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Basic endocrinological disorders in chronic renal failure

Podstawowe zaburzenia endokrynologiczne w przewlekłej niewydolności nerek

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Abstract

The aim of this study was to look at basic endocrinological disorders in chronic kidney disease, acquainting endocrinologists with information about the definition and classification of kidney diseases and basic metabolic disorders in uraemia. Secondary hyperparathyroidism, insulin resistance and hyperinsulinism, growth hormone disorders and the possibility of growth hormone treatment, the reasons for and the consequences of hyperprolactinaemia are presented in a practical way. Thyroid hormones management, a problem which requires further study, is portrayed extensively. Hypothalamic–pituitary–adrenal axis disorders are equally complex and not yet fully examined. We have largely concentrated on the practical aspects of diagnostics of the presented disorders. **(Pol J Endocrinol 2012; 63 (3): 250–257)**

Key words: *renal failure, insulin resistance, growth hormone, hyperprolactinaemia, thyroid hormones, cortisol*

Streszczenie

Autorzy przedstawili podstawowe zaburzenia endokrynologiczne w przewlekłej chorobie nerek, zapoznając endokrynologów z informacjami na temat definicji i klasyfikacji chorób nerek oraz podstawowymi zaburzeniami metabolicznymi w mocznicy. Wtórna nadczynność przytarczyc, insulinooporność i hiperinsulinemia, zaburzenia w zakresie hormonu wzrostu, a także możliwości leczenia hormonem wzrostu oraz przyczyny i konsekwencje hiperprolaktynemii zostały przedstawione w sposób praktyczny. W szerokim zakresie omówiono ponadto hormonalną gospodarkę tarczycową oraz osi podwzgórze–przysadka–nadnercza. Nie wszystkie aspekty są wyjaśnione i wymagają dalszych badań. Autorzy w dużej mierze skoncentrowali się na praktycznych aspektach diagnostyki przedstawianych schorzeń. **(Endokrynol Pol 2012; 63 (3): 250–257)**

Słowa kluczowe: *niewydolność nerek, insulinooporność, hormon wzrostu, hiperprolaktynemia, hormony tarczycy, kortyzol*

Introduction

Chronic kidney disease (CKD) has become a great problem throughout the world. It is connected to increased morbidity and mortality and also to decreased quality of life in patients compared to the general population [1, 2].

The National Kidney Foundation — Kidney Disease Outcomes Quality Initiative (NKF-K/DOQI) defined CKD as the presence of structural and functional symptoms of renal damage for at least three months with or without a glomerular filtration rate (GFR) decrease [1].

The classification of CKD depending on GFR value is:

- stage 1 — normal GFR (above 90 mL/min/1.73 m^2) with persistent microalbumin;
- stage 2 — GFR 60–89 mL/min/1.73 m^2 with persistent microalbumin;
- stage 3 — GFR 30–59 mL/min/1.73 m^2;
- stage 4 — GFR 15–29 mL/min/1.73 m^2;
- stage 5 — GFR below 15 mL/min/1.73 m^2 or end-stage renal disease (ESRD).

Stages 3–5 are defined as chronic renal failure (CRF).

Diabetes, hypertension, chronic glomerulonephritis, and tubulointerstitial diseases are the commonest reasons for CRF. Morbidity and CRF progression rate are higher in the USA than in Europe. Scientists link this fact with the greater obesity and more frequent diabetes and hypertension occurrences in the American population [1–3].

Chronic renal failure complications

The gradual deterioration of renal functions initially proceeds asymptomatically, but in the further stages of CRF, various symptoms and disorders including water-electrolyte balance disorders (volume overload, hyperkalaemia), metabolic acidosis, hypertension, anaemia and hyperphosphataemia with bone disease may be observed. Uraemia symptoms include disorders of the gastrointestinal tract (lack of appetite, nausea, vomiting), circulatory system (pericarditis, muscle overgrowth in left ventricle), nervous system (peripheral

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neuropathy, concentration disorders, coma, brain death) which have no direct connection to the absolute concentration of blood urea nitrogen (BUN) or creatinine.

Volume overload is not a significant problem in the first stages of CKD, but may be dangerous in the CRF period, particularly if a patient does not have residual diuresis. This problem is frequently connected to insufficient sodium removal from the system [4, 5].

