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ORIGINAL ARTICLE

Cardiovascular risk factors in patients with chronic renal failure Nine months follow up for cardiovascular disease events

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Background: Cardiovascular morbidity and mortality in patients with chronic renal failure (CRF) is higher than in general population. The consideration that this patients are a " higher risk" group for subsequent cardiovascular disease events is based on detection of multiple cardiovascular risk factors- "traditional" and unique for chronic renal failure.

Material and Methods: We evaluated cardiovascular risk factors (CVF) in patients with CRF and followed them for a 9 month period for clinical presentation of cardiovascular disease.

Seventeen pts were examined – 10 F and 7 M, average age 49 years with glomerular filtration rate from 10 to 58 ml/min. Four pts were with primary glomerulonephritis (GN), 4- secondary GN, 2- I type diabetes, 1 –II type diabetes, 2 -chronic pyelonephritis, 2 with hypertensive nephropathy and 3 others - with interstitial nephritis, amyloidosis and Balkan endemic nephropathy each. Elevated blood pressure was detected in all pts. Immunosuppressive therapy was needed in 2 pts with GN.

We examined "traditional" CVF (age, gender, body mass index, smoke, blood pressure, hyperlipidemia, carbohydrate metabolism- diabetes or glucose intolerance) as well as related to CRF CVF (anemia, hyperphosphatemia, left ventricular hypertrophy, hyperhomocysteinemia, hyperinsulinemia, based on the values of IRI, proteinuria and need for pathogenic treatment with steroids.

Results: After 9 month period 7 pts (35%) had coronary incident: 1 -died from myocardial infarction; in 2- ischemic heart disease was manifested by arrhythmia; in other 3-ECG criteria for heart ischemia was detected. All of these patients had moderate or advanced renal failure, diabetes or hyperinsulinemia and were positive for all related to CFR CVF.

Conclusion: In patients with chronic renal disease a straight forward search and correction of the classical and uremia-related cardiovascular risk factors are necessary even at the earliest stages. Primary and secondary prevention of all risk factors will decrease the serious cardiovascular complications in patints with chronic renal failure and will prolong and better their lives.

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Over the last 30 years the incidence and prevalence of end stage renal disease (ESRD) have been increasing**.** It is more pronounced in USA, where the prevalence of ESRD is doubled during the 10 years period and the mean age of ESRD pts has been increasing over time[1].

The morbidity and mortality in patients with chronic renal failure remains so high that the 5 years survival of pts age with more than 64 years is significantly lower than that of patient with malignancies[2]. Cardiovascular disease (CVD) is the leading cause of morbidity and mortality, accounting for about 50 % of deaths, which is approximately 30 times higher than that in general population, and 30% of hospitalizations of these patients[3].

The pathogenesis of cardiovascular damage in CRF is far more complicated than in general population since the risk factors include those identified in general population: age, gender, smoking, physical activity, hypertension, prothrombotic and inflammation-related factors, diabetes mellitus and additional risk factors typical for CRF. The common factors in CRF group are important because of the progressive aging of the ESRD population, the increased frequency of diabetes and hypertension as a cause of CRF. Unique for CRF CVF are anemia, hyperphosphatemia, left ventricular hypertrophy, hyperhomocysteinemia, hyperinsulinemia, proteinuria increased oxidant stress, lipid metabolism deragements, electrolyte and water imbalance with plasma volume expansion. Because of that, chronic renal failure has recently been defined as "vasculopathetic state". The understanding and proper management of the determinants of CVD now become a major focus of Nephrology care.

Patients and methods

Seventeen pts, 10 F and 7 M, average age 49 years, with glomerular filtration rate from 10 to 58 ml/min were hospitalized in our clinic because of renal failure, during a three month period. All of them (without any selection) were examined and were followed up for 9 months for the presentation of cardiovascular events. The leading causes for CRF were shown in Table 1.

Table 1. *The primary renal diseases in examined patients*

Primary renal disease	Primary GN	Lupus nephropathy	type I D.m.	type II D.m.	Chronic PN	Hypertensive nephropathy	Interstitial nephritis
Number of patients	4	4	2	1	2	2	2

GN- glomerulonephritis; D.m- diabetes mellitus; PN-pyelonephritis

Hypertension was detected in all pts. According to the guidelines published in the seventh report on treatment of high blood pressure the levels of blood pressure were less then 130 /80 mmHg. Many of the patients received aggressive blood pressure management with 3 or more drugs to reach the target levels. All patients received ACE inhibitors alone or in combination with others antihypertensive drugs- (Ca blockers, B -blockers, diuretics, vasodilatators). Immunosuppressive therapy with steroids alone or in combination with cytotoxic drug-Cyclophosphmide was needed in 2 pts with GN.

We examined the "traditional" CVF age, gender, smoke, family history for cardiovascular diseases, hypertension, changes in carbohydrate metabolism- diabetes or glucose intolerance (GIT) and body mass index

$$(\text{BMI}) = \frac{\text{weight (in kg)}}{\text{height (in m)}} \quad \{\text{normal range from 20 to 23}\}$$

Hyperlipidemia is well known CVF that we examined. Dyslipidemia was defined as elevated total cholesterol and LDL and low levels of HDL. Increased levels of triglycerides were considered as cardiovascular risk factor too.

