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VIII ADVANCED COURSE OF ENDOCRINOLOGY

Welcome Words

Davide Carvalho[1]

[1] *Presidente da Sociedade Portuguesa de Endocrinologia, Diabetes e Metabolismo*

Dear Friends

Welcome to the VIII Advanced Course of Endocrinology. This course brings together interns, young specialists of Endocrinology, and well-known specialists, and is a melting pot of different perspective and diverse interests, with but one focal challenge: to improve the quality of care of patients.

Real World Evidence is a worldwide trend in Health and Life Sciences. New kinds of data, such as electronic health records and data mining tools are now available, which allow us to extract information and knowledge. We can detect not only medical treatment costs and treatment efficiency (cost, benefits, and risks), but also references to drugs, side effects, and long-term results.

A nick-name for the VIII Advanced Course could be 'Real World Evidence'.

For the first time we are going to have an insulin-pump therapy course, which we expect to be very practical, enabling all the participants to have an opportunity to update their practical knowledge of a disease that has had a marked increase over the last years.

Evidence of Real World in the management of diabetes will also be discussed, as well as for phosphocalcic metabolism. Sharing experiences from our country with colleagues from other countries is important for building a new clinical perspective.

The challenges of precision medicine will be discussed during the pituitary conferences, in an attempt to tailor therapeutic algorithms according to patients' characteristics.

I hope that you will all enjoy the VIII Course and I look forward to receiving suggestions for the subject matter of the next one!

Davide Carvalho

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4200-319 Porto
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VIII ADVANCED COURSE OF ENDOCRINOLOGY

7APRIL2018
CONGRESS CENTRE OF PORTO PALÁCIO HOTEL

ORGANIZATION
Associação dos Amigos do Serviço de Endocrinologia do Hospital de S. João

COLLABORATION
Serviço de Endocrinologia, Diabetes e Metabolismo do Centro Hospitalar S. João / Faculdade de Medicina da Universidade do Porto

6th April - Friday

17H45 **Welcome words –** Davide Carvalho

18H00 – 20H00 **From the scientific evidence to the clinical practice: CSII efficacy and safety**
Chairmen: Helena Cardoso, Celestino Neves

18H00 – 18H30 **The Spanish perspective: The experience of a National Reference Center: Diabetes –** Alfonso Soto, Complejo Hospitalario Juan Canalejo- La Coruña

18H30 – 18H45 **The Portuguese perspective**: César Esteves

18H45 – 19H00 **How to use specific features of CSII therapy. The example of Bolus Calculator for meals and corrections. The use of computer´s downloading supports and softwares**… Alfonso Soto, Complejo Hospitalario Juan Canalejo- La Coruña

20H00 – 21H00 ***Dinner***

21H00 – 23H00 **Chairmen:** Francisco Carrilho, Joana Queirós
Workshop: Clinical cases – Alfonso Soto, Complejo Hospitalario Juan Canalejo- La Coruña

7th April - Saturday

08h30 – 10h00 **What is new in diabetes management**
Chairmen: José Luís Medina, Ana Agapito
Moderators: João Filipe Raposo, Silvestre Abreu

08h30 – 09h00 **Why we need Real World Evidence? –** Jukka Westerbacka

09h00 – 09h30 **Real World Evidence Portuguese data: does matter?** – Miguel Gouveia

09h30 – 10h00 **Panel Discussion:** JL Castedo, Daniel Braga, Pedro Melo

10h00 – 11h00 **Moderators:** Maria João Oliveira, Carlos Vasconcelos

10h00 – 10h20 **Impaired awareness of hypoglycaemia** – Eduardo Sepúlveda

10h20 – 10h50 **Hypoglycaemia: risks and management** – Mark L Evans

10h50 – 11h00 **Panel Discussion:** Paula Freitas, Joana Guimarães, Eva Lau

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Moderators: Mário Mascarenhas, Manuel Lemos

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16h45 **Closing ceremony and posters award**

JURY OF THE LUIS MARQUES PRIZE

Valeriano Leite, Ana Maia Silva, Paula Freitas, Manuel Lemos

JURY OF THE MANUEL PINHEIRO HARGREAVES PRIZE

Mário Mascarenhas, Mariana Martinho, Duarte Pignatelli

VIII ADVANCED COURSE OF ENDOCRINOLOGY

Conference Abstracts

L01. FROM THE SCIENTIFIC EVIDENCE TO THE CLINICAL PRACTICE: CSII EFFICACY AND SAFETY THE PORTUGUESE PERSPECTIVE

César Esteves[1]

[1] *Department of Endocrinology, Diabetes and Metabolism, Centro Hospitalar S. João, i3S, University of Porto, Porto, Portugal*

Continuous subcutaneous insulin infusion therapy, once relevant only in a small subset of type 1 diabetic patients, is currently viewed as preferencial treatment in motivated patients with active lifestyles, with increased need of a flexible insulin regimen. In some countries, the prevalence of insulin pump use exceeds 40% in type 1 diabetic patients. In Portugal, the SNS (Portuguese National Health Service) initiated the distribution of insulin pumps, free of charge, to type 1 diabetics according to recognized indications, in 2008. Those cases included the failure of multiple daily injections to achieve good glucose control, the occurrence of severe hypoglycemia or hypoglycemia unawareness, the need of a flexible lifestyle, the use of low total daily insulin dose or current/planned pregnancy. Since then, more than 1000 patients (adult and pediatric) were initiated in insulin pump therapy, distributed by 16 treatment centers. However, in 2005, only 2.3% of type 1 diabetic patients were treated with an insulin pump. In 2016, the Directorate – General of Health determined that, to keep up with European best practice, the SNS should be able to deliver insulin pumps to all children up to 10 years of age until 2017, up to 14 years of age until the end of 2018 and up to 18 years of age until the end of 2019. It also determined that, every year, insulin pumps will be made available to pregnant women. Unfortunately, as the number of available pumps is limited, a wider group of individuals will not be able to get an insulin pump as expected and health professionals still can not help these patients as they needed and hoped for. Hence, although progress has been made, there remains relevant gaps in access to advanced technology in the treatment of diabetes.

L02. REAL WORLD EVIDENCE PORTUGUESE DATA: DOES IT MATTER?

Miguel Gouveia[1], Francesca Fiorentino[2], Raquel Ascensão[2], João Costa[2], Miguel Melo[3], Margarida Borges[2]

[1] *Catolica Lisbon School of Business and Economics, Lisbon, Portugal*
[2] *Centro de Estudos de Medicina Baseada na Evidência, Lisbon, Portugal*
[3] *Faculdade de Medicina da Universidade de Coimbra, Coimbra, Portugal*

This communication reports the results obtained by a research project using *big data* from the Lisbon and Tagus Valley Regional Health Administration (ARS LVT). The objectives of the research were 1) to measure the insulin gap, 2) to estimate the health gains that might be obtainable by closing the gap, and 3) to estimate the cost-effectiveness of that intervention.

The analysis begins by selecting patients over 18 with type 2 diabetes from 2.2 million patients in ARS LVT. These include patients with a code of type 2 diabetes or patients taking oral antidiabetic drugs. This leads to a choice of 250 391 patients. We then exclude patients with no HbA1c data and other anomalous cases, resulting in 136 977 patients for analysis. A set of criteria was then applied sequentially identifying patients not being treated with insulin but with an indication for that treatment. The procedure identified 8475 patients. This represents 6.2% of the total patients under analysis and a group equal to 59% of the patients already being treated with insulin.

The second step in the analysis simulates what the changes in HbA1C would be if all the 8475 patients in the gap were treated with insulin. On average HbA1c would decrease by 1.5% with a standard deviation of 1.9%.

In the third step, the United Kingdom Prospective Diabetes Study (UKPDS) equations are used to simulate the incidence of diabetes related health problems over a ten-year horizon in two scenarios, the "status quo" and the "intervention" closing the insulin gap. The analysis shows a decrease in the incidence of events and in mortality. Overall there is a gain of 419 years of life (discounted at 5%).

In the fourth and final step the present value of direct and indirect costs for each scenario are calculated. The average patient has a present value of discounted costs for the ten-year horizon that is higher in the intervention scenario, with a *per capita* cost increase of €366. This implies that the incremental cost-effectiveness ratio (ICER) of the intervention is €7390 per year of life gained.