Hyperkalaemia develops more frequently in patients with oliguria but may be generated by excessive sodium consumption in a diet or connected to tissue damage or hypoaldosteronism. It is often caused by adhibiting medicines from the ACEI and ARB groups or aldosterone antagonists [4, 6].

Metabolic acidosis occurs more frequently in the last stage of CKD [7, 8]. Acidosis may be one of the important reasons for metabolic disorders increase including endocrine [4].

One of the greatest problems in CKD is hyperphosphataemia connected to a decrease of phosphate clearance and insufficient correction of calcium and phosphate concentrations by PTH. This disorder is considered to be an important reason for cachexia, inflammation and the development of vascular atherosclerosis conducive to acute cardiovascular episodes [9, 10].

Another clinical problem is hypertension, which is present in approximately 85% of patients with chronic kidney disease. Although hypertension treatment (ACEI, ARB, diuretics, beta-blockers) contains the development of CKD, it may alter the activity of metabolic pathways [11].

More than half of patients in stage 4 of CKD have anaemia, many with a haemoglobin level below 10 g/dL [12]. This is the effect of erythropoiesis disorder connected to deficiency of iron and disturbances of erythropoiesis excretion in damaged kidneys, receptor resistance to erythropoiesis, and also decrease of erythrocyte survival in patients with uraemia. Additionally, in the course of renal replacement therapy with the use of extracorporeal methods, a disintegration of corpuscles may be observed, which also intensifies anaemia. Anaemia influences a great number of symptoms and increases disorders connected to chronic kidney disease, particularly an increase of complications in cardiovascular diseases, including mortality [13]. Currently, treatment for anaemia is commenced according to its degree, even in the predialytic period, and continued in the course of renal replacement therapy. In the treatment, erythropoietin preparates are employed, but only after balancing iron administration. Both anaemia and erythropoietin preparates may influence the activity and disorders of physiological pathways [14].

Possibilities of chronic renal failure therapy (dialysis therapy)

A number of kidney diseases inevitably lead to end stage renal failure.

Following a judgement that renal replacement therapy will be necessary, renal replacement therapy education should be started with GFR below 30 mL/min/1.73 m^2 and renal replacement therapy itself with GFR 10 mL/min. The clinical condition of a patient is a decisive factor here. Most patients can be treated with haemodialysis or peritoneal dialysis [15]. Various factors influence the selection of dialysis type, including patient preference, the possibility of ambulatory treatment, and also patient co-operation in peritoneal dialysis treatment. Both methods require several months of preparation. Qualification for kidney transplantation should be considered for every patient. If possible, this is the preferable method. The effectiveness of various dialysis therapy methods is similar, although there are slight differences in survival rates during the first months of treatment in favour of peritoneal dialysis [16].

Endocrinological complications in chronic kidney disease

In patients with CKD, numerous extrarenal complications may be frequently observed. As a result of GFR decrease, metabolic disorders occur leading to increased morbidity and death risk, principally because of cardiovascular disease. Hormonal disorders also occur frequently. The kidneys play a significant part in maintaining homeostasis in an organism. They participate in the excretion of various hormones: cortisol, aldosterone, sex hormones, thyroid gland hormones, catecholamine and in biodegradation of peptide hormones such as parathormone, calcitonin and insulin. In patients with uraemia, impairment of hormone excretion and biodegradation has been observed, as well as disorders affecting excretion, transportation and binding hormones with target cells, frequently as a result of receptor resistance. Renal replacement therapy in the advanced stages of renal failure insignificantly influences the compensation of endocrine disorders [17–19].

PTH and kidneys

All stages of CKD are accompanied by calcium-phosphorus balance disorders, and severe secondary hyperparathyroidism is a frequent complication in advanced CKD and in dialysed patients [20]. Parathormone (PTH) is considered to be a uraemic toxin, and its concentration in serum increases when GFR drops below 50–70 mL/min. Prolonged excess of PTH leads to bone

mass loss and extraskeletal calcifications, primarily in the cardiovascular system [21]. Excessive retention of phosphorus due to its decreased ejection by the kidneys commences in stage 3 of CKD. In this period, active renal parenchyma mass decreases, which leads to a decreased production of vitamin D active form (calcitriol; 1,25-OH D_3) and impaired calcium absorption from the gastrointestinal tract.

