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20th ESE Postgraduate Training Course on Endocrinology Diabetes and Metabolism Abstracts and clinical cases

МЕДИА СФЕРА

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20th ESE Postgraduate Training Course on Endocrinology Diabetes and Metabolism

Abstracts and clinical cases

In accordance with the resolution of the Higher Attestation Commission of the Ministry of Education and Science of the Russian Federation, the Problems of Endocrinology was included in the List of Leading Peer-Reviewed Journals and Periodicals issued in the Russian Federation where the main results of Candidate and Doctor Theses are recommended to be published.

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Abstracts and clinical cases

FROM INSULIN PUMP TO BIONIC PANCREAS: THE STEP FORWARD IN PUMP THERAPY

J. Hans de Vries

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Insulin pumps will soon celebrate their 40th anniversary. They lower HbA1c in people with type 1 diabetes, especially in motivated people with high baseline HbA_{1c} values. Similarly, their use reduces severe hypoglycaemia, especially in those who encounter severe hypoglycaemia frequently. Some 15 years after its introduction in clinical practice, Continuous Glucose Monitoring has become an established treatment modality. There is sound evidence that patients can lower their HbA_{1c} when using this technology, and spend less time in hypoglycaemia. Evidence supports the notion that CGM can also decrease the incidence of severe hypoglycemia. The added value of CGM during pregnancy is unclear, but larger trials are under way. Insulin pumps and Continuous Glucose Monitoring combined with a control algorithm constitute an artificial pancreas or closed-loop. In several trials with a duration up to three months, time in target increased through a decrease in both time above target and time below target. In parallel to several pivotal trials, a first product will come to the market in 2017. Bihormonal closed-loop, employing both insulin to lower glucose and glucagon to increase glucose, may show further benefits.

KEYWORDS: diabetes mellitus, CGM, insulin pumps.

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GLUCOSE CLAMP TECHNIQUE IN ENDOCRINOLOGY

Alexander Y. Mayorov

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Mathematical models of glucose homeostasis (HOMA-IR, Matsuda etc.) are usually used in clinical practice for quantitative assessment of insulin resistance. However those methods are not accurate enough (high variability of glucose and insulin levels) and have a number of limitations. That is why hyperinsulinemic euglycemic clamp test is the gold standard of quantitative assessment of insulin resistance. Glucose clamp technique is being used to measure insulin resistance since late 1970s. Hyperinsulinemic euglycemic clamp test is based on peripheral glucose disposal assessment in conditions of inhibited endogenous insulin secretion and gluconeogenesis. To achieve these conditions acute increase of insulin concentration in blood (100 mU/ml at average) is created by its constant intravenous infusion with the rate 1 mU/kg/min and simultaneous intravenous infusion of glucose in order to maintain euglycemia (around 5 mmol/l). To calculate the amount of the infused glucose fast and multiple venous blood glucose measurements are needed (every 5 min during several hours). When the rate of glucose infusion is equal to the rate of its peripheral disposal, euglycemic steady state is achieved. M-value is calculated: it is the rate of whole body glucose metabolism at a single level of hyperinsulinemia during steady state conditions of glucose during clamp test. In order to achieve a maximal possible suppression of endogenous insulin, glucagon and growth hormone release during hyperinsulinemic clamp tests, a concomitant infusion of somatostatin can be applied. There are other types of clamp tests, each of them can be used to study a particular problem. For example, hyperglycemic clamp technique is a method for the quantification of beta-cell sensitivity to glucose. In this case the stimulation of endogenous insulin secretion takes place, which can be used to study functional activity of pancreatic beta-cells, insulin secretion phases, and pharmacokinetic properties of some antidiabetic drugs. Hyperinsulinemic hypoglycemic clamp technique is used for assessment of counterregulation and other metabolic parameters during hypoglycemia. For assessment of hepatic glucose production glucose clamp with tracers is used. Euglycemic insulin clamp technique is also used to study time-action profiles (pharmacokinetics and pharmacodynamics) of insulin preparations (including biosimilars). In this case glycemic level lowering is expected in some period of time after subcutaneous injection of the study drug and is corrected back to euglycemic level by increasing the glucose infusion rate. The increase of glucose infusion rate will reflect most precisely the beginning, peak and end of action of the study insulin, i.e. it will characterize its biological activity profile. It is preferable to study rapid- and short-acting insulins on healthy volunteers, as they usually demonstrate less intraindividual variability. Patients with type 1 diabetes are more suitable for the studies to determine the time-action profile of long-acting insulins. Thus, clamp test is the most reliable and accurate diagnostic method for both evaluation of the properties of insulin resistance and studying pharmacodynamic and pharmacokinetic characteristics of antidiabetic drugs. Its infrequent use in clinical practice is due to considerable manpower input of this method, which requires additional technical equipment and specially trained staff.

KEYWORDS: glucose clamp, diabetes mellitus, insulin resistance.

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UPDATE ON TREATMENT OF TYPE 2 DIABETES MELLITUS

JORGEN RUNGBY

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Type 2 diabetes is a heterogeneous disease and therefore it may be complicated to treat hyperglycaemia. Treatment is ideally based on pathophysiological knowledge about the causes of hyperglycaemia in the individual patient:

«The right pill in the right mouth».

The lecture will focus on anti-hyperglycaemic treatment, including an introduction to recently introduced drugs and a discussion of recently published outcome trials.

KEYWORDS: diabetes mellitus, treatment, drugs.

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LIPODYSTROPHY AND DIABETES

Ekaterina Sorkina

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Lipodystrophy syndromes form a heterogeneous group of rare disorders of deficient body fat associated with potentially serious metabolic complications, including diabetes, hypertriglyceridemia, and steatohepatitis. Lipodystrophies can be categorized based on their etiology (genetic or acquired) and the degree of fat loss: affecting the entire body (generalized), some regions of the body (partial) or localized lipodystrophy (eg, from injectable drugs). It has been shown in the last 20 years that the cause of the majority of inherited forms of lipodystrophy is the mutation in one of the genes involved in adipogenesis. Acquired lipodystrophies are often associated with autoimmune diseases, although the most common form is HIV-associated lipodystrophy. Major causes of mortality in lipodystrophic patients include heart disease, liver disease, kidney failure, acute pancreatitis and sepsis. Diabetes is common in patients with congenital forms of generalized and partial lipodystrophy as well as in acquired generalized lipodystrophy and is known as a special type of diabetes — lipoatrophic diabetes. Major characteristic of the lipoatrophic diabetes is marked insulin resistance, usually associated with acanthosis nigricans, hypertriglyceridemia, liver disease and arterial hypertension in young patients with no signs of obesity. Due to the rarity of lipodystrophy syndromes, many clinicians are unfamiliar with their diagnosis and management, and lipoatrophic diabetes is usually misdiagnosed as diabetes mellitus type 2 or type 1. This lecture summarizes the diagnosis and management of lipodystrophy syndromes and lipoatrophic diabetes in particular, based on the International practice guideline and local experience of studying different forms of lipodystrophies in Russia.

KEYWORDS: diabetes mellitus; lipodystrophy; lipoatrophic diabetes.

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DIABETES AND CANCER

Itamar Raz

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To date, the medical literature has indicated that diabetic patients experience an increase in the incidence of cancer. The main organs that are involved are liver, pancreas, lungs, ovaries and breast. The risk for early mortality also seems to be increased when compared to non-diabetic patients. Better glucose control has not been shown to necessarily influence mortality. There is also a strong link between obesity and cancer. It is estimated that $^{1}/_{3}$ of breast cancer can be prevented by adopting a healthy lifestyle. Intentional weight loss was shown to reduce the incidence of cancer. Both diabetes and obesity are the cause and result of insulin resistance, resulting hyperinsulinemia and increase in free IGF1, enhanced cell replication and growth. In both obesity and diabetes there is an increase in cytokines that enhance/promote cell growth. In women with breast cancer, recurrence of the tumor was strongly related to high insulin levels. Observational studies have demonstrated an increased risk to develop cancer in patients treated with insulin or sulphonylurea. Exogenous hyperinsulinemia can directly enhance cell growth. However, the ORIGIN study which followed 12,000 patients under insulin therapy over a period of 6 years did not show any increase in the risk to develop cancer. The thiazolidinedione family of drugs was expected to reduce the risk to develop cancer by reducing insulin resistance and deleterious cytokines and also by having a direct inhibitory effect on cell growth. Metaanalyses of various studies with rosiglitazone suggest that this drug may indeed reduce the risk for cancer. On the other hand, some studies have suggested that pioglitazones may increase the risk of bladder cancer. In mice treated with high doses of metformin (equivalent to 18 gm/per day in humans) the free recurrence time from breast carcinoma was increased. Observational studies have demonstrated a reduction in the incidence of liver, lung and GI cancer under metformin therapy. Metformin inhibits the progression of breast carcinoma cell line and seems to improve survival in patients with lung cancer. Metformin affects carcinoma cells by increasing AMP-Kinase which inhibits mTOR and enhances tumor suppressors, thereby preventing cell proliferation. At the end of 2014 there were 213 studies registered in the NIH dealing with metformin to prevent cancer development and progression. In my lecture I will discuss new data on the relationship of anti-diabetic drugs to cancer development and progression.

KEYWORDS: diabetes mellitus, cancer, metformin.

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CHRONIC KIDNEY DISEASE IN TYPE 1 AND TYPE 2 DIABETES: EARLY DIAGNOSTICS AND NEPHROPROTECTION

Marina Shestakova

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Diabetic kidney disease (DKD) is still a widespread complication both in type 1 and type 2 diabetes and the leading cause of end stage renal disease, accounting for 30—50% of cases in different countries. The routine markers of kidney dysfunction such as decrease of glomerular filtration rate (GFR) and increase in urinary albumin excretion (UAE) come too late in the natural history of DKD. It seems to be promising to find new urinary proteomic biomarkers of glomerular, tubular and interstitium damage in DKD much earlier than UAE increases. The «metabolic memory» mechanism in predicting a risk for DKD through 20 years of follow-up since the onset of the disease will be discussed. Genetic polymorphic markers may serve as a useful tool for prediction the risks of DKD in type 1 and type 2 diabetes as well. The efficacy of renal protection agents such as renin-angiotensin system blocking drugs is rather high but not enough to stop the DKD. The renal protective capacity of novel classes of glucose-lowering drugs such as DPP-4 inhibitors, GLP-1 receptor agonists, SGLT-2 inhibitors will be discussed.

KEYWORDS: diabetes mellitus, diabetic kidney disease, metabolic memory.

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CARDIOVASCULAR OUTCOME STUDIES: PRESENT AND FUTURE IN DIABETES

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Cardiovascular disease is one of the most common diabetes-associated complications. Before 2008 almost all randomized controlled studies were «glucocentric», concentrating on the glycaemic effect of antidiabetic drugs. In 2008 paradigm was changed to look for cardiovascular complications as the leading cause of death in type 2 diabetes patients.

This lead to the series of cardiovascular outcome trials with new antidiabetic drugs, mostly showing cardiovascular safety. Once more paradigm changed in 2015, when first superiority results with antidiabetic drugs were archived. Since that time lots of questions rise, concerning the drug choice in different populations and the possibility to extend trial results on primary prevention patients and on the all molecules in classes of SGLT-2 inhibitors and GLP-1 receptor agonists. Deep investigations into the mechanisms of cardiovascular prevention with antidiabetic drugs are required. Despite the amount of data provided by cardiovascular outcome trials, this approach still has certain limitations.

KEYWORDS: diabetes mellitus; cardiovascular disease; complications.

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THE STATES OF THE ART MANAGEMENT OF ACROMEGALY: FROM DIAGNOSIS TO TREATMENT AND 10 YEARS FOLLOW UP

AJ van der Lely

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Acromegaly is a rare disease, most often caused by a GH producing tumor of the anterior pituitary. Available treatment modalities to date aim at normalizing serum IGF-I levels via reduction of either GH overproduction or GH actions. The obvious advantage is that the efficacy of different treatments can be easily compared by means of serum IGF-I measurements as this is more practical than frequent GH measurements. This also applies to comparisons between the effects of long-acting somatostatin therapies (LA-SMSA) and the GH-receptor antagonist, pegvisomant (PEGV). This approach, however, is based on the assumption that serum IGF-I levels adequately and uniformly reflect disease activity. This assumption, however, is not necessarily valid. In a hypothesis paper, published in the EJE, Negers et al addressed the relationship between the GH — IGF-I axis with a specific emphasis on the significant differences in the modes of action of LA-SMSA and PEGV. In doing so, they introduced the novel hypothetic paradigm of hepatic and extra-hepatic acromegaly and its potential clinical implications. The effects of GH are tissue specific and concentration dependent. The physiological effects of GH versus IGF-I remain controversial. Historically, it has been difficult to isolate the individual effects of GH and IGF-I at the tissue level during physiological conditions. But the fact that GH possesses a diabetogenic or 'anti-insulin' activity while IGF-I (as the name implies) is similar to insulin in its actions, clearly demonstrates that physiological differences exist between the actions of the two peptide hormones. Medical treatment of acromegaly with LA-SMSA and PEGV has made it possible to achieve normal serum IGF-I concentrations in a majority of patients with acromegaly. These two compounds, however, impact the GH-IGF-I axis differently, which challenges the traditional biochemical assessment of the therapeutic response. Neggers et al postulated that LA-SMSA in certain patients normalizes serum IGF-I levels in the presence of elevated GH actions in extra hepatic tissues. This may result in persistent disease activity for which they proposed the term extra-hepatic acromegaly. Pegvisomant, on the other hand, blocks systemic GH actions, which is not necessarily reliably reflected by serum IGF-I levels, and this treatment causes a further elevation of serum GH levels. Medical treatment is, therefore, difficult to monitor with the traditional biomarkers. Moreover, the different modes of actions of LA-SMSA

and PEGV make it attractive to use the two drugs in combination. Maybe it is time to challenge the existing concepts of treatment and monitoring of patients with acromegaly.

KEYWORDS: acromegaly, IGF-I, somatostatin, pegvisomant.

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CUSHING'S SYNDROME: HOW TO SCREEN, DIAGNOSE AND TREAT TODAY WITH LINK TO THE FUTURE

R. Feelders

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Cushing's disease (CD), caused by a corticotroph pituitary adenoma, is associated with multi-system morbidity resulting in an impaired quality of life. When untreated or suboptimally treated, CD can lead to an increased mortality with cardiovascular disease as leading cause of death. Recently an etiological role for somatic mutations in ubiquitin specific peptidase 8 gene (USP8) has been identified in a subset of corticotroph adenomas. Inactivation of USP8 leads to increased epidermal growth factor receptor (EGFR) signaling and subsequently ACTH synthesis. EGFR may become a new therapeutic target in CD. Because of the gradual development of symptoms and the overlap in features of the metabolic syndrome, it can take years before the diagnosis CD is established. First-line screening tests are available to identify patients with CD, i.e. 24 h urinary free cortisol excretion, the overnight 1 mg dexamethasone suppression test and measurement of late night salivary cortisol levels (LNSC). LNSC can also be helpful to differentiate CD from conditions that are accompanied by activation of the pituitary-adrenal axis ('pseudo-Cushing states'), e.g. psychiatric disorders. Rarely, CD has a cyclical pattern which can hamper biochemical diagnosis. Preliminary data show that measurement of cortisol in scalp hair can reveal episodic cortisol overproduction in these patients. Transsphenoidal adenomectomy is the first choice of treatment for CD and remission rates vary between 60 and 90%. Treatment modalities for patients with persistent or recurrent disease include repeat surgery, radiotherapy, medical therapy and bilateral adrenalectomy. Medical therapy for CD can be classified into pituitary-directed drugs, adrenal-blocking drugs and glucocorticoid receptor antagonists. Dopamine and somatostatin receptors have been identified as targets for pituitary-directed drug therapy. The majority of ACTH-secreting pituitary adenomas expresses the dopamine receptor subtype 2 (DA2) and several studies show that the DA2 agonist cabergoline can normalize cortisol production in 25—40% of CD patients. Of the 5 known somatostatin receptor subtypes (sst), corticotroph pituitary adenomas predominantly express sst5, whereas sst2 expression is low due to down-regulating effects of high cortisol levels. Pasireotide is a universal somatostatin analog with high affinity for sst5 and the formulation for subcutaneous administration was recently approved for treatment of CD in Europe and the USA. A study with longacting pasireotide in CD is underway. Combined targeting of DA2 and sst5 with cabergoline and pasireotide showed promising results. Another potential therapeutic target includes cyclin-dependent kinases which were shown to be upregulated in corticotroph adenomas and which can promote cell growth via deregulation of the cell cycle. Metyrapone and ketoconazole are the most widely used adrenal blocking drugs. LCI699 and COR-003 are recently developed inhibitors of steroidogenesis and are currently under investigation in multicenter trials. Mifepristone is the only available glucocorticoid receptor antagonist and was recently approved in the USA for treatment of hyperglycemia related to CD. Importantly, morbidity of CD is not or only partially reversible in a substantial number of patients which is possibly related to the duration of pre-existing hypercortisolism. Therefore, after diagnosis cortisol production should be rapidly normalized with concomitant careful treatment of (cardiovascular) co-morbidity. Long-term follow-up is needed for CD patients to monitor complications of hypercortisolism and to detect recurrent disease.

KEYWORDS: cushing's syndrome, pituitary adenoma, ACTH, cortisol.

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UPDATE ON THE MULTIDISCIPLINARY MANAGEMENT OF PITUITARY TUMOURS

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The pituitary gland is one of most fascinating organs of the body, as it has centrally important functions and also it is located in a unique anatomical position. It is the leader of the endocrine orchestra regulating multiple functions and it is sitting below the optic crossing and in-between the carotid arteries therefore no surprise that management of diseases of the pituitary requires an orchestra of expert colleagues itself. Starting with the diagnosis, we rely on family doctors, neurologists, rheumatologists, dermatologists, orthopaedic specialist, neurosurgeons, dentists, gynaecologists, cardiologists, ophthalmologists and optometrists but even jewellers (ring enlargements) and to make or at least suggest the diagnosis of acromegaly, Cushing's disease, prolactinoma, TSHoma, diabetes insipidus etc. While the diagnosis often is simple, in other cases numerous tests and discussions are needed to come to the right conclusions: skills of an interventional radiologists doing venous catheterisation or a vigilant biochemist testing for macroprolactin or the hook effect or special tests to solve the thyroid hormone resistance-TSHoma dilemma, helps out the endo-

crinologist to make the correct diagnosis. More recently clinical geneticist are helping to make the genetic diagnosis and therefore sometimes changing the nature of a planned operation and helping families to prevent major morbidities. Characterisation by a pathologist is crucial as treatment options are also widening and special assessment such as immunostaining for somatostatin receptors or MGMT. Special imaging with metomidate PET-CT could lead to the right choice of next step. The role of radiotherapist and oncologist intervening in the severe cases can be life-prolonging for many patients. Importantly the endocrinologist is keeping this orchestra of specialist together and guides the patient management and long-term follow-up.

KEYWORDS: pituitary tumours, treatment options, patient management.

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TREATMENT OF GH DEFICIENCY IN ADULTS GROWTH HORMONE IS THE MOST FREQUENT PITUITARY HORMONE DEFICIT AND IS AFFECTED FIRST

V. Popovic[1,2]

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Hypopituitarism results from complete or partial deficiency of pituitary hormones and is caused by a variety of structural lesions or trauma involving the hypothalamus or pituitary gland (most often pituitary adenomas). There is a varying sensitivity of the different anterior pituitary hormones to pathological damage. The usual sequential pattern of hormonal deficiencies is the loss of growth hormone (GH) followed by gonadotropins, TSH and ACTH. The reason why GH is the most frequent pituitary hormone deficit and affected first is not known. GH axis is most vulnerable to cranial irradiation. Patients who received cranial irradiation frequently develop isolated GH deficiency. GH deficiency is more common as part of multiple pituitary hormone deficiency. Hypopituitary patients have increased sick days, lower health status and those with GH deficiency have less working capacity. Furthermore, findings of several studies have shown excess mortality in patients with hypopituitarism. Hypopituitarism removes the natural survival advantage that women have over men. Highest mortality is among younger patients, women and patients with diabetes insipidus. A recent study from Sweden shows a decline in mortality in patients optimally replaced including GH replacement therapy.

Diagnosing adults with GH deficiency

Adult GH deficiency is associated with adverse physical, metabolic and quality of life symptoms. Adults with GH deficiency have reduced body lean mass ,excess abdominal fat mass (truncal fat, weight waist circumference), decreased bone mineral density, decreased energy level ,social isolation, inadequate initiative and generally decreased quality of life. The clinical features of GH deficiency are not distinctive and clinical suspicion should be confirmed by GH stimulation tests. A GH stimulation test with abnormally low peak serum GH concentrations and low insulin growth factor-I (IGF-I) concentrations is diagnostic in a patient with high pretest probability of having GH deficiency. Normal IGF-I concentrations do not exclude a diagnosis of GH deficiency in adults. Insulin tolerance test is recommended as the gold standard test. If contraindicated other stimulation tests are suggested. If GH deficiency is isolated then two stimulation tests may be required. Severe GH deficiency can be diagnosed without any testing if the patient has three pituitary deficiencies and low serum IGF-I concentrations. In obesity GH secretion is reduced, GH clearance is enhanced and stimulated GH secretion is reduced thus causing functional hyposomatotropism. This functional hyposomatotropism in obesity is reversed by weight loss. Considering the rising prevalence of obesity, GH stimulation tests should be avoided in obese subjects with very low pretest probability.

