Dyslipidemia and Anemia in Chronically Hemodialyzed Patients

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Received June 6, 2007; Accepted June 28, 2007.

Key words: End-stage renal disease – Atherosclerosis – Heart failure – Anemia – Dialysis

Abbreviations: ESRD – end-stage renal disease; ESO – erythropoiesis stimulating agents; K/DOQI – Kidney/Dialysis Outcomes Quality Initiative; EBPG – European Best Practice Guidelines

This study was supported by the grant of Internal Grant Agency, Ministry of Health ČR NR 8334.

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**Abstract:** More than 50% of end-stage renal disease subjects treated by chronic hemodialysis die from cardiovascular events. Although there is some information regarding to anemia compensation and to the levels of biochemical risk factors of atherosclerosis in other countries, the data from the Czech Republic are missing. The aim of this study was to estimate mean cholesterol, triglyceride and hemoglobin levels in hemodialyzed subjects in the Czech Republic and to compare them with current guidelines. During the years 2001–2006, nephrologists of all subjects screened by duplex Doppler ultrasonography of our department were asked to fill in questionnaires with basic history and laboratory data. Hemoglobin concentration was calculated separately for years 2001–2004 and 2005–2006 because of the change of recommended target value from 105 to 110 g/l in 2004. A total of 258 subjects were included, aged 65 ± 14 years, 93 of them males. Patients came from 46 different hemodialysis centers in the Czech Republic. The presence of hypertension and diabetes was in 72.5% and 39.5%, respectively. Only 13.2% of subjects had the smoking history, and another 10% currently smoked.

The mean ± SD laboratory results were as follows: total cholesterol 5.0 ± 1.1 mmol/l, triglycerides (2.5 ± 1.4 mmol/l). Hemoglobin concentration was 104.4 ± 14.4 g/l (mean ± SD) in years 2001–2004 and 110.1 ± 16.2 g/l in years 2005–2006. Hemoglobin full blood concentration was lower than recommended 105 g/l in 55% of hemodialyzed subjects during years 2001–2004, and it was lower than 110 g/l during years 2005–2006 in 47% of patients. Hypercholesterolemia above recommended 5.17 mmol/l was present in 39 % of subjects. Triglycerides were elevated above 1.69 mmol/l in 64 % of patients. Only 10 % of subjects were treated by lipid-lowering drugs. We can conclude that in the Czech Republic, patients treated by chronic hemodialysis frequently suffer from anemia, despite the growing evidence of erythrocyte stimulating agents treatment benefit. Similarly, considerable number of these subjects has hypercholesterolemia and hypertriglyceridemia, only rarely treated by lipid-lowering drugs. However, this therapy is still not adequately supported by clinical research evidence.

**Introduction**

High mortality in end-stage renal disease (ESRD) patients was documented in several studies. General risk of death is 10–20 times higher in hemodialyzed patients than in the general population [1]. More than 50% of ESRD subjects die from cardiovascular events [2].

Schematically, we can divide the causes of high cardiovascular mortality into 2 groups: 1. consequences of accelerated atherosclerosis and 2. chronic heart failure caused by causes specific for the hemodialyzed population. **Atherosclerosis** is accelerated by the high prevalence of classical risk factors,
namely hypertension, dyslipidemia and growing proportion of diabetic subjects. Furthermore, some factors specific for ESRD also play role: phospho-calcium metabolism abnormalities, inflammation, oxidative stress, malnutrition and increased levels of circulating ADMA (asymmetric di-methyl-arginine, endogenous inhibitor of nitric-oxide synthase).

*Chronic heart failure* is caused by coronary artery disease, hypertension (nephrogenous or reno-vascular) with left ventricle hypertrophy and hyperkinetic circulation as a result of water volume gain between hemodialyses in subjects with oliguria or anuria, by higher vascular access flow and anemia. The latter represents a treatable factor of hyperkinetic circulation, mainly by erythropoiesis stimulating agents (ESA), because the synthesis of erythropoietin is decreased in ESRD subjects.

Common levels of serum lipids and of hemoglobin in hemodialyzed Czech ESRD patients are not known. The aim of this study was to estimate mean cholesterol, triglyceride and hemoglobin levels in hemodialyzed subjects in the Czech Republic and to compare them with current guidelines.

**Population and Methods**

Nephrologists of all subjects screened by duplex Doppler ultrasonography of our department during the years 2001–2006 were asked to fill in questionnaires with basic history and laboratory data. Vast majority of them were patients with polytetrafluoroethylene graft accesses.

