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Haemodialysis - clinical and diagnostic challenges

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Pathophysiological basis of laboratory parameter changes we monitor in dialysis patients

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Chronic kidney disease is a state where kidney loses one of it functions during time, as the results of an illness primarily affecting kidneys or any other illness which damages kidneys as part of its multiorgan damage. The stage of renal failure is assessed through creatinine clearance. Several modified formulas today aim to assess renal function as precisely as possible, on individual level, and are based on a number of variables. The loss of renal function (excretory, metabolic, endocrinological) leads to disorders of many organ systems, which is first detected through blood and urine laboratory tests. Anaemia of chronic disease is developed through the reduced production of erythropoietin in kidneys, suppressed erythropoiesis due to chronic inflammation or even blood loss in the dialysis system or frequent blood draws for laboratory tests. The excretory kidney function is reduced, which changes the dilution of urine, causes water retention, electrolyte disorders often accompanied by blood acidosis. The reduced excretion of calcium and phosphate as well as the reduced vitamin D activation in kidneys (calcitriol), leads to enhanced secretion of parathyroid hormone, and then to hyperplasia of parathyroid glands and the development of secondary hyperparathyroidism with complications such as renal osteodystrophy and calcification. The damage and the increased permeability of glomerular basal membrane for proteins (selective or non-selective) often results in the development of severe hypoalbuminemia, a coagulation disorder occurring after the loss of clotting factor as well as failure of medicine and hormone effects directly connected to plasma proteins. At the final stage of renal failure (creatinine clearance is lower than 15 mL/min/1.73m^2), it is necessary to commence treatment with one of the kidney function replacement forms (haemodialysis, peritoneal dialysis or kidney transplant). The choice of treatment modality is subject to the expertise of a nephrologist, surgeon, urologist together with the patient, in order to ensure an optimal quality of life. Each method has its advantages and possible complications that need to be considered. The start of treatment of the chronic renal disease with one of the forms of kidney function replacement demands a thorough clinical monitoring of the patient's condition, the assessment of the dialysis process adequacy and prompt reaction by clinicians, which is greatly based on fast, available and reliable laboratory test values.

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Preanalytical and postanalytical problems in laboratory analysis of haemodialysis patient samples

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Accurate, reliable and clinically useful laboratory test results for the right patient at the right time is one of the goals of laboratory medicine. It is important to keep in mind that patient outcome can be affected by preanalytical errors. Patients with end-stage kidney failure are treated with complex therapeutic procedures which is why guidelines for obtaining analytically adequate sample should be followed. Wide variety of sample types can be submitted for numerous laboratory testing, such as: samples from a central line or peripheral vein, dialysate samples, sample drawn before or after the dialysis treatments. For right clinical interpretation of a laboratory result, in relation to a reference group or longitudinally monitored, clinicians should know whether the test results were obtained on point of care devices or in core laboratory.

Peritoneal equilibration test (PET) that is performed in peritoneal dialysis patients requires several laboratory measurements in dialysate samples. Proper specimen labelling and type of units of measurement is needed for the right interpretation of the PET. Measurements such as complete blood count, parathyroid hormone, potassium, phosphorus, calcium balance determination, blood gas analysis, serum protein electrophoresis or the concentration of immunosuppressive drugs have their own characteristics. Continuous education and cooperation are very important for all health professionals that participate in the process from ordering to interpretation of the test results.

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Mineral metabolism monitoring in haemodialysis patients with secondary hyperparathyroidism

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Chronic kidney disease (CKD) is a global public health problem affecting 5-10% of the world population. Disorders of bone and mineral metabolism are common complications of dialysis patients that can manifested as one or more abnormalities in laboratory parameters (calcium, phosphorous, parathyroid hormone (PTH), and vitamin D), volume, growth and structural bone changes and pathological calcifications. The pathophysiology of chronic kidney disease-mineral and bone disorder (CKD-MBD) is very complex and involves a number of feedback loops between the kidney, bone, intestine and the vasculature. The main hormones and factors that contribute to the kidney regulation of phosphorus and calcium include PTH, fibroblast growth factor 23 (FGF-23), klotho and 1,25-dihydroxyvitamin D ($1,25(OH)_2D$). Secondary hyperparathyroidism develops as a consequence of mineral metabolism disturbances and is characterized by elevated serum PTH and parathyroid hyperplasia. To help clinicians recognize abnormalities in mineral metabolism markers target ranges have been defined for serum PTH, calcium and phosphorus concentrations in clinical practice guidelines. Recommended frequencies for mineral metabolism monitoring in haemodialysis patients also vary between guidelines with no firm consensus on optimum frequency. In Japan, biweekly or monthly measurement is recommended for calcium/phosphorus, which is more frequent than values defined in the KDOQI (Kidney Disease Outcomes Quality Initiative) or KDIGO (Kidney Disease Improvement of Global Outcomes) guidelines. Regarding PTH trimonthly measurement is recommended in Japan whereas less frequent measurement (every 3-6 months) is recommended in the KDIGO guideline. Early detection, optimal treatment and regular monitoring CKD-MBD in accordance with current guidelines can reduce the all-cause and cardiovascular mortality in haemodialysis patients.