GH dosing and patient monitoring

In adults with GH deficiency, the goal of growth hormone replacement is to improve wellbeing, reduce cardiovascular risk, increase bone density and normalize body composition. Recombinant human growth hormone is available for daily subcutaneous injections. Initial low GH doses are preferred and the recommended starting dose is 0.2—0.4 mg/day for patients younger than 60 years and 0.1—0.2 mg /day for patients older than 60 years. For younger transition patients (<30 years) the starting dose is 0.4—0.5 mg/ day. After initiation of GH replacement treatment**,** follow up is usually planned at intervals of 2—3 months, when the dose of GH can be adjusted by increments of 0.1—0.2mg/day based on clinical response, IGF-I and side effects. The GH dose should be titrated towards mid-normal IGF-I concentration adjusted for age. The dose should be reduced if side effects occur such as fluid retention, muscle and joint stiffness and pain, peripheral edema and carpal tunnel. Thyroid and adrenal function need to be assessed before and after starting growth hormone replacement because GH replacement may unmask central hypothyroidism and secondary adrenal insufficiency so the doses of replacement need to be adjusted. Dose adjustments needs to be done in women who are on oral estrogen. Higher GH doses are needed since estrogen attenuates the serum IGF1 response to GH. Once the dose is stabilized, clinicians should monitor for efficacy.

Efficacy of GH replacement therapy in adult GH deficiency

Overall GH replacement results in improvement in body composition and bone mineral density in particular in men and those with low bone mass. Visceral adipose tissue mass decreases by 9% and lean body mass improves up to 7%. Muscle strength improves. Results from a re-

cent study, using accurate assessment of left ventricular (LV) mass by cardiac magnetic resonance, demonstrated reduced cardiac mass in patients with adult onset GH deficiency and increase in cardiac mass after 1 year of GH replacement. Improved quality of life after seven years of GH replacement is reported with most marked improvement in patients with low baseline quality of life. Most of the improvement is seen during the first year of treatment but it improves further with time. All effects of GH replacement therapy are sustained for long period of time (over 10 years). What is helpful in evaluating the success of GH replacement therapy and in the deciding to continue GH replacement therapy? A recent study shows that IGF-I concentrations, quality of life, total cholesterol and waist circumference response to 2 years of GH replacement therapy predict the response.

Safety of GH replacement therapy

Safety concerns with GH replacement therapy are diabetes mellitus, malignancies occurring de novo and re-growth of residual pituitary mass .GH reduces insulin sensitivity and therefore the concern that this therapy might induce diabetes mellitus. Data from two large data bases report a slightly increased prevalence of diabetes mellitus in particular in those who are obese and who have a strong family history of diabetes mellitus while data from the most recent database show that four years of GH replacement therapy did not adversely affect glucose homeostasis in the majority of adults with GH deficiency. Available data do not suggest an increased risk of de novo malignancies or recurrence or re-growth of residual pituitary tumor. **Conclusion.** GH replacement treatment in adult GH deficient patients appears to have favorable long-term efficacy and safety profile.

KEYWORDS: growth hormone, IGF-I, GH replacement therapy.

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CHALLENGES IN PROLACTINOMA MANAGEMENT

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Case1: A woman with a long history of cabergolin treatment

Patient *B.*, 40 years, after a long period (17 years) of cabergoline treatment due to a residual prolactinoma after transnasal adenomectomy (because of bromocriptine intolerance) at 19 years of age. In the ensuing years the patient had 4 spontaneous pregnancies at the age of 27, 28, 31 and 33 years. During gestation period and breastfeeding agonist therapy was discontinued, Cabergoline therapy was discontinued during the intergestational periods due to high levels (30 000—40 000 mu/ml) of prolactin. On her last visit to the endocrinologist normprolactinemia was confirmed (0,25 mg/wk Carbegoline). FSH was on reproductive levels. According to the MRI, a cystic tumor is visualized of endoparacellular localization, sized 13×15×20 mm, with signs of postoperative alterations. Echocardiologic examination was performed, no valve pathology was found.

Case 2. A case of galactorrhea due to self-prescribed estrogene-treatment in a male-to-female transgender

This story began at the early 70's, while in the former USSR no law regulation existed on gender dysphoria and even the mere idea about the existence of such a problem was unfamiliar to Russian physicians. Patient *P.* was a normal full term male baby. At the age of 10, he started feeling a desire to wear girls' clothing. At the age of 15, he came to a firm conclusion that he was a girl, and thus started urinating like one (squatting), wearing lipstick and makeup. He also greatly suffered from having a «deformity» — his male reproductive organs. At the age of 17, working as a hospital cleaner, he began injecting himself with estrogenes and progesterone which lead to the development of mammary glands and, in the end, constant milk flow from the breasts. To receive a passport he showed this effect to the police staff and officially changed his gender to female. At the age of 23 the mammary gland showed a development stage corresponding to that of a 15—16 year old girl (due to periodical intake of estrogens) with a nipple discharge (sizable droplets upon applying pressure — galactorrhea ++). He insisted on castration and penile amputation due to feelings of shame which came from having a «deformity» inappropriate to his gender. Skull x-ray revealed normal sella turcica in terms of form and size, however there were signs of increased intracranial pressure. The thyroid gland functions were within normal limits. Radioimmunoassay was performed using standard radioimmunoassay kits (Sorin). A slightly elevated prolactin level in the blood was revealed — 24 ng/ml (normal range for males, 4—15 ng/ml). Given multiple suicide attempts, unsuccessful psychiatric treatment, female gender, and a female social role, the patient ultimately underwent castration and feminizing genitoplasty at the age of 27 as a means of social rehabilitation. Some time after surgery, the patient regained interest in life. Surgical and hormonal treatment resulted in the patient exhibiting an overwhelming maternal instinct. Being single, the patient secured her right to adopt a child, simulated pregnancy and was discharged from a maternity hospital with a son. Immediately after «labor», the patient showed significant increase in galactorrhea (+++) and forceful milk ejection reflex. The baby was nursed until the age of 6 months. These findings lead us to believe that galactorrhea in the patient may be due to several factors.

1. Increased prolactin level as a result of estrogen use and treatment with cyproterone acetate. Estrogens have long been known to increase prolactin levels in the blood, and similar properties of cyproterone acetate were shown by *K. Schmidt-Golewizer et al.*

2. Increased intracranial pressure. Its role in disorders of the neuroendocrine system (galactorrhea in particular) was demonstrated by *R. Paterson*.

3. Our report describes the second case of galactorrhea in a male-to-female transsexual in the world. The first case was reported by *R. Flückiger et al.* in 1983.

4. These findings indicate that the mechanism of lactation is independent of chromosomal sex. The possibility of drug-induced galactorrhea in males does exist.

KEYWORDS: prolactinoma, cabergoline, bromocriptine intolerance, spontaneous pregnancy, drug-induced galactorrhea, transgender, lactation.

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ELEVATED T4 AND TSH, APPROACH TO DIFFERENTIAL DIAGNOSIS

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The 'inappropriate secretion of thyrotropin (TSH)' syndrome includes two types of central hyperthyroidism: TSH-secreting pituitary adenomas (TSH-omas) and thyroid hormone action resistance (RTH). Both types are characterized by high levels of FT4 and FT3 in the presence of unsuppressed TSH concentrations in contrast to primary hyperthyroidism, where TSH levels are always undetectable. Failure to diagnose these different disorders may result in improper thyroid ablation in patients with TSH-omas or unnecessary pituitary surgery in patients with RTH. Several diagnostic steps should be carried out to differentiate the two types of central hyperthyroidism: laboratory evaluation (alpha-subunit of glycoprotein pituitary hormones (α-GSU), sex hormone-binding globulin, C-terminal telopeptide (CTx); MRI visualization; functional tests should be performed (T3 suppression test and thyrotropin releasing hormone (TRH) stimulation test); genetic analysis. The presence of pituitary lesions on an MRI scan strongly supports the diagnosis of TSH-oma. However, the usefulness of such imaging is limited by the known prevalence of pituitary incidentalomas in healthy subjects. A partial inhibition of TSH secretion after T3 suppression test is seen only in RTH patients. The TSH response to TRH stimulation is usually preserved in RTH patients. The finding of a similar thyroid biochemical phenotype in other first-degree relatives is highly suggestive of RTH. Mutations in the thyroid hormone receptor beta gene are identified in ~ 75—80% of RTH. High α-GSU concentrations and/or high α-GSU/TSH molar ratios are typically present in patients with TSH-omas. Circulating sex hormone-binding globulin levels are usually high in patients with TSH-omas, whilst being of normal level in RTH. Chronic administration of long-acting somatostatin analogs caused a marked decrease of free T4 and free T3 levels in nearly all patients with TSH-omas, while patients with RTH did not respond at all. Echocardiologic examination was performed, no valve pathology was found.

KEYWORDS: TSH-secreting pituitary adenoma, thyroid hormone action resistance, differential diagnosis, somatostatin.

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DIABETES INSIPIDUS

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Diabetes insipidus is a disorder that dramatically interferes with a patient's everyday life due to the need to constantly replenish the fluids lost in increased urination, which comes amid shortage of synthesis, secretion or action of pituitary hormone vasopressin. Differential diagnosis of types of diabetes insipidus in patients with polydipsia-polyuria syndrome is the main difficulty, for a correct diagnosis predetermines the safety and efficacy of further treatment. This session will present current concepts on the etiology, diagnosis and treatment of central diabetes insipidus (CDI). Comparative characteristics of various preparations of desmopressin for the treatment of the central form of the disease will be discussed, and features of the management of selected patient populations with CDI will be taken in consideration: during pregnancy and lactation, pathology of the thirst sensation, after traumatic brain injury and neurosurgery.

KEYWORDS: diabetes insispidus, differential diagnosis, safety, efficacy, treatment.

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PITUITARY CAUSES OF BONE LOSS

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Different hormonal disorders can influence bone metabolism and cause secondary osteoporosis. In childhood, pituitary diseases can hamper gaining of proper peak bone mass and skeletal size. In the adult life they can stimulate bone loss by increasing bone resorption and decreasing bone formation. The consequence of these processes are decreased bone mineral density (BMD) and trabecular bone score (TBS), deterioration of bone quality, diminished bone strength and finally increased bone fracture risk. Among pituitary disorders such effects are possible in patients with hyperprolactinemia, Cushing's disease, acromegaly and hypopituitarism. Hyperprolactinemia increases bone resorption and loss of BMD, there is increased fracture risk in patients with prolactinoma. Hypercortisolism due to Cushing's disease (ACTH-dependent Cushing's syndrome) diminishes formation and increases resorption of bone, causing trabecular bone loss and increased fracture risk. Moreover, there are decreased calcium absorption and disturbances in sex steroids secretion. In acromegaly, GH excess stimulates bone formation, but concomitant hyperprolactinemia and hypogonadism caused by pituitary

macroadenoma lead to increase of bone resorption and spinal fractures. In hypopituitarism, disturbances in GH and gonadotropins secretion lead to osteopenia or osteoporosis. There is an increased fracture risk in GHD patients. Sometimes, additional effects of secondary hypogonadism, hyperprolactinemia and GHD are observed in hypopituitarism due to pituitary tumor.

KEYWORDS: pituitary disorders, bone metabolism, disruption, osteoporosis.

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MODERN PRINCIPLES OF TREATING OBESITY

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In the last couple of decades obesity rapidly increased together with obesity related co-morbidities. Comprehensive lifestyle interventions, including nutrition, physical activity and behavioral therapy are the foundation for obesity management. Drug treatment, medical devices or bariatric surgery for obesity are indicated when diet, physical exercise and behavioural methods did not achieve satisfactory results. Pharmacotherapy for obesity is introduced in patients with a body mass index ⩾ 30 kg/m2 and in patients with a body mass index ⩾27 kg/m^2 with co-morbidities. The FDA approved the following drugs for chronic therapy of obesity in the US: orlistat; lorcaserin; phentermine/topiramate; bupropion/naltrexone and liraglutide, while EMEA approved the following drugs for the treatment of obesity in Europe: orlistat; bupropion/naltrexone and liraglutide. Orlistat is a powerfull selective inhibitor of pancreas lipase which decreases fat absorption from the gut. Lorcaserin is a selective 5-HT 2 C receptor agonist. Activation of serotonin-2 C receptors in hypothalamus decreases the food intake. Combination of phentermine/topiramate decreases body weight in a way that phentermine suppresses apetite while topiramate affects energy homeostasis. Fixed combination of naltrexone (antagonist for opiate receptors) and bupropion (inhibitor of uptake for dopamine and norepinephrine) has a synergistic effect on apetite decrease and body mass decrease. Liraglutide is a GLP-1 analog which is injected in 3 mg dose daily to decrease hunger and induce fulness in stomach and satiety. Therapeutic efficacy for most of the obesity drugs is assessed by determining body weight decrease by ⩾5% of initial body weight after three months (for liraglutide ⩾4% after 16 weeks) and in case of having achieved such a response, therapy is continued. These data suggest the existence of specific responder phenotypes in which the use of adequate antiobesity therapy could result in a significant decrease of body weight. In the future we can expect that different drug combinations may be used, having different mechanisms in mind which are contributing in the rise of global obesity epidemic. Intragastric balloons are a newly developed endoscopic therapy for weight loss. Balloons occupy space in the stomach, inducing satiety and decreasing food intake. The implantable weight loss device was approved by FDA in 2015. The device works by interruption of vagus nerve signalling which leads to a delay in gastric emptying, early satiety and reduced hunger. Bariatric surgery is the most effective treatment for severe obesity and its comorbidities. Major clinical procedures are: adjustable gastric banding, vertical sleeve gastrectomy, Roux-en-Y gastric bypass and biliopancreatic diversion.

KEYWORDS: obesity, approved drugs, drug combination, efficacy criteria, intragastric balloons.

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BARIATRIC SURGERY: THE MESSAGE FROM SURGEON TO ENDOCRINOLOGIST (OR WHAT TO EXPECT FROM DIFFERENT SURGICAL TECHNIQUES)

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Diabetes mellitus is a chronic disease, 85% of all diabetics suffered from DM2. The expected spreading of DM2, high frequency of complications (nephropathy, retinopathy, polyneuropathy, angiopathy), early disability of patients, high mortality rate dictates a necessity of the effective treatment of DM2, which was called by WHO as a non-infectious epidemy. Bariatric (Metabolic) surgery initially intended for the treatment for severe (morbid) obesity proven to be very effective for the patients suffering from Diabetes Mellitus type 2 (DM2) — well-known obesity-related disease. Moreover, some kinds of metabolic operations were appeared to have «specific action» which means high probability of compensation of DM2 and correction of Hypercholesterolemia independently on weight loss. During the last decade metabolic surgery could extend its opportunities not only for severe obese patients but also for the patients suffering from DM2 with obesity class 1 (BMI 30—35) or even without obesity. The latest cohort of surgically — treated patients with DM2 is of high scientific interest. It is important to select appropriate patients whose prognosis for DM2 compensation would be high. The more obese is patient — the better prognosis of remission of DM2 he (she) has. Non-important factors for the prognosis of compensation of DM2 are: level of fasting glycemia, level of HbA_{1c} preoperatively, kind of hypoglycemic therapy including Insulin. Less optimistic prognosis for compensation of DM2 can be expected in patients with C-Peptide level <1.0 pmol/ml, anamnesis of DM2 >10 years, positive tests for autoimmune antibodies (GAD, beta-cels etc). However, in case of LADA-Diabetes or DM2 with severe impaired beta-cell secretory function metabolic surgery can also be helpful while lowering of doses of Insulin and providing more predictable limited

food consumption. The choice of kind of operation in the patient suffering from DM is a key factor for success and a discussible question among bariatric specialists. Although all kinds of operations are effective the effectiveness is in direct proportion with the complexity of surgery. Mechanisms of action of pure restrictive operations (Gastric Banding, Sleeve Gastrectomy, other Gastroplasties) are: 1) food restriction; 2) visceral fat loss. Mechanism of food restriction starts working since the first days after surgery. This can explain compensation of DM2 since the first weeks after surgery in many patients. Rather than other Gastroplasties Sleeve Gastrectomy has probably additional mechanism of action: 3) removal of Grelin-producing zone of the fundus. In general, restrictive operations can achieve 55—70 % rate of compensation of DM2 but chance of obesity and DM2 recidivism is high after pure restrictive procedures. Gastric Bypass is still a popular operation and currently is used in some modifications with addition of some degree of malabsorption (long-limb R-Y-Gastric Bypass, mini-Gastric Bypass etc). Gastric Bypass provides better compensation of DM2 (~ 80% of cases) than pure restrictive operation. Besides mentioned mechanisms of action Gastric Bypass includes additional ones: 4) incretine effect due to early release of small bowel peptides like GLP-1, PPY etc 5) duodenal exclusion with interruption of postprandial impulses from Duodenum to the pancreas. Some hormonal stimulus (GIP etc.) are proven to be of importance. Due to strong incretine effect episodes of hypoglycemias can occur after Gastric Bypass. Life-long vitamin – mineral supplementation is mandatory. Biliopancreatic Diversion (BPD) is the most «metabolically» effective operation (~ 95% of compensation of DM2 plus lowering of LDL-Cholesterol) and currently is used in some modifications (Scopinaro's type, BPD/Duodenal Switch, SADI's BPD). Together with other mechanisms of action BPD has «specific» mechanism of action: 6) selective malabsorption of fats leading to low concentration of FFA in the portal vein system. To our data compensation of DM2 was achieved in 98.5% of 70 patients with obesity and DM2 and results were stable 5 and more years after surgery. Careful monitoring including blood tests and life-long Vitamin-mineral supplementation is necessary after BPD.

Metabolic surgery for treatment of DM2 has been promoting in Russia since 2000 but nowadays it becomes a reality. In standards — 2017 American Diabetes Association recommends metabolic surgery in patients with BMI >40 or BMI >35 when diet modification and medical treatment are ineffective. Metabolic surgery can also be considered in patients with BMI >30 when appropriate antidiabetic treatment including insulin therapy are non-effective in compensation of DM2.

KEYWORDS: bariatric surgery, obesity, biliopancreatic diversion, diabetes mellitus.

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CALCIUM METABOLISM AND BONE LOSS AFTER BARIATRIC SURGERY

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Bariatric surgery results in the most significant and stable weight reduction in MO patients. The most commonly performed bariatric procedures are RYGP and SG. RYGSB and BPD are hybrid bariatric surgical procedures incorporating gastric restrictive and extensive malabsorptive components. Consequently, digestion and absorption of macronutrients and micronutrients are largely limited. Weight loss after bariatric surgery lasts about 12—18 months postoperatively, with weight maintenance during the next period. Malabsorption is a result of the anatomic changes imposed by bariatric surgery, and most of the patients are predisposed to calcium and vitamin D deficiency. Secondary hyperparathyroidism (SHPT) and osteoporosis may occur in the absence of adequate supplementation. Postoperative nutritional deficiencies were studied mostly in patients who underwent RYGBP. During the 2 years after RYGBP, in spite of routine supplementation by standard multivitamin preparation, the incidence of specific nutrient deficiencies is reported to be up to 80% for vitamin B_{12}, 60% for iron, 60—80% for calcium and vitamin D and 40—45% for folic acid. The decrease of vitamin D level and progressive increase of PTH are related to the length of bypass limb and to the follow-up period after surgery. At the same time, not all patients whose vitamin D levels were lower than 30 ng/ml also had elevated PHT levels: only 49.0% of those who underwent short limb bypass and 78.9% of those who underwent long limb bypass. It is interesting that 42.1% of the individuals with laboratory normal vitamin D levels had an elevation in PTH. It is interesting that in morbidly obese patients there is a direct relationship between the level 25(OH)D and the level of PTH, but in patients who undergo bypass surgery the correlation between 25(OH)D and PTH can't be revealed. When patients undergo GBP, the preferential sites for the absorption of calcium, the duodenum and proximal jejunum are bypassed, so they have a risk of hypocalcaemia that only partially depends of vitamin D. In the study by R. Clements et al. patients were recruited one year after GBP: vitamin D deficiency was found in 23.6% cases, elevated PTH — in 25.7% cases. Only 28.6% patients with SHPT had low 25(OH)D and in patients with vitamin D deficiency only 36 % had PTH elevation. Bone metabolism changes and BMD loss after bariatric surgery are widely discussed. BMD loss is reported after malabsorbtive surgery, but also after restrictive operations such as SG.

KEYWORDS: bariatric surgery, vitamin D, secondary hyperparathyroidism, bone metabolism.