As a result of these abnormalities, decreased concentration of ionised calcium and increased excretion of PTH occur, and PTH excess leads to the development of secondary hyperparathyroidism mobilising calcium and phosphorus ions from osseous tissue [21, 22]. These disorders are intensified by resistance on calcium and vitamin D receptor level as well as an excessive number of factors restraining the production of active vitamin D [22]. In stage 4 of CKD, hypocalcaemia, hyperphosphataemia, decreased concentration of vitamin 1,25D and an approximately 4-fold increase in PTH concentration are common. In stage 5 of CKD, PTH concentration increases greatly. Therapy in a case of secondary hyperparathyroidism is the domain of nephrology [23].

Insulin

In numerous patients with CRF, disorders in carbohydrate management are observed. Hyperinsulinaemia and insulin resistance occur rather early, although glucose concentrations are generally normal. However, an increase of HOMA-IR value is reported which is also a recognised indicator of insulin resistance in patients with CRF [24].

It has been documented that insulin resistance in patients with CRF is an independent factor of mortality risk due to cardiovascular reasons [25]. Increased insulin concentration in CRF is generated by deterioration of glomerular filtration and insulin excretion in proximal tubules, and also disorders of insulin metabolism in proximal tubular cells which leads to a prolonged period of insulin half-life. Tubular secretion increases along with a drop in GFR, and therefore only at approximate 15–20 mL/min GFR values decreases significantly [26–28].

The molecular mechanisms of insulin resistance are not fully understood. It may result from overexpression of potential inhibitors in receptor activity of tyrosine kinase restraining insulin transfer in a cell PC-1-plasma cell membrane glycoprotein-1 [29]. In haemodialysed patients, an increased activity of PC-1 in lymphocytes has been indicated. It has also been established that EPO treatment and anaemia correction connected to a decrease of insulin resistance in these patients are related to a decrease of PC-1 expression [30].

In consideration of uraemia, secondary hyperparathyroidism and disorders resulting from endocrine activity of adipose tissue (hyperleptinaemia) in patients with CRF increased insulin excretion by pancreatic islets explained as a result of insulin resistance has been observed [31–33]. However, not all scientists confirm the increase of insulin excretion in this group of patients. It supposedly results from a direct activity of uraemic toxins, acidosis and calcitriol deficiency on insulin secretion [26, 34]. It is documented that insulin resistance is independent of the stage of renal failure [35]. Gluconeogenesis intensification in the liver, a decrease of glucose uptake by the liver and skeletal muscles, and disorder of intracellular pathways in glucose transformation, also lead to impaired glucose metabolism in patients with CRF [26]. Insulin resistance may also be a result of inflammation in dialysed patients [36].

Prolonged dialysis therapy probably eliminates factors reducing insulin degradation by extrarenal tissues, which improves tissue sensitivity to its impact. The study by Tuzcu et al. indicated the improvement of insulin resistance only in HD as opposed to CAPD [37]. Haemodialysis therapy may accelerate metabolic clearance of insulin [38]. Souza et al. evaluated the influence of kidney transplantation on insulin resistance. After three months of transplantation, HOMA-IR indicator was significantly lower (2.4 ± 1.5 before transplantation *v.* 1.5 ± 1.1 after three months, $p < 0.001$), but in the following markings it increased. However, it did not reach statistical significance (2.0 ± 1.7 — 12 months after transplantation) [39]. This problem requires further studies.

Clinical conclusions

The role of insulin resistance in the development of protein energy wasting (PEW) syndrome is not as unequivocal as was previously believed. Insulin resistance is higher in malnutritioned patients, and is connected to inflammation, hyperleptinaemia, calcitriol deficiency and acidosis.

It appears that the most important factor for a decrease of insulin resistance in patients with CRF is efficient and productive haemodialysis.