Collected data included the presence of hypertension, diabetes mellitus, prescription of lipid-lowering drugs, blood hemoglobin concentration, serum levels of total cholesterol and triglycerides.

Internationally accepted expert group guidelines “European Best Practice Guidelines” (EBPG) [3] recommended to increase the target values of hemoglobin concentration in hemodialyzed patients from 105 to 110 g/l. The guidelines were published in 2004. Therefore, we performed separate hemoglobin analysis of years 2001–2004 and years 2005–2006.

Target values of total cholesterol and triglycerides are established for subjects with the 1st to 4th stage of chronic kidney disease by the K/DOQI (Kidney/Dialysis Outcomes Quality Initiative) guidelines: total cholesterol below 5.17 mmol/l a triglycerides below 1.69 mmol/l [4]. The same values are recommended also for the 5th stage – ESRD, but not enough evidenced.

Results were expressed as means ± SD.

**Results**

A total of 258 ESRD subjects were included in. They were 65 ± 14 years old, 165 of them were women. Patients came from 46 hemodialysis centers throughout the Czech Republic (see acknowledgment with the list of centers).
Laboratory results in the whole group were as follows: total cholesterol 5.0 ± 1.1 mmol/l and triglycerides 2.5 ± 1.4 mmol/l. Hemoglobin concentration was 104.4 ± 14.4 g/l (mean ± SD) in years 2001–2004 and 110.1 ± 16.2 g/l in years 2005–2006. Hypertension was documented in 72 % of patients, diabetes mellitus 39.5 % of patients.

Total cholesterol level higher than 5.17 mmol/l (K/DOQI recommendation) was found in 39% of patients and elevated triglycerides above 1.69 mmol/l (K/DOQI recommendation) in 64% of subjects. Hemoglobin full blood concentration was lower than recommended 105 g/l in 55% of hemodialyzed subjects during years 2001–2004 and lower that 110 g/l (EBPG guidelines) during years 2005–2006 in 47% of patients.

Lipid-lowering medication was prescribed only to 10% of subjects, in case of diabetics to 21 %.
Smoking: 13 % of patients were current smokers and another 10 % ex-smokers.

Discussion
Presented study documents insufficiently treated anemia in Czech hemodialyzed patients. Hyperlipidemia is also frequent and only rarely treated.

Anemia
Recommended hemoglobin concentration by the EBPG is 110–120 g/l in ESRD patients [3]. This value was recommended in 2004; until this year it was >105 g/l. The lower limit of this interval represents the value, when the therapy of anemia should be initiated. On the contrary, levels over 120 g/l an increase the risk of cardiovascular events and of vascular access thrombosis. During the years 1998–2000, first part of the DOPPS study (Dialysis Outcomes and Practice Patterns Study) was performed in more than 4500 hemodialyzed patients. The aim of DOPPS was to study the actual status of anemia treatment and its relation to morbidity and mortality [5]. The improved treatment of anemia, especially with the use of ESA, lead to statistically significant decrease of morbidity and mortality. According to DOPPS, patients with hemoglobin level below 100 g/l has 29% higher probability of acute hospitalization than subjects with hemoglobin 110–120 g/l. Anemia below 100 g/l was associated with 22% higher risk of death. Similar results were obtained in recent study by Robinson in USA, who observed similar outcome of hemoglobin concentration above 110 g/l, but not above 120 g/l [6]. Novel results of the DOPPS study from 11 countries of the Western Europe revealed the average hemoglobin levels at 111–120 g/l [5]. In DOPPS 23–77 % of patients hemodialyzed for more than 6 months reached the target value 110 g/l. We can conclude that there is enough evidence of the profit of appropriate anemia correction in hemodialyzed subjects. Unfortunately, the level of anemia therapy is still far from being...
optimal in the Czech Republic also in case of intravenous iron therapy [7].
It is caused mainly by high cost of ESA therapy and limited coverage by the
health insurance companies. However, it is known that inadequate anemia
correction lead to increased number of acute hospitalizations, which are also
expensive.