L03. IMPAIRED AWARENESS OF HYPOGLYCAEMIA

Eduardo Sepulveda[1]

[1] *Faculty of Psychology and Educational Sciences, University of Porto, Porto, Portugal*

Repeated exposure to hypoglycaemia leads to impaired awareness of hypoglycaemia (IAH) and protection from severe hypoglycaemia (SH). Impaired awareness of hypoglycaemia, defined as the diminished ability of the patient to perceive the

onset of hypoglycaemia, increases risk of SH in adults with type 1 diabetes (T1D) three- to six fold, affects 19.5% to 40% of patients with T1D**,** and is associated with lack of motivation to changes in insulin regimens. Severe hypoglycaemia requiring external help for recovery, and occurs in 17% - 41% of adults with T1D. In adults with T1D has an annual prevalence of around 30%, and an annual incidence rate of one episode/patient-year. Current methods have been used to assess IAH in T1D, particularly the Gold and Clarke scores. Structured education in flexible intensive insulin therapy and use of diabetes technologies (pumps and sensors) reduce SH, and education improves IHA without relaxing overall glycaemic control (e.g., Dose Adjustment for Normal Eating [DAFNE]; Comparison of Optimized Multiple Daily Injections and Pumps with and without Sensors in Severe Hypoglycaemia [HypoCOMPaSS trial]), but some people with T1D with IHA (around 50%) fail to achieve benefit. However, awareness of hypoglycaemia can be restored by rigorous avoidance of hypoglycaemia, and addressing psychological barriers that have been described in people with persistent IHA. These barriers may inhibit patients' attempts to avoid hypoglycaemia and regain awareness, and include underestimating the consequences of hypoglycaemia and persistent IHA, needing to "soldier on" through episodes, and overestimating the consequences of high glucose readings. The DAFNE-Hypoglycaemia Awareness Restoration Training (DAFNE-HART), which is a psychological intervention aimed for individuals who had previously attended DAFNE and still had persistent IAH, has shown to reduce the incidence of SH and to improve awareness of hypoglycaemia (with no deterioration in HbA1c). Structured education should be part of routine management for all patients with T1D.

L04. HYPOGLYCAEMIA: RISKS AND MANAGEMENT

Mark Evans[1]

[1] *University Lecturer and Honorary Consultant Physician, Institute of Metabolic Science and Department of Medicine, University of Cambridge, United Kingdom*

Hypoglycaemia is a major burden for people with diabetes with fear of hypoglycaemia being ranked as highly as fear of long term complications by those treated with insulin. This carries personal, social, occupational and economic costs. In addition, it there are potential medical consequences. Fear of hypoglycaemia may mean that people with diabetes choose to run their blood glucose levels higher than target values, increasing risk of complications. Acute hypoglycaemia increases risk of accidents for example. Hypoglycaemia is also associated with increased mortality in a number of interventional and observational studies.

There are a number of risk factors for severe hypoglycaemia. Individual episodes may have identifiable precipitants (activity, alcohol, injection site problems, insulin errors). Longer term risk factors include the syndrome of reduced awareness/impaired counter-regulatory responses, long duration of diabetes, age and previous problematic hypoglycaemia). Hypoglycaemia tends to cluster so that a small number of individuals represent a disproportionately large number of events, suggesting individual behavioural or biological factors may contribute.

Management includes both prevention of severe episodes (identifying those at risk and changing risk factors where possible), managing the acute episodes/ supporting people and carers/ families to manage and trying to reduce risk of recurrence. This includes adjusting therapies, glycaemic targets, providing structured education to support insulin dosing decisions, use of technology such as continuous glucose sensing. Finally, there is current interest in testing cognitive interventions in type 1 diabetes to overcome the "thinking traps" that lead some to suffer recurrent episodes.

L05. HYPERPARATHYROIDISM: A SURGICAL PERSPECTIVE

João Capela[1]

[1] *Cervical and Endocrine Surgery Unit, Department of General Surgery, Centro Hospitalar São João, Porto, Portugal*

Primary hyperparathyroidism (HPTP) has a prevalence of 0.2%, but more than 90% of the cases are undiagnosed. If it is not identified early, it can cause marked morbidity. On the other hand, the number of asymptomatic patients at presentation can reach 80% if biochemical screening is performed systematically. The correct identification of the parathyroids is the main difficulty of the surgery of the hyperparathyroidism (HPT) and fundamental for its success. Their number, size and shape can be variable. The probability of ectopic glands is 15% - 20%. Its existence is determined by embryonic development and parathyroid weight, by the negative pulling force of the thoracic at the end of inspiration, and by the swallowing movements that mobilize the upper glands. Parathyroid adenomas are the most frequent cause of pseudopseudohypoparathyroidism (PPHP) and therefore the surgical treatment has evolved from the classic approach to the mini-invasive anomalous parathyroid, localized by ultrasound and scintigraphy. It has a cure rate >95% if the surgeon is experienced. In the reinterventions, the preoperative imaging location is paramount. In cases of multiglandular disease, a subtotal or total parathyroidectomy with an implant should be performed. The excision of mediastinal glands is frequently performed with opening of the thorax, but can be performed by cervicotomy and eventually endoscopically. Parathyroid carcinoma accounts for <1% of cases of parathyroid hormone (PTH). The differential diagnosis with adenoma is difficult. The rapid onset of symptoms and very high serum calcium and parathormone levels are the most important data for the suspected case. The observation of a greyish, voluminous and fixed parathyroid should always alert the surgeon. However, the only criteria for the diagnosis of carcinoma are invasion and metastasis. Block excision of the gland and invaded neighbouring tissues is the only method of cure. Relapses occur mainly in the first 2 to 5 years, but the prognosis varies greatly, from cases of slow progression to fulminant situations. The guidelines for action to HPTP are a valuable tool to support surgeons. We carried out an Iberian Inquiry to evaluate its use. We had 16 responses from Portugal corresponding to 1119 parathyroidectomies. Operative indications for asymptomatic PHPT were followed by 93% of the centres, although 47% also considered other indications, such as simultaneous thyroidectomy. Ultrasound and scintigraphy were routinely used at the glandular site. In cases where they were negative or discordant, 44% of surgeons asked for more imaging. Selective parathyroidectomy is performed in 93% of centres.

L06. HYPOPARATHYROIDISM: FROM GUIDELINES TO REAL WORLD

Maria Luisa Brandi[1]

[1] *University of Florence, Department of Surgery and Translational Medicine, Florence, Italy*

Hypoparathyroidism is a rare disorder characterized by hypocalcemia and absent or deficient parathyroid hormone (PTH).

The prevalence of hypoparathyroidism is an estimated 37 per 100 000 person-years in the United States and 22 per 100 000 person-years in Denmark. The incidence in Denmark is approximately 0.8 per 100 000 person-years. Estimates of prevalence and incidence of hypoparathyroidism are currently lacking in most other countries.

Hypoparathyroidism is often associated with complications and comorbidities. It is important for endocrinologists and other physicians who care for these patients to be aware of recent advances in the epidemiology, diagnosis, and genetics of this disorder.

Current information about epidemiology, presentation, diagnosis, clinical features, and management and proposals to help clinicians diagnose, evaluate, and manage this disorder have been published in 2016.

Conventional management of hypoparathyroidism has focused upon maintaining the serum calcium with oral calcium and active vitamin D, often requiring high doses and giving rise to concerns about long-term consequences including renal and brain calcifications. Replacement therapy with parathyroid hormone (PTH) has recently become available.

Under normal circumstances, interactions between PTH and active vitamin D along with the dynamics of calcium and phosphorus absorption, renal tubular handing of those ions, and skeletal responsiveness help to maintain calcium homeostasis and skeletal health. In the absence of PTH, the gastrointestinal tract, kidneys, and skeleton are all affected, leading to hypocalcemia, hyperphosphatemia, reduced bone remodeling, and an inability to conserve filtered calcium. Acute hypocalcemia can be a medical emergency presenting with neuromuscular irritability. The recent availability of recombinant human PTH (1-84) has given hope that management of hypoparathyroidism with the missing hormone in this disorder will provide better control and reduced needs for calcium and vitamin D.

Control with calcium and active vitamin D can be a challenge. The availability of PTH (1-84) replacement therapy may usher new opportunities for better control with reduced supplementation requirements.

Treatment with rhPTH(1-84) may improve health-related quality of life (HRQoL) in adults with hypoparathyroidism.