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Haematological parameters in samples of dialysis patients

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Haemodialysed patients have an increased risk of developing haematological disorders due to the nature of underlying disease as well as the therapeutic procedures themselves. In addition to thrombocytopenia and platelet dysfunction, the most common disorder is anaemia. Etiological background is multifactorial, primarily caused by the long-term endocrinological, mechanical, metabolic, toxic and nutritional issues. Inadequate erythropoietin synthesis, hyperparathyroidism, blood loss during venipuncture or dialysis might

develop, besides membrane and intracellular erythrocyte changes, reduced availability of iron, folate and other nutrients. According to Kidney Disease Improvement of Global Outcomes guideline (KDIGO) for diagnosis and evaluation of anaemia in chronic kidney disease, as well as for monitoring therapeutic procedures, a complete blood count, reticulocytes, ferritin, transferrin saturation, vitamin B12 and folate measuring are recommended. However, due to the complex and interdependent pathophysiological mechanisms, including volemic and cardiovascular disorders, inflammatory reaction, immune dysregulation, disturbed erythropoiesis and the influence of therapeutic protocol, these standard markers in samples of dialysis patients are changed and may be unreliable indicators of their erythroid status. More informative and diagnostically accurate indices are still needed to help clinicians in adjusting therapy as well as maintaining haemoglobin within the recommended limits. Although erythrocytes are primarily used in clinical practice, reticulocyte parameters more directly reflect changes in the hemoglobinization of erythron and can provide the fastest information about the functional iron availability in patients receiving erythropoietin.

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Are laboratory biomarkers of cardiovascular changes in dialysis patients sufficiently informative?

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Cardiovascular disease (CVD) is the leading cause of morbidity and mortality in patients with chronic kidney disease (CKD). Numerous studies have found a strong association between decrease of glomerular filtration rate as a marker of renal disease progression and increasing prevalence of clinical manifestations of CVD. In patients with CKD, especially patients with end-stage renal disease and patients on dialysis, besides traditional risk factors for the development of CVD, such as diabetes, hypertension, high cholesterol, obesity *etc.*, there could be found additional uremic-related factors such as anaemia, inflammation, oxidative stress and lipid and mineral metabolism disorders. An additional challenge for early diagnosis and managing CVD in CKD patients is the interpretation of reno-cardiovascular biomarkers. Commonly used biomarkers are brain natriuretic peptides (BNP/NT-proBNP), as biomarkers of heart failure, and high-sensitivity troponins (hsTnI), as markers of ischemic myocardial damage. The blood values of these biomarkers in patients with CKD, compared to the cut-off values obtained for the general population, are often elevated even when there are no clear clinical signs of cardiovascular changes. This increase is probably associated with two mechanism: decreased clearance of biomarkers due to decreased renal function, and renal disease-related pathophysiological mechanisms that also lead to damage of the heart muscle. In addition, in haemodialysis patients, the type of dialysis itself or the materials of dialytic membrane may affect biomarker blood concentrations. Because of all this, in CKD patients for both, BNP/NT-pro BNP and hsTn, the cut-off values should be set higher than in the general population. On the other hand, by raising the cut-off values diagnostic accuracy decreases and a single determination of blood concentration for CVD diagnosis is not recommended. Serial estimation for the basal blood value of natriuretic peptides might provide more useful information. Similar, only serial determination of hsTn and dynamic changes of more than 20% should be used in diagnosing acute coronary syndrome. For early recognition of CVD in CKD patients, as multi-organ pathophysiological mechanisms are involved, multi-biomarker estimation could be beneficial.

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Nutritional status monitoring of patients undergoing chronic dialysis

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Patients with chronic kidney disease (CKD), especially those with end-stage renal disease who are undergoing chronic haemodialysis, are at high risk for developing protein-energy malnutrition (PEM). Protein-energy malnutrition is a complex clinical condition characterized by a progressive decrease in protein reserves and disturbance of energy balance leading to increased hospitalization and death rates.

During the renal function deterioration and development of uremic syndrome, there is a conforming decline of nutritional status partly due to loss of appetite, various comorbidities affecting digestive function, depression, socioeconomic situation, patient isolation, and mostly because of loss of nutrients during dialysis (amino acids, peptides, proteins, glucose, water-soluble vitamins, and other bioactive compounds). Therefore, the early diagnosis of PEM justifies regular and vigilant monitoring of nutritional status.

Several indicators are available to assess the nutritional status of renal patients, which are used independently or jointly as part of a systematic evaluation. It is recommended to use several different methods simultaneously to achieve a comprehensive assessment of nutritional status by examining different parameters. The National Kidney Foundation (USA) has developed guidelines which propose that patients on chronic haemodialysis should be routinely assessed for nutritional status by a panel of tests at certain time intervals. The proposed panel of complementary tests includes pre-dialysis serum albumin, percent of usual body weight, percent of standard bodyweight, subjective global assessment (SGA), dietary interviews and diaries, and nPNA (normalized Protein Equivalent of Total Nitrogen Appearance).

Serum albumin is currently most common parameter used for screening patients at high-risk of developing PEM. For assessment of nutrition several other biochemical parameters such as: serum prealbumin, transferrin, serum creatinine and total cholesterol can be used.

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