Growth hormone (GH)

In patients with CKD, growth hormone concentration is generally elevated and increases with disease progression, although correct GH excretion may be observed following GHRH stimulation [40]. Elevated concentration of this hormone is a result of increased GH excretion by the pituitary gland, but also by impairments of hormone degradation in the kidneys (GH is reabsorbed and metabolised in a proximal tubule) [41]. Additionally, the increase of concentration of

proteins binding GH is observed which may influence its concentration. Paradoxically, in patients with CKD, growth hormone excretion intensifies with increased glucose concentration, and hypoglycaemia after insulin administration causes only a slight increase of GH concentration [42]. GH concentration increases excessively following intravenous administration of arginine. Unlike in healthy people, patients with CKD have been reported to have increased GH concentration following TRH stimulation [43]. Despite elevated GH concentration in patients with CKD, among children with CKD growth disorders may be observed. It seems that this results from resistance of peripheral tissues to GH but also to IGF-1 and IGF-2. Additionally, activity of IGF-1 and IGF-2 is decreased by increased binding with IGFPB [41, 44, 45]. Therefore, when marking IGF concentrations with the use of biological tests, the results may be lowered, and with the use of radioimmunological tests, results may be overstated [41]. GH administration in children with growth deficiency is a routine treatment as it has been proven that GH analogue administration enables normal growth in children with CKD [46]. In adults, GH analogue administration generates muscle mass gain and may be a suitable treatment for protein energy wasting (PEW) [47, 48]. However, considering the cost of treatment, it cannot be a routine procedure. The condition of GH analogue administration is a correction of acidosis, secondary hyperparathyroidism and zinc deficiency [49]. Similar results were acquired following GHRH administration [50]. The most frequent marginal symptoms of exogenous GH administration are oedemas [47, 50].

After commencing dialysis therapy, GH concentration decreases and HD treatment leads to the increase of IGF-1 activity, probably due to elimination of low molecular weight inhibitors from circulation [44]. Administration of recombined human erythropoietin in the course of dialysis also leads to a decrease of basic growth hormone concentration [51]. After kidney transplantation, normalisation of GH metabolism is obtained [46].

Clinical conclusions

The initial GH analogue dose is 0.35 mg/kg/week. The most frequent marginal symptoms are oedemas.

GH administration in children with growth deficiency is a routine treatment, and in adults with ESRD is tolerable in PEW syndrome treatment.

Prolactin in CKD

PRL concentration in patients with CRF treated with HD, PD and during the predialysis period is increased in 30–50% of patients, but the clinical consequences of this state are not yet fully understood. The concentration of this hormone increases along with kidney function deterioration, and is highest in patients on renal replacement therapy with the employment of extracorporeal circulation. The curve of daily PRL concentration is flat, and nightly increase of PRL excretion has not been indicated [52]. It is connected with PRL overproduction secondarily to a decrease of dopaminergic system activity and disorder of restraining pituitary PRL excretion. However, impairments of stimulation of PRL excretion have not been reported, because after TRH stimulation a proper increase of PRL concentration is observed [53].

Peripheral mechanisms with the participation of hormones such as oestrogens, thyroid hormones, GKK and catecholamine also influence prolactin excretion [54]. Besides, impaired biodegradation by inefficient kidneys leads to hyperprolactinaemia, although some authors claim that kidneys are not the only place of PRL degradation [55]. It is believed that hyperprolactinaemia may be a compensatory mechanism counteracting hypocalcaemia as PRL is one of the factors stimulating $1,25(OH)_2D_3$ synthesis [56]. Hyperprolactinaemia may lead to hypogonadism. In order to diagnose hyperprolactinaemia, it is advised that a single PRL measurement in blood plasma be performed [57].

The result of a metoclopramide test in patients with end-stage renal disease is inadequate, and response of PRL excretion is lower. The diagnostic value of a metoclopramide test in patients with ESRD is inconsiderable [58].

Neither EPO treatment and haemoglobin level increase nor general improvement of health induce normalisation of transformed PRL profile, and does not normalise the results of a metoclopramide test [52, 58]. Bromocriptine treatment in patients with CKD may be effective in cases of the presence of menstrual disorders [57].

Clinical conclusions

A single measurement of PRL concentration above the upper limit of normal confirms a diagnosis of hyperprolactinaemia. When diagnosing hyperprolactinaemia in patients with CKD, a dynamic testing of prolactin excretion is not advisable.

Diagnostic imaging may be performed only in cases of very high PRL concentration.

Treatment in CRF is rare, only in menstrual disorders in young women.