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THE GENETICS OF FAMILIAL ADRENAL TUMORS

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For a tumor type, the concept of «familial tumors» encompasses germline mutations predisposing either directly to this tumor, or to a syndrome to which the tumor type belongs. This general concept applies to adrenal tumors, and will be developed here. Adrenal tumors gather a broad range of diseases, scattered on two main categories depending on whether they are arising from adrenal cortex or medulla. From adrenal cortex, the dreadful adrenocortical carcinoma is in a large majority of cases sporadic and non syndromic. A germline mutation is found in less than 5% of cases, mainly related to Li Fraumeni syndrome (*TP53* mutations), or to Lynch syndrome (mutations in mismatch-repair genes). A vast majority of adrenocortical adenomas are sporadic, related to sporadic mutations — mainly *PRKACA* and *CTNNB1*. In terms of germline predisposition, adrenocortical adenomas seem more common in rare tumor predisposition syndromes such as Multiple Endocrine Neoplasia type 1 (mutations of *MENIN*) and Gardner syndrome (mutatons of *APC*). Primary macronodular adrenocortical hyperplasia is related to germline *ARMC5* mutations in $^1/_3$ of cases. Pigmented primary nodular adrenal dysplasia are often syndromic, part of the Carney complex (mutations of *PRKAR1A*). Other adrenocortical hyperplasias/dysplasias are rare, and several mutated genes have been reported. Tumors arising from adrenal medulla are called pheochromocytoma. These tumors are parented to paragangliomas, of extra-adrenal location. Approximately $^1/_3$ of pheochromocytoma and paragangliomas are related to germline mutations. The most commonly mutated genes are part of succinate deshydrogenase complex (mutations of *SDHB*, *C* and *D* mainly). Syndromic forms of pheochromocytoma include Multiple Endocrine Neoplasia type 2 (mutations of *RET*), Von-Hippel-Lindau syndrome (mutations of *VHL*) and neurofibromatosis type 1. Mutations in >10 other genes have been reported so far. An up-to-date catalogue of these mutations will be presented for each of this disease, with a special emphasis of their pathophysiological and clinical consequences.

KEYWORDS: familial adrenal tumors, genetics, mutations, multiple endocrine neoplasia.

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HYPERALDOSTERONISM

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Primary aldosteronism is the most common cause of secondary hypertension with the estimated prevalence of around 5—10% in hypertensive patients and up to 20% in those with refractory hypertension. However, it is still underdiagnosed in clinical practice. The disease is characterized by autonomous aldosterone overproduction, independent of renin-angiotensin system, which is caused by bilateral adrenal hyperplasia or aldosterone-producing adenoma in more than 90% of cases. Several studies have demonstrated that primary aldosteronism is associated with high cardiovascular, cerebrovascular and renal morbidity and mortality. Although hypokalemia is the hallmark of the disease, most of the patients are actually normokalemic. Recommended diagnostic evaluation involves measurement of plasma aldosterone and renin with subsequent calculation of aldosterone to renin ratio (ARR) which serves as the screening test for primary aldosteronism. In patients with elevated ARR this is followed by one of the four available confirmatory tests; oral salt loading, saline infusion, captopril challenge or fludrocortisone suppression test. If confirmatory testing is positive, further diagnostic investigations are directed toward identification of the primary aldosteronism subtype as the treatment differs between aldosterone producing adenoma and bilateral adrenal hyperplasia. Selective adrenal venous sampling for aldosterone is recommended as the only reliable way to separate unilateral from bilateral disease. Patients with unilateral disease are candidates for surgery whereas those with bilateral hyperplasia are treated with mineralocorticoid receptor antagonists. Early detection and appropriate treatment of primary aldosteronism could reduce morbidity and mortality to the levels seen in patients with essential hypertension.

KEYWORDS: hyperaldosteronism, secondary hypertension, aldosterone-producing adenoma, hypokalemia.

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MANAGEMENT OF PHEOCHROMOCYTOMA

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The report focuses on catecholamine-secreting tumors that develop from chromaffin cells of adrenal medulla and sympathetic ganglia, which are referred to as pheochromocytomas and catecholamine-secreting paragangliomas. Catecholamine-secreting tumors are rare, with an annual incidence of two to eight cases per a million people. There are 6—8% of pheochromocytomas among incidentally discovered adrenal tumors. Nevertheless, it is important to suspect, confirm, localize, and remove these tumors because associated hypertension is treated with surgical removal of a tumor. There is mortality risk (especially when the diagnosis is unknown). At least 5—6% of tumors are malignant; up to 30—35% of tumors are familial. Thus, detection of these tumors in the proband may result in early diagnosis in other family members. The report summarizes epidemiological data; pathogenesis; laboratory, genetic and topical diagnostic

options of chromaffin tumors. It emphasizes important aspects of preparing for surgery, and discusses prognosis.

KEYWORDS: pheochromocytoma, adrenal tumors, hypertension, management.

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THYROID DISORDERS ASSOCIATED WITH IODINE DEFICIENCY IN PRACTICE OF ENDOCRINOLOGISTS

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Iodine deficiency (ID) impairs thyroid hormone production and has many adverse effects throughout the human life cycle. The most serious effect of ID is mental impairment in children, adolescents and adults. Goiter is the most visible and well known effect of insufficient iodine nutrition. Management of goiter and other thyroid disorders caused by ID is an important part of routine clinical practice of endocrinologists. Moreover, in dealing with thyroid disorders the clinicians should be well aware of changing patterns of iodine intake to make necessary amendments to their clinical practices. Effective goiter prevention program (combination of massive use of iodized salt and distribution of iodine supplements in vulnerable groups of population) was conducted in the USSR until 1990 and reduced goiter prevalence to nearly sporadic level. Collapse of iodized salt production in 1991—1992 led to a significant increase in goiter morbidity, especially in areas with severe ID. It took nearly half decade before this negative trend had been realized and another 10 years or more before situation had improved in the former USSR countries that had adopted universal salt iodization (USI) strategy. However, this progress has been much less spectacular in Russia and Ukraine that are still relying only on a voluntary use of iodized salt. In Russia, certain regions (Moscow, Tyumen, St.-Petersburg) with move advanced voluntary salt iodization programs may have median UIC in children in the optimum range (100—300 mcg/l). In other regions and, especially, in rural areas ID still remains widespread. Several sub-national surveys conducted in Russia regions (oblasts) in the past 10—15 years showed mild-to-moderate ID (median UIC in the range of 40 to 80 mcg/l). This uneven pattern of iodine nutrition provides another challenge to endocrinologists who should adapt their clinical strategy in dealing with thyroid disorders to potential status of iodine deficiency (or sufficiency) in the given territory. Thus, major benefits of increasing iodine intake though salt iodization in populations with mild-to-moderate ID are decrease in prevalence of goiter, thyroid autonomy and thyrotoxicosis in adults and increase in IQ in children. In the situation of optimum iodine nutrition populations, especially children, are better protected from radioactive iodine exposure in case of nuclear accident. These benefits occur at the expense of a small increase in the prevalence of subclinical hypothyroidism in adults that could be minimized by avoiding excessive iodine intakes.

KEYWORDS: iodine deficiency; goitre; universal salt iodization.

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THYROID CANCERS: THE STATE OF THE ART MANAGEMENT

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Thyroid nodules are a common clinical problem, and differentiated thyroid cancer (DTC) is becoming increasingly prevalent. High-resolution ultrasound can detect thyroid nodules in 20—70% of randomly selected individuals, with higher frequencies in the elderly. The main clinical problems concerning thyroid nodules are US-based categorization of the malignancy risk and indications for US-guided fine-needle aspiration biopsy (FNA), cytological classification of FNA samples, the roles of immunocytochemistry and molecular testing applied to thyroid FNA, therapeutic options, and follow-up strategy. Recent advances in research on thyroid carcinogenesis have yielded applications of diagnostic molecular biomarkers and profiling panels in the management of thyroid nodules. Differentiated thyroid cancer (DTC), which includes papillary and follicular variants, comprises the vast majority (>90%) of all thyroid cancers. Most of the detected tumours are very small and have unknown clinical importance and malignant potential. 25% of the new thyroid cancers diagnosed in 1988—1989 were less than 1 cm compared with 40% of the new thyroid cancer diagnoses in 2008—2009. This tumour shift can be explained due to the increasing use of neck ultrasonography or other imaging very often without clear clinical indications and switch last clinical recommendations to less aggressive initial treatment with organ-saving in patients with thyroid microcarcinomas. Nevertheless clinical controversy still exists in many areas of thyroid cancer management. The management of very rare medullary thyroid cancer is now generally based on molecular testing of RET-proto-oncogen mutations. The main directions for further research in the field of thyroid cancer and nodules are optimizing molecular markers for diagnosis, prognosis, and therapeutic targets, improvement of the risk stratification and understanding of the risks and benefits of DTC initial treatment options.

KEYWORDS: thyroid nodules, differentiated thyroid cancer, fine-needle aspiration biopsy.

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GRAVES' DISEASE

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Graves' disease is an autoimmune disease where activating thyroid-hormone receptor antibodies cause thy-

roid hormone overproduction. It is the most common cause of hyperthyroidism, with 20—50 cases per 100 000 persons annually. The incidence peaks at 30—50 years. The annual incidence of Graves' ophthalmopathy is 18/100 000 women and 3/100 000 men yearly. The diagnostic work-up of hyperthyroidism is presented below (Smit and Hegedus, N Engl J Med, 2016). Treatment of hyperthyroidism is initiated by an antithyroidal drug (methimazole/carbimazole is first-line, propylthiouracil is an alternative option). The final choice of treatment (12—18 months of antithyroid drug therapy, radioiodine or total thyroidectomy) should be individually tailored. Patients should be advised to stop smoking. In this session, we will discuss these different treatment options, treatment of hyperthyroidism during pregnancy, as well as the diagnosis and treatment of Graves' ophthalmopathy.

KEYWORDS: Graves' disease, thyroid-hormone receptor antibodies, hyperthyroidism.

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ADRENAL INSUFFICIENCY

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Adrenal insufficiency (AI) is a condition associated with decreased secretion of steroid hormones from adrenal cortex resulting in a decrease of their biological effects on cells, tissues and organs of human body. Primary AI is a consequence of destruction of the entire adrenal cortex resulting wit loss of both, glucocorticoid and mineralocorticoid activity. By contrast, secondary adrenal insufficiency reflects an inability to sufficiently stimulate adrenal cortex by ACTH that results mainly in glucocorticoid deficiency whereas mineralocorticoid secretion is largely preserved. Among peripheral (primary) causes autoimmune destruction of adrenal cortex is most frequent in developed countries. Other possible peripheral causes of AI are: infections, bilateral metastases, bilateral adrenalectomy, adrenoleukodystrophy, amyloidosis, hemochromatosis, vascular causes (bilateral adrenal hemorrhage or thrombosis). Central (secondary) causes of adrenal insufficiency are: structural lesions of the hypothalamus or pituitary gland (tumours, infiltrating disorders, irradiation, lymphocytic hypophysisits) and some other rare conditions. One of most frequent causes in clinical practice is functional suppression of HPA axes caused by exogenous glucocorticoids. Proper replacement therapy is essential for patients' survival and also for maintaining their quality of life a normalizing morbidity and mortality.Treatment of acute AI should be performed and ICU setting with a close monitoring of patients. It has to start with immediate intravenous application of 100 mg of hydrocortisone followed by daily dose 200—400 mg continuously or divided in 3—4 partial doses. At the same time volume resuscitation with intravenous saline infusion and hypoglycaemia correction with intravenous glucose has to be carried out. Treatment of chronic AI of all causes consists of oral administration of glucocorticoid, commonly hydrocortisone in basal doses in approximate dose of 10—15 mg/m^2. Basal dose has to be adjusted before and during stress conditions properly. In primary AI patients usually require an addition of mineralocorticoid (Fludrocortisone in oral dose of 0,5—2 mg daily). On the other hand in cases with secondary AI hydrocortisone could be replaced by selective glucocorticoid in equipotent dose (e.g. prednisone or prednisolone). Proper and careful education of patients is essential and patients have to be equipped with steroid emergency card.

KEYWORDS: adrenal insufficiency, replacement therapy, exogenous glucocorticoids.

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MALE HYPOGONADISM

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The scientific and medical topic of male hypogonadism is one of the most growing and discussable problems in endocrinology in our days. Hypogonadism in male patients defined as testosterone level decrease in serum associated with specific symptoms and/or signs can be observed in case of abnormal changes in testes and/or pituitary such as Klinefelter syndrome, Kallmann syndrome and also in male patients with idiopathic, metabolic or iatrogenic disorders resulting in androgen deficiency. Among the classical reasons pointed above the growing number of hypogonadal elderly men are now in focus of clinicians. The main guidelines' for diagnosing and treatment options of hypogonadal adolescents and adults will be discussed. Also the introduction into Russian Guidelines for diagnosing and treatment of testosterone deficiency will be discussed during the talk.

KEYWORDS: male hypogonadism, Klinefelter syndrome, Kallmann syndrome, testosterone deficiency.

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BONE BIOLOGY AND FUTURE TARGETS FOR OSTEOPOROSIS TREATMENT

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Novel therapeutic approaches to osteoporosis have not only provided better treatment modalities but also shed new light on the cellular and molecular mechanisms by which trabecular and cortical bone skeletal homeostasis is regulated. Skeletal homeostasis is ensured by the balanced activities of bone resorption and bone formation in bone remodeling. Osteoclasts are responsible for the resorption of bone, but also for the local recruitment

of osteoblasts at resorption sites (coupling) ensuring repair of resorbed areas. In turn, osteoblasts are responsible for the formation of new bone at these sites but also for the differentiation of osteoclasts, mostly through the local production of RANKL and OPG, also secreted by osteocytes. Consequently, inhibition of osteoclast differentiation leads to a decrease in both resorption and formation, with suppression of bone remodeling. Denosumab treatment nevertheless allows a continued increase in bone density and reduction in fracture risk over time. The mechanisms by which bone mass continues to increase despite very low remodeling activity appears to involve bone modeling activity, during which bone formation continues independent of bone resorption, particularly in cortical bone. Although not pursued anymore as a therapeutic target, inhibition of cathepsin K in humans decreases bone resorption while maintaining bone formation, allowing cross-talk between osteoclasts and osteoblasts and a robust and prolonged increase in BMD at trabecular and cortical sites. The other, most promising approach involves not the inhibition of resorption but the stimulation of bone formation with osteo-anabolics. Bone formation occurs in the context of bone remodeling or bone modeling, and activation of the PTH and/or Wnt signaling pathways increase bone formation by osteoblasts via both processes. Daily PTH1-34 (Teriparatide) injections increase bone formation but also bone resorption, increasing bone turnover, albeit with a positive balance. Although bone density is efficiently increased, the secondary increase in bone resorption may affect intracortical remodeling and increase cortical porosity, limiting the benefits of PTH treatment. Weekly administration of PTH1-34, the use of PTHrP analogs (Abaloparatide) or the combination of PTH with Denosumab may avoid in part the increase in resorption and increasing bone density further. Other osteo-anabolics target the Wnt signaling pathway, which is a key regulator of the differentiation and function of osteoblasts as well as their ability to cross talk with osteoclasts. Inhibition of endogenous inhibitors such as Sclerostin, secreted locally by osteocytes, leads to massive increases in bone formation and production of OPG, thereby also reducing resorption. Sclerostin antibodies (Romosozumab and Blozosumab) enhance locally, at the level of osteoblasts and osteocytes, Wnt signaling. These compounds have both an anabolic and an anti-resorptive effect that, albeit limited in time, increase very quickly and efficiently bone density at trabecular and cortical sites, in large part via bone modeling. Taken together, these new therapeutic developments provide not only promising prospects for the future treatment of osteoporosis but also important insights into bone biology.

KEYWORDS: osteoporosis, osteoclasts, Denosumab, PTHrP analogs.

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OSTEOPOROSIS: HOW AND HOW LONG TO TREAT

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Osteoporosis is the most prevalent bone disease and a major health-economic problem worldwide. It is defined as a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue with a consequent increase in bone fragility and susceptibility to fracture. The disease is still underdiagnosed and undertreated in spite of rich armamentarium of different drugs. The aim of treatment is to prevent a fracture. Each patient with osteopenia or osteoporosis should take cholecalciferol 1,000—2,000 IU daily or 7,000—14,000 IU once weekly in addition to food rich in calcium (dairy products) or calcium supplements. Patients who sustained an osteoporotic fracture or those who are at high risk of a major osteoporotic fracture (>20% in next 10 years) or hip fracture (>5%) as assessed by FRAX or other fracture risk assessment algorithm, should receive an antiosteoporotic medication. The most commonly used drugs are antiresorptive medications such as the nitrogen-containing bisphosphonates (BPs) and the receptor activator of nuclear factor kappa B ligand inhibitor denosumab. Whereas both BPs and denosumab inhibit osteoclastic bone resorption (and, to a lesser degree, bone formation), they do so by different cellular and molecular mechanisms. The skeletal effects of denosumab resolve quickly and completely when treatment is stopped while BPs can stay in bone for years. Less commonly used and generally reserved for patients with severe and established osteoporosis are the anabolic agents PTH [PTH-(1—84)] and teriparatide [PTH-(1—34)]. These peptides potently stimulate osteoblastic bone formation but also stimulate bone resorption. The treatment is limited to two years. Immediately after anabolic treatment an antiresorptive medication should be introduced to sustain the benefits. Concomitant teriparatide and denosumab therapy increases BMD more than therapy with either medication alone and more than has been reported with any current therapy. The combination of these agents might be an important treatment option in patients at very high risk of fracture. In case there is a need for prolonged treatment the effect is better when starting with the anabolic drug teriparatide for two years and following with an antiresorptive like bisphosphonate or denosumab. There are new medications in the pharmaceutical pipeline: anti-sclerostin monoclonal antibodies, anti katepsin K monoclonal antibodies, PTHrP analog abaloparatide. How long treatment should last depends on the individual fracture risk assessed by FRAX. This is performed before and every two to three years during the treatment. Continuous long-term therapy with antiresorptive drugs can cause late complications like osteonecrosis of the jaw or atypical femur fractures.

KEYWORDS: osteoporosis, antiresorptive drugs, denosumab, PTHrP analogs.

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DIABETES AND BONE

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Diabetes mellitus type 1 and 2 (T1DM and T2DM) are associated with increased fracture risk in both male and female individuals. The relative risk (RR) of hip fractures in patients with T1DM ranges from 1.7 to 12.3, and increases with age, particularly after the age of 40. The outcome of a single study showed that the prevalence of morphometric vertebral fractures was higher in young (30 year old) patients with T1DM (24%) than in a control population (6%). Patients with T2DM in general have a moderately increased risk of hip fractures (RR 1.7, 95% CI 1.3—2.2). However, when restricting the analysis to the cohorts with more than 10 years of follow-up observation, the RR of hip fractures increased to 2.7 (95% CI 1.7—4.4). Fractures of the wrist and the foot also appeared to be more frequent in patients with T2DM than in healthy individuals. A single study conducted in Japan found that T2DM was associated with an increased risk of vertebral fractures in women (OR 1.9; 95% CI 1.11—3.12) and men (OR 4.7; 95% CI 2.19—10.20). Drs. Albright and Reifenstein first suggested that there was a link between BMD loss and T1DM over 50 years ago. Nowadays, it has been proven that individuals with T1DM have 22—37% less BMD than the non-diabetic control. The effects of T2DM on bone metabolism have remained less clear. Many studies have found a 5-10% increase in BMD above an age-matched non-diabetic population. By contrast, the trabecular bone score (TBS) at the lumbar spine decreased in patients with T2DM. It appeared that fracture risk in T2DM is higher for a given BMD T-score and age or for a given FRAX score (a web-based tool for estimating the 10-year probability of bone fracture risk). Both MRI and high-resolution peripheral quantitative CT revealed an increase in cortical porosity and trabecularization of the bone cortex. Bone material strength (assessed by *in vivo* microindentation) appeared to be lower in T2DM patients compared with non-diabetic controls, which is consistent with the alteration in collagen structure induced by hyperglycemia. The cellular and molecular mechanisms of increased bone fragility are rather complicated and probably not fully understood yet. At the tissue level, a decreased number of osteoblasts and diminished quantities of osteoid have been documented in patients with T2DM. The activation frequency of the bone remodeling units is decreased in diabetic patients. At the same time, the degree of bone mineralization and of non-enzymatic collagen crosslinking by pentosidine increased and positively correlated with HbA1c levels. These findings are consistent with a relatively low bone turnover state. Other determinants of bone fragility include Wnt dysregulation and increased marrow fat, adipokine alterations, oxidative stress, inflammation, use of thiazolidinediones or some SGLT2 inhibitors. Complications of diabetes mellitus increase the risk of falls and risk of fracture. In addition to this, recent investigations have identified the crucial role of osteocalcin in regulating insulin metabolism in a hormonal manner. The use of osteoblast-specific knockout mice produced a strong body of evidence that glucose homeostasis is controlled by the amount of osteocalcin in the circulation. Observational data in humans has provided strong evidence of a link between the levels of circulating osteocalcin and type 2 diabetes mellitus, although clinical trials of osteocalcin have not been initiated. In conclusion, patients with diabetes have an increased risk of low-traumatic fracture, particularly with hip fractures, yet the common approach to osteoporosis diagnostics appears to be inefficient. The mechanism of bone fragility in patients with diabetes is not fully understood, but it certainly related to hyperglycemia and the consequent changes in bone tissue and bone remodeling regulation. The role of osteocalcin on glucose metabolism and its potential therapeutic advantages in diabetic patients remains to be investigated.

KEYWORDS: FRAX score, bone fragility, vitamin D deficiency.