The following "unique" for chronic renal failure CVF were evaluated at the beginning of the study:

- Anemia (hemoglobin < 110 g/l, hematocrit < 25%)
- Hyperphosphatemia, (serum P >1.6 mmol/l).
- Hyperhomocysteinemia >15 μmol/l (in healthy controls homocystein level was from 10 -15 μmol/l, mean value- 13,9±1,5)
- Hyperinsulinemia, based on the levels of immunoreactive insulin (IRI normal range from 5 - 25 U/l). Hyperinsulinemia was considered if IRI before meal was > 30 U/l and at the 120 min after meal was > 50 U/l.
- Left ventricular hypertrophy (LVH) was detected by echocardiography and defined as left ventricular mass > 130 g/m^2 and increased left ventricular wall thickness > 13 mm.
- Proteinuria (g/24h) was examined and patients with more the 3 g/24 h protein loss from the kidney were considered to have active renal disease and immunosuppressive treatment was needed.

Four hours creatinine clearance was used to measure the glomerular filtration rate (GFR).

Cardiovascular risk factors were streamed into two groups: Group I- Standard CVF and Group II – CVF related to chronic renal failure

Results

The distribution (% of all patients in whom the examined CVF was detected) of the standard CVF is shown in table 2.

The summary of the results for distribution of unique for CRF CVF is shown in Table 3.

More than 50% of all examined patients had all CVF related to CFR. The GFR in these patients was below 40 ml/min. This high risk group includes all patients with diabetes and age > 55 years .

After a nine month period **35%** of all pts had coronary incident: 1 patient died from myocardial infarction; in 2-ischemic heart disease was manifested by arrhythmia; in other 3-ECG criteria for heart ischemia were detected.

The distribution of CVF in patients with cardiovascular events is shown in Table 4.

Discussion

Cardiovascular morbidity and mortality in patients with chronic renal failure in predialysis stage is far higher compared to the general population[4]. The left ventricular hypertrophy and coronary artery disease are the basis of the cardiovascular complications[5]. Risk factors (hypertension, diabetes mellitus, obesity, hyperlipidemia) that contribute to cardiovascular disease events in general population are present in patients with chronic kidney disease, but they do not explain the whole risk of cardiovascular disease in the general population as well as in the patients with chronic renal failure. The high prevalence of CVD at the beginning of renal replacement therapy indicates that the mechanism leading to the cardiovascular impairment have been operating early in the course of the chronic renal disease. This was con-

Table 2. *Standard cardiovascular risk factors*

Age		BMI		Smoke		Hyperlipidemia	RR	Carbohydrate metabolism		
<55	>55	<30	>30	yes	no	In all pts	Elevated in all pts.	D.m	IGT	Normal
42 %	58 %	65 %	35 %	35 %	65 %	100 %	100 %	17 %	23 %	60 %

Table 3. *Cardiovascular risk factors related to chronic renal failure*

Anemia		Hyperphosphatemia		LVH		IRI		Hyperhomocystein		
yes	no	yes	no	yes	no	Normal	Elevated	>25 μmol/l	<25 μmol/l	norma μmol/l
58 %	42 %	76 %	24 %	94 %	6 %	45 %	55 %	26 %	53 %	21 %

Table 4. *Standard cardiovascular risk factors in pts with clinical signs of cardiovascular disease*

№	age	BMJ	smoke	RR	hyperlipidemia	Carbohydrate metabolism
1	80	22	no	?	yes	D.m II type
2	75	26	no	?	yes	Normal
3	55	30	yes	?	yes	D.m. I type
4	50	28	yes	?	yes	Normal
5	68	29	no	?	yes	Normal
6	63	23	yes	?	yes	IGT

Table 5. *Cardiovascular risk factors related to chronic renal failure in pts with clinical signs of cardiovascular disease*

№	Anemia	Hyperphosphatemia	LVH	IRI	Hyperhomocystein	GFR
1	yes	yes	yes	?	yes	10
2	yes	yes	yes	Normal	yes	45
3	yes	yes	yes	?	yes	33
4	no	no	yes	?	yes	55
5	yes	yes	yes	Normal	no	50
6	yes	yes	yes	?	yes	32

firmed by Levin in a Canadian cohort of patients with CFR[6,7]. In these studies investigators concluded that prevalence of the related to CRF CVF were very high in patients with early stage of renal failure and they increased with the decline of the glomerular filtration rate.

Many studies focus on the specific uremia-related risk factors associated with cardiovascular disease outcomes in renal failure patients. The relation between anemia and left ventricular hypertrophy is best described. It has been proved that in patients with hemoglobin <8 g/dl the risk for cardiovascular disease is twice as high as in those with hemoglobin = 10 g/dl. Each hemoglobin decrease with 1 g/dl gives an increase of left ventricular mass index with 10 g per square meter[8].