**Hyperlipidemia**
Internationally accepted guidelines K/DOQI recommend target values of serum
lipids in subjects with chronic kidney disease stage 1–4 as follows: total
cholesterol below 5.17 mmol/l, LDL cholesterol below 2.59 mmol/l, HDL
cholesterol above 1.03 mmol/l and triglycerides below 1.69 mmol/l [4]. Subjects
with stage 1–4 of chronic kidney disease are recommended to use statins if their
LDL-cholesterol is above 2.59 mmol/l. However, these guidelines are not valid in
case of ESRD (stage 5) patients and are not supported by large clinical trials as in
case of anemia therapy [8]. Some papers report inverse relationship between
serum lipids and mortality. One example is the study of Kilpatrick et al. [9], who
documented in a large study (over 1500 subjects) poor prognosis in subjects
with low LDL cholesterol. Afro-Americans were the only exception having
better prognosis in case of low LDL-cholesterol. These data could be, at least in
part, explained by the fact that low LDL-cholesterol frequently occurs in
catabolism – i.e. terminal phase of ESRD.

The trial 4D [10] tested the effect of atorvastatin on cardiovascular mortality
in hemodialyzed type 2 diabetics. This therapy lowered LDL-cholesterol, but
it did not reduce the prevalence of cardiovascular deaths, non-fatal myocardial
infarctions, or strokes. These neutral effects could be theoretically explained by
the fact that high cardiovascular mortality in hemodialyzed patients is not caused
only by atherosclerosis, but also by other factors leading to vasculopathy, such as
medial calcinosis. The latter is influenced by alterations in phospho-calcium
metabolism, malnutrition etc. Another possible explanation is that 20 mg of
atorvastatin in one dose per day is not enough to stop accelerated atherogenesis.
This interesting question will be, hopefully, answered after finishing other
randomized clinical trials (SHARP, AURORA).

**Diabetes mellitus**
Diabetes mellitus is the most frequent cause of ESRD in many developed
countries. The proportion of diabetics increases together with their life
prolongation and with hemodialysis availability. In Europe and in Canada and
USA, more than 30% of hemodialyzed subjects are diabetics [11].

According to the statistics of the Czech Society of Nephrology
(www.nefrol.cz ), 37% of hemodialyzed subjects in this country have diabetes
mellitus. In diabetics, the quality of life and life expectancy is significantly lower
than in non-diabetics despite generally decreasing mortality of ESRD subjects
Five-year life expectancy of hemodialyzed diabetics is 20–50%, of non-diabetics 35–70% [13].

In general (non-dialyzed) population, diabetes mellitus is a powerful risk factor of atherosclerosis. Indeed, also in otherwise healthy diabetics hyperlipidemia therapy should follow the guidelines of secondary prevention of coronary artery disease [14]. Available clinical trial data support the recommendation to administer statins in diabetic patients without nephropathy and in those with milder forms of nephropathy. Are the statins really useless in hemodialyzed diabetics as shown in the 4D study? This question should be answered by further research.

Improvement of dialyzed patients' prognosis largely depends on improving cardiovascular health in the early phase of chronic kidney failure. Therefore, all atherosclerosis risk factors should be searched and treated as soon as possible. Higher cardiovascular risk is related already to the slightly reduced glomerular filtration rate [15]. Pravastatin was shown to be effective in the secondary prophylaxis of cardiovascular events in subjects with mild renal insufficiency [16].

A limitation of this study is that laboratory examinations were performed in different laboratories, which co-operate with the hemodialysis units. However, the advantage of this fact is that we took into account concrete values available for the nephrologists and thus these values reflect better the routine care. Another limitation is that mainly subjects with arteriovenous grafts were included. Arteriovenous graft is used when native veins are depleted, so one could hypothesize that the included subjects were in average more seriously ill than general hemodialyzed population.

Clinically the most important finding of this study is the fact that anemia is not sufficiently compensated in the Czech Republic. It is not a criticism of nephrologists, but rather of the health insurance system, which limits prescription of ESA. Data present in this study represent the first, although slightly non-homogenous information about the presence of cardiovascular risk factors in Czech ESRD patients. More detailed data are expected in the near future in the recently established Registry of Dialyzed Patients (www.nefrol.cz).

Acknowledgements: We would like to express our thanks to the staff of the following hemodialysis units for their long-time co-operation (in alphabetical order of the cities/towns): HDS nemocnice Rudolfa a Stefanie, Benešov; HDS NsP Česká Lípa; HDS nemocnice České Budějovice; HDS nemocnice Český Krumlov, HDS nemocnice Děčín; FMC-DS Chomutov; HDS nemocnice Jihlava; HDS MMN Jilemnice; HDS ON Jindřichův Hradec, HDS nemocnice Karlovy Vary; HDS nemocnice Kladno; Nefrologicko-dialyzační centrum Liberec; Renart Litoměřice; FMC-DS Louny; FMC-DS Mariánské Lázně; HDS nemocnice Mělník; HDS
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