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Homocysteine and Cystatin C level changes in haemodialysed patients and connection with cerebro- and cardiovascular complications

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Plasma homocysteine and Cystatin C levels of 360 chronic haemodialysed patients were measured in fasting (191 men, mean age: 55.5 years; and 169 women, mean: 62.9 years). The patients were divided into subgroups: diabetes mellitus (34 men and 38 women 7 vs 8 IDDM). obliterative arteriosclerosis (68 men and 61 women), cardiovascular complications (75 men and 84 women) and stroke (16 men and 12 women), and after renal transplantation in chronic rejection (15 men and 5 female).

Homocysteine was determined by IMx analyser from Abbott by FPIA method. Immunoturbidimetric method was used for quantification of Cystatin C (PETIA). The lowest Cystatin C concentration was found in diabetic patients (4.35±0.15 mg/l in men and 3.18± 1.77 mg/l in women) and the highest one occurred in anuric and bilateral nephrectomised and transplanted chronic rejected patients (6.075 mg/l in men and 6.35 mg/l in women: $p<0.001$). The homocysteine levels (24.98±2.94 μmol/l in men and 23.88±1.76 μmol/l in women) exceeded the upper limit of reference range (<15.0 μmol/l). There was a significant difference in favour of subgroup of cardiovascular (27.25 μmol/l in men and 26.87 μmol/1 in women) and stroke patients (27.16 μmol/l in men and 30.76 μmol/l in women $p<0.001$). Elevated levels were found in chronic rejected patients with accelerated arteriosclerotic events (25.94 μmol/l in men and 27.43 μmol/l in women). Good positive linear correlation was found between serum homocysteine and Cystatin C levels ($r=0.2393$ and 0.2252). The authors demonstrated hyperhomocysteinaemia associated with high Cystatin C concentration in four subgroups of haemodialysed patients (obliterative and accelerated arteriosclerosis. cardiovascular disease, and cerebrovascular complications and stroke).

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Infections, cerebro- and cardiovascular events are the major causes of morbidity and mortality of renal patients. Arteriosclerosis is multifactorial disease. The smoking, diabetes mellitus, hypertension and other systemic diseases play an important role in the diasese process. The lipid level changes (hyper-, and dyslipidaemia), hyperfibrinogenaemia and other independent risk factors are also involved. Recently homocysteine has gained considerable attention. Homocysteine is a sulphur-containing amino acid. Due to increased production and abnormal elimination hyperhomocysteinaemia has been reported to develop in renal failure (1–4, 9–12). Several studies have been dealing with the abnormal methionine metabolism, disturbances of remethylation, deficiences of vitamins (folic acid and B-6, B-12) and genetic background of hyperhomocysteinaemia (8, 13, 19, 20). In the present study the serum homocysteine and Cystatin C concentrations were measured in chronic haemodialysed patients and investigated connection between homocysteine levels and cerebro- and cardiovascular complications.

Patients and Methods

The serum fasting homocysteine and Cystatin C concentrations of 191 men (age: 16–87 years, mean 56.1 y) and 169 women (age: 17–83 years, mean: 62.9 y) were comparatively measured. All the patients were treated in chronic haemodialysis programme. The homocysteine levels was measured in Abbott-IMx immunoassay FPIA method. The Cystatin C quantification was performed by immunoturbidimetric PETIA method (5–7). The studied subgroups of dialysed patients are summarized in Table I. All dialysis treatments utilized bicarbonate based dialysate (HCO_3: 36.0-, Sodium: 140-, Potassium: 2.0-, Magnesium: 0.65-, Calcium: 1.75-, glucose: 11.5 mmol/l concentration). The patients received 2×1 pills of B 6 and 3×1 pills of (15 mg) folic acid supplement daily.

Table I

Patients and vessel complications

	DM	Cardiovascular complications	Stroke	Obliterative vessel alterations	TRx
Male	34	75	16	68	15
Female	38	84	12	61	5

Results

The Cystatin C concentrations are presented in Figure 1. The Cystatin C concentrations of haemodialysed patients was higher than the upper limit of reference range (<1.5 mg/l). The Cystatin C concentration were lower in the diabetic group and was not different between with IDDM and NIDDM patients. This may by explained by the residual hyperfiltration and the earlier onset of haemodialysis of these patients. The highest Cystatin C levels found in anuric, bilateral nephrectomised and graftectomised in chronic-rejected patients. According to cardio- and cerebrovascular complications the patients were categorized. More complications were found in women, than in age-mathed men.