Hyperphosphatemia and high levels of parathyroid hormone have a key role in the genesis of the cardiovascular changes. They participate in the genesis of endothelial dysfunction, oxidative stress, hypertension as well as affect the myocardial contractility, change the myocyte metabolism and stimulate the myocardial fibrosis[9]. The increase of Ca X P > 5,5 presupposes the calcium deposits on the vessel walls, myocardium and valves and stimulates the process of atherogenesis[10].

Homocystein is a sulfur -containing amino acid that is formed from the metabolism of methionine. High levels of homocystein have been associated with vascular disease. Homocystein is high in patients with renal failure. Although there are no convincing data that the decrease in the level of homocystein reduces the cardiovascular risk its diminishing levels favors the endothelial function[11].

Hyperinsulinemia and hyperlipidemia caused by metabolic changes as a result of renal failure have been recorded to have unfavorable effect on the cardiovascular system[12].

The results in this article are very close to the conclusion made by Levin and coworkers. Patients with clinical evidence for cardiovascular event were with moderate renal failure and were positive for all CVF related to CRF. Three out of six patients were with impairment of carbohydrate metabolism- diabetes or impaired glucose tolerance. All pts have hypertension and hyperlipidemia of long duration. Hypertension and diabetes have been present many years before initiation of CRF and for this period they have already determined cardiovascular damage.

In our study we assessed CVF in non selected patients with CRF and although the follow up period was nine months short we detected a serious cardiovascular event. We did not focus on the relation between decline of GFR and the increased prevalence of CVF. This will be our next step and a long follow up period with a large group of patients with renal insufficiency in different stages is needed to draw correct conclusion.

We can conclude based on our results that the strategies for CVF identification and reduction in patients with CRF should target not only to traditional ones but also to those related to the renal failure. Identifing patients with CRF especially those with diabetes at an earlier stage, performing primary and secondary prevention by earlier risk factor reduction results in better patients outcome and quality of life.

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ORIGINAL ARTICLE

The socioeconomic impact of hemodialysis

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Background: Hemodialysis is the most widely approach to treat End Stage Renal Disease (ESRD) patients in Greece. The purpose of the paper is to provide a microeconomic evaluation for the cost of dialysis in a public hospital setting, along with an estimate of the loss of production for these patients.
Methods: A socioeconomic prevalence-based analysis was performed attempting the micro-economic evaluation of the resources consumed in order to provide hemodialysis therapy for ESRD patients. The loss of production for the patient and family were estimated and the method used was the human capital approach.
Results: It was estimated that the healthsector cost for hemodialysis has surpassed €171 million. The potential years of productivity lost due to mortality were, according human capital approach, 2,046 years leading to a cost of €9,9 million, in 2000. The total morbidity cost due to absence from work and early retirement was estimated to be more than €273 million.
Conclusions: Results indicate that the total direct cost of hemodialysis constituted approximately 2% of the national health expenditure in Greece, providing care for 0.05% of the population. In addition to the costs imposed on the National Health System, it was estimated that production losses due to mortality and morbidity from the disease are also very significant. Organ-donation campaigns, introduction of satellite units in Greece and telemedicine are some recommendations which may hold some promise for the future and prove more cost-effective and psychologically advantageous for patients.
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One of the most dominant health policy issues over the last twenty years has been the rising cost of health care and consequently the efficiency and effectiveness needed in resource use[1]. It has been clearly established that health care technology is a major cost-driving factor[2,3], but, its appropriate utilization improves quality and the effectiveness in health care delivery. One of the important factors in determining appropriate patterns of technology utilization is the cost and the cost-effectiveness associated with its purchase, maintenance and use.

In comparison to other European countries, Greece was late to introduce, and cover through public reimbursement, provision and use of expensive health technology, innovations and treatments in the National Health Service (NHS) hospitals. Coronary Artery Bypass Grafting (CABG), for instance, was reimbursed only as late as 1993. However, recent years have seen considerable progress in technology diffusion in some areas, such as Telemedicine and Telematics[4]. In a similar fashion, Greece is characterized by one of the highest rates of hemodialysis stations for the treatment of ESRD, though unfortunately also with one of the lowest rates of kidney transplantation, and this despite the already proven effectiveness and cost-effectiveness of the method[5,6].

Hemodialysis is the most widely approach to treat ESRD, but has a very high cost (direct and indirect) and a major limitation which is associated with the duration and frequency in which it needs to be delivered. Continuous Ambulatory Peritoneal Dialysis (CAPD), on the other hand, is characterised by a high incidence of complications (hospitalisation rates among CAPD patients are higher than that for haemodialysis patients)[7]. Perhaps for this reason, there is a steady growth in the numbers of patients treated with haemodialysis[8,9]. This is also the case in Greece, where the number of patients on dialysis in Greece increases by approximately 7% each year. In 1997, there were 6,942 patients treated with in-center haemodialysis, CAPD and with a functioning kidney transplant, and by the year 2000 this number increased to 8,601 (74% of which are patients on dialysis)[10]. The number of patients on Renal Replacement Therapy (RRT) and the rate of increase for the last five years are shown in Figure 1. It is also worth mentioning that 70% of the patients are between the ages of 20-65, that is the productive age band.

Treatments usually take place in well-equipped NHS or private hospital dialysis units and are therefore expensive to deliver, which begs the question as to which