Influence of kidney disease on thyroid hormone functions

In chronic kidney disease, disorders of thyroid functions are observed. Approximately 8% of patients with

chronic kidney disease have symptoms of subclinical hypothyroidism, and a reduction in the degree of thyroid hormone concentrations depends on intensification of kidney disease [59, 60].

TSH concentration is normal or elevated but with a disturbed rhythm of daily TSH excretion and weakened reaction to TRH. Concentration of fT4 is normal or decreased. TT4, TT3, fT3 and rT3 concentrations are reduced, unlike in other chronic diseases [61]. In cases of reference concentrations of thyroid hormones, rT3 concentration may yet be increased [61–64].

In haemodialysed patients in uraemia, there is a tendency towards a decrease (but generally still within the reference range) of T4 concentration, and low T3 and rT3 concentrations but without lowering its basic concentration compared to patients with kidney disease in the predialysis period and dialysed peritoneally. Besides, decreased coefficient values of thyroid hormones bindings with proteins (fT4/TT4, fT3/TT3, T4/TBG) and elevated concentration of TBG and thyroglobulin have been observed [61, 63, 65–67]. It has been indicated that increased concentration of uraemic toxins results in selective restraint of transcription by receptor blockade for T3, which may partially explain disorders of thyroid hormones metabolism [68, 69].

Iodum accumulation in an organism along with intensified kidney damage generates an increase of iodum quantity stored in the thyroid, which may block production of thyroid hormones (Wolff-Chaikoff effect) [70]. It is believed that because of this, in patients with CRF one may more frequently observe hypothyroidism, thyroid nodules, thyroid neoplasm and also goitre which may occur increasingly frequently with advancing age. The influence of the length of renal replacement therapy on occurrences of goitre is not fully understood [65, 71–73].

In advanced CRF stages acidosis persists, which may be the reason for decreased fT4 and fT3 concentrations and increased TSH concentration. A significant improvement in fT3 concentration in patients cured of acidosis has been confirmed which was not indicated for fT4, TT4 and TSH. Normalisation of inflammation parameters concentration after acidosis compensation has not been indicated [61, 74].

Except for disorders of acid-base management, disorders of electrolyte management are present in chronic kidney disease and elevated phosphate ion concentrations may disturb T4 binding with transport proteins and increase free thyroxine concentrations [75].

In uraemia, significant changes in transport proteins (TBG and albumin) concentration were not indicated, although decreased concentrations of these proteins may be observed in cachetic patients with present inflammation and increased levels of proinflammatory cytokines. Besides, accumulated uraemic toxins such as urea, creatinine, indoles, and phenols may lead to decreased bindings of thyroid hormones and proteins (principally prealbumins and albumins) [76].

Some authors have described improvement of thyroid functions and decrease of TBG affinity to thyroid hormones after haemodialysis [61, 77, 78]. They indicate a significant improvement of hormonal state of thyroid in patients with ESRD haemodialysed daily [79]. However, there are other scientists who have not observed a positive effect of treatment on disorders of thyroid hormones management in dialysis programme [61, 80]. Following haemodialysis, a decrease of T3 receptor restraint by uraemic toxins has been reported which reduced organism resistance to the activity of thyroid hormones [69].

Even after administration of an insignificant quantity of heparin which is normal for patients dialysed in extracorporeal circulation, increased FFA concentration is observed which may result in elevation of free thyroxine fraction (fT4) through decreased ability of thyroid hormones bindings by TGB [77, 81, 82].

After administration of erythropoietin preparates in patients haemodialysed and dialysed peritoneally, improvement of T4 and T3 concentrations and TSH excretion, including reaction to TRH, has been observed, but only a slight influence of this treatment on a daily rhythm of hormone excretion has been reported. TSH reaction to TRH improves along with an increase of haemoglobin (Hb) level [64, 83, 84].

Besides, there has been an indication of a relationship between fT4 and residual kidney function, fT3, length of dialysis, concentration of calcium, proteins, triglycerides and between TT3 and length of dialysis, albumin concentrations and also inverted dependence between fT4 and Kt/V [85].

Another important problem is the treatment of patients with renal failure and coexisting hyperthyroidism. In the treatment of this group of patients, similar procedures are applied but the treatment of l131 requires a significant decrease of dosage in connection with a prolonged period of l131 half-life in thyroid [86].