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RARE BONE DISEASE WITH ABNORMAL BONE MASS

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The group of genetic skeletal disorders comprises a total of almost 500 entities. Obviously this a very heterogeneous group with a clinical picture ranging from lethal over (very) severe to almost asymptomatic. Also the mechanisms that are disturbed vary, depending on the time, the skeletal sites as well as the cell types being affected. Despite the fact that these monogenic conditions are in general very rare, they can provide us with nice models for more complex, multifactorial diseases that are more common in the population. This is definitely the case for osteoporosis and a subset of the genetic skeletal disorders. For many of the latter, the disease causing genes have been identified and the underlying pathogenic mechanisms provided novel insights with relevance towards understanding and treatment of osteoporosis. Some monogenic conditions present with an increased fracture rate as seen in osteoporosis. This can be due to structural abnormalities within the bone matrix as is the case in some forms of osteogenesis imperfecta or osteopetrosis. But in other conditions the increased fracture risk is simply caused by a reduced bone mass, as seen in osteoporosis pseudoglioma syndrome. Also the pathogenic mechanisms of sclerosing bone dysplasias associ-

ated with an increased bone mass and in some cases protection against fracturing, are of relevance for osteoporosis. One of the major breakthroughs in the field of bone metabolism has been the role of canonical Wnt signaling in bone formation. The unraveling of several sclerosing bone dysplasias have been instrumental for this. Furthermore, in other conditions the regulation of this pathway turned out to be disturbed resulting in an increased bone formation rate. This is nicely exemplified in sclerosteosis and Van Buchem disease lacking sclerostin, a bone specific inhibitor of canonical Wnt signaling. Finally, the study of monogenic skeletal diseases not only contributed towards the understanding of mechanisms and regulation of bone homeostasis but also provided some novel targets for drug development for the treatment or prevention of osteoporosis. For example, monoclonal antibodies against sclerostin and cathepsin K are currently under development. This supports the idea that the study of rare monogenic conditions has important implications also for more common related conditions.

KEYWORDS: genetic skeletal disorders, Wnt signaling, sclerostin, cathepsin K.

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PRIMARY HYPERPARATHYROIDISM: CHALLENGES IN NORMOCALCEMIC AND MILD CASES

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The clinical presentation of primary hyperparathyroidism (PHPT) has changed dramatically in Western societies after increased accessibility to biochemical analyses. Thus, the diagnosis is today often made by change in patients without specific symptoms. Operative treatment is always an option and recommended in patient with markedly increased calcium levels or typical symptoms. However, the vast majority of patients in the modern Western clinic do not present organ related symptoms and their calcium levels are only slightly increased, or even within the upper limit of normal. Several consensus development conferences have discussed management of these patients with mild, borderline PHPT during the last twenty years. In developing countries in The Middle East, Asia and Latin America, patients still present with classical symptoms, severe hypercalcaemia, osteitis fibrosa and prevalent fractures. The female preponderance is much less pronounced in these areas and the presentation and severity of the disease related to vitamin D deficiency. With the recent change in socio-economic status in these areas, the clinical presentation of PHPT has drifted towards the more non-classical presentation with non-specific symptoms raising the same discussion on treatment indications. As disease severity in PHPT seems to be related to vitamin D deficiency and as the true calcium level might be masked by low levels, patients might be repleted with vitamin D during work-up and in preparation for surgical treatment. Only few studies have so far addressed this question, however based on recent randomized and controlled studies, pre-surgical Vitamin D treatment in PHPT seems to be safe and beneficial regarding PTH levels and BMD. Thus, in the modern clinic, most patients will present with few if any symptoms, high normal or slightly increased calcium levels with only slightly or moderately elevated PTH. Differential diagnoses must be ruled out and familiar or syndromic forms identified. Before decision for active treatment or observation is made, the patient should be handled to optimize vitamin D levels and ensure that no medical treatment is interfering with calcium levels.

KEYWORDS: primary hyperparathyroidism (PHPT), hypercalcaemia, vitamin D.

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GENETIC CAUSES OF HYPERPARATHYROIDISM

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Primary hyperparathyroidism (PHPT) is caused by autonomous hypersecretion of parathyroid hormone (PTH) by solitary parathyroid adenoma (~85%), parathyroid hyperplasia/multiple adenomas (~15%) or less frequently by parathyroid carcinoma (~1—5%). The majority of cases of PHPT are sporadic. Only 10—20% occur as a part of one of familial syndromes which include multiple endocrine neoplasia type 1, type 2A, type 4, hyperparathyroidism-jaw tumour syndrome, familial hypocalciuric hypercalcemia and familial isolated hyperparathyroidism, and has specific features in each of them. To date only two genes (tumor suppressor gene *MEN1* and oncogene *CCND1*) have been proven to play a role in tumorigenesis of sporadic parathyroid adenomas. Somatic *CDC73* mutations are frequently associated with parathyroid carcinomas. The role of somatic mutations in other genes in parathyroid tumorigenesis remains controversial.

KERWORDS: hyperparathyroidism, genetics, adenoma.

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SECONDARY HYPERPARATHYROIDISM DUE TO CHRONIC KIDNEY DISEASE. THE MANAGEMENT OF CALCIUM — PHOSPHOROUS DISTURBANCE

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Chronic kidney disease (CKD) is a widespread disease, which is characterized by progressive deterioration of kidney function. CKD is not only limited to negative effects on the kidney but is associated with a multifactorial dysregulation of bone and vascular calcification and is closely linked to increased cardiovascular disease and concomitant bone disease. These comorbidities are responsible for increased and premature mortality in CKD pa-

tients. Therefore, an early detection of bone related and cardiovascular problems in this patient group will help to improve the therapeutic approach. Secondary hyperparathyroidism due to CKD is possibly one of the most important and most frequent comorbidities which is associated with CKD and a multifactorial dysregulation of bone and mineral metabolism. The respective systemic disorder has been named chronic kidney disease-mineral bone disorder (CKD-MBD), associated with increased cardio- and cerebrovascular calcification in this group of patients. Disturbances of mineral metabolism including parathyroid hormone (PTH), calcium, phosphorus, vitamin D, acidosis, and alkaline phosphatase (AP) are increasing during CKD, abnormalities in bone turnover, mineralization, volume, linear growth, or strength and vascular or other soft tissue calcifications contribute to the clinical outcomes. Bone biomarkers, e.g. PTH and isoforms of AP are increasingly important to generate diagnostic information independently of kidney function to predict underlying bone turnover and fracture risk, as well as diagnostic bone biopsies, which are underutilized. The KDIGO Clinical Practice Guideline for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD–MBD) has focussed on the specific problems in CKD patients with regard to their mineral metabolism first in 2009. Since then, not only the attention of clinical doctors and scientists for CKD-MBD patients has increased, there is a number of new insights into bone regulation and its importance via therapy options. Hemodialysis systems, kidney transplantation as well as nutrition and hydratation balance have a large impact on mineral and bone metabolism, but also a large number of medications e.g. phosphate binders and vitamin D supplements, or calcimimetic drugs, based on allosteric activation of the calcium-sensing receptor expressed in various human tissues. Future developments include more sensitive biomarkers to define disease risks in CKG patients and new therapeutic options, e.g. via molecular modulations of new metabolic targets.

KEYWORDS: hyperparathyroidism, chronic kidney disease, diagnosis.

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ACROMEGALY AND MULTIPLE TUMORS

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Acromegaly is associated with increased growth hormone (GH) and insulin-like growth factor-1 (IGF-1) levels which, in addition to the characteristic signs, symptoms and complications of acromegaly, may support tumor development and growth. In 1993 a 52 year old female patient was operated due to a medulla oblongata tumor (no histopathology available). In 2012, aged 71 years she was diagnosed with acromegaly due to typical clinical and hormonal characteristics (IGF-1 586 ng/mL, GH in OGTT 2.38, 3.48, 1.96 ng/mL). However, contrast-enhanced MRI did not reveal a pituitary adenoma. The rest of the pituitary function was normal. We have started to search for ectopic source of GH/GHRH. Firstly, we made abdominal and chest CT (June 2012), which revealed three tumors: solid stomach tumor located on the border of the gastric cardia and corpus, right adrenal gland tumor and right lung tumor, communicating with pleura and lymphatic nodes up to 1.5 cm, located in the mediastinum. The CT also showed hypodense lesion in liver (segment IV b, 1.6 cm in diameter) and heterogeneous echostructure of thyroid gland with right lobe enlargement and left lobe solid-cystic tumor (2.6 cm in diameter). Somatostatin receptor scintigraphy revealed increased tracer accumulation in the right thyroid lobe. No tracer accumulation was noted in the location of the lungs and stomach. Circulating GHRH levels were assessed 3 times with normal values. All tumors were radically resected. The histopathological examination of these neoplasms did not reveal GH secretion. The repeated MRI pituitary gland revealed hypodense lesion 5 mm in diameter, could represent microadenoma. Revision of first MRI pituitary gland showed also this small adenoma on first pituitary MRI imaging. We also made control abdominal CT which showed left kidney tumor: 1.7×1.6×2.0 cm, with clear border, showing a strong contrast enhancement. Patient refused pituitary and kidney surgery. Acromegaly is well-controlled with monthly somatostatin analogue therapy (Octreotide LAR 30 mg i.m.). Despite of numerous further tests, the cause of the disease remains unknown. AIP and MEN1 mutations were excluded. Next-generation cancer panel containing 99 cancer genes did not identify possible unifying gene abnormality in her germline DNA. **Conclusions.** Coexistence of acromegaly and occurring tumours suggests a common aetiology of these disorders. To this time, no genetic abnormality could be identified with the tests that have performed. Whole exome or genome sequencing using germline and tumor sample DNA might further help the identification of a tumour-predisposing genetic alteration.

KEYWORDS: acromegaly, growth hormone, somatostatin, tumors.

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ALCOHOL-INDUCED PSEUDO-CUSHING SYNDROME WITH CHRONIC HYPOKALEMIA CAUSED BY DIURETIC ABUSE: CLINICAL CASE REPORT

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Background. Diagnosis of Cushing's syndrome often remains a challenge, as well as distinction between Cush-

ing's syndrome and pseudo-Cushing. In case of pseudo-Cushing, glucocorticoid excess may be due visceral obesity, anorexia nervosa, depression or alcohol abuse. Here we present a patient with pseudo-Cushing syndrome caused by excessive alcohol consumption and chronic hypocalemia due to diuretic abuse. **Case report.** 39-year-old woman attended neuroendocrinology and bone diseases department with complaints of cramping in the feet, nausea and vomiting, fatigue, weight loss (7 kg for the last 6 months) and lower back pain. Previous medical history included hypertension, low trauma left hip fracture (osteosynthesis was made after) and bleeding gastric ulcer. Cramps presented after the hip fracture. BMD was assessed by hip DEXA: Z-score −1.5SD neck, −1.0 whole hip. In 2015, patient attended general medicine department, where following laboratory investigations were made: calcium 0,97 mmol/l, repeated measurements showed hypokalemia from 2.6 to 3.5 mmol/l. From this point, patient was prescribed with intravenous potassium chloride injections, but potassium blood level remained low (up to 3.0 mmol/l). By the time of admission to neuroendocrinology and bone diseases department, the patient took 12 tablets of potassium chloride (7200 mg) daily, spironolactone 100 mg and calcium carbonate 500 mg twice a day. Physical examination showed no distinct cushingoid signs. Laboratory investigations showed following evidence: ASAT 312 U/l (5—34), ALAT 88 U/l (0—55), bilirubin 32.6 umol/l (3.4—20.5), gamma GT 842 U/l (9—36), potassium 3.2 umol/l (3.5—5.1). Levels for sodium, chloride, calcium, creatinine, alkaline phosphatase (AF) and PTH were normal. Circadian rhythm for ACTH and cortisol was preserved. Levels for plasma ACTH were normal, serum cortisol levels were elevated: morning cortisol 1750 umol/L (123—626), late evening cortisol 1233 umol/L (42—270). Late evening salivary free cortisol was also elevated (15.55 umol/L; reference 0.5—9.4) and urinary free cortisol level was within normal range. A short dexamethasone suppression test showed inadequate suppression of a morning plasma cortisol (355.2 umol/L; reference value <50 umol/L). During the ward round, the patient had breath-alcohol odor, but denied alcohol abuse. Toxicology screen could not be performed due to technical issues. In addition, nurse reported seeing the patient taking unprescribed tablets. Taking all these results into consideration, the diagnosis of Pseudo-Cushing was made. To exclude diuretic abuse, the patient was moved to another ward under strict supervision. Subsequently repeated laboratory investigations did not revealed hypokalemia. **Conclusion.** In cases of clinical and laboratory data mismatch, careful observation is important to exclude drug and alcohol abuse. Setting the diagnosis is troublesome without having technical capability to perform urine diuretic test and toxicology screen.

KEYWORDS: pseudo-Cushing syndrome, hypokalemia, diuretics abuse.

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TYPE 2 POLYGLANDULAR AUTOIMMUNE SYNDROME «SCHMIDT SYNDROME». CASE REPORT

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Introduction. Schimdt Syndrome (Type 2 Polyendocrine autoimmune syndrome) is defined as the co-existence of Addison's disease (insufficiency of surrenalis) associated with autoimmune thyroid disease or Type 1 Diabetis. In our study case we have co-existence of Addison's disease with autoimmune thyroid disease. Over time these patients have a development of other autoimmune disorders in various organs. These include hypergonadotropic hypogonadism, vitiligo, chronic atrophic gastritis, pernicious anemia, autoimmune chronic hepatitis and celiac disease. Antibodies detected are 21 hydroxylase antibodies (21OH antibodies) against adrenal cortex, thyroperoxidase antibody (TPO antibodies). **Clinical case.** Patient *B.T* 28 years old presented in emergency with weakness, fatigue, nausea, vomiting, profuse diarrhea, hypotension (TA=90/60 mm Hg), tachycardia (heart rate =110 beats/min) and widespread hyperpigmentation of the skin and oral mucosa. The patient had an anamnesis approximately 3 years ago that occasionally showed signs of weakness, nausea, diarrhea but not the hyperpigmentation of skin.The patient has made a previous consultation to the infectious disease doctor.

Technique: Cutting 5mm with oral and IV contrast and reconstruction multiplanar.

Data: Thorax parenchymal lesions inferior-free, without the liquid freely;

Liver: normal size, without evident parenchymal lesions without dilatation of bile intra hepatic roads;

Cholecystis has no obvious lesions, without dilatation of bile roads extra hepatic;

Pancreas without obvious lesions;

Spleen, slightly enlarged without visible lesions, the kidneys has no obvious lesions;

Kidneys, without evident lesions;

Glandula surrenalis no obvious lesions;

No stomach lesions evident;

Gout intestine without evident lesions;

Colon without evident lesions;

Retroperitoneal space without adenopathy;

Blood vessels with normal dimensions;

Pelvis without evident lesions.

Treatment: treatment of Type 2 Polyglandular Autoimmune Syndrome is the same as that of the individual disorders. Treatment of primary hypothyroidism: physiologic thyroid hormone replacement with levothyroxine. Our patient's treatment is 50 m.c.g levothyroxine (1.6 m.c.g/kg body) and adjusted every 4—6 weeks to maintain TSH and thyroxine in mid normal range. Chronic treatment of Addison disease: glucocorticoid and mineralocorticoid replacement. The dose of hydrocortisone

	BEFORE	After	Normal Range
Blood test	Treatment may 2016	Treatment October 2016	
WBC	5.81×109/L	4.5×109/L	4.0—12.0
RBC	5.51×1012/L	5.9×1012/L	3.85.80
HGB	16.9 g/dL	16.4 g/dL	11.0—16.5
HCT	35%	51.6%	30.0—50.0
PLT	216×109/L	133×109/L	100—300
MCV	68.5 fL	87 fL	80.0—99.0
MCH	30.7 pg	27.6 pg	26.5—33.5
MCHC	483 g/L	31.7 g/L	320—360
GLYCEMIA	72 mg/dL	79 mg/dL	70—110
UREA	40 mg/dL	30 mg/dL	15—40
CREATINEMIA	1.1 mg/dL	1.0 mg/dL	0.7—1.2
URIC ACID	4.1 mg/dL	5.8 mg/dl	4.0—8.5
CHOLESTEROL	170 mg/dL	147 mg/dl	150—200
TRIGLYCERIDES	108 mg/dL	64 mg/dl	50—150
TOTAL PROTEIN	6.4 g/dL	6.8 g/dL	6.4—8.3
Na+	127 mmol/l	134 mmol/l	135.37—145.00
Cl-	102 mmol/l	114 mmol/l	96.00—106.00
Ca++	1.8 mmol/l	2.3 mmol/l	2.2—2.7
K+	8.3 mmol/l	5.1 mmol/l	3.48—5.50
Albumin	3.6 g/dL	3.8 g/dL	3.5—5.5
CORTISOLI 8.00 A.M	0.34μg/dL	2.41 μg/dL	5—25
ACTH 8.00 A.M	712.9	522.3	6—80 pg/Ml
TSH	6	3.63	0,4—4 μIU/ml
ANTI TPO	381	105	3—45 μIU/ml
ANTI 21-HYDROXILAZA	48.5	40.1	<0.1

used was 15—25 mg per day given as $^{2}/_{3}$ in the morning (20 mg) and $^{1}/_{3}$ in the evening (10 mg). Usual mineralocorticoid regimen is fludorcortisone 0.1 mg/day with monitoring of blood pressure, volume status, weight, plasma rein activity, sodium and potassium. **Discussion.** Type 2 Polyglandulare Syndrome typically occurs in early adulthood with a peak during the third or fourth decades and is three times more common in females than in males. This patient with, autoimmune thyroid disease and Addison disease has two major components of Schmidt's Syndrome. 10% of Schimidt's Syndrome patients have all three major DM, Addison and Hashimoto. Patients with autoimmune thyroiditis disease are prone to develope other autoimmune disease .In this case the patient with Addison is associated with Hashimoto thyroiditis.

KEYWORDS: polyglandular autoimmune syndrome, Schmidt syndrome, case report.

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A CASE OF HYPOPITUITARISM AND A SPONTANEOUS REGRESSION OF MASSIVE LESION OF HYPOTHALAMIC AREA

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Introduction. Hypopituitarism is a complex of one or more pituitary hormone deficiency due to diversity of underlying etiology, including rare poor studied forms. Clinical case presentation: we present a case of 57 years old woman with intracranial and extracranial mass lesions localized in medial part of the middle cranial fossa, skull base, third ventricle walls, chiasma opticum, sphenoid sinus and panhypopituitarism. The disease debut was associated with reactivation of chronic polypous sinusitis and left side otitis. It was suggested as a neoplasm due to aggressive progress of neurologic signs such as diplopia, vertigo, facial numbness and typical visualization feature with high contrast accumulation by MRI and positron emission tomography. But histological examination of sphenoid sinus mass, cytological liquor assessment did not reveal any tumor cells and alpha fetoprotein level was normal in contradiction to malignant lesion. Compensation of vital functions by substitution therapy by hydrocortisone 10—15 mg per day, L-thyroxine 75 mkg and desmopressin 0.1 mg twice a day improved overall health of the patient. Spontaneous regression of the vast majority of mass lesion within 6 months confirmed inflammatory process as a probable cause of this accident. **Conclusions.** Infection process could mimic tumor. Clear understanding of etiology of pathologic process in each case is necessary for accurate prognosis and treatment individualization.

KEYWORDS: hypopituitarism, case report.

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A CASE REPORT OF PITUITARY GIGANTISM OF 27-YEAR-OLD MALE PATIENT IN CHELYABINSK REGION OF RUSSIA

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Pituitary gigantism is a rare disorder. It refers to growth hormone (GH) excess that occurs before fusion of the epiphyseal growth plates. We report a 27-year-old male patient with a pituitary macroadenoma who underwent transsphenoidal surgery in 2004 at the age of 15 with the height up to 215 cm. He had history of visual impairment and severe headache. The patient's condition improved after the surgery but GH and insulin-like growth factor (IGF-I) levels did not normalize; as a consequence, he was referred for postoperative somatostatin analogue injection (30 mg per 28 days) with poor response. He continued to grow. In 2014 his height and body weight were approximately 235 cm and 142 kg, respectively, with a BMI of 25,7 kg/m^2. The concentration of plasma GH and IGF-1 levels maintained a high level, which were 15.67 ng/mL and 408 ng/mL, respectively. Pituitary magnetic resonance imaging (MRI) revealed macroadenoma 33×28×23 mm without negative dynamic compared with 2008 year sizes 23×31×28 mm. The patient suffered from back pain, restriction of movement because of difference in length of the legs. Valgus deformation of knee joints was detected. For this reason he decided to undergo surgery in traumatology department in 11.2014 before he stabilized GH secretion. Osteosynthesis of the left hip with the extension apparatus, osteology of the femur in the distal third (clinoid resection of the femur) were performed. Postoperative period was more then 3 months and patient walks with crutches till nowadays. He has edema of the left ankle experienced over a 1-year period and the huge strained left knee. In this consideration, he had a disability and impossibility to move. He needs more examinations in the National Research Center for Endocrinology. In conclusion all surgical manipulation should be provided after achieving the target level of GH and IGF-I secretion.

KEYWORDS: pituitary gigantism, case report.

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A CASE OF ASSOCIATION OF TYPE 1 DIABETES MELLITUS AND PRECOCIOUS PUBERTY

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Introduction. The processes of intensive growth and puberty are regulated by growth hormone and sex hormones, which are contrinsular. During the pubertal period the metabolic control is getting worse in the most of patients with type 1 diabetes mellitus (T1DM). One of the reasons of bad diabetes control at prepubertal children can be precocious puberty. **Case report.** A 4-year-old girl was diagnosed with T1DM 6 months ago. The daily dose of insulin was 0.5 units/kg. But during the last month glycemic control become worse and she was admitted to hospital for treatment correction. The daily dose of insulin increased to 1 units/kg and glucose levels according to continuous glucose monitoring system (CGMS) were very variable (from 2,9 to17,7 mmol/L). HbA_{1c} level was 10,1%. On examination, girl was found to have Tanner stage 2 breast development. There was no axillary or pubic hair. Her height was above the 90th percentile (6 months ago it was above 50th percentile, familial target height – 50th percentile). Bone age was 4 years and 6 months (Greulich Pyele). There was no thyroid swelling, café au lait spots or any bone abnormality. Her investigations showed normal hemogram, liver and renal functions. Thyroid functions were normal. Her basal hormonal profile was as follows: LH 0,133 mIU/ml, FSH 1,67 mIU/ml. On ultrasonography, increase in ovarian volumes (bilateral) and uterus was found (uterus measured 35×7,8×12,5 mm, OS — 20×10 mm, OD — 27×15 mm). On the GnRH stimulation test, the peak LH and FSH levels were 10 times higher than basal levels, which was compatible with a diagnosis of central precocious puberty. Brain magnetic resonance imaging (MRI) was performed and the organic cause of precocious puberty was excluded. **Conclusion.** Association of T1DM with precocious puberty is rare. But in the case of an unexplained severe course of the disease, this reason must also be considered.

