, lack of expression of PGC-1α is associated with age. Thus, irisin and betatrophin levels may decrease in both aged people and type 2 diabetes patients. Consequently, exercise is an important tool to activate this pathway, thereby decreasing insulin resistance and improving glucoregulation in T2D patients. However, the activation of this pathway may fail during the aging process due to lack of expression of PGC-1α, gradually increasing insulin resistance.

Aim of the study

Aim of this project is to evaluate betatrophin-irisin axis in obesity, type 2 diabetes and polycystic ovary syndrome in order to characterise the role of these hormones in glucose and lipid metabolism and insulin resistance.

Methods and preliminary results

Due to recent controversies about circulating irisin including difficulties of its specific detection in human serum, we decided to evaluate firstly the expression of irisin by Western Blot.
First of all, we detected irisin in serum using a specific antibody, that also is used in ELISA assay. The major problem faced in the analysis of human serum is the broad range of its protein constituents. High abundance proteins, such HAS, IgG inhibit the analysis of lower abundances protein such irisin.
So we decide to depletethe serum with albumin/IgG depletion kit and furtheranalyzed depleted serum in Western immunoblot.
In particular with Western Blot we immunodectedirisin in human muscle protein, to confirm the real presence in muscle and in human serum. We detected a strong band around 25 kDa in these sample and also using rec irisin, to confirm the specificity of the antibody.

Further step of investigation will be:

- Deglycosilation experimentto see in which form irisin circulates in serum as irisin may undergo protein modification by glycosylation
- ELISA for quantification in obesity, polycystic ovary syndrome and type 2 diabetes of irisin and betatrophin.

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- Meet the experts in Endocrinology and Metabolism. Novara, 11 December 2014. ScientificManagers: Prof. Gianluca Aimaretti, Prof. Paolo Marzullo

- XVIII Corso Post-specialistico di Formazione in Endocrinologia Clinica. Pisa, 29-31 January 2015. Scientific Manager: Nicola Sicolo
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SEMINARS

- European International Workshop on Tolerogenic Vaccination in Autoimmune Diseases. November 20th 2014, Novara
- Lesson of Prof Prat "Stem cell in the regeneration and repair of the tissues and organs". November 21st 2014, Novara.
- Seminar of Professor Arvind Patel "Humoral responses to HCV infection and clinical outcomes". November 28th 2014, Novara.
- Seminar of Professor Girish Patel: "Uncovering the role of β-HPV in field cancerization: a collaboration in progress". December 4th 2014, Novara.
- Seminar of Prof. Rifaat Safadi M.D: "Focus on the liver: from basics of NAFLD to hot topics in HBV & HCV infections". December 5th 2014, Novara.
- Seminar of Prof. Antonio Musarò "From the legend of Prometheus to regenerative medicine". 16th December 2014, Novara
- Seminr of Prof. Furlan "Microglia microvesicles: messengers from the diseased brain". 17th December 2014, Novara.
- Michele Mishto "Proteasome-catalysed peptide splicing: mechanisms and implications in immunology". DecemberTuesday 23rd 2014, Novara.
- Prof. Dr Yong-Sang Song "Anticancer strategy Targeting cancer cell metabolism in ovarian cancer". JanuaryMonday 19th 2015, Novara
- DrToninoAlonzi, "Different molecular mechanisms regulate hepatocyte differentiation during the transitions between epithelial and mesenchymal states".JanuaryTuesday 20th 2015, Novara
- Prof. Valeria Poli "Targeting the liver to cure myocarditis: a lesson from a model of STAT3-dependent auto-immune myocarditis". January Wednesday 21st 2015, Novara
- Prof. Antonio Sica "Myeloid cells as therapeutic target in cancer", January Wednesday 27th 2015, Novara
- Prof. Bosnakovski "Proof of principle for cell therapy: from autologous transplantation of tissue specific progenitors to gene corrected patient specific injured pluripotent stem cells". March 11st 2015, Novara
- Prof Zhong "Signal control in iNKT cell development and function". April 9th 2015, Novara
- Prof. Percipalle "Actin-based mechanisms in the control of gene expression and cell fate". - April 21st 2015, Novara
- Prof John McDonald "An Integrated Approach to the Diagnosis and Treatment of Ovarian Cancer". MayThursday 7th 2015, Novara
- DrFeltkamp "Recent Developments in (cutaneous) Human Polyomavirus Research". June 5th 2015, Novara

- Prof. DarkoBoshnakovski “Cell based models for studying molecular mechanism of Facioscapulohumeral Muscular Dystrophy (FSHD)” Thursday 3rd September 2015, Novara
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POSTERS

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