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

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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

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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

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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-