KEYWORDS: diabetes mellitus type 1, case report, precocious puberty.

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PITUITARY MACROADENOMA IN ADDISON'S DISEASE

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Introduction. Long-standing primary failure of pituitary-dependent endocrine glands may lead to hyperplasia of the pituitary cells. Particularly, primary adrenal failure may predispose to corticotroph hyperplasia and in some patients to the development of corticotroph adenoma. We describe a rare case of a pituitary macroadenoma in a patient diagnosed with Addison's disease (AD). **Case report.** A 57-year-old female presented to the endocrinology outpatient department with complaints of weakness, dizziness and easy fatigability, nausea with occasional vomiting and darkening of the skin in the last 3 years. She also noticed progressive weight

loss over the 12 months prior to presentation (15 kg). About 10 years before, she had been diagnosed with polymyalgia rheumatica and was treated with corticoids for some periods. Prior to our observation, in the context of headaches, a brain CT was performed revealing a pituitary macroadenoma. Laboratory tests showed hyperkalaemia (6.7 mmol/L) and hyponatremia (129 mmol/L), an elevated ACTH (3353 pg/mL) and low cortisol (9.7 ug/dL). The ACTH stimulation test with tetracosactide was also consistent with primary adrenal insufficiency. Adrenal antibodies were positive and the adrenal CT was normal. There was no evidence of other autoimmune endocrinopathies. Considering the high levels of ACTH and the pituitary lesion, the patient was treated with dexamethasone plus fludrocortisone, leading to clinical improvement and normalization of ACTH. 12 months after, a brain-MRI was done, showing a significant reduction of the pituitary lesion. **Conclusion.** Primary adrenal failure may lead to corticotroph hyperplasia and pituitary adenomas. The aggressive treatment of AD, aiming to achieve a normalization of the ACTH level, can lead to a reduction or remission of the pituitary masses.

KEYWORDS: addison's disease, pituitary adenoma, cortisol.

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PLASMA LEPTIN AND NEYROPEPTIDE Y CONCENTRATION IN PATIENTS WITH IMPAIRED GLUCOSE TOLERANCE

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Background. Leptin, an adipose tissue-derived product of the obesity (OB) gene, is an important regulator of energy metabolism and may be associated with the occurrence of insulin resistance and diabetes in humans. At present the leptin problem in impaired glucose tolerance (IGT) is widely discussed. **Aim.** The aim of the present study was to determine the change of leptin and neuropeptide Y (NPY) levels in patients with IGT. **Material and methods.** 46 patients (20 males, 26 females), mean age 58,2±13,2, mean BMI 28,9 ±6,47 kg/m^2, waist-to-hip ratio (WHR) 0,82±0,11. The average fasting plasma glucose (FPG), 2-hour plasma glucose concentrations (2-h PG) following a 75-g oral glucose tolerance test, HbA_{1c}, total cholesterol, triglycerides. Serum leptin and NPY levels were measured by ELISA and results were compared by Statistica 10.0. **Results.** The averages were FPG 7,47±1,27 mmol/l, 2-h PG 8,9±1,2 mmol/l, HbA_{1c} 6,3±0,2% total cholesterol 5,6±0,9 mmol/l, triglycerides 1,5±0,7 mmol/l. In patients with IGT serum leptin levels 22,4 ±15,97 ng/ml, serum NPY levels 0,78±1,12 ng/ml. The relationships leptin/NPY 28,7±14,1 ng/ml. There was no significant correlation between serum NPY levels and BMI and WHR, but relationships leptin\NPY correlated with BMI (r=0.89; p<0.05), HbA_{1c} (r=0.62; p<0.05), FPG (r=0.78; p<0.05) and triglycerides (r=0.74; p<0.05) in patients with IGT. **Conclusions.** These data suggest that the relationships leptin/NPY significant in-creases in patients with impaired glucose tolerance.

KEYWORDS: leptin, neyropeptide Y, impaired glucose tolerance.

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CONGENITAL HYPERINSULINISM IN INFANCY

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Introduction. Congenital hyperinsulinism — is a rare condition, which characterized with inadequate increased insulin secretion and severe hypoglycemia. **Case.** A girl, born at 23.12.16 (1st, delivery by caesarian session at the 35 week of pregnancy). Birth weight 4570 gr., length 55 sm. Due to the presence of severe hypoglycemia (1,4—2,8 mmol/l), prematurity and respiratory insufficiency, she was transferred to the intensive care department. Hormonal evaluation was made: cortisol 197,45 nmol/l (norm 170—720), insulin 321,8 mUE/ml (norm 3—25,5). Sodium and potassium were in normal range. A high glucose levels (13—14 mg/kg/min) and prednisolone (3—6 mg/kg) treatment were given from birth without any effect. After that a child came to the Republican Endocrinological Center in the intensive care department in severe condition due to hypoglycemia. Additional examination of computed tomography was made: diffuse hyperplasia of left adrenal, hepatomegaly, symptoms of spina bifida Th 11,L5—S2. Due to the clinical-laboratory features a clinical diagnosis was made: congenital hyperinsulinism, prematurity (35 weeks gestational age). Intravenous glucose titration (1 g/kg) and octreotide (45 mg/day with increasing 240 mg/day due to the presence of hypoglycemia). Despite this treatment glucose levels were low, so treatment with diazoxide 75 mg/day (instead of octreotide) was started. On this dosage child had severe vomiting (was diazoxide treatment side effect), that's why we lowered dosage to 50 mg/day and gave antireflux food and domperidone to her. Hormonal evaluation: insulin 33,8 mUE/ml (norm 3—25,5), C-peptide 5,05 ng/ml (norm 1,1—4,4). Genetical evaluation: no mutation was determined (50% of congenital hyperinsulinism cases didn't evaluate any mutations due to genetical testing). A child was discharged from the hospital with weight 4850 g, length 57 sm. She takes now diazoxide 50 mg/day, eat antireflux food and need in subsequent observations by pediatric endocrinologist. **Conclusions.** This case demonstrates the importance of timely diagnosis and treatment of congenital hyperinsulinism in early in-

fancy. The most severe complication of this condition is brain injury due to severe hypoglycemia.

KEYWORDS: hyperinsulinism, hypoglycemia, infancy.

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THE INFLUENCE OF DPP-4 INHIBITORS ON FAT METABOLISM IN TYPE 2 DIABETES PATIENTS

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Background. To evaluate the effect of sitagliptin in combination with metformin on glucose toxicity and lipotoxicity in patients with type 2 diabetes and obesity. **Material and methods.** The study involved 82 patients (55 women, 27 men, mean age 56,1±5,47 years) with obesity, lipid metabolism disorders, who have not reached target levels HbA_{1c} (average HbA_{1c} 8,3±1,6%) after metformin and diet therapy. The first group of patients (42 patients) received co-formulated drug, consisting of sitagliptin 100mg and metformin 2g once a day; the second comparison group (40 patients) received metformin 1.5—2.0 g/day. Dynamics of fasting glycemia, postprandial glycemia, glycated hemoglobin, weight, BMI, WC, WHR, lipid profile (total cholesterol, triglycerides, LDL, HDL, apoβ protein), insulin, proinsulin, leptin, adiponectin, insulin resistance using the index HOMA IR and functional activity of β-cells (by HOMA-β index) was evaluated at baseline and at 6 months of therapy. In addition, MRI was performed to assess visceral fat in all the patients. **Results.** At 6 months patients in both groups demonstrated significant positive changes in the levels of fasting glucose, postprandial glycemia and glycosylated hemoglobin. In group I, HbA_{1c} decreased from 8.3±1.6 to 6.6±1.24% (p<0.01), in group II there was a decrease from 8.35±1.75 to 7.62±1.39% (p<0.01). FPG and late products of glycosylation levels in group I reduced on average by 2.67 and 3.3 mmol/L, correspondingly, in group II by 2.1 and 1.8 mmol/l. No significant differences in the dynamics of total cholesterol, HDL between the groups were found. LDL in group I lowered by 0.7 mmol/l, in group II by 0.3 mmol/l (p<0.05); in group I, TG decreased by 1.33 mmol/l. in group II by 0, 63 mmol/l (p<0.05); in group I IRI reduction was 3.45 mcU/ml in group II 1.63 mcU/ml (p=0.05). Proinsulin level dropped down in group I by 2.93±3.02, in group II by 1.26±1.1, C-peptide level increased by 1.4±1.6 ng/ml, in group II 0.16±0.1 ng/ml, HOMA-β grew up in group I by 23.4 standard units, in group II by 4.8 standard units (p<0.005). The ratio of proinsulin/insulin dropped down in group I by 0.19±0.7, in group II by 0.02±0.2. There were no significant differences between the groups in the dynamics of HOMA IR and both groups demonstrated positive dynamics. Adiponectin levels were different between the groups, there was an increase by 1.9 ng/ml in group I, in group II by 0.49 ng/ml. (p<0.01). Leptin lowered by 7.37 ng/ml in group I, in group II by 1.21 ng/ml (p<0.01). Also groups showed dramatic difference in anthropometric parameters dynamics (p<0,001). Average weight loss was 4.9±3.2 kg in group I, in group II 2.0±0.94 kg correspondingly. BMI in group I decreased by 1.8±1.3, in group II by 0.68±0.3. WC shortened by 6.5±4.7 sm in group I, in group II by 2.42±1.02 sm. WHR in group I decreased from 0.95±0.06 sm to 0.91±0.05 sm, in group II from 0.94±0.03 sm to 0.93±0.03 sm respectively. Also MRI showed a significant reduction of visceral fat area by 20.6±13.5 sm^2 (7.5%) in group I, compared to group II with 5.7±3.75 sm^2 reduction(1.76%; p<0.01), while in the dynamics of the area of the subcutaneous fat there is no reliable dynamics between groups. Episodes of hypoglycemia have not been registered in any of the groups during the treatment. **Conclusion.** The administration of sitagliptin and metformin decreased glucose toxicity and lipotoxicity that generally led to the improvement of glycemic control.

KEYWORDS: DPP-4 inhibitors, type 2 diabetes mellitus, obesity.

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THE IMPACT OF LOCAL NEGATIVE PRESSURE WOUND THERAPY ON TISSUE REPAIR PROCESSES IN PATIENTS WITH DIABETIC FOOT ULCES

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Aim. To evaluate clinical, histological and immunohistochemical effects of NPWT in comparison to standard management in diabetic foot ulcers (DFUs). **Material and methods.** Clinical examination, transcutaneous oxygen monitoring, ulcer biopsies (haemotoxylin-eosin and immunohistochemistry for CD68 (macrophages), MMP-9 and TIMP-1(proteolytic activity), CD31 (vessels) before and after local treatment. **Results.** 42 patients were enrolled (28 men; 14 women) with DFUs after surgical debridement and divided into 2groups. Group1 (n=21) was treated with NPWT (−90—120 mm Hg), group 2 (n=21) was treated with atraumatic dressings for 9±2 days. The groups matched by DM type, age (group 1 60 (52; 64), group 2 60 (57; 72) years), HbA_{1c} in group1 8.8% (7.4; 10.6%), in group 2 8.8% (7.6; 9.7%), severity of microvascular complications, form of diabetic foot (neuropathic — 41, neuroischemic-1(after revascularization)), wound size (group 1 — 25,0 (16,2; 44,5) cm^2, group 2 — 23.5 (12.3; 55.3) cm^2, wound depth (group 1 — 3,3 (1,5; 6,5) cm, group 2 —3.2 (2.4; 5.2) cm), $tcpO_2$ (group 1 46 (38; 52) mm Hg; group 2 — 43 (38; 47) mm Hg; p>0.05). Histologically both groups presented edema, poorly organized extracellular matrix (ECM), small quantity of fibroblast-like cells and severe inflammation (p>0.05). Immunohistochemically: increased staining of

MMP-9, low TIMP-1 levels were found in both groups (p>0.05). Amount of vessels according to CD31 staining was 43 (19; 62) in group 1 and 58 (30; 95) in group 2. In follow-up period wound size and depth decreased, $tcpO_2$ increased more significantly in group1 (p<0.05). Histological exam showed significant reduction of edema, formation of ECM, high quality of granulation tissue, reduction of inflammation in group1 compared to group 2(p <0.05). Amount of blood vessels increased more than twice, but there was no significant difference between 2 groups (p=0.33). TIMP-1 expression slightly increased and MMP-9 levels decreased more significant in group 1 (p=0.04). The majority patients in group 2 had low quality of granulation tissue and excessive exudation after treatment, which required surgical debridement. **Conclusion.** Histological and immunohistochemical exams confirm more clinical effect of NPWT.

KEYWORDS: diabetic foot ulcers, local negative pressure wound therapy, diabetes mellitus.

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REIFENSTEIN SYNDROME — NEEDS AND POSSIBILITIES OF IMPROVING THE OUTCOMES

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Introduction. Reifenstein syndrome or Partial Androgen Insensitivity Syndrome PAIS represents a rare form of male hypogonadism, caused by a mutation of gene encoding the androgen receptor, resulting in partial resistance to androgens. In consequence a disorder of sex development appears, in which 46,XY individuals do not virilize normally despite the presence of bilateral testes and serum testosterone concentrations within or above the normal male range. Men have varying degrees of ambiguous external genitalia, hypogonadism, and infertility. As it is primarily rare disease, usually it is only mentioned in professional guidelines, no medical consensus has been reached about the treatment of these patients. We present a case of Reifenstein syndrome treated with high doses of testosterone for 12 months, resulting in improved masculinization and even obtaining sperm by testicular extraction for ICSI. **Case presentation.** A 33-year-old male presented with complaints of infertility and reduced libido. His personal history is remarkable for hypospadias (several surgical corrections have been done, the last one — at the age of 16) and gynecomastia (at the age of 13—14, was solved by surgery). His family history is noticeable — brother and cousin have had hypospadias and gynecomastia. Physical exam revealed high-pitched voice, sparse pubic and axillary hear and absent facial hair, micropenis, testes located in the scrotum, but small in size. Lab test results in December 2015: karyotype 46XY; AZF deletions negative, azoospermia in semen analysis; double increased total testosterone with increased SHBG; LH-16 (with upper normal level of 8.7); FSH on the upper normal level. The diagnosis of Reifenstein syndrome was supposed. Based on some professional articles we decided to try high doses of androgens. In March 2016 the administration of testosterone undecanoate 1000mg/4 weeks (X3 usual doses) was initiated. After 12 months of treatment patient remarked refined libido, development of facial hair, improved quality of life. Lab test revealed normalization of LH level. As patient extremely desires descendants, the mutual agreement for TESA was obtained. During the procedure, on 7th of March, we faced 2 unexpected things: 1) presence of blind vagina (images are available), 2) microsurgical testicular sperm extraction resulted in obtaining mobile spermatozoa, which will be used for intra-cytoplasmic sperm injection. **Conclusion.** Administration of androgens in more masculinized patients with PAIS can improve patient's condition and ameliorate prognosis; this approach should be systematically assessed, to describe more extensively dosage, administration, benefits, as well as adverse effects and recommended follow-up.

KEYWORDS: reifenstein syndrome, hypogonadism, androgens.

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EATING BEHAVIOR IN CONNECTION WITH BODY MASS INDEX IN WOMEN

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The European Medical Agency defines obesity as a chronic disease associated with genetic, metabolic, behavioral factors, as well as environmental factors, resulting in increased morbidity and mortality. The etiological factor underlying primary obesity are an absolute or relative prevalence of energy processes (overeating) over processes of energy expenditure. Overeating is usually a result of eating disorders. **Objective.** To explore the features of eating disorders among groups of women according to body mass index. **Material and methods**. The study included 139 women aged 18—61. All participants were divided into three groups according to body mass index (BMI): the first group included women with normal weight (n=21), the 2nd group — women with overweight (n=34), the third one — obese women (n=84). Eating disorders (ED) were evaluated using the Dutch eating DEBQ questionnaire. **Results.** ED were found in all groups. The frequency of different ED was 47% in the first group, in the second group — 55.9%, in the third — 76.2% of cases. The emotiogenic eating behavior was significantly higher in obese women (1.5±0.9 points) compare to normal weight women (1.1±0.7 points; p=0.04) and overweight women (1.1±0.6 points; p=0.02), respectively. Compulsive ED was more frequent among women in the 3rd group (2.25±1.0 points), compared to women in the 1st (1.7±0.7 points; p=0.02) and 2nd groups

(1.8±0.8, points, p=0.08). Obese women also showed a tendency to increase ED of the external type (2.6±0.8 points) compared to groups 1 (2.3±0.6 points, p=0.075) and 2 (2.3±0.6 points; p=0.070). Restrained food intake was negatively correlated with weight, the ED was more significant in the 1 group (2.3±1.0 points) relative to the 3 group (1.9±0.8 points; p=0.09). A noteworthy finding was the higher amount of combined types of ED with higher BMI. Combined types of ED were detected among obese women (50%). The most frequent combinations were emotional-compulsive and external-compulsive types of ED. **Conclusion.** Certain types of ED can be detected independently of BMI levels, but obese women suffer of ED more frequently than women with normal weight and overweight women. ED occur in isolated and combined variants, the number of combined variants increases with rising BMI. Women with normal weight and overweight women demonstrated a more frequent accurance of restrained type of ED probably due to concern about their outward appearance and higher care for quantity and quality of food intake.

KEYWORDS: eating disorders, body mass index, overweight, obesity.

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SOMETHING NEW ON THE REAL HISTORY OF KETOACIDOSIS

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Aim. To estimate the frequency of different risk factors appearance for diabetic ketoacidosis developing in a real clinical practice in Rostov-on-Don. **Material and methods.** Patients with a diagnosis of ketoacedosis were enrolled in the reserach. A survey to determine the type of nutrition, alcohol intake and other risk factors was conducted. All patients were divided into two groups according to their age. The 1st group — 12 patients younger than 65 y.o. — Nutritional Risk Screening survey, the 2nd group — 3 patients (65—90 y.o) – Mini Nutritional Assessment survey. «Alcoholic agnosia» survey for the identification of alcohol addiction. **Results.** 15 patients (11 men and 4 women), average age — 36±0,93 y.o. According to type of diabetes: 11 patients of type 1 diabetes mellitus, 4 patients wth type 2 diabetes mellitus. Out of 15 patients 10 (66,66%) had nutrition problems. 5 (33,33%) patients were closed to the nutrition risk questions. According to «Alcohol agnosia» survey: 5 (33,33%) patients had alcohol abuse problems, 3 (60%) of them were aware of this problem, 2 (40%) were indifferent to it. 10 (66,66%) patients did not have alcohol addiction problems. The risk factors of developing ketozcedosis: inadequate insulin therapy — 7 (46,66%) patients, 5 (71,42%) of them with alcohol abuse problems, 2 (13,33%) of them with a sober life style. Took drugs 2 (13,33%) patients, but also experienced alcohol abuse problems. Exacerbation of concomitant diseases — 6 (40%) patients, 4 (66,66%) of them had alcohol abuse problems. **Conclusion.** The most significant risk factors for developing ketoacedosis were inadequate insulin therapy, exacerbation of concomitant diseases (40%), abuse of alcohol (33,33%), drugs intake (13,33%). 66,66% had nutritional problems but this state is rather the result than the cause of developing ketoacedosis.

KEYWORDS: developing ketoacedosis, risk factors, inadequate insuling therapy, alcohol abuse, concomitant diseases.

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ALPHA-LIPOIC ACID CYTOPROTECTIVE THERAPY IN TYPE 2 DIABETES PATIENTS

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Objective. To study the alpha-lipoic acid (ALA) efficacy in oxidative stress (OS) modification in type 2 diabetes mellitus (T2DM) patients with diabetic polyneuropathy (DPN). **Material and methods.** 61 patients were included in the research: 29 (48%) female, 32 (52%) male, average age — 50.1±0.5 years, mean T2DM duration — 5.9±0.4 years, DPN — 4.9±0.5 years, AH — 6.7±0.3 years. Neuropathic status (NS) indices: Neuropathy Symptoms Score (NSS), Total Symptoms Score (TSS), Neuropathy Disability Score (NDS), Douleur Neuropathique 4 (DN4); oxidative stress parameters: total oxidative capacity (TOC), total antioxidant capacity (TAC), oxidized LDL antibody level (ab-oxLDL); carbohydrate metabolism state: pre-, post-prandial glycemia, HbA_{1c} were defined in patients. Depending on therapy patients were divided into 2 groups: control (n=30) and basic (n=31) with 50 ml (600 mg) ALA ready for use solution for 14 days was prescribed; then (600 mg) oral ALA 1 tablet once a day for 12 weeks was prescribed. Statistical analysis was carried out with Excel 2013 («Microsoft») and Statistica 8.0 («StatSoft, Inc.») software, investigated parameters were presented in M±m, Mann—Whitney test (U) was used for group comparison and significance critical level (p) was accepted at 0.05 or lower. **Results.** ALA therapy in the basic group patients contributed to the reduction of the severity of DPN clinical and laboratory manifestations in comparison to the same parameters in the control group. OS parameters modifications were observed: TOC value decreased by 13.9%, ab-oxLDL — by 12.9%, OSI — by 32.4% whereas TAC increased ones by 27.3% (U, $p<0.05$). In the basic group of hospital patient ALA treatment led to reduced glycemia at 8, 11 and 14 o'clock and HbA_{1c} level in 12.0, 9.1, 11.8 and 8.2% accordingly compared to the same ones in control group patients (U, $p<0.05$). NS indices were reduced significantly: NSS — 16.1%, TSS — 17.6%, NDS

— 12.4%, DN4 — 22.9% (U, $p<0.05$). **Conclusion.** Alpha-lipoic acid cytoprotective therapy contributes to significant improvements of neuropathic status indices, oxidative stress parameteres, and reduces glycemia and HbA_{1c} levels.