L07. ACROMEGALY MANAGEMENT: A PRECISION MEDICINE PERSPECTIVE

Mônica Gadelha[1, 2, 3]

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[2] *Neuroendocrine Research Center, Hospital Universitário Clementino Fraga Filho, Universidade Federal do Rio de Janeiro, Rio de Janeiro, Brazil*
[3] *Neuroendocrine Section and the Molecular Genetics Laboratory, Instituto Estadual do Cérebro Paulo Niemeyer, Rio de Janeiro, Brazil*

Acromegaly is a chronic systemic disease associated with high morbi-mortality when not adequately treated. Nowadays, three treatment modalities (surgery, medical therapy and radiotherapy) are available and we are able to attain disease control in the vast majority of the patients. Surgery is the first-line treatment for most patients as it is the only therapy that can lead to immediate disease control. However, in around 50% of cases, surgical cure does not occur, and medical treatment is necessary. Radiotherapy is considered the third-line treatment and is reserved for aggressive tumors not controlled with surgery and medical therapy.

Medical treatment is currently started on a trial-and-error approach: First-generation somatostatin receptor ligands are initiated for most patients, however in only approximately 40% disease control is attained. Second-generation somatostatin receptor ligand, pasireotide LAR, and pegvisomant are usually used as second-line medical therapy. Some biomarkers of treatment outcome have been investigated, with the goal of categorizing patients into different groups to personalize their treatments. This important shift towards precision medicine allows better treatment results with expedite acromegaly control and cost reduction. During this talk, the biomarkers that support the development of precision medicine for the treatment of acromegaly will be discussed as well as future perspectives on the use of personalized medicine.

L08. THE YEAR IN CUSHING'S DISEASE

Davide Carvalho[1,2,3]

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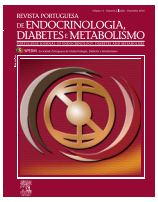
[2] *Faculty of Medicine, University of Porto, Porto, Portugal*
[3] *i3s, Porto, Portugal*

Cushing's disease is a rare disease (1 per 10,000) whose pathogenesis has seen recent advances. Somatic mutations of the *USP8* (encoding ubiquitin-specific protease 8) gene account for about 40% - 60% of corticotrophinomas. More rare (2.2%) are mutations of the *CABLES1* (Cdk5 and ABL enzyme substrate 1) (18q11.2) gene, which has functions of cell cycle inhibition. A possible cause of early childhood Cushing's disease may be the *DICER1* gene, which encodes an endoribonuclease that is responsible for processing precursors of microRNAs into functional miRNAs. As far as screening and diagnosis are concerned, the measurement of nocturnal salivary cortisol (between 23 and 24 hours) seems to be a valuable tool. Its variability has recently been characterised in patients with proven, new, or recurrent Cushing's disease. It had already been shown that in the determination of urinary free cortisol (UFC), the intra-patient coefficient of variation may be 52%, with patients showing fluctuations of between 217.5 and 5081.5 ug / day. Fluctuations of nocturnal salivary cortisol are large, and patients with recurrence/persistence may often have normal levels. With regard to surgery, the long-term results of transphenoidal resection guided by the anti-ACTH antibody seem to improve efficacy to 85.7%, which is significantly better than historical controls of the same centre, which was 71.9%. Regarding radiosurgery, a study of 278 patients was patients was published, where hypercortisolism control was

obtained in 80% of them at the 10-year follow-up. The enthusiasm for the results should, however, be moderated by the fact that the symptoms were controlled by medical therapy in 11% of these patients, and in the long term, a recurrence rate of 18% was observed. γ-knife-radiosurgery gave rise to cure in 50% of the 278 patients treated after an average follow-up of 5 years. The time to obtain remission was lower than expected (14.5 months). Long-term follow-up is required to detect recurrences (the mean time of recurrence was 38 ± 44 months). Regarding medical therapy, the results of the use of two drugs have recently been reported: one with central (pituitary) action – pasireotide, and the other with a peripheral (adrenal) action – osilodrostat. Pasireotide reduces levels of UFC and causes normalisation of these levels in about 40% of patients. Pasireotide also induces a reduction in ACTH levels, which are associated with the improvement of BP, lipids, body weight, and quality of life. This drug has a safety profile that is similar to the other somatostatin analogues, although it induces diabetes or hyperglycaemia in a significant number of cases. The glycaemic status (FPG/A1c) should be evaluated prior to the initiation of treatment. In patients with impaired glucose tolerance or diabetes, glycaemic self-monitoring should be intensified before and during and treatment: weekly during the first 2-3 months, and periodically thereafter. Furthermore, pasireotide seems to inhibit insulin secretion, but maintains glucagon secretion, and therefore incretinic drugs are the preferred choice to treat pasireotido-induced hyperglycaemia. Osilodrostat is an oral inhibitor of 11β-hydroxylase, which catalyses the final step of cortisol synthesis. Although this mechanism of action is similar to that of metyrapone, osilodrostat has a longer plasma half-life (4-5 *vs* ~ 2 h), allowing twice daily administrations (instead of 3-4 times per day) and it is more potent blocker for 11β-hydroxylase (IC 50 in vitro of 2.5 versus ~ 7.5 nM for metyrapone), allowing for a more convenient overall treatment.



VIII ADVANCED COURSE OF ENDOCRINOLOGY

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Introduction: Alterations in GH – IGF-1 axis play an important role in pathogenesis of HIV-associated lipodystrophy and the serum levels of IGF-I are associated with the percentage of body fat, lipid metabolism, diabetes, cardiovascular disease (CVD) and metabolic changes.
Aim: Evaluate the levels of IGF-1, IGFBP-3, IGF-1/IGFBP-3 ratio and insulin resistance and their relationship with metabolic syndrome, fat redistribution, lipodystrophy and BMI categories, in HIV-infected patients treated with cART.
Methods: Anthropometric and metabolic parameters, HOMA-IR, body composition (DXA and CT), IGF-1 and IGFBP-3 were evaluated in 236 HIV-infected patients on cART (154 men and 82 women).
Results: IGF-1 was significantly higher in patients without MS. No other significantly differences were found in IGF-1, IGFBP-3 and IGF-1/IGFBP- 3 ratio in relation to fat redistribution, presence of lipodystrophy and BMI categories. HOMA-IR was positively correlated with the presence of lipodystrophy, isolated central fat accumulation and mixed forms of lipodystrophy. HOMA-IR was higher in obese patients and in patients with MS.
Conclusion: In HIV-infected patients on cART, alterations in body composition were associated with IR. No associations were found between fat redistribution syndrome and IGF-1, IGFBP-3 and IGF-1/IGFBP-3 ratio. A negative association between IGF-1 levels and the presence of MS was observed.
Keywords: Body Composition; Combined Antiretroviral Therapy; HIV Infection; Insulin-Like Growth Factors; Insulin-Like Growth Factor Binding Protein; Insulin Resistance; Lipodystrophy; Metabolic Syndrome

P02. THE IMPACT OF NUTRITIONAL STATUS AND INSULIN RESISTANCE ON IGF-1 AND ITS BIOAVAILABILITY

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Introduction: IGF-1 and IGFBP-3 are commonly assessed in the diagnostic work-up of short stature, however their significance is still controversial. The effects of obesity on their serum levels remain unclear. There is evidence that insulin is a strong regulator of the circulating IGF system.
Aim: To assess the relationship between IGF-1 SDS and IGF-1/IGFBP-3 with BMI and insulin resistance in children with idiopathic GH deficiency.
Methods: Retrospective study of 60 children. IGF-1/IGFBP-3 molar ratio was calculated to determine the IGF-1 bioavailability. Insulin resistance was calculated according to HOMA-IR.
Results: We found moderate positive correlations between IGF-1/IGFBP3 and baseline BMI ($r=0.531$, $p<0.001$), serum insulin ($r=0.683$, $p=0.014$) and HOMA-IR ($r=0.713$, $p=0.009$). Applying a multiple linear regression model, a significant regression equation was found ($F[3,8]=6.262$, $p=0.017$, $R^2=0.701$). Subjects predicted IGF-1/IGFBP-3 was equal to -0.012 + 0.078 (HOMA-IR). In contrast, we haven't found any correlation between IGF-1 SDS and the analysed variables. BMI SDS subgroups - overweight/obesity (7), normal range (48) and thinness (0) had no effect on IGF-1 SDS and IGF-1/IGFBP-3.
Conclusion: Insulin resistance seems to affect free IGF-1 levels, possibly by inhibiting some of its binding proteins. The result is not an increase in total IGF-1 levels but rather in the tissue bioavailability of this hormone.
Keywords: Idiopathic GH Deficiency; IGF-1; IGFBP-3; Insulin Resistance