Clinical conclusions

In approximately 30% of patients with CRF, a decrease of thyroid hormone concentrations, particularly T3, is observed and only approximately 8% are characterised by subclinical hypothyroidism. An increase in rT3 concentration is not indicated as opposed to other chronic diseases.

A diagnosis of a thyreological state in patients with CRF requires a complex estimation. Renal replacement therapy insignificantly improves a thyreological state in patients with ESRD. The substitution treatment of hormonal disorders connected to uraemia is not advised.

The treatment of hyperthyroidism in dialysed patients with ESRD may be performed with reduced doses of l131 in specialised facilities. The dialysis therapy following l131 administration requires special precautions.

Disorders of the hypothalamic–pituitary––adrenal axis functions in CKD

Evaluating ACTH and cortisol concentrations in patients with CKD is complex. However, ACTH and cortisol concentrations in serum in this group of patients are believed to be normal or insignificantly increased, although the daily rhythm of cortisol excretion remains unchanged [87].

In healthy people, the kidneys take part in removing cortisol and its metabolites soluble in water, and are an important site for active cortisol conversion to inactive cortisone with a participation of 11β-hydroxysteroid dehydrogenase type 2 (11-βHSD2) which prevents excessive activation of mineralocorticosteroid receptor by cortisol, thus protecting against sodium retention and the development of hypertension [88–90]. In CRF, the activity of this dehydrogenase is reduced which leads to an extended period of cortisol half-life and accumulation of its metabolites which may disturb measurements of cortisol concentration [87, 91].

Free cortisol level in plasma is increased in a higher degree than total, which suggests decreased cortisol bindings with albumins, although binding with transcortin (corticol binding globulin) remains unchanged [92]. Hypercortisolaemia may be the reason for osteopenia, disturbed distribution of adipose tissue, and increase of protein catabolism due to elevation of GKS concentration [93–95].

It has been indicated that interventions in renal replacement therapy (HD) do not significantly improve disorders of the hypothalamic–pituitary–adrenal axis; however, in dialysed patients, decreased intensification of hypercortisolaemia and ACTH concentration in comparison with CKD patients on conservative management and also normalisation of the cortisol half-life period has been observed [95–97]. It has been reported that despite a decrease of CRH concentration, ACTH and cortisol concentrations increased during HD [97]. Besides, it has been observed that elevated cortisol concentration was frequently an indication of increased morbidity and cachexia, and could be connected to a necessity for hospitalisation [88].

Tests of adrenal gland stimulation (ACTH, CRH, metyrapone) are generally normal; cortisol concentration increases after ACTH and CRH stimulation, although the response to ACTH excretion after CRH stimulation is, just like in a chronic stress situation, generally suppressed [95, 96]. Improvement of reaction to CRH following EPO administration is indicated as well [93, 94].

The test of adrenal restraint with dexamethasone does not produce unequivocal results, something which is explained by disturbances in absorption and/or slower metabolism [95, 96]. However, in the diagnostics of hypercortisolaemia, it is advised to employ a 1 mg dexamethasone test since marking a concentration of free cortisol in the urine of patients with renal failure is non-diagnostic [98].

Clinical conclusions

In patients with CKD, it is possible to observe an inconsiderable increase of ACTH and cortisol concentrations.

The results of stimulation tests in patients with CKD do not alter, and in the diagnostics of hypercortisolaemia a 1mg dexamethasone test is advised.

Dialysis therapy does not significantly influence the hypothalamic–pituitary–adrenal axis.

Conclusion

The kidneys play an important role in hormonal management. Endocrine disorders are one of the most crucial elements of 'uraemic syndrome' which is underestimated and has not been fully examined. Pathogenetic relationships are very complex and not always obvious. Knowledge of the subject of hormonal disorders and their mechanisms in 'uraemic syndrome' is not widespread among endocrinology doctors.

In the treatment of disorders, the most important seem to be the treatment of malnutrition, improvement of the general health state, optimisation of renal replacement therapy, and only in exceptional cases hormone substitution. Diagnosis, due to the complexity of disorders and the dependency of employed test results on their type, is difficult.

In CRF, apart from the discussed disorders, there are also complex disorders in the section connected with the hypothalamus and pituitary functions, and also as far as sex hormones and adipose tissue hormones management is concerned. A study of this type is currently being prepared by the authors.

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