KEYWORDS: type 2 diabetes mellitus, alpha-lipoic acid, oxidative stress, glycemia levels, $HbA_{1c.}$

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A CASE OF CYCLIC ECTOPIC CUSHING'S SYNDROME DUE TO A NEUROENDOCRINE TUMOR OF THE APPENDIX

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Cyclic Cushing's syndrome (CS) is a rare disorder, characterized by repeat episodes of cortisol excess interspersed by periods of normal cortisol secretion. The so-called cycles of hypercortisolism can occur regularly or irregularly with intercyclic phases ranging in duration from days to years. A 24-year-old woman with fluctuating symptoms of hypercorticolism: weight gain, "moon" face, large purple striae on the trunk and breasts, hair loss on the head, acne, hypokalemia, diabetes. Disease duration was 6 years. Laboratory investigations showed a cyclic ectopic ACTH syndrome. Levels of adrenocorticotropic hormone fluctuated in the range from 34,0 to 299,0 pg/ml (7,0—66,0), and serum cortisol 457,0—1590,0 nmol/l (123,0—626,0). According to the results of hormonal tests, hypercorticolism cycle length varied from 2 to 11 months, with intervals of normal cortisol secretion from 2 weeks to 3 years.

CT scan revealed a mass in the ileocaecal area (2,5×2,5×4,4 cm). Right hemicolectomy was performed. Histological examination showed a neuroendocrine tumor of the appendix, G2. Our patient remained in clinical remission during a 6-years follow-up.

KEYWORDS: cyclic Cushing's syndrome, appendix, neuroendocrine tumor, ectopic ACTH syndrome.

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BONE MINERAL DENSITY — ONLY BODY MASS MATTERS IN HAVING STRONG BONES?

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There is a known association of body mass index and bone mineral density, but relative contribution of fat and lean tissue is not so well analysed yet. We aimed to investigate the effect of selected anthropometric parameters including BMI, fat content and lean body mass on BMD in postmenopausal women. Deferred to routine bone MD screening because risk of osteoporosis in menopausal women or additional risk factors. We could say, our group of 110 women aged 43.4—83.2 years/mean 63.7 y./ is a good representative of the average population of postmenopausal women. **Material and methods.** We included a randomly chosen group of postmenopausal women, deferred to routine bone MD screening because risk of osteoporosis in menopausal women or additional risk factors. We could say, our group of 110 women aged 43.4—83.2 years/mean 63.7 y./ is a good representative of the average population of postmenopausal women in our region of Subotica, northern Serbia. For measuring BMD, Dual energy X-ray absorptiometry was performed, with Lunar type model, wich gives simultaneous data of body mass, and content of lean and fat body mass. As first step multivariate ANOVA was used to find correlations between BMI, fat and lean body mass and BMD. Afterwards, Mann Whitney test was used to differentiate groups and localisations correlations. **Results.** The effect of BMI on BMD in L1—L4, femoral neck and hip is statistically highly significant with risk of mistake 0.5, 3.3 and 0.1% consecutively. T score reaches highest values in pre-obese group of patients / BMI 25—29.9 kg/m^2. The percentage of fat and lean body mass has no significant effect on having osteoporosis or osteopenia in this region. **Conclusion.** BMI and BMD are in tight positive correlation, regardless of the body composition — fat or muscle content. Seemingly, the most important is the mass our bones carry, which is a stimulus for osteoblast activity. We are planning further analyses to investigate eventual additional factors including age, physical activity, comorbidities, medications.

KEYWORDS; bone, postmenopausal, osteoporosis, mineral density.

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THE CASE OF TSH-PRODUCTION PITUITARY ADENOMA WITH LATE DIAGNOSIS

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A pituitary adenoma is frequent endocrine pathology. It more commons in women. The first place of hormone-activity adenoma belongs to prolactinoma, the second place — somatotropinoma. The TSH-production adenoma is very rare type of hormone- pituitary neoplasias. In the report we will focus on the patient *B.*, she is resident of a remote area of Primorsky Krai. For the first time she was hospitalized in Primorsky regional centre of diabetes and endocrinological diseases in January 2015 with referral diagnosis multinodular toxic goiter. **Of history.** The patient had three cases of hyperthyroidism (in 1983, 1988, 1995). Thyroid resection was carried out three times over the multinodular goiter with symptoms of hyperthyroidism. After the last resection appointed replacement therapy with thyroid medications (levothyrox-

ine 50 mcg in the morning). First hormonal studies conducted in the early 2000s. There was revealed a high level of TSH, but replacement therapy was continued despite the manifestations of thyrotoxicosis. Free T4 Episodic study revealed increased rates of medical and regarded as thyrotoxicosis. Clinically, the patient had symptoms of hyperthyroidism DC with lesions predominantly cardiovascular system, since 2007 atrial fibrillation, mitral and tricuspid insufficiency, replacement of heart valves. The first pair of hormones (TSH and FT4) on a clean background was investigated in 2016. In the repeated trial (which excluded a laboratory error) at the same time an elevated level of TSH (20.8 mMe/ml) and FT4 (34 pmol/l). The differential diagnosis with resistance to thyroid hormone. The study of the brain and pituitary MRI with dynamic contrast. Pituitary adenoma was found 0.2 cm in diameter. Exhibited a clinical diagnosis of TSH-producing pituitary adenoma. The patient was operated in neurosurgical center of Far Eastern federal university's medical centre. Performed transnasal transsphenoidal adenomectomy with endoscopic video navigation in January 2017. According to the results of immunohistochemistry. According to the results of immunohistochemistry: Ki-67, Alpha ingiban — negative expression. Chromogranin — weak expression in 10—20% of the cells. TSH — strong expression in 90—100% of the cells, prolactin expression severe 80—90% of the cells. **Conclusion.** IHC tumor profile best fits multigormonalnoy pituitary adenoma with minimal formation of proliferative activity of cells. When hormonal study TSH decreased to 3.45 mMe/l, retained a higher level of St. T4 30.4 pmol/l. The patient was recommended treatment with somatostatin analogues (octreotide Long 40 mg of p 1 to 28 days/m) and dopamine agonists (cabergoline 0.5 mg 2 p per week) - on 6 months follow-up examination. The patient entered into the register of entities gipotalyamo pituitary region of Primorsky Krai. This case is the second in the coastal region.

KEYWORDS: pituitary adenoma, endocrine pathology, prolactinoma, somatotropinoma.

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SECONDARY AND TERTIARY HYPERPARATHYROIDISM: CASE REPORT

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Introduction. In the treatment of secondary hyperparathyroidism of chronic kidney disease, allosteric modulators of the calcium-sensing receptor — inhibit glandular hyperplasia, reduce parathyroid hormone (PTH) levels, impact on bone turnover and mineral density (BMD). But the use of calcimimetic did not reduce the need for parathyroidectomy for refractory hyperparathyroidism. Tertiary hyperparathyroidism is a state of excessive secretion of PTH after a long period of secondary hyperparathyroidism and renal transplantation. **Case report.** We present the case of a 43-year-old caucasian male undergoing chronic hemodialysis since 2006. Laboratory investigations showed elevated levels of phosphorus 1.95 mmol/l, calcium 2.6 mmol/l, CaxP 5.07 mmol2/l2, iPTH 817 pg/ml, CTx 3.1 ng/ml, OC >300 ng/ml, ALP 469.6 U/L, vitamin D deficiency 7.9 ng/ml. Ultrasound revealed multiple enlarged parathyroid glands: right superior 1.08 cm3; right inferior 0.04 cm^3; left superior 0.3 cm^3 and left inferior d=0.6 sm. DEXA revealed osteoporosis (Z-sc): Rad 33% –4.0; L2—L4 —1.1; total femur —2.2 SD. We have recommended dialysis with low calcium (1.25 mmol/L) and cinacalcet 30 mg/day. Laboratory investigations were done during the treatment. After normalization of serum calcium and phosphorous concentrations we have added cholecalciferol. Six months later mean iPTH and Ca×P levels decreased by 60.2 and 20.4%. Bone markers decreased by CTx 19.4%; OC 1.4%; ALP 16.8%. 25-D levels increased by 123.4%. The dynamics of BMD from baseline: L2—L4 +5.4%; Rad 33%: +9.3; total femur +6.4%. On ultrasound 3 parathyroid glands (right inferior, left superior and inferior) involute to normal size, but right superior enlarged 1.9 cm^3 (+75%). Patient underwent renal transplantation in 2010 (CKD stages 1—2). After successful kidney transplantation right superior parathyroid gland did not involute. One months later he developed the tertiary hyperparathyroidism with an iPTH 815 pg/ml, calcium 3.4 mmol/l. Was recommended cinacalcet initially in dose 30 mg, then was dose-increased to 180 mg/day in 2011 (calcium 2.4 mmol/l, iPTH 634 pg/ml), added alfacalcidol 6 mcg/week, but did not control hyperparathyroidism. In 2011 performed a right superior-gland parathyroidectomy to treat severe hyperparathyroidism refractory to cinacalcet and alfacalcidol treatment. **Conclusion.** Our case study shows that cinacalcet treatment is an effective therapy of hyperparathyroidism. But enlarged gland (larger than 0.5 cm^3 or 1 cm in diameter) became refractory to medical therapy and patient need for parathyroidectomy.

KEYWORDS: hyperparathyroidism, mineral density, bone, chronic hemodialysis, chronic kidney disease, parathyroid hormone.

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LONG-TERM MANAGEMENT OF RESISTANT ACROMEGALY WITH PASIREOTIDE LAR IN A PATIENT FROM AN AIP MUTATION POSITIVE FIPA FAMILY

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Introduction. AIP-related somatotropinoma patients with active acromegaly after surgery tend to be resistant to adjuvant medical therapy with somatostatin receptor

(SSTR) subtype 2 specific somatostatin analogues (SSA). Pasireotide is a newer multiple SSTR binding SSA with actviity primarily at SSTR5 and SSTR2, which has not been widely studied in AIP mutated patients. **Clinical case and results.** A male patient was diagnosed aged 29 with a GH-producing pituitary macroadenoma (25×18×23 mm); he was from a FIPA kindred and his sister also had acromegaly due to a pituitary macroadenoma (25 mm) at age of 24 and was cured by neurosurgery. A familial AIP mutation p.Gln217X was revealed in the index patient, his sister and an unaffected nephew. The patient underwent transsphenoidal surgery, with partial resection of a GH and prolactin positive adenoma. He was treated for post-operative corticotroph, thyrotroph and gonadotroph deficiencies but GH hypersecretion by the residual tumor required adjuvant medical treatment. He was treated with SSTR2 specific agents (lanreotide autogel and octreotide LAR), but without hormonal control. Addition of cabergoline did not improve hormonal suppression. An increase of tumor residue size was observed on SSA treatment and the residual tumor approximated the chiasma, which precluded safe surgery and pegvisomant therapy, while the patient declined radiotherapy. The patient began pasireotide LAR and was uptitrated to 60 mg/month. The clinical signs of acromegaly improved, GH/IGF-1 was controlled and tumor size was stable. Pasireotide was associated with worsening of existing impaired glucose control and treatment with metformin, gliclazide and liraglutide was required. After 2 years of treatment the dose of paseriotide was decreased to 40 mg/4 weeks and further follow-up showed tumor shrinkage and an empty sella. However, glucose metabolism worsened over time despite existing therapy and exogenous insulin treatment was required. **Conclusion.** In this patient from an AIP-mutation positive FIPA family, resistance to surgery, SSTR2-spcific SSA and cabergoline was seen. Pasireotide permitted clinical, hormonal and tumoral improvement, albeit at the cost of long-term worsening of hyperglycemia requiring increasing antidiabetic therapy.

KEYWORDS: somatotropinoma, acromegaly, AIP, FIPA family, pasireotide LAR.

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CARBOHYDRATE METABOLISM IN PATIENTS WITH CUSHING DISEASE AND ACROMEGALY: A GLANCE AT THE INCRETIN SYSTEM

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Introduction. The relevance of carbohydrate metabolism studying in patients with Cushing disease (CD) and acromegaly can be explained by frequent occurrence of glucose metabolism disturbances on the one hand, and difficulties in glucose-lowering therapy in these patients on the other. The effectiveness of hyperglycaemia treatment may be reduced due to difficulties in remission/cure of the underlying disease, as well as to the use of specific drug-therapy, leading to hyperglycaemia. There is a growing interest in research aimed at studying the role of incretin system in the pathogenesis of secondary hyperglycemia associated with neuroendocrine diseases recently. **Aim of the study.** To analyze the rhythm and levels of incretins and neuropeptides secretion in patients with CD and acromegaly and therefore to specify the pathogenesis of carbohydrate metabolism disturbances. **Material and methods.** 42 patients with Cushing disease and acromegaly were included; the mean age was 37.5 years. All of the patients were newly diagnosed with Cushing disease (using urinary free cortisol levels, evening saliva cortisol levels and low-dose dexamethasone suppression test) and acromegaly (in absence of GH suppression during OGTT and high IGF-1 levels); none of them had a history of previous drug therapy, radiotherapy or pituitary surgery. All patients underwent OGTT, during which glucose, glucagon, GLP1, GLP2, GIP, ghrelin were measured at 0, 30 and 120 min respectively. **Results.** During OGTT glucose levels were not significantly different in all groups. The mean HbA_{1c} level was 5.8% (5.3—6.2). However the relevance of prediabetes was higher in CD patients. In CD patients glucagon levels were significantly higher at all cut off points compared to controls (p=0.001). In acromegaly patients, no significant differences were found. GIP secretion was slightly lower in CD patients; in acromegaly patients, no differences were found. Acromegaly group was characterized by inverse rhythm of GIP secretion, with no peak level at 30': GIP 0 min — 194.2 pg/ml, GIP 30 min — 178.8 pg/ml/. GLP-1 levels were significantly higher in CD patients (p=0.047). In acromegaly group, no significant differences in GLP-1 secretion were found. GLP-2 levels were significantly higher in CD patients compared to acromegaly and controls (p=0.001). Ghrelin levels were significantly higher in CD (p=0.013) and acromegaly (p=0.023) patients. **Conclusion.** More pleotropic actions of glucocorticoids can possibly explain higher relevance of carbohydrate metabolism disturbances in CD patients. This can be also explained by higher levels of glucagon secretion, which does not depend on type of carbohydrate metabolism disorder and is stimulated by a direct action of glucocorticoids on glucagon receptor. GIP and GLP-1 secretion in CD and acromegaly patients are characterized by inverse rhythm with no peak levels which means that these hormones are not playing the crucial role in carbohydrate disturbances development in these patients. On the contrary, GLP-2 and ghrelin seem to influence and potentially regulate glucose homeostasis in CD and acromegaly patients.

KEYWORDS: Cushing disease, acromegaly, glucose metabolism disturbances, hyperglycemia, incretin system.

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UNUSUAL CAUSE OF HYPOGLYCEMIA

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Anamnesis. Girl, a 1st child. In the 3rd trimester was found polyhydramnios — susp. esophageal atresia. Term vaginal delivery at 38 weeks' gestation. Birth weight 2650 g, birth lengths 48 cm, Apgar score 8/9. Esophageal atresia with tracheoesophageal fistula, anal atresia with rectovestibular fistula. 1st day performed surgical repair of tracheoesophageal fistula and anal atresia; primary repair of esophageal atresia with cervicostomy and gastrostomy. 14 months - definite esophageal reconstructions reverse gastric tube from the greater gastric curve method. Until the time of admission no difficulties with swallowing, barium swallow exam — no signs of stricture; slow weight gain and well controlled asthma, otherwise normal PM history. At the age of 3 years recurrent brief episodes of pallor, tremor, sweating, fatigue and confusion; episodes resolved promptly after ingestion of sweet beverages and food. General practitioner provided neurological exam, cardiological exam, EEG, echocardiography, abdominal ultrasound: no abnormal founding. At the age of 5 years, during one such episode of pallor and fatigue, girl's grandmother (type 2 diabetic) measured glucose 2.0 mmol/l, during the following months, parents continued measuring the glucose-recurrent episodes of symptomatic hypoglycemia with glucose levels as low as 1.2 mmol/l. On admission: symptomatic hypoglycemia occurred 90 minutes after breakfast, glucose 2.3 mmol/l, no urine ketones, glycosuria of 28 mmol/l, increased plasma insulin of 23.7 mIU/l, normal levels of cortisol and growth hormone. Glucagon challenge test: glucose — 0 minute (2,3 mmol/l)- 30 minute (9,4 mmol/l). Critical sample analyses confirmed the diagnosis of nonketotic hyperinsulinemic hypoglycemia. Oral glucose tolerance test: delayed and hyperinsulinemic response to oral glucose, hyperglycemia during the first 60 minutes, followed by a rapid lowering of blood glucose level during the second hour of oral glucose tolerance test. **Diagnosis.** Postprandial hyperinsulinem, caused by a delayed and hyperinsulinemic response to carbohydrate intake, as a result of esophagogastric surgery. It represents one end of the «post-bariatric surgery hypoglycemia» spectrum, distinct from the «dumping syndrome». Initial treatment: diet with complex carbohydrates, no sweets or juices, higher dietary fat intake, first week of diet, no hypoglycemic events were detected, occasional episodes of postprandial hyperglycemia12-month follow-up: without symptoms and no hypoglycemic events were detected, apart from occasional sweets, the girl's diet was as prescribed, HbA_{1c} 5.2%, CGM: frequent postprandial hyperglycemia up to 21.1 mmol/l. **Conclusion.** Case of a child with PHH following esophageal reconstructions benefits of using the CGM/FGM in the diagnosis, therapy of hypoglycemia.

KEYWORDS: hypoglycemia, postprandial hyperinsulinism, post-bariatric surgery, hypoglycemia.

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MAGNETIC RESONANCE SPECTROSCOPY OF THE BRAIN IN PATIENTS WITH TYPE 1 DIABETES MELLITUS

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Introduction. Currently, there are more and more techniques to assess the state of the brain in patients with type 1 diabetes mellitus (DM type 1). Proton magnetic resonance spectroscopy (1H-MRS) of the brain provides detailed information on the structure, dynamics, status of reactions and the chemical state of molecules. This method was approved by the United States Food and Drug Administration (FDA) in 1995, however, according to the literature, it has not yet found wide application in patients with type 1 diabetes. **Aim.** To study the data of 1H-MRS of the brain in patients with DM type 1. **Material and methods.** Were examined 22 patients at the age 24.6±0.4 years with DM type 1, the control group consisted of 10 healthy young adults, matched by sex and age. All patients underwent clinical and laboratory diagnostics. Magnetic resonance imaging (MRI) and 1H-MRS of the brain performed on apparatus Siemens Magnetom 1,0 T. in the standard method. Statistical analysis was performed using the R-system package. **Results.** In assessing the state of carbohydrate metabolism average blood glucose levels in patients with T1DM 10.2±4.7 mmol/l, HbA_{1c} 8.1±1.6%. According to the standard MRI in patients with type 1 diabetes was found expansion arachnoid spaces liquorocystic character, spaces of Virchow-Robin and convexity spaces. Also detected a correlation between the expansion of liquorocystic spaces and indexes HbA_{1c} (r=0.4; p=0.001), and fasting blood glucose (r=0.5; p=0.001), as well as with the expansion of Virchow—Robin spaces (r=0.5; p=0.001, r=0.5; p=0.001) and convexity spaces (r=0.4; p=0.003; r=0.4; p=0.003). During the 1H-MRS identified changes in metabolite ratios in the thalamus, namely the reduction of NAA/Cho ratio of 1.07±0.14 to the right, left 1.14±0.02 (the rate of more than 1.6), a significant increase in Cho/Cr ratio of 2.16±0.34 right, left 2.23±0.17 (rate of less than 1.2). **Conclusions.** Conducting 1H-MRS in patients with DM type 1 allows studying the metabolism of the brain, predicting possible cognitive impairment, as well as carry out adequate correction of the revealed disorders. However, the study requires an increase in the sample of patients for a more thorough analysis.

KEYWORDS: type 1 diabetes mellitus, proton magnetic resonance spectroscopy (1H-MRS) of the brain, carbohydrate metabolism.