P03. OBESITY PARADOX IN PATIENTS WITH HYPERTENSION AND HIGH CARDIOVASCULAR RISK

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Introduction: In the general population, overweight and obesity are established risk factors for cardiovascular disease. However, in patients with increased cardiovascular risk, the effects of overweight and obesity are uncertain.
Methods: We examined the association of overweight and obesity with major cardiovascular events and death in 9361 patients of the Systolic Blood Pressure Intervention Trial (SPRINT). We evaluated the occurrence of the primary composite outcome (acute coronary syndrome, stroke, acute decompensated heart failure, or death from cardiovascular causes) among patients with normal weight, overweight and obesity. We used cox proportional hazards regression models unadjusted and adjusted for relevant confounders.
Results: Overweight and obesity groups were younger, more likely to be male, had a lower prevalence of current smoking and a higher prevalence of dyslipidemia. In the unadjusted analysis, we observed a decreased hazard of primary outcome in overweight (0.71 [0.57-0.80], p=0.003) and obesity (0.75 [0.60-0.93], p=0.010) comparing with normal weight. After adjustment, obesity was no longer protective for primary outcome (0.94 [0.73-1.20], p=0.605), while overweight remained associated with a decreased hazard of primary outcome (0.76 [0.60-0.96], p=0.022).
Conclusion: Among patients with increased cardiovascular risk, overweight was associated with a decreased hazard of major cardiovascular events and mortality.
Keywords: Cardiovascular Events; Hypertension; Obesity

P04. AUTOIMMUNE THYROIDITIS IN PATIENTS WITH TYPE 1 DIABETES MELLITUS - INFLUENCE IN METABOLIC CONTROL: A SYSTEMATIC REVIEW

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Aim: To synthesize evidence about the relationship between the presence of autoimmune thyroiditis (AIT) in patients with T1DM and metabolic disarrangement.
Methods: Systematic review. Inclusion criteria: cross-sectional or case-control articles with a prospective or retrospective nature, comparing patients with T1DM versus patients with both T1DM and AIT; AIT should be defined by the presence of thyroid autoantibodies with or without ultrasound abnormalities; authors must have studied at least one of the outcomes of interests: A1c levels, insulin demand, lipid profile, TSH, FT4 and BMI; the articles must have been written in English or Portuguese. Data sources: MEDLINE and EMBASE databases. Vote-counting method was used to summarize the results.
Results: Approximately 64%, 75%, 71%, 75% and 67% of the studies did not demonstrate a statistically significant difference in A1c levels, lipid profile, daily insulin dose, body mass index and FT4 levels, respectively. Approximately 63% of the studies demonstrated a statistically significant higher level of TSH in patients with T1DM and AIT.
Conclusion: This systematic review highlights a high risk of AIT in individuals with T1DM. Statistically significant higher level of TSH in patients with T1DM and AIT may predict the progression to hypothyroidism.
Keywords: Autoimmune Thyroiditis; Autoimmunity; Glycemic Control; Thyroid Autoantibodies; Type 1 Diabetes Mellitus

P05. STEROID-UNMASKED LATENT AUTOIMMUNE DIABETES OF THE ADULT – CRITICAL APPRAISAL AND REVIEW OF THE LITERATURE

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Introduction: Steroid-induced diabetes mellitus (SID) is a common and potentially severe clinical problem, although it is undervalued and underdiagnosed. Limited information is available regarding pathophysiology and diagnosis. Treatment is not optimized. Furthermore SID is not consistently predicted by traditional risk factors and there is clinical heterogeneity.
Case Report: A 64-year-old male, without a prior history of diabetes mellitus, developed persistent polydipsia after the administration of intramuscular methylprednisolone. Weight at diagnosis 50.1 kg, BMI 19.33 kg/m², HbA1c 10.7%, fasting glycaemia 264 mg/dL, C-peptide 0.2 ng/mL (0.78 – 5.19), anti-IA2 antibodies 1.27 U/mL (positive> 0.75), anti-GAD65 antibodies negative, no diabetic retinopathy or microalbuminuria. Insulin therapy was initiated 6 months after diagnosis, having achieved good glycaemic control with the daily dose of 1.3 UI/kg of body weight.
Discussion: Anti-IA2 antibodies increase significantly the probability that insulin therapy is required in less than 6 years after a diagnosis of LADA. Glucocorticoid therapy could have unmasked and precipitated latent autoimmune diabetes in adults (LADA). On the other hand a significant number of cases of SID could actually correspond to LADA. We propose the measurement of antibodies for autoimmune diabetes as a novel “risk factor” for SID allowing for the proper reclassification and management of antibody positive patients.
Keywords: Anti-IA2 Antibodies; Diabetes Mellitus; Glucocorticoids; Latent Autoimmune Diabetes in Adults

P06. A PRELIMINARY ANALYSIS OF THE IMPACT OF PROLONGED USE OF CONTINUOUS SUBCUTANEOUS INSULIN INFUSION (CSII) IN THE CONTROL OF DIABETES TYPE 1: TWENTY YEARS OF EXPERIENCE

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Introduction: The use of continuous subcutaneous insulin infusion (CSII) therapy in type-1 diabetes (DM1) has increased due to its benefits in glycaemic control.
Aim: Analyse the impact of CSII on glycaemic control and total daily dose of insulin (TDD), during twenty years of follow-up.
Methods: This retrospective study included DM1 patients that started CSII therapy before 2006. We evaluated HbA1c and TDD immediately before initiation of CSII therapy, at 6 months, 1 year, 5 years, 10 years, 15 years and 20 years after. Data was analysed using SPSS (v.22).
Results: We included 26 patients (7 men; 19 women) with mean duration of disease until CSII initiation of 17.73 ± 7.92, mean age at insulin pump placement of 31.92 ± 8.75 years and mean follow-up time of 13.12 ± 2.07 years. The main reasons for pump placement were: inadequate metabolic control (80.8%), history of hypoglycaemia without symptoms or severe hypoglycaemia (15.4%), and pregnancy/pregnancy planning (3.8%). The mean HbA1c before CSII therapy was 9.51 ± 2.29% and decreased to 7.32 ± 1.06% at 6 months of therapy (p=0.00029). HbA1c decrease remained statistically significant in the first 10 years of follow-up. The mean daily insulin requirement was reduced from 60.61 ± 16.69 U/day to 44.96 ± 10.61 U/day at 6 months without statistical significance throughout this study.
Conclusion: CSII therapy improved glycaemic control, especially during the first 10 years of follow-up.
Keywords: Glycated Hemoglobin A; Insulin Infusion Systems; Long-Term Care; Type 1 Diabetes Mellitus

P07. INTENSIVE INSULIN THERAPY WITH A CONTINUOUS SUBCUTANEOUS INSULIN PERFUSION DEVICE

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Aim: To compare intensive insulin therapy through continuous subcutaneous insulin perfusion device (CSIPD) and multiple insulin daily injections (MIDI) in patients with type 1 diabetes.
Methods: We included 59 type 1 diabetic patients followed by Endocrinology at the Centro Hospitalar São João to perform intensive insulin therapy through CSIPD for more than 6 years, having previously used the MIDI strategy for more than 6 months.
Results: 59 patients with a mean age of 41+10 years were diagnosed with type 1 diabetes at 16+10 years of age and had average disease duration of 17+9 years at the time of CSIPD start. HbA1c values were significantly lower in the 3 CSIPD periods compared to the MIDI period (-0.998, -0.659 and -0.774 at 1, 3 and 6 years post CSIPD start). Microalbuminuria showed only a statistically significant difference (increase) at 6 years after CSIPD. Lipid profile, ISF and I: CH ratio did not show statistically significant differences in any of the periods. Regarding BMI, a statistically significant increase was found 6 years after MIDI start.
Conclusion: The change from MIDI to CSIPD strategy allowed better glycaemic control over the first 6 years, with no change in lipid profile.
Keywords: Insulin; Type 1 Diabetes Mellitus

P08. LOSS OF SMALL FIBERS IS ALREADY PRESENT IN TYPE 1 DIABETES PATIENTS WITHOUT NEUROPATHY AND PAIN: QUANTITATIVE SENSORY TESTING (QST).

