

*Original Article*

## **Anaemia is common after kidney transplantation, especially among African Americans**

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### **Abstract**

**Background.** Anaemia is a major cardiovascular risk factor in renal disease. It might be appropriate to extrapolate this association of anaemia with cardiovascular disease to renal transplant recipients who continue to have a significant cardiovascular risk. There are very few studies addressing the issue of anaemia after renal transplantation.

**Methods.** We studied 192 consecutive kidney transplant recipients over a 5-year period in a tertiary referral centre in Michigan, USA. Patients who were followed up at the ambulatory transplant clinic for at least 1 year after transplantation were studied. Haemoglobin (Hb) level at 6 months and 1 year after renal transplantation was recorded. Risk factors for anaemia were evaluated using multivariate regression analysis.

**Results.** Significant anaemia (Hb <11 g/dl in females and <12 g/dl in males) was common (19.3% at 6 months, 19.8% at 1 year). Anaemia was more common in African American (AA) than in non-AA patients both at 6 months and 1 year after transplantation. Multivariate analysis showed that serum creatinine was an independent risk factor for anaemia. Female gender was associated with significant anaemia at 1 year. Intriguingly, AA race was also an independent risk factor at 6 months and strong trend for risk at 1 year.

**Conclusions.** Anaemia is common during the first year after kidney transplantation. AA race as well as high serum creatinine and female gender are independent risk factors for post-transplant anaemia. The importance of anaemia as a risk factor in AA patients after renal transplantation should be more recognised.

**Keywords:** anaemia; African American race; female; kidney transplantation; multivariate analysis

### **Introduction**

Anaemia is one of the most common consequences of chronic kidney disease (CKD). The consequences of anaemia in CKD are well documented. Anaemia in CKD is strongly associated with significant cardiovascular morbidity [1], hospitalization [2] and mortality [3]. Correction of anaemia with iron or erythropoietin (EPO) has been shown to reverse left ventricular hypertrophy in CKD [3]. Perhaps more importantly, a recent study has shown that correction of even mild anaemia [mean entry haemoglobin (Hb) of  $10.16 \pm 0.95$  g/dl] resulted in improvement of cardiovascular symptoms and hospitalization in patients with congestive heart failure [4]. From this study, we may extrapolate that even mild anaemia should be corrected, especially in patients with cardiac dysfunction, which is well known to be common in renal transplant recipients [5]. In addition, cardiovascular disease (CVD) is the leading cause of mortality in kidney transplant recipients and the death rate from CVD in this population is twice as high as in the general population