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INCIDENCE OF INCREASED REACTIVE OXYGEN SPECIES ACTIVITY AND RAPID HYPOTHYROIDISM DEVELOPMENT IN PATIENTS WITH GRAVES' DISEASE DURING ANTITHYROID TREATMENT

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Introduction. Autoimmunity plays an important role in the development of thyrotrophin (TSH) receptor antibodies and the pathogenesis of Graves' disease (GD). The mechanism underlying the functioning status of thyroid stimulating antibodies (TSAb) and antibodies that block TSH action (TBAb) is still unclear. Clinical case. A-54-year-old woman was admitted to the hospital with manifest hyperthyroidism. She was diagnosed with GD. She had no ophthalmopathy similar to GD and had high titer of plasma TSH receptor antibodies (30,34 ED/L (0—1,0). The following characteristics of spontaneous chemiluminescent (CL) and zymosan-induced (ZiCL) activity of blood neutrophilic granulocytes (BNG) was studied: time to maximum (Tmax), maximum intensity value (Imax), reflecting the maximum reactive oxygen species (ROS) level synthesis, area under the curve (S), describing total ROS synthesis. In our patient we observed the increased Imax during luminol-dependent spontaneous- and Zi-CL. Index S changed depending on the kinetics of CL: from low index during luminol-dependent spontaneous to high S level in luminol- and lucigenin-dependent ZiCL. In her thyroid ultrasonography there were the alternation of hypoechoic and increased echogenicity areas, the volume of the gland were 31.03 ml. Color flow Doppler imaging showed typical findings of GD. Antithyroid drugs therapy were initiated in total daily dose of thiamazol 30 mg. Under additional beta-blockade the patient's condition significantly improved. After 3 weeks antithyroid treatment the clinical features and hormonal control of thyroid status demonstrated hypothyroidism, TSH – 37,96 mIU/ml (0.2—3.2), fT4 — 5.9 pmol/L (9.0—22.0). The block and replaced scheme was performed. We measured that the kinetics of BNG CL was varied with thyroid status and accompanied by increased of Imax in luminol-dependent spontaneous- and Zi—CL. Variability of S in luminol-dependent spontaneous CL markedly depressed, suggesting an immunosuppressive effect of the antithyroid drugs, and, than, increased only during lucigenin-dependent ZiCL. In contrast with manifest thyrotoxicosis, the hypothyroidism under antithyroid treatment of our patient entailed by high index T during luminol-dependent spontaneous and lucigenin Zi—CL. Sequentially after reversion euthyroid state and 2 weeks before radioiodine therapy (RIT) all medications were discontinued and given as treatment a fixed dose of 500 MBq radioiodine. Patient became hypothyroid at the 12 day post RIT and was maintained on 100 mcg of levothyroxine daily. **Conclusion.** This case demonstrates that both, the hyperthyroid state and antithyroid drugs mediated immunity upon BNG activity, release assay for ROS cytotoxicity. This phenomenon implies that pathogenesis of GD might be associated not only with self-limited changing TSAb or TBAb antibodies, but, also, the antithyroid drugs immunosuppressive exerted effects upon the BNG activity should be considered.

KEYWORDS: Graves' disease, antithyroid treatment, autoimmunity.

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EFFECT OF SUPPRESSION OF PUBERTY AND CROSS-SEX HORMONE THERAPY ON BONE TURNOVER MARKERS AND BMAD IN TRANSGENDER ADOLESCENTS

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Background. Puberty is highly important for the accumulation of bone mass. Bone turnover and bone mineral density can be affected in transgender adolescents when puberty is suppressed by gonadotropin-releasing hormone analogues (GnRHa), followed by treatment with cross-sex hormone therapy (CSHT). **Objective**. To investigate the effect of GnRHa and CSHT on bone turnover markers (BTMs) and bone mineral apparent density (BMAD) in transgender adolescents. **Material and methods.** Thirty four female-to-males (FtMs) and 22 male-to-females (MtFs) were divided into a young and old pubertal group, based on the bone age of 14 years in the FtMs and 15 years in the MtFs. All patients received GnRHa triptorelin. CSHT was prescribed in incremental doses from the age of 16 years. FtMs received testosterone ester mixture and MtFs were treated with 17-β estradiol. BTMs P1NP, osteocalcin and ICTP and the BMD of lumbar spine (LS) and femoral neck (FN) were measured at three time points. Furthermore, BMAD and Z-scores were calculated. **Results.** P1NP and 1CTP decreased during GnRHa treatment, indicating decreased bone turnover. Osteocalcin showed an aberrant pattern. A low BMAD Z-score of both FN and LS was observed in the MtFs at start of GnRHa treatment. The decrease in bone turnover upon GnRHa treatment was accompanied by an unchanged BMAD of both FN and LS, however BMAD Z-scores of predominantly the LS decreased. Twenty-four months after CSHT the BTMs P1NP and ICTP were even more decreased. During CSHT BMAD Z-scores increased and returned towards normal, especially of the LS. **Conclusion.** Suppressing puberty by GnRHa leads to a decrease of BTMs in transgender adolescents. The increase of BMAD and BMAD Z-scores predominantly in the LS as a result of treatment with CSHT

is accompanied by decreasing BTM concentrations after 24 months of CSHT. Therefore, the added value of evaluating BTMs seems to be limited and DEXA-scans remain important in follow-up of transgender adolescents.

KEYWORDS: transgender adolescents, gonadotropin-releasing hormone analogues, bone mineral density.

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DIFFERENT FORMS OF CONGENITAL ADRENAL HYPERPLASIA IN TWO SIBLINGS IN A FAMILY: A CASE REPORT

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Introduction. CAH — is a group of diseases with autosomal recessive type of inheritance. 21-hydroxylase deficiency is responsible for 95% of all cases of CAH. Depending on the severity of 21-hydroxylase deficiency the disease is divided into three forms: salt wasting, simple virile, and nonclassic. If both parents are known to be heterozygous carriers of pathogenic genes, each sib has only 25% chance of being affected. **Clinical case.** A 7-day-old female girl was referred to our hospital with ambiguous genitalia. According to the medical history, she was born at term to a 28-year old healthy mother from her second gestation with a spontaneous delivery without any complications. Birth weight was 3290 g. Genital examination revealed clitoromegaly, single urogenital onfice, posterior labial fusion. Karyotype analysis showed normal female karyotype 46XX. Biochemistry revealed hyponatriemia (Na 131 mmol/l), hyperpotassemia: (K 6,55 mmol/l). Blood hormone analysis showed increased levels of 17-hydroxyprogesterone (811 ng/mL) and dehydroepiandrosterone (989,8 mcmol/l), hypocortisolemia (69,6 nmol/l).These results suggested a salt wasting form of CAH. In the gene analysis of CYP21 heterozygous mutations IVS2-13A/C>G and 30-kb deletion were detected.Replacement treatment, including hydrocortisone at the dose of 41 mg/m^2/day and fludrocortisone at the dose of 0,15 mg/day was initiated. The dose of hydrocortisone was gradually decreased to 24 mg/m^2/day. On the therapy the child showed positive dynamics of electrolytes levels, the general status was compensated. Weight at the age of 37 days was 4060 g (meant weight 4090 g.).During collection of the family history the baby's mother marked special features of her older son. By the time of sister's birth the boy was 2 years 8 months old. The parents reported high velocity of growth since birth and acne after 2 years of age. Laboratory investigation showed high level of 17-hydroxyprogesterone (299,8 ng/l) and testosterone (12,6 nmol/l). The boy was admitted to the hospital. Physical examination revealed acne on the face and upper back, penile enlargement, pigmentation of the scrotum, though both testis were prepubertal in size. Height was 106 cm (> 97th percentile). Bone age was 6 years 10 months. His predicted height (159 cm) was significantly lower than genetic one (177 cm). Levels of blood electrolytes were normal. A diagnosis of virile form of CAH was considered. Hydrocortisone treatment at the dose of 13,3 mg/m^2/day was initiated. The boy showed a compound heterozygous mutation (IVS2-13 A/C>G and 30-kb deletion). **Conclusion.** Although the sibs had similar mutations, they exhibited different phenotypes. According to the literature, presence of IVS-2 mutation may determine both salt wasting and simple virile forms. It might result from the variable splicing of this mutation due to variation in RNA splicing factors.

KEYWORDS: congenital adrenal hyperplasia, 17-hydroxyprogesterone, hydrocortisone treatment.

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INDICATORS OF RESPIRATORY MITOCHONDRIAL FUNCTION IN DIABETES MELLITUS

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Changes in the level of mitochondrial dehydrogenases in the respiratory cells in patients with diabetes mellitus had been found in the earlier studies. However, the diagnostic criteria for verification of energy disturbances in the respiratory system in subjects with type 1 diabetes are not established. **The aim** of the study was to perform the cytochemical analysis of mitochondrial function in patients with diabetes. A total of 116 Caucasian subjects were recruited and studied: 57 person with type 1 diabetes, aged 54.2±1.3 years and 59 participants without diabetes, aged 47.8±3.5 years. Those with the history of respiratory disease and smoking history were specifically excluded. Cytochemical analysis was performed by analyzing the activity of succinate dehydrogenase (SDH) and lactate dehydrogenase (LDH) using computer morphometry. The substrate for the study was the bronchoalveolar secret. The viability of epithelial cells and alveolar macrophages of the bronchi was significantly decreased in patients with type 1 diabetes compared to control group — 49.6±1.5% and 73.2±2.8% vs 57.6±1.9% and 85.3±2.7%, respectively ($p<0.001$). Phagocytic number and phagocytic index was also decreased in those with type 1 diabetes compared to controls — 39.4±1.7% and 7.1±0.4% vs 48.8±1.3% and 8.7±0.3%, respectively ($p<0.05$). The levels of mitochondrial activity SDH and LDH in patients with type 1 diabetes were 12.4±0.9 and 11.5±0.9 standard units and in the control group — 19.8±0.7 and 23.6±1.1 standard units ($p<0,01$). In subjects with diabetes it was the negative correlation between the activity of SDH and LDH of the cellular elements of the respiratory system and hyperglycemia and of index endobronchitis activity, with $r = -0.39$ ($p=0.003$) and $r=-0.29$ ($p=0.03$) and $r=-0.53$ ($p=0.02$) and $r = -0.39$ ($p=0.01$), respectively. We can speculate that the level of dehydrogenase activity may serve as a diagnos-

tic marker of the functional state of mitochondria and their disturbances for the evaluation of respiratory system in patients with type 1 diabetes mellitus.

KEYWORDS: diabetes mellitus, mitochondrial function.

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EFFICIENCY OF THE CRITERION OF NEONATAL THYROID-STIMULATING HORMONE IN MONITORING OF IODINE DEFICIENCY IN THE ENDEMIC TERRITORY

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Aim. To evaluate the effectiveness of using the criterion of neonatal hyperthyrotropinemia in monitoring of iodine deficiency in an endemic area. **Material and methods.** The analysis of thyrotropic hormone (TSH) indices in the whole blood of newborns was performed, determined within screening for congenital hypothyroidism in the Tyumen region for the period from 1994 to 2015. The study of neonatal TTG was performed based on the Tyumen regional perinatal center by the method of bilateral fluorometric linked immune ferment assay. Results of medical and biological monitoring during this period were used to establish the correlation: the frequency of iodine deficiency goiter among prepubertal children. Statistical processing of the material was done using the Statistica software package («StatSoft.Inc.», USA, 8.0). **Results.** In 1994, the World Health Organization (WHO) included the level of neonatal hyperthyrotropinemia above 5 mU/l, in the list of criteria for severity of iodine deficiency (ID) in the territory. According to WHO recommendations, for regions with a safe iodine supply, this indicator is determined in no more than 3% of newborns. The level of neonatal hyperthyrotropinemia above 5 mU/l in 2015 is defined in 5.3% of newborns (n=1253), which characterizes the Tyumen region as a territory with a slight iodine deficiency. During the implementation of the iodine deficiency prevention programs in the region, significant improvements were achieved in the 20-years period — the frequency of goiter among schoolchildren in the Tyumen region decreased from 87% in 1995 to 6.8% in 2016 ($p<0.001$). The incidence of neonatal TSH> 5 mU/l decreased from 44.7% in 1995 to 5.3% in 2015 ($p<0.001$). A highly positive statistically significant association was revealed between the neonatal TSH> 5 mU/l and the frequency of iodine deficiency goiter in prepubertal children group ($r = 0.94$, $p<0.05$), which indicates the effectiveness of neonatal hyperthyrotropinemia as a monitoring criterion for ID, which has a number of advantages comparing to other criteria of ID: at first, screening for congenital hypothyroidism covers all newborns, and secondly, the use of neonatal TSH data, determined within program, does not require additional financial costs. Thus, frequency of neonatal hyperthyrotropinemia criterion can be used both to evaluate the severity of ID in the region, and as a criterion for monitoring of the preventive programs implementation in endemic areas.

KEYWORDS: iodine deficiency, thyrotropic hormone.

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FEATURES OF DISTAL FOREARM FRACTURE IN PERSONS 50 YEARS OLD AND OLDER

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Objective. To identify the prevalent fracture risk factors in the group of persons 50 years and older. Assess their impact on BMD in patients with a distal forearm fracture (DFF-fracture of the radius) over 50 years at low injury. **Material and methods.** A comparative study among patients with DFF in the age group 50 years and older. Study based on medical records of city hospital traum depatment. Analised period 2009—2012. All patients underwent R-densitometry on the unit DTX-200, provided by Nicomed Takeda in the framework of the program «Russian Osteoscreening». **Results.** Hospital records of patients 50 years and older who suffered from low-energy fracture of the distal forearm were analyzed retrospectively for the period of 2009—2012. 791 patients were interviewed using standardized questionnaires «Osteoscreening Russia». According to the survey the metabolic syndrome (MS) diagnosed in 70.8% (560 persons). It included type 2 diabetes mellitus (T2DM) —14.8% (117 persons), prediabetes — 22.9% (181 people) — (Impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)), obesity (33.1%) — an isolated cohort of patients with overweight and obesity without disrupting glycemic indices. All patients had DFF that occurred at a low injury. Among the investigated cohort of patients with highnormal bone mineral density (BMD above — 1.0 standard deviation (SD) we revealed 66.0% of patients with MS; 64.1% — with obesity; 65.4% — with the presence of pre-diabetes; 65.3% — with a history of type 2 diabetes. BMD — 1,0—2,5 SD: 20.6% with MS; obesity, 20.2%; prediabetes, 19.7%; type 2 diabetes —19.5%; BMD below 2.5 standard deviations (SD): MS at 13.5%; obesity, 15.7%; prediabetes, 14.7%; Type 2 DM —15.3%. Patients with low-energy DFF with a history of metabolic syndrome differed from the group of patients without this disease by its high and highnormal % normal BMD. Almost $^2/_3$ (70.8%) of patients with metabolic syndrome have normal BMD. **Conclusion.** The prevalence of low BMD in patients of investigated groups has not been established. Proposed mechanism of fracture is focused not on the performance of T-score (BMD) but the bone quality due to changes caused by abnormality of bone metabolism. Suppression of medullary osteoblastogenesis by adipocytes of bone marrow and stimulation of

proinflammatory cytokines synthesis leads to increased bone fragility without decreasing BMD.

KEYWORDS: fracture risk, osteoporosis.

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TRANSFORMATION OF PROLACTINOMA INTO CORTICOTROPIN-SECRETING ADENOMA IN PATIENT WITH MEN 1 SYNDROME: A CASE REPORT

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Multiple endocrine neoplasia syndrome type 1 (MEN 1 type, Wermer's syndrome) is a group of heterogeneous inherited diseases, pathogenesis of which is based on hyperplasia or neoplasia of several endocrine glands, characterized by autosomal dominant mode of inheritance, high penetrance and similar prevalence among males and females. Prevalence of MEN 1 is estimated as 2—10 people per 100,000 of population. The patient turned to the doctor for the first time at the age of 20 with her primary amenorrhea. Examination revealed pituitary adenoma with pronounced secretion of prolactin (11,370 IU/L). She underwent transspenoidal adenomectomy, followed by drug treatment with dopamine agonists which normalized prolactin level, and restored menstrual function. At the age of 31 the acute gastrointestinal bleeding was the reason for further investigations and subsequent surgery. There were found gastrin-secreting tumor of the pancreatic gland and small tumors in the spleen area, as well as carcinoid in the mesentery area. At the age of 39 primary hyperparathyroidism (hypercalcemia, osteoporosis, high PTH level and parathyroid adenoma) was diagnosed. Parathyroidectomy was performed. Genetic analysis has revealed nonsense mutation Y77X in the Gene *Menin* in that patient and in her brother, thus MEN 1 type was confirmed. Nodular hyperplasia of both adrenals was visualized on CT. Disturbance of adrenocorticotrophic hormone secretion (in the morning 27 pg/mL, in the evening 33, 8 pg/mL) and cortisol secretion (in the morning 581 nmol/L, in the evening 338 nmol/L), high urinary free cortisol to 2,178 nmol/day, no suppression of cortisol secretion by 1 mg of dexamethasone were measured, and at the same time no clinical symptoms were detected. Cushing's disease was confirmed by inferior petrosal sinus sampling and functional tests. Pituitary surgery was not performed due to the absence of clinical manifestations of hypercortisolism. For the next 7 years active hypercortisolism was persisting, however clinical features appeared only last year. The patient underwent neurosurgical intervention in March 2017, remission of hypercortisolism was achieved. The clinical case may be called unique due the following reasons: multiple lesions of endocrine organs, of gastrointestinal tract; absolute synchronism of tumor development in various organs similar to those observed in her brother except hypercortisolism, as well as transformation of tumorigenesis in pituitary from prolactin-secreting tumor to ACTH-secreting tumor.

KEYWORDS: MEN 1 type; Wermer's syndrome; pituitary tumor; gene analysis.

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MOBILE APP ELECTRONIC DIARY IMPROVES THE MOTIVATION IN PATIENTS WITH GESTATIONAL DIABETES

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Introduction. In the course of gestational diabetes (GDM) treatment, it is significantly important to keep track on records in a personal diary, which helps physicians and patients to understand the problems appearing during blood glucose (BG) compensation. At the same time, the lack of motivation can lead patients to stop making records and exchanging them with their doctor. In our study we analyzed, how the electronic diary app can improve the motivation of patients in comparison with traditional means of perceiving data on blood glucose. **The aim** of the study is to improve the motivation in gestational diabetes patients by providing them with helpful tools to keep track on their records. **Material and methods.** Android and desktop application DiaCompanion was developed and given to a group of patients with diagnosed GDM. Another group of GDM patients received a traditional diary via Excel spreadsheet. Patients from both groups were asked to fill the diaries with the data on BG levels, insulin injections (when prescribed) and, if possible, food intakes, physical activity, sleep and ketones (when prescribed). **Results.** By the middle of march 2017, a total of 179 patients with GDM received an application DiaCompanion and 36 patients recorded their BG levels via Excel spreadsheet. A total of 24914 and 4247 BG records were analyzed correspondingly. A significant difference was shown in the amount of women quitting keeping records (6.0% vs 19.4% patients with less than 2 weeks of reports, p=0.029) and the average number of days with records (53.0 days against 40.2 days, p=0.006). Considerable amount of patients used an app to track additional records, while patients with traditional diary rarely reported any (98.6% against 44.4% reported food intakes (p=9.97·e-8), 59.6% vs 22.2% reported physical activity (p=6.64·e-6), 37.2% vs 5.6% sleep (p=6.37·e-9) and 21.6% vs 11.1% ketones (p=0.044) correspondingly). Average fasting BG levels during the whole course of monitoring were lower in women who used the app (4.88 vs 5.01 correspondingly, p=0.048), while postprandial BG values didn't show significant dif-

ference (6.27 vs 6.30 correspondingly, p=0.374). **Conclusion.** The use of the application helped to increase the length of monitoring period, the amount of data that patients perceived in the diary and improved glycemic control. This can be due to an increased motivation to keep records and to a reduction of burden associated with traditional diaries. More detailed analysis on achieving BG goals and delivery outcomes will be held in further studies.

KEYWORDS: gestational diabetes, mobile app.

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EFFECT OF FAMILY INTERVENTION TO CONTROL TYPE 2 DIABETES IN YOUNG: A CONTROLLED CLINICAL TRIAL

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Introduction. With the increasing number of young type 2 diabetes mellitus (T2DM) patients in India, it has become a great challenge for clinicians to achieve strict glycemic control and prevent complications in this population of patients. We studied the effectiveness of a family oriented intervention designed to improve glycemic control of these patients in a specialised diabetes clinic. There are very few studies have ever been done on this aspect on type 2DM. **Aim.** Our aim of this study was to see the effect of family intervention in these patients on glycemic control as reduction of HbA_{1c} to ⩽6.5 % over and above standard care. **Material and methods**. Young (18—25 years) newly diagnosed ,drug naïve T2DM patients from our clinic were selected for the study as per patient'. Patients were selected with type 2DM with HbA_{1c} between >7% to < 9% and living with at-least one family member(not alone). One group (A) of patients received the family oriented intervention; patients from the other group (B) received standard care. The intervention involved family members which included one amongst "father ,mother, wife or husband " and included family counselling during clinic visits, family meetings and home visits by a dedicated diabetes educator . The primary outcome was HbA_{1c}, measured at 6 and 12 months. **Result**. A total of 205 patients were enrolled and they were divided into group A (n=103) and group B (n=102). All patients completed the study. The HbA_{1c} from baseline to 12 months was a significantly different between groups (p<0.005). During the later period (6—12 months), when the patients in the group A showed further improvement in their HbA_{1c} reduction (p<0.001) compared to Group B patients. **Conlcusions.** In T2DM in young patients a significant reduction in HbA1c was seen when the family intervention was provided over standard intervention.

KEYWORDS: young type 2 diabetes mellitus, diabetes clinic, family intervention.