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Introduction: Neuropathy is one of the most frequent complications of diabetes. QST is a psychophysical method of quantifying somatosensorial function large (Aβ), small (A-δ/C) nerve fibers and central tracts. Can detect negative/positive sensitive signs, latter not being accessed by other methods.
Aim: To evaluate the frequency of large/small nerve fibres and the signs of gain in type 1 diabetes (T1D) with or without clinical neuropathy or pain.
Methods: Cross-sectional study, 70 T1D (3 subgroups: B–without neuropathy/pain (n=21);C–with neuropathy/without pain (n=22); D– with neuropathy/pain (n=27) compared to 21 healthy control (A). MNSI, NRS, LANSS, DN4 scales were applied. All cases underwent QST evaluation in foot (test) and face (control). Proportion of loss (L) /gain (G) threshold were calculated after z transformation of QST data according to sex, age and local reference values. T test/ Kruskal-Wallis test were used.
Results: T1D: 54% women; mean age: 37.8 ± 12.3 years, T1D duration: 21.57 ± 1 years, BMI: 24.1 ± 3. Group A: 95% presented L0/100% presented G0; Group B had mainly thermal hypoesthesia (TH, 28.6%), mechanical hyperalgesia (MHp). Group C: 18%

TH, 18% HM, 64% MHp, without thermal hyperalgesia. Group D: 66.7% mixed loss (L3); 44% mechanical hyperalgesia, 4% thermal hyperalgesia. Results in four groups are statistically significant (p<0.001).
Conclusion: Our results show T1D patients without neuropathy and no pain have early loss of function of small fibers (A-δ/C). QST is a useful tool in early evaluation of small fibres in diabetic patients.
Keywords: Quantitative Sensory Test; Sensory Phenotype; Small Fibers; Type 1 Diabetes Mellitus

P09. METFORMIN IN OVERWEIGHT AND OBESE WOMEN WITH GESTATIONAL DIABETES MELLITUS

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Introduction: Gestational diabetes mellitus (GDM) is more prevalent in overweight and obese women. Excessive gestational weight gain (EGWG) has been linked to adverse outcomes.
Aim: To evaluate possible benefits of metformin in overweight/obese women with GDM.
Methods: We studied 353 women with GDM and pregestational body mass index (BMI)≥25 kg/m^2.
Results: After diagnosis of GDM, 120 (34%) women were treated with metformin. Those treated with metformin had higher pregestational weight (87.5 *vs* 78.4 kg, p<0.001) and BMI (33.1 *vs* 30.2 kg/m^2, p<0.001), but lower gestational weight gain (5.9 *vs* 7.9, p=0.024). The percentage with EGWG was significantly lower in metformin group (29.1% *vs* 41.1%, p=0.033). The risk of EGWG was reduced in 40% when treated with metformin (OR=0.588, 95% CI 0.364-0.950). There were no differences in insulin utilization rate, total daily insulin and HbA1c in third trimester. No significant differences were found regarding preterm birth, need for cesarean section, pregnancy-induced hypertension, pre-eclampsia, hydramnios and results of oral glucose tolerance test for reclassification. Fenton growth parameters, neonatal hypoglycemia, hyperbilirubinemia, respiratory distress syndrome, hospitalization in the Intensive Care Unit, congenital anomalies and neonatal death did not differ between groups.
Conclusion: Metformin can be a therapeutic option to prevent EGWG in overweight and obese women with GDM.
Keywords: Gestational Diabetes; Metformin; Obesity; Overweight

P10. TYPE 2 DIABETES MANAGEMENT AFTER BARIATRIC SURGERY – THE EXPERIENCE OF REFERENCE CENTER

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Introduction: There is an ongoing discussion on oral antidiabetic drugs (OADs) withdrawal after bariatric surgery and on the role of metformin after type 2 diabetes (T2DM) remission.
Methods: Cross-sectional study of 114 T2DM patients followed 5 years after bariatric surgery.
Results: Among patients treated exclusively with OADs, 49% discontinued OADs in the first post-operative year (Y1). Younger age, lower pre-operative A1c and higher weight loss percentage (WL%) (p<0.05) were independent factors that led clinicians to withdraw them. These patients had a 12-fold chance of achieving a final A1c ≤6% than those that continued OADs (OR=11.99; p=0.001), even after adjusting for potential confounders (pre-operative HbA1c, age, WL%) (p=0.01). OADs were reintroduced in 22% of those patients. After Y1, OADs were withdrawn in 30% of the remaining patients (mean A1c at withdrawal of 5.88% ± 0.56%). Remission rates were at average 21.8% ± 2.33% higher when metformin was allowed. Patients there were kept on metformin during all follow-up presented with higher final A1c than those maintained without OADs (mean difference 0.69%; p<0.001), even after adjustment (p<0.05).
Conclusion: OADs are mostly withdrawn in Y1 and patients' age, pre-operative A1c and WL% are the factors that most influence clinicians to attempt it. Keeping metformin did not seem to have a clear benefit but further studies are needed.
Keywords: Bariatric Surgery; Hypoglycemic Agents; Metformin; Type 2 Diabetes Mellitus

P11. PEPTIDE RECEPTOR RADIONUCLIDE THERAPY WITH 177LU-DOTA-TATE AS A PROMISING TREATMENT OF MALIGNANT INSULINOMA

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Introduction:Insulinomas are rare neuroendocrine tumours characterized by insulin hypersecretion. They are malignant when metastases are present. Traditional therapies often promote only temporarily symptomatic relief and may be associated with severe adverse effects. There is scarce experience in treating malignant insulinomas with peptide receptors radionuclide therapy (PRRNT).
Methods: We describe PRRNT results in four patients with inoperable malignant insulinomas with poorly controllable hypoglycaemia. All received ^{177}Lu-DOTA-TATE after conventional therapies failure. The activity administered was 4.8-7.4 GBq/cycle, with 10-16 weeks interval between cycles. Haematology, liver and kidney function tests were performed before, five and ten weeks after each cycle.
Results: Patient 1 presented clinical benefit for 13 months after PRRNT, with imaging partial response. Patient 2 obtained reduction of the number and severity of hypoglycaemic episodes during 15 months after therapy. Patient 3 is asymptomatic since PRRNT first cycle performed 20 months ago and revealed significant imaging response. Patient 4 had resolution of hypoglycaemia 3 days after PRRNT first cycle and today, 13 months after, the disease seem to be in remission and the patient is euglycaemic. PRRNT was globally well tolerated.
Conclusion: After the start of ^{177}Lu-DOTA-TATE all patients achieved hypoglycaemia symptomatic control and had evident improvement of their quality of life. Three patients showed partial response with reduced imagiological tumour load.
Keywords: Insulinoma; Lutecium; Neuroendocrine Tumour; PRRNT; Radiolabeled Somatostatin Analogues; Somatostatin Receptors

P12. METASTATIC PAPILLARY THYROID CARCINOMA TREATED WITH LENVATINIB

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Introduction: Lenvatinib, a tyrosine kinase inhibitor (TKI), is used in papillary thyroid carcinoma (PTC) with metastatic disease refractory to radioiodine therapy (RAIT).
Case Report: A 34-year-old female presented with a 45 mm thyroid nodule with suspicious lymph nodes. Cytology indicated PTC. In January/2013 she was submitted to a thyroidectomy with right modified radical neck dissection. Histology confirmed PTC (pT4N1bR1). Following surgery, she underwent RAIT with 150 mCi. In March/2014, because of high thyroglobulin a PET-scan was performed and showed pulmonary metastases. The patient underwent a second RAIT (200 mCi). In June/2015, due to local and lymphatic disease, she was submitted to a new surgery and three months later diagnosed with liver metastases. She was proposed for treatment with lenvatinib 24 mg/day. There was a decrease in thyroglobulin and reduction in metastatic lesions. The 24 mg/day dose was not tolerated and reduced until 14 mg/day. Nine months later she was admitted due to abscesses in lung metastasis and treatment was discontinued for one month. Lenvatinib was resumed but despite the maximum dose there was progression of disease. The patient was proposed for sorafenib and died some days after.
Conclusion: TKIs may control the progression of metastatic, radioiodine-refractory PTC. The management of negative side effects of these drugs can be challenging.
Keywords: Lenvatinib; Papillary Thyroid Carcinoma

P13. NIVOLUMAB-INDUCED ENDOCRINE DISORDERS – REPORT OF A CASE

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Introduction: Nivolumab is an anti-programmed death-1 monoclonal antibody used in the treatment of malignant tumours and may induce autoimmune adverse effects. We report a case of nivolumab-induced thyroid dysfunction followed by isolated ACTH deficiency.
Case Report: Male, 55-year-old with stage IV pulmonary carcinoma. He had no history of thyroid disease and thyroid function prior to the treatment was normal. Four months after nivolumab was started, thyroid evaluation showed hyperthyroidism (TSH 0.01 uUI/mL, FT4 1.91 ng/dL). Patient was asymptomatic, thyroid antibodies were negative and thyroid scintigraphy showed a very low uptake (0%). Two months after, the patient became hypothyroid and was started on levothyroxine. One year after thyroid dysfunction, patient recalled severe fatigue, asthenia and weight loss. Laboratory testing showed low morning cortisol with normal ACTH. Other pituitary hormones were normal. Magnetic resonance imaging showed no space-occupying lesions and homogeneous enhancement of the pituitary gland. He was started on hydrocortisone.
Conclusion: This case intends to alert clinicians to possible adverse endocrine effects from nivolumab. Thyroid dysfunction can occur and other glands may also be affected. In the setting of unexpected fatigue or hypotension, the possibility of adrenal insufficiency should be considered once it is a potentially life-threatening condition that requires immediate treatment.
Keywords: Adrenal Insufficiency; Immunotherapy; Nivolumab, Thyroid Dysfunction

P14. METASTATIC ADRENOCORTICAL CARCINOMA: A SUCCESSFUL CASE?