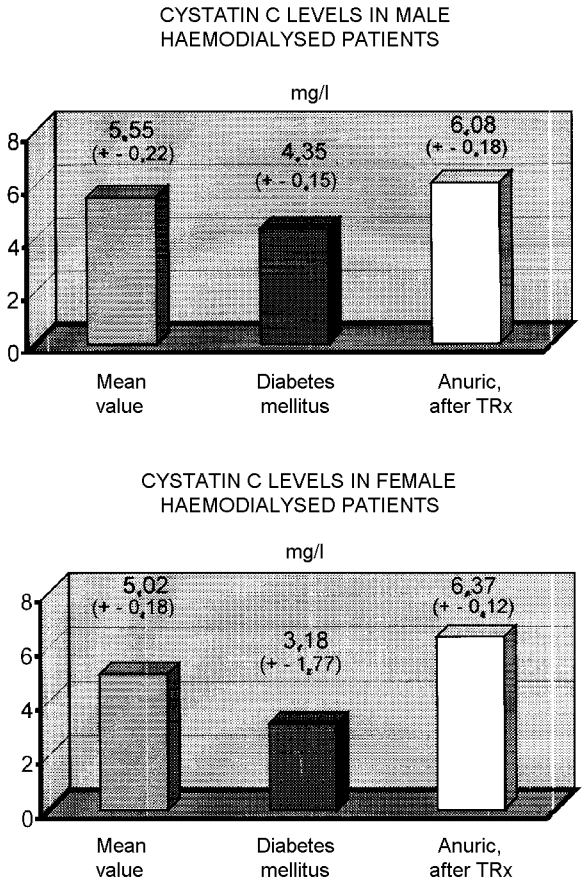

Fig. 1. Cystatin C levels in haemodialysed patients

The prevalence of obliterative arteriosclerosis was strikingly high in both genders (Table I). The mean value of serum homocysteine levels were significantly elevated in dialysed patients compared to the upper limit of the reference intervals (<15 μmol/l). Very high homocysteine concentration was found in patients with stroke and cardiovascular events ($p<0.001$) and in earlier transplanted, chronic-rejected patients ($p<0.01$). The homocysteine levels of the diabetic- and obliterative arteriosclerotic group did not differ significantly from dialysed one. The results of homocysteine levels measurements are shown in Figure 2. Positive good correlation was found between serum homocysteine and Cystatin C levels ($r=0.2393$ in female and $r=0.2251$ in men). The change of hyperhomocysteinaemia are shown in Fig. 3