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ASSOCIATIONS OF THE POLYMORPHISMS KCNJ11, ADIPOQ, ADIPOR2, IGF1B2 OF THE GENES WITH INSULIN RESISTANCE AND FUNCTIONAL ACTIVITY OF PANCREATIC B-CELLS IN WOMEN WITH METABOLIC SYNDROME

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Purpose. To evaluate the association of alleles and genotypes of the polymorphisms KCNJ11 ADIPOQ, ADIPOR2, IGFBP2 genes with insulin resistance and functional activity of pancreatic β-cells in women with metabolic syndrome. **Material and methods.** A survey of women in the Russian population with obesity and metabolic syndrome. Insulin resistance (IR) and functional activity of pancreatic β-cells were determined using the HOMA-IR ⩾2.77 and HOMA-β ⩾180% indices (D. Matthews et al., 1985). The polymorphisms of the genes candidate for IR and insulinopenia were determined: rs16928751 of the *ADIPOR2* gene, rs2241766 of the *ADIPOQ* gene, rs5219 of the *KCNJ11* gene, rs4402960 of the *IGFBP2* gene. Genotyping of the polymorphisms of candidate genes of IR and insulinopenia was carried out on the basis of the Laboratory of Molecular Diagnostics and Genomic Dactyloscopy of the State Scientific Center of the Russian Federation «GosNIIGenetika», Moscow (Doctor of Biological Sciences, professor V.V. Nosikov). **Results.** Higher values of the HOMA-IR index [6.3 (3.6, 10.8)] in women with the Lys/Lys genotype of the polymorphism rs5219 of the *KCNJ11* gene were determined than in the carriers of the genotypes Glu/Glu and Glu/Lys 3,8 (2,2, 7,0) and 3,6 (2,3, 5,6) (p<0,01). It was established that HOMA-β index ⩾180% is more often detected in carriers of genotypes G/A + A/A (34.2%) than in persons with genotype G / G of the polymorphism rs16928751 of the *ADIPOR2* gene (18.8%) (p=0.04). The homozygous carrier of the T/T genotype of the polymorphism rs2241766 of the *ADIPOQ* gene was more often detected in obese and MS patients (94.3%) than in healthy individuals (72.1%)) (p=0.009). In women with obesity and IR, the carrier of the T allele and the T/T genotype of the polymorphism rs2241766 of the *ADIPOQ* gene increases (OR=3.21 95% CI 1.01—10.24; p<0.05 and OR=6.39 95% CI 1.32—30.86; p=0.009), and the carriage of the G allele and the G/T genotype of rs2241766 of the *ADIPOQ* gene reduces the risk of developing IR (OR=0.31 95% CI 0.10—0.99; p<0.05 and OR=0.04 95% CI 0.1—0.80; p=0.009). Carriers of the T/T genotype of the polymorphism rs4402960 of the *IGF1B2* gene had a higher HOMA-IR index, along with a low HOMA-β index of 7.0 (5.9; 8.9) and 59.1% (37.7; 153.8%) than individuals with genotypes G/G and G/T [3.9 (2.3, 7.4), 105.3 (53.1, 157.50 and 3.4 (2,2; 4.9), 121.3 (76.3, 170.9; p<0.05)]. **Conclusions.** These data suggest that the relationship between insulin resistance and the functional activity of β-cells of the pancreas of the polymorphisms rs5219 KCNJ11, rs2241766 *ADIPOQ*, rs4402960 *IGF1B2*,

rs16928751 *ADIPOR2* genes in women of the Russian population.

KEYWORDS: obesity, metabolic syndrome, genotypes of the polymorphisms.

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FERTILITY RESTORATION IN A PATIENT WITH RESISTANT PROLACTINOMA AFTER COMPLEX THERAPY OF DOPAMINE AGONIST AND SELECTIVE ESTROGEN RECEPTOR MODULATOR

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Introduction. Prolactinomas are the most common pituitary adenomas and dopamine agonists (DA) still remain the first choice of treatment. Nevertheless it does not always exert an adequate effect and endocrinologists face the challenge of resistant prolactinomas more frequently. This problem is very important for women of reproductive ages who desire to recover fertility. We present a clinical case of a woman with DA resistant prolactinoma and primary amenorrhea who had recovered regular menstrual cycle and ovulation after one year of combination treatment with cabergoline and tamoxifen. **Clinical case.** In 2002 a 12-year old woman was referred to our tertiary care center with hyperprolactinemia (prolactin (PRL) level 5000 IU/l (90—540), no macroprolactinemia) and macroprolactinoma 10×18×10 mm by MRI. Administration of cabergoline with maximum dose 3.5 mg a week did not result in significant clinical or laboratory improvement. In 2004 transnasal transsphenoidal adenomectomy was performed. Postoperative prolactin levels remained high. For short period the patient received injections of octreotide without effect. In 2006 the repeat operation was conducted because of additional tumor tissue of 8×7×10 mm on MRI. After surgery PRL decreased to 3000 IU/l, cabergoline therapy was restarted in dose 1 mg per week with gradually increasing up to 4.5 mg that allowed to stabilize tumor growth, but without recovery of menstrual cycle. During examination in 2015 PRL level was 6000 IU/l, endoparasellar adenoma visualized on MRI and hypoplasia of the uterus with the lineal endometrium were detected. As an antitumor agent, the patient was assigned a treatment with selective estrogen receptors modulator (SERM) tamoxifen — in a dose 20 mg per day in combination with cabergoline in a dose 4.5 mg per week. After one year of such therapy the prolactin was 15000 IU/l, adenoma's MR-characteristics didn't reveal any negative trend. At the same time the patient noted that menstrual function restored in 3 months after starting tamoxifen. Ultrasound examination confirmed normal uterus size and adequate endometrial thickness; also, the left ovary contained corpus luteum. The therapy was prolonged with recommendations of careful ultrasound control of endometrium state and barrier contraception. **Conclusion.** This case demonstrates reversion of symptoms of hyperprolactinemic hypogonadism in a patient with DA resistant prolactinoma due to SERM treatment without prolactin level normalization. The pathophysiological mechanisms underlying the phenomenon are not clear but may be due to the changers in interactions of kisspeptin neurons involved in GnRH secretion due to modulation of negative and positive estrogen feedback.

KEYWORDS: hyperprolactinemia, plolactinoma, tamoxifen, cabergoline.

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EPIGENETIC ASPECTS OF BONE METABOLISM REGULATION IN PATIENTS WITH ENDOGENOUS HYPERCORTISOLISM

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Objective. To investigate mRNA and microRNA related to bone of remodeling in bone tissue samples from patients with Cushing's disease (CD). **Material and methods.** Patients with clinically evident and biochemically proven active CD and patients with hormonally inactive pituitary adenoma matched by age, sex and BMI were invited to participate. Bone samples were taken during transsphenoidal adenomectomy from the base of the sella-turcica, immediately placed in lysis buffer (QIAzol) and subjected to homogenization. 24h urine free cortisol (24hUFC) was measured by an immunochemiluminescence assay on a VitrosECi (60-413 nmol/24 h). Total RNA isolation from bone tissue with on-column digestion of the genomic DNA was carried out with miRNeasy Mini Kit on the automatic station «QIAcube». Reverse transcription was carried out using a High-Capacity RNA-to-cDNA Kit. Gene expression analysis was performed by Real-Time PCR on StepOnePlus instrument with Custom TaqMan Array 48 Plus plates. MicroRNA expression analysis was carried out by TaqMan Advanced miRNA Assays. **Results.** We enrolled 24 subjects (15 patients with CD and 9 with hormonally inactive pituitary adenomas); 18 females and 6 males, the mean age was 41 years (confident interval (CI) 95% 36—46) mean BMI — 29 (CI 95% 26—32) kg/m^2. There were no significant difference between the groups. Mean 24h UFC in subjects with CS — 1168 (CI 95% 702—1634) nmol/24h. Expression of osteoblast activity and bone formation genes was decreased in patients with CD: ALPL 0.34 (CI 95% 0.24—0.43; p<0.001), BGLAP 0.41 (CI 95% 0.28—0.54; p<0.001), COL1A1 0.26 (CI 95% 0.14—0.37; p<0.001), COL1A2 0.51 (CI 95% 0.33—0.69; p<0.001), MMP2 0.52 (CI 95% 0.41—0.62; p<0.001). The expression of SOST 5.3 (CI 95% 1.8—8.8; p<0.001), WNT10B 10.24 (CI 95% 5.26—15.22; p<0.001), WNT3A 1.44 (CI 95%

0.3—2.57; p=0.016), CD40 3.5 (CI 95% 3.13—3.91; p<0.001), BMP7 2.03 (CI 95% 1.22—2.83; p<0.001) was increased in subjects with hypercortisolism as compared to inactive pituitary adenoma. An increase in the expression of microRNA 133a-3p 1,74 (CI 95% 0.14—3.34; p=0,037), that stimulate osteoclastogenesis, and microRNA 204-5p 0,54 (CI 95% 0.06—1.02; p=0.031), that block the differentiation of osteoblasts was found. **Conclusion.** Suppression of osteoblastogenesis in patients with endogenous hypercortisolism is explained by an increase in the expression of the SOST, which codes the main inhibitor of the Wnt signaling pathway — sclerostin. Reduction of osteoblast differentiation is also realized through increased expression of 133a-3p microRNA and 204-5p microRNA.

KEYWORDS: microRNA, osteoblastogenesis, hypercortisolism.

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MCCUNE-ALBRIGHT SYNDROME (MAS): CLINICAL CASE

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Introduction. McCune-Albright syndrome (MAS) — a systemic disease associated with a mutation in the gene GNAS1, responsible for the activation of a G protein subunit (Gsa), is characterized by symptoms: fibrocystic dysplasia, skin pigmentation, precocious puberty. **Clinical case.** A 29 — y. o. male patient during past 12 years noted a gradual change in his appearance. Began to seek a medical attention only 3.5 years ago due to reduced vision. Hormonal tests revealed marked elevation of GH to 106 (<20 mIU/ln), and IGF-1 to 567 (121—336 ng/ml), decrease in testosterone levels to 1.91 (3-12 ng/ml), other gormons within the reference range. MRI of the brain showed a 4×7 mm adenoma of the anterior part of the pituitary. CT brain scan with contrast described poliostic dysplasia of the skull bones. Octreotide depot injections therapy was initiated 20 mg/28 d. Than levels of GH and IGF-1 were still high in spite of medical treatment — 119 (<20 mIU/ln) and 1033 (121—336 ng/ml), respectively. At the age of 27 years the patient was 205 cm tall (BMI 29.5 kg/m^2) at admission to Endocrinology Research Centre. His facial features were acromegaloid with sloped towered skull. "Café au lait" pigmentation of the skin was noted at the chest, back, and abdomen. Lab tests confirmed the presence of the active acromegaly (GH — 117 (< 20 mIU/ln), IGF-1 — 1412 (121—336 ng/ml)). Brain MRI with contrast showed a marked increase in the size of previously described adenoma 17×23×14 mm, and progression of the fibrous dysplasia (predominantly hypointense on T1) of the skull base, parietal, temporal bones, scales of the frontal and occipital bones, hypopneuma-tization of frontal sinus and ethmoidal labyrinth, narrowing of the internal and the external auditory canals on the left. All these symptoms allowed us to suspect the MAS. The progressive clinical course of the disease, insensitivity to octreoride treatment was the basis for the choice of further surgical treatment despite the pronounced fibrous dysplasia of the skull base. Then the patient underwent endoscopic endonasal removal of tumor using navigation BrainLab at Burdenko Neurosurgical Research Institute. Postoperatively levels of GH and IGF-1 decreased to - 27 (<20 mIU/ln) and 856 (121—336 ng/ml), visual function had improved markedly. He was then followed on depo octreotide injections 30 mg/28d and cabergoline 2 mg/w with later dose adjustments. The high-performance parallel sequencing was implemented with the gene panel (*MEN1, CDKN1B, PRKAR1A, GNAS, AIP, SDHA, SDHB, SDHC, SDHD, PRKCA, CDKN2C, CDKN2A, POU1F1, PTTG2*). **Conclusions.** The treatment of acromegaly in the setting of the MAS is characterized by multiple challenges that require the participation of a team of experienced endocrinologists and neurosurgeons. This patient with the MAS was identified heterozygous p.S163P replacement in *SDHB* gene.

KEYWORDS: McCune-Albright syndrome, acromegaly, parallel sequencing, pituitary adenomas.

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OBESITY PARADOX: CARDIOVASCULAR COMPLICATIONS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND OBESITY

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Introduction. Obesity and type 2 diabetes mellitus (T2DM) are commonly associated with cardiovascular complications. At the same time, obesity paradoxes are not new to the field of cardiovascular disease and have been observed in heart failure, acute coronary syndromes, and chronic kidney disease. **Clinical cases.** Two patients (both non-smoking men) comparable for age (48—50 years), BMI (32.1—34.4 kg/m^2) glycated hemoglobin (HbA_{1c}) (6.0—6.3%), hypoglycemic therapy (Sulfonylureas with Metformin) and diabetes duration (3—5 years) were treated in Endocrinology Research Centre during 2016 year. There was no significant differences in routine laboratory tests (total cholesterol, low-density cholesterol, high-density cholesterol, triglycerides, fasting glucose, microalbuminuria). First patient (50 years old, BMI 32.1 kg/m^2) had several cardiovascular complications at the time of hospitalization: including Myocardial infarction, coronary angiography revealed multi-vascular atherosclerotic lesion of coronary vessels (left anterior descending coronary artery, right coronary artery and circumflex artery were stenosed up to 90%) and athero-

sclerosis of lower limb arteries (up to 40%). There was no option for endovascular treatment for the patient, so he was recommended coronary artery bypass grafting. Leading cause of hospitalization was the presence of an ulcerative defect of the posterior surface of left tibia associated with neuropathic form of diabetic foot. Second patient (48 years old, BMI 34.1 kg/m^2) had no clinical and instrumental sings for the coronary artery disease (excluded after Tredmil-Test) or any other complications of T2DM. **Conclusion.** Patients with obesity need personalized strategy for management and treatment. Further studies are needed to evaluate novel markers for cardiovascular disease development in this group of patients. Promising can be the determination of the expression of cardiovascular associated microRNA and several growth factors.

KEYWORDS: microRNA, obesity, diabetes.

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MODY 3 AND PREGNANCY: COURSE AND TREATMENT

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Introduction. Diabetes caused by mutations in the HNF1-alpha gene (encoding hepatocyte nuclear factor-1 alpha) is one of the most common types of MODY. This gene contains is a blueprint for a transcription factor that is important in for the normal development of beta cells. MODY 3 is typically diagnosed before 30 years of age and is often misdiagnosed as Type 1 diabetes mellitus. MODY 3 usually manifests with symptoms associated with high blood sugars. These include increased frequency of urination (polyuria), increased thirst (polydipsia), and weight loss. Mutations can occur spontaneously but usually are passed on from a parent to a child. If a parent has MODY 3 there is a 50% chance that a child will inherit the mutation and be at risk of developing diabetes at a young age. Distinguishing MODY 3 from Type 1 diabetes can be difficult. In this case, we presents a woman with MODY 3 and pregnancy. **Clinical case**. A 44-year-old female patient diagnosed with MODY 3 Diabetes, during the first pregnancy, Ten years ago (GEN HNF_1A) mutation c.511 C> T (p.Arg171X.Treatment initial was insulin aspart 30 units day, after gestation received during 8 years glyclazide 30 mg daily. Second gestation was a year ago, treated with insulin lispro 14 units day. In both gestations there was hypertension treated with Trandate. In both gestations the delivery was cesarean due to fetal distress. Both deliveries were male, and the APGAR at 5 minutes was 10. No congenital anomaly was detected in any of the offspring. 8 months ago presented hypothyroidism due to Hashimoto's disease treated with 50 micrograms of levothyroxine. The patient's current state is stable. **Conclusion.** Monogenic diabetes is frequently mistakenly diagnosed as either type 1 or type 2 diabetes, yet accounts for approximately 1—2% of diabetes. Identifying monogenic forms of diabetes has practical implications for specific therapy, screening of family members and genetic counselling. The most common forms of monogenic diabetes are due to glucokinase (GCK), hepatocyte nuclear factor (HNF)-1A and HNF-4A, HNF-1B, m.3243A>G gene defects. In this case it was a MODY 3 diabetes that responded well to the use of Insulin. This knowledge is important for all physicians managing diabetes in pregnancy, given this is a time when previously unrecognised monogenic diabetes may be uncovered with careful attention to atypical features of diabetes misclassified as type 1, type 2, or gestational diabetes.

KEYWORDS: diabetes, HNF1-alpha gene, MODY 3.

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LIPODYSTROPHY SYNDROMES AND ASSOCIATED METABOLIC DISORDERS IN RUSSIAN POPULATION

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Background. Lipodystrophies are heterogeneous disorders characterized by selective loss of body fat, which can be generalized (GL) or partial (PL), inherited or acquired, and usually are associated with different metabolic disorders, like diabetes with marked insulin resistance, dyslipidemia, arterial hypertension, hepatic steatosis and hepatosplenomegaly, and so often remain not diagnosed, especially familial partial lipodystrophy (FPL). GL may be a sign of progeroid syndromes (PS). Genetic diagnostics may be challenging because of many candidate genes and similar phenotypes. There is a lack of information on clinical and molecular-genetic characteristics of lipodystrophy syndromes in Russian population and the condition is usually misdiagnosed. **Objective.** To assess the clinical and molecular-genetic characteristics of lipodystrophies in Russian population. **Material and methods.** 58 patients (45 adults and 13 children) from 51 families with different lipodystrophic fat loss patterns were included in the study: 40 (69%) patients with PL, 12 (20.7%) patients with GL, and 6 (10.3%) patients with PS. Detailed clinical examination and the assessment of metabolic abnormalities was performed. For genetic confirmation of the diagnosis 16 congenital lipodystrophies and progeroid syndromes with lipodystrophies candidate genes (*AGPAT2, BSCL2, CAV1, PTRF, LMNA, PPARG, PLIN1, AKT2, LIPE, LMNB2, POLD1, CIDEC, WRN (RECQL2), PPP1R3A, ZMPSTE24, BANF1*) were sequenced using a Custom Ion Ampliseq panel and PGM semiconductor sequencer (Ion Torrent). **Results.** There were considerable age differences between the groups with GL and PL: mean age

of the GL patients was 20.17±14.78 years, comparing to 36.07±16.13 years in the PL group (p=0.005). The median age of the diagnosis of lipodystrophy also differed significantly in those 2 groups: 2.5 (1; 14.8) years for GL comparing to 15.5 (8.5; 29.5) for PL (p=0.005). 87.5% of PL patients were female, comparing to the 58% in GL and 33% in PS. In the GL group 66.7% of patients had diabetes, 8.3% had pre-diabetes and 16.7% had relatives with diabetes, in the PL group 57.5% of patients had diabetes, 25% had pre-diabetes and 16.7% had relatives with diabetes, and in PS patients 50% had diabetes, 16.7% had pre-diabetes and 33.3% had relatives with diabetes. Mean HbA_{1c} levels were not significantly different in all 3 groups: GL — 7,4% (4,8; 8,2), PL — 6,7% (6,0; 9,2), PS — 5.85% (5.34; 10.03). However, patients with PL demonstrated significantly higher insulin resistance than patients with GL (HOMA-IR index for GL 1.36 (0.72; 6.22), for PL 8.0 (3.7; 18.86; p=0.024). Predictably, patients with GL had significantly lower leptin levels 0.95 (0.58; 2.00 ng/ml than patients with PL 5.2 (1.93; 11.4 ng/ml; p=0.004). Many patients had acanthosis nigricans: 41.7% of GL, 50% of PL, 16.7% of PS. Dyslipidemia was found in 33.3% in GL, 80% of PL and 50% of PS. Arterial hypertension was diagnosed in 57.5% of PL patients and in 16.7% of GL patients. As many as 41.7% of the GL patients had associated autoimmune disorders and there were no mutations in the candidate genes found for them. In 25% of GL patients mutations in *AGPAT2* (n=2) and *BSCL2* (n=1) were found. In PS group there were 3 patients with Werner syndrome in whom *WRN* mutations were found, 1 atypical progeria due to *LMNA* mutation, and in 2 patients no mutations in the studied genes were found: one with atypical Werner syndrome and one with mandibuloacral dysplasia. In 35% of PL patients mutations in the following genes were found: 4 in *LMNA*, 1 in *PPARG*, 1 in *AKT2*, 1 in *LMNB2*. The most common mutation was a heterozygous R482W mutation in the 8 exon (hotspot) of the *LMNA* gene found in 4 families (7 patients) with PL. Genetic variants with the unknown pathogenicity in candidate genes were found in 20% of PL patients and 8.3% of GL patients. **Conclusion.** Lipodystrophy syndromes in Russian population are very heterogeneous and can affect both children and adults. PL is more likely to be diagnosed in female young adults, and GL manifests in childhood. We recommend suspecting the possibility of a lipodystrophy syndrome in young patients with multiple metabolic disorders and the decrease of subcutaneous fat tissue. In case of FPL the search for the genetic cause should start from the 8 exon of *LMNA*. In other cases candidate genes panel is an effective diagnostic tool for differential diagnostics and confirmation of the diagnosis of the different forms of inherited lipodystrophies. When lipodystrophy is associated with autoimmune disorders it is less likely to find a mutation in a candidate gene.

KEYWORDS: lipodystrophy syndromes, *LMNA,* autoimmune disorders, insulin resistance.