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Introduction: Adrenocortical carcinoma (ACC) is a rare neoplasm with a variable but overall poor prognosis. Complete resection is the only potentially curative treatment and mitotane is important as an adjuvant therapy due to high recurrence rate.
Case Report: A 69-year-old female with type 2 diabetes and hypertension had a suspicious right adrenal lesion in an ultrasound. She performed an abdominal computed tomography (CT) that showed an 11 x 10 cm heterogeneous right adrenal mass. The patient was referred to Urology and the study revealed normal

24-hour urinary free cortisol and total metanephrines. She underwent open right radical nephro-adrenalectomy with total resection (R0). Histology revealed a 12 cm ACC classified in ENSAT stage II (modified Weiss score 6, Ki67 20%). Three months later, hormonal profile and CT did not reveal any recurrence and she began mitotane. Five months post-surgery CT showed multifocal millimetric lung metastasis, without uptake on FDG-PET/CT. She performed 6 cycles of EDP-M (etoposide, doxorubicin, cisplatin and mitotane). The patient remains under mitotane without evidence of active disease 43 months after the last cycle of chemotherapy.
Conclusion: The management of ACC is challenging. This is a case of success in remission of ACC despite initial unfavourable course.
Keywords: Adrenocortical Carcinoma; EDP-M; Lung Metastasis; Mitotane

P15. LITHIUM-INDUCED NEPHROGENIC DIABETES INSIPIDUS – A CASE REPORT

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Case Report: A 61-year-old woman, under lithium therapy since the diagnosis of bipolar disorder 15 years ago was referred to our hospital Intermediate Care Unit with the diagnosis of a necrotizing pneumonia complicated with a pneumothorax. At the admission, the patient presented moderate hypernatremia (151 mEq/L). She also presented polyuria (3410 mL/24 hours) with normal renal function (pCr 0.58 mg/dL) and normal blood glucose levels. The review of the patient's medical records revealed persistent hypernatremia (maximum value of 155 mEq/L) in the previous 2 weeks despite 5% dextrose in water infusion (63 mL/hour) and oral water replacement (1500 mL/day). Additional study revealed plasmatic osmolarity of 322 mOsmol/kg and urinary osmolarity of 199 mOsmol/kg. Although lithium was withdrawn 2 weeks prior to this diagnosis, lithium-induced nephrogenic diabetes insipidus was assumed and hydrochlorothiazide/amiloride 50/5 mg was initiated. After starting this therapy sodium levels normalized in 2 days (151 > 148 > 141 mEq/L) and polyuria was obviated (3410 > 2890 > 2270 mL/24 hours).
Conclusion: Chronic therapy with lithium causes a clinical picture of diabetes insipidus through a progressive impairment in the kidney concentration ability that can be irreversible even after drug discontinuation. Counterintuitively, diuretic therapy can improve polyuria and solve hypernatremia.
Keywords: Diabetes Insipidus; Iatrogenic; Lithium; Nephrogenic

P16. AGRESSIVE MACROPROLACTINOMA: A CHALLENGING CASE

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Introduction: The majority of prolactinomas respond to dopamine agonists (DA). Rarely surgery and radiotherapy are needed. Temozolomide is the first oral chemotherapeutic agent with substantial response rates in aggressive tumours.
Case Report: In 1998, a 20-year-old female presented with a pituitary macroadenoma, prolactin (PRL) 400 ng/mL, without visual deficits. Due to bilateral visual field defects, tumour enlargement (45 x 30 x 29 mm) and resistance to DA, she underwent two surgeries (histology: prolactinoma, Ki67 8%, p53 32%, negative MGMT). In 2008, she did radiotherapy with partial tumour regression (30 x 30 x 30 mm). Two years later, the tumour increased and she underwent a third surgery. Study did not reveal metastatic lesions. She underwent "salvage therapy" with temozolomide (21 months), with PRL normalization and significant tumour reduction. In 2016, the tumour increased again. She underwent a second cycle of temozolomide, only for 3 months by tumour growth. Due to clinical deterioration without effective treatment options, PPRT therapy was considered. GA-DOTA-NOC PET showed an intense pituitary uptake but the therapy was refused. Despite a new surgery (Ki67 15%, p53 30% - 40%), she is getting worse and the tumour keeps growing (64 x 43 x 33 mm).
Conclusion: Resistant prolactinomas are rare and their treatment is very challenging. We report a case in which all treatment options were not effective.
Keywords: Aggressive Tumours; Prolactinoma; Resistant; Temozolomide

P17. BILATERAL INFERIOR PETROSAL SINUS SAMPLING IN THE DIAGNOSIS OF CUSHING'S SYNDROME IN MRI NEGATIVE PATIENTS: A SINGLE-CENTER EXPERIENCE

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Introduction: ACTH-dependent Cushing's syndrome (CS) is characterized by excessive adrenocorticotropic hormone (ACTH) secretion from a pituitary or ectopic tumour, resulting in hypercortisolism. Despite low sensitivity and specificity, non-invasive tests may be used to differentiate these aetiologies.

If fail to localize the site, invasive tests are advocated. Bilateral inferior petrosal sinus sampling (BIPSS) is the current diagnosis gold standard of Cushing's disease (CD). Our aim is to determine the diagnostic value of this procedure to evaluate patients with suspected CD.

Methods: We retrospectively analysed 27 patients with confirmed hypercortisolism, measurable level of plasma ACTH and negative or inconclusive findings on pituitary magnetic resonance imaging (MRI) who underwent BIPSS. Patient files were used to identify demographics, laboratory, MRI, surgery and pathology findings. Basal >2 or after CRH stimulation > 3 central/peripheral ratio were considered diagnostic of CD. Pituitary or ectopic tumours, identified in histologic samples, were the gold standard of diagnosis.

Results: Twenty seven procedures were performed in 27 patients (22 F, 5 M), mean age 39 years. Sampling was successful following catheterization in all patients. No thromboembolic complications were found. In this series, 2 patients were excluded from further statistical analyses for lack of final diagnosis. Among the 25 patients, 20 had CD (80%) and 5 ectopic secretion (20%). Among the 20 CD patients, 14 had centralizing BIPSS after corticotropin-releasing hormone (CRH) stimulation, therefore the sensitivity was 70%. All ectopic tumours had negative gradient, consequently the specificity was 100%.

Conclusion: BIPSS is a safe procedure and remains the 'gold standard' for diagnosing CD. Though its accuracy is not 100%, it presents higher sensitivity and specificity than other biochemical tests.

Keywords: Adrenocorticotropic Hormone; Bilateral Inferior Petrosal Sinus Sampling; Corticotropin-Releasing Hormone; Cushing Disease; Cushing Syndrome

P18. 48,XXYY SYNDROME: A VARIANT OF KLINEFELTER SYNDROME OR A DIFFERENT CONDITION? CASE REPORT

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Introduction: Klinefelter syndrome (KS) is the most common congenital abnormality causing primary hypogonadism (~1:1000 male births). The most common genotype is 47,XXY but different karyotypes have been reported. 48,XXYY syndrome (occurring in 1:18,000–1:40,000 males) was often characterized as a variant of KS due to a shared physical and endocrinologic phenotype (tall stature, hypergonadotropic hypogonadism and infertility). However, these patients have more significant neurodevelopmental/psychological involvement, reason why recent literature considers it a separate condition.