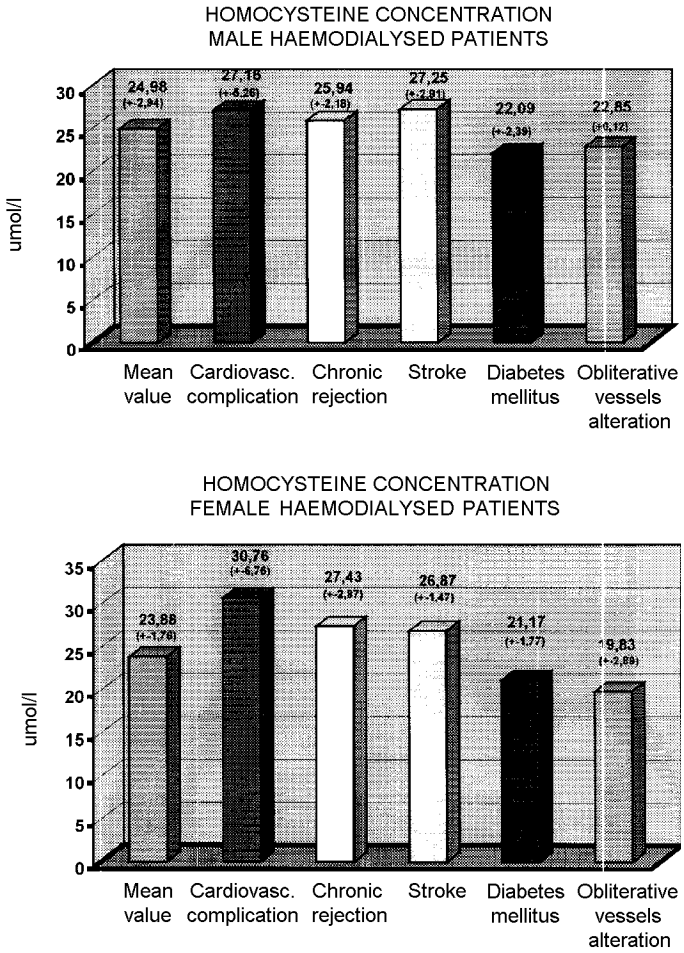

Fig. 2. Homocysteine concentration in haemodialysed patients

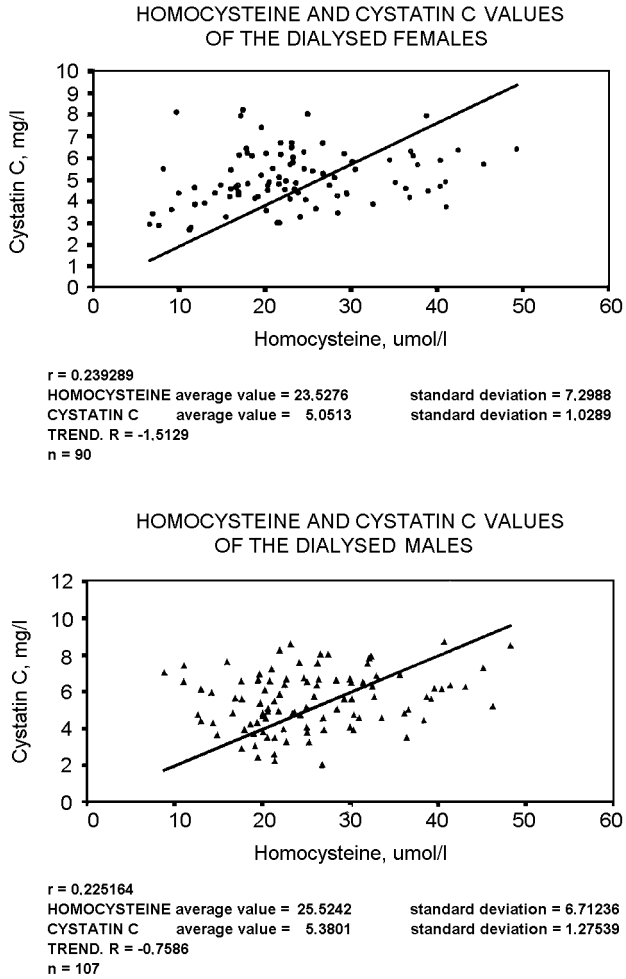

Fig. 3. Correlation between the Homocysteine and Cystatin C levels in haemodialysed patients

Discussion

During dialysis treatment the renal function worsens and the urine excretion decreases to anuria. The endogen creatinine clearance cannot be determined because of difficulties of urine collection. The Cystatin C may be an objective parameter for the assessment of renal function, renal failure progression and graft function monitoring (3, 5, 11, 12, 15). In our study we have found hyperfiltration of Cystatin C and diabetic patients. The highest Cystatin C concentration was measured in anuric, graftectomised

patients. Hyperhomocysteinaemia is an independent risk factor for cardiovascular disease and arteriosclerosis (14–17). The hyperhomocystein-aemia plays an important role in morbidity and mortality of end-stage renal failure patients with cerebrovascular complications (18). The Vitamin B and folic acid supplementation are homocysteine lowering therapy (14, 19–21). Similarly to other organic compounds homocysteine may be lowered by dialysis, but due to metabolic accumulation its level fluctuates during the treatment (2, 14).

We have found significantly increased hyperhomocysteine levels in patients under dialysis treatment. The elevation was most pronounced in patients at high risk (coronary heart disease-CHD). A relatively low homocysteine concentration was found in diabetics (16–20) which may be explained with an altered homocysteine metabolism or with enzyme receptor deficiency (1, 11, 13, 21).

The hyperhomocysteinaemia has gained considerable attention, because elevated concentrations of homocysteine may be associated with an increased risk of cardio- and cerebrovascular disease.

The patients survival and life expectancies may be influenced by these events.

The homocysteine concentration may be a prognostic factor for graft function and rejection. In hyperhomocysteinaemic patients obstructive arteriosclerosis, repeated unsuccessful Cimino fistula operations, and cerebro- and cardiovascular complications are common. Hyperhomocysteinaemia itself causes various deleterious effects on vascular endothelial dysfunction and smooth muscle cells through direct toxic effect. An unfavorable impact on muscle cell proliferation and LDL modification may also be observed. Increased the LDL internalisation and degradation, accelerated lipid peroxidation, oxidized LDl production, increased the platelet aggregation, elevated haemostatic factors (V, X, XII), and decreased plasminogen activator, antithrombin III, protein C levels may be observed. These unfavorable effects results in endothelial dysfunction, haemostasis impairment and increased occurrence of thrombotic events.

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