Case Report: A 20-year-old male, non-consanguineous parents, with personal history of cardiac interatrial communication and inguinal hernias during childhood. He had learning and linguistic impairments, hyperactive disorder and behavior and impulsivity problems, being currently under psychiatric and psychological guidance. His karyotype, performed at 3 years-old, was 48,XXYY. He has heterosexual orientation with coprophilia. On physical examination, weight of 84 kg, height of 193 cm and arm span of 194 cm. Blood tests revealed hypergonadotropic hypogonadism. Bone osteodensitometry showed no alterations.

Conclusion: Unlike KS, which is difficult to diagnose before puberty, 48,XXYY syndrome is diagnosed earlier (on average at 7.7 years of age) due to developmental delays that are noted from 2nd to 5th year. The authors emphasize the importance of early diagnosis of this entity to allow an adequate multidisciplinary approach.

Keywords: Hypergonadotrophic Hypogonadism; Klinefelter Syndrome

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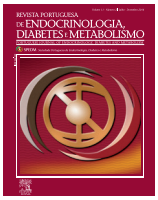

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VI. Resumo Estruturado

Um resumo estruturado, com as etiquetas de secção apropriadas, deve fornecer o contexto e objectivo do estudo, procedimentos básicos (seleção dos sujeitos de estudo ou animais de laboratório, métodos observacionais e analíticos), principais resultados (significância estatística, se possível) e principais conclusões. Deve enfatizar aspectos novos e importantes do estudo ou das observações. Secções: Introdução, Métodos, Resultados e Conclusões.

VII. Os autores também incluirão nesta página de título, sob a designação "Considerações éticas" a declaração de "**Protecção de pessoas e animais"**, **Confidencialidade dos dados e consentimento informado e Conflitos de interesse.**

Prémios e Apresentações prévias

Devem ser referidos os prémios e apresentações do estudo, prévias à submissão do manuscrito

Texto

Artigos Originais

Os artigos originais devem incluir as seguintes secções: Introdução, Material e Métodos, Resultados, Discussão e Conclusão, Agradecimentos (se aplicável), Referências, Tabelas e Figuras.

Os artigos originais não devem exceder 4000 palavras, até 6 tabelas ou figuras e até 60 referências. Um resumo estruturado com o máximo de 350 palavras.

Article structure

Introduction

State the objectives of the work and provide an adequate background, avoiding a detailed literature survey or a summary of the results.

Material and methods

Provide sufficient detail to allow the work to be reproduced.

Article type	Abstract	Keywords	Main text structure	Max. words	Tables/figures	References
Original Article	Max. 350 words; structured (Introduction and Objectives, Methods, Results and Conclusion(s)) Portuguese and English	Up to 6 Portuguese and English	Introduction; Methods; Results; Discussion; Conclusion(s); Acknowledgments, if any; References; and figure legends, if any	4000	Total up to 6	Up to 60
Review Article	Max. 350 words; unstructured Portuguese and English	Up to 6 Portuguese and English	Introduction; thematic sections at the discretion of the authors; Conclusion(s); Acknowledgments, if any; References; and figure legends, if any	4000	Total up to 6	Up to 100
Systematic Review	Max. 350 words; structured Portuguese and English	Up to 6 Portuguese and English	PRISMA	4000	Total up to 6	Up to 100
Case Report	Max. 150 words; unstructured Portuguese and English	Up to 6 Portuguese and English	Introduction; Case report; Discussion; Conclusion(s) (optional); References; and figure legends, if any	2000	Total up to 4	Up to 25
Images in Endocrinology	None	Up to 6 Portuguese and English	Unstructured	500	Total up to 4	Up to 5
Editorial	None	None	Unstructured	1500	Total up to 2	Up to 20
Letter to the Editor	None	Up to 6 Portuguese and English	Unstructured	600	Total up to 1	Up to 10
Current Perspectives	None	Up to 6 Portuguese and English	Unstructured	1200	Total up to 2	Up to 10

Methods already published should be indicated by a reference: only relevant modifications should be described.

Results

Results should be clear and concise.

Discussion

This should explore the significance of the results of the work, not repeat them. A combined Results and Discussion section is often appropriate. Avoid extensive citations and discussion of published literature.

Conclusions

The main conclusions of the study may be presented in a short Conclusions section, which may stand alone or form a subsection of a Discussion or Results and Discussion section.

Artigos de Revisão

Os artigos de revisão são artigos abrangentes que sintetizam ideias antigas e sugerem novas. Abrangem áreas amplas. Podem ser de ciência clínica, investigação ou básica. Embora geralmente por convite do Editor-Chefe, ocasionalmente aceitamos artigos de revisão não solicitados sobre assuntos importantes ou sobre avanços recentes. Antes de submeter uma revisão, pedimos que envie ao Editor-Chefe um breve esboço (não mais de 500 palavras) indicando a importância e novidade do assunto, e por que está qualificado para escrevê-lo. Um convite para submissão não garante aceitação.

Os artigos de revisão não devem exceder 4000 palavras, até 6 tabelas ou figuras e até 100 referências. Um resumo não estruturado com o máximo de 350 palavras.

Revisões Sistemáticas e Meta-Análises

As revisões sistemáticas podem ou não utilizar métodos estatísticos (meta-análises) para analisar e resumir os resultados dos estudos incluídos.

As Revisões Sistemáticas podem ser apresentadas no formato Introdução, Métodos, Resultados, Discussão. O assunto deve ser claramente definido. O objectivo de uma revisão sistemática deve ser produzir uma conclusão baseada em evidências. Nos Métodos devem fornecer uma indicação clara da estratégia de pesquisa da literatura, extracção de dados, classificação das evidências e análise. Deve ser seguida a normativa PRISMA (http://www.prisma-statement.org/).

O texto não deverá exceder 4000 palavras, excluindo um resumo estruturado (máximo de 350 palavras). Não poderá incluir mais de 10 referências, e até 6 tabelas ou figuras**.**

Caso Clínico

O relato de Casos Clínicos deve incluir as seguintes seções: Introdução, Caso Clínico e Discussão.

O texto não poderá exceder 2000 palavras, e não poderá exceder as 25 referências bibliográficas. Deve incluir um resumo não estruturado, que não exceda 150 palavras.

Deve ser seguida a normativa CARE (http://www.care-statement.org/).

Editoriais

Os Editoriais são da responsabilidade do grupo editorial ou solicitados por convite do Editor-Chefe e constituirão comentários sobre tópicos actuais ou comentários sobre artigos publicados na revista. Não devem exceder as 1200 palavras, um máximo de 20 referências bibliográficas e podem conter uma tabela e uma figura. Não têm resumo.

Cartas ao Editor

As cartas ao Editor consistem em comentários críticos sobre um artigo publicado na revista ou uma nota curta sobre um determinado tópico ou caso clínico. Cartas ao Editor não devem exceder 600 palavras e 10 referências e pode conter uma figura ou tabela. Não têm resumo.

Imagens em Endocrinologia

Esta secção destina-se à publicação de imagens clínicas, radiológicas, histológicas e cirúrgicas relacionadas com casos de endocrinologia, diabetes ou metabolismo.

O título não deve ter mais de oito palavras. Os autores devem ser no máximo quatro. As imagens devem ser de alta qualidade e valor educativo. São permitidas até 4 figuras**.** As legendas devem ser breves e informativas. Setas ou outros símbolos devem ser incluídos conforme necessário para facilitar a compreensão das imagens. O texto não deve exceder 500 palavras, até cinco referências, e deve incluir uma breve história clínica e dados relevantes do exame físico, testes laboratoriais e progressão clínica, conforme apropriado. Não têm resumo.

Perspectiva

Este é o tipo de manuscrito é submetido a convite do Conselho Editorial. Pode abranger uma ampla diversidade de temas relacionados com endocrinologia, diabetes, metabolismo e saúde: problemas atuais ou emergentes, políticas de gestão e saúde, história da medicina, questões de sociedade e epidemiologia, entre outros. Um Autor que deseje propor um manuscrito nesta seção deverá enviar um resumo ao Editor-Chefe, incluindo o título e a lista de autores para avaliação. O texto não deve exceder 1200 palavras, até 10 referências, e até 2 tabelas ou 2 figuras. Não têm resumo.

Guidelines

Os guias de prática clínica não devem exceder 4000 palavras, até 6 tabelas ou figuras e até 100 referências. Resumo até 350 palavras.

Referências

I.Citação no texto

Certifique-se de que todas as referências citadas no texto também estão presentes na lista de referências (e vice-versa). As referências devem ser listadas usando algarismos árabes pela ordem em que são citados no texto.

As referências a comunicações pessoais e dados não publicados devem ser feitas diretamente no texto e não devem ser numeradas. Citação de uma referência como “in press” implica que o item tenha sido aceite para publicação. Os nomes das revistas devem ser abreviados de acordo com o estilo da Medline.

As referências a artigos publicados em revistas devem incluir o nome do primeiro autor seguido dos nomes dos restantes autores, o título do artigo, o nome da revista e o ano de publicação, volume e páginas.

Certifique-se de que os dados fornecidos nas referências estão corretos. Ao copiar referências, tenha cuidado porque já podem conter erros.

A lista de referências deve ser adicionada como parte do texto, nunca como uma nota de rodapé. Códigos específicos do programa de gestão de referências não são permitidos.

II. Formato

Uma descrição detalhada dos formatos de diferentes tipos de referência pode ser consultada em ICMJE *Recommendations* (http://www.icmje.org/recommendations/). Liste todos os autores se houver seis ou menos. *Et al* deve ser adicionado se houver mais de seis autores. Título do artigo, nome da revista, ano, volume e páginas.

III. Estilo de referência

Texto: Indicar as referências no texto por número (s) em expoente. Os autores podem ser referidos, mas o número de referência deve ser sempre dado.
Lista: Ordene as referências na lista pela ordem em que aparecem no texto
Exemplos:
Referência de artigo:

1. Isidori AM, Sbardella E, Zatelli MC, Boschetti M, Vitale G, Colao A, et al. Conventional and nuclear medicine imaging in ectopic Cushing's syndrome: a systematic review. J Clin Endocrinol Metab. 2015;100:3231-44.

Referência de livro:
2.Ware JE, Kosinski M, Dewey JE. How to score version 2 of the SF-36 Health Survey: standard & acute forms. Lincoln: Quality Metric Incorporated; 2000.

Referência de capítulo de livro:
3. Castellano Barca G, Hidalgo Vicario M, Ortega Molina M. Transtorno del comportamento alimentário. In: Castellano Barca G, Hidalgo Vicario M, Redondo Romero A, editores. Medicina de la adolescência – atención integral. 2ª ed. Madrid: Ergon; 2004. p.415-29.

Referências Web:
4. No mínimo, o URL completo deve ser dado e a data em que o documento foi consultado. Qualquer outra informação, se conhecida (nomes de autor, datas, referência a uma publicação de origem, etc.), também deve ser dada.

Notas de Rodapé

As notas de rodapé devem ser evitadas. Quando imprescindíveis, devem ser numerados consecutivamente e aparecer ao pé da página apropriada.

Agradecimentos (facultativo)

Devem vir após o texto, e antes das referências, tendo como objectivo agradecer a todos os que contribuíram para o estudo mas que não têm peso de autoria. Nesta secção é possível agradecer a todas as fontes de apoio, quer financeiro, quer tecnológico ou de consultadoria, assim como contribuições individuais.

Abreviaturas

Não use abreviaturas ou acrónimos no título e no resumo e limite o seu uso. Abreviaturas não consagradas devem ser definidas na primeira utilização, por extenso, logo seguido pela abreviatura entre parenteses. A menos que a sigla seja uma unidade padrão de medição. Uso excessivo e desnecessário de acrónimos e abreviaturas deve ser evitado.

Unidades de Medida

Devem ser utilizadas as unidades Sistema Internacional de Unidades. As medidas de comprimento, altura, peso e volume devem ser expressas em unidades do sistema métrico (metro, quilograma ou litro) ou seus múltiplos decimais. As temperaturas devem ser dadas em graus Celsius (ºC) e a pressão arterial em milímetros de mercúrio (mm Hg) ou a hemoglobina em g/dL. Todas as medições hematológicas ou bioquímicas serão referidas no sistema métrico de acordo com o Sistema Internacional de Unidades (SI).

Nomes de Medicamentos

Identifique com precisão todos os medicamentos e produtos pelo nome genérico. Não é recomendável a utilização de nomes comerciais de fármacos (marca registrada), mas quando a utilização for imperativa, o nome do produto deverá vir após o nome genérico, entre parênteses, em minúscula, seguido do símbolo que caracteriza marca registada, em sobrescrito (®).

Tabelas e Figuras

Tabelas/Figuras devem ser numerados na ordem em que são citadas no texto e assinaladas em numeração árabe e com identificação, Figura/Tabela.

Cada figura e tabela incluídas no trabalho têm de ser referidas no texto: Uma resposta imunitária anormal pode estar na origem dos sintomas da doença (Fig. 2). Esta associa-se a outras duas lesões (Tabela 1).

Figura: Quando referida no texto é abreviada para Fig., enquanto Tabela não é abreviada. Nas legendas ambas as palavras são escritas por extenso.

Cada tabela e figura deve ser acompanhada da respectiva legenda, sucinta e clara. As legendas devem ser auto-explicativas (sem necessidade de recorrer ao texto).

Em relação aos gráficos deve ser explícito se a informação inclui valores individuais, médias ou medianas, se há representação do desvio padrão e intervalos de confiança e o tamanho da amostra (n).

As fotografias deverão incluir identificadores (setas e asteriscos). Poderão ser publicadas fotografias a cores, desde que consideradas essenciais.

Cada tabela deve ser utilizada para mostrar resultados, apresentando listas de dados individuais ou sumariando os mesmos, não devendo no entanto constituir duplicação dos resultados descritos no texto. Devem ser acompanhadas de um título curto mas claro e elucidativo. As unidades de medida usadas devem ser indicadas (em parêntesis abaixo do nome que encabeça cada categoria de valores) e os números expressos devem ser reduzidos às casas decimais com significado clínico.

Para as notas explicativas nas tabelas devem ser utilizados os seguintes símbolos e sequência: *, †, ‡, §, ||, ¶, **, ††, ‡‡ .

Se fotografias de doentes forem usadas, estes não devem ser identificáveis ou as fotografias devem ser acompanhadas de autorização por escrito para usá-las.

As imagens a cores são reproduzidas gratuitamente.

Princípios gerais:

• Numere as ilustrações de acordo com a sua sequência no texto.

• Forneça as legendas das ilustrações separadamente.

• Dimensione as ilustrações próximas das dimensões desejadas da versão publicada.

• Envie cada ilustração em ficheiro separado.

A inclusão de figuras e/ou tabelas já publicadas, implica a autorização do detentor de *copyright* (autor ou editor).

A submissão deve ser feita separadamente do texto, conforme as instruções da plataforma.

Os ficheiros das figuras devem ser fornecidos em alta resolução, 800 dpi mínimo para gráficos e 300 dpi mínimo para fotografias.

A publicação de ilustrações a cores é gratuita.

Material gráfico deve ser entregue em um dos seguintes formatos:
JPEG (. Jpg)
Portable Document Format (. Pdf)
PowerPoint (.ppt)
TIFF (. Tif)
Excel

Permissão para publicação: No caso de publicação de tabelas de livros ou revistas os autores são responsáveis por obter permissão, junto dos autores dos trabalhos de onde forem reproduzidos, para a referida publicação, e terão de a apresentar na submissão.

Ficheiros Multimedia

Os ficheiros multimedia devem ser enviados em ficheiro separado com o manuscrito. O material multimedia deve seguir os padrões de qualidade de produção para publicação sem a necessidade de qualquer modificação ou edição. Os ficheiros aceitáveis são: formatos MPEG, AVI ou QuickTime.

Anexos/ Apêndices

Quando necessário, os anexos devem ser utilizados para apresentar inquéritos longos ou detalhados, descrições de extensos cálculos matemáticos e / ou listas de itens. Devem ser colocados depois da lista de referências, se necessário, com legendas. Anexos longos, tais como algoritmos, pesquisas e protocolos, serão publicados apenas *online*; o URL será fornecido no artigo impresso onde o anexo é citado.

Se houver mais de um apêndice, eles devem ser identificados como A, B, etc. As fórmulas e equações em apêndices devem ser numeradas separadamente: Eq. (A.1), Eq. (A.2), etc .; Em apêndice posterior, a Eq. (B.1) e assim por diante. Da mesma forma para tabelas e figuras: Tabela A.1; FIG. A.1, etc.

Estilo

Rev Port Endocrinol Diabetes Metab segue AMA Manual Style (10ª edição).

Última revisão **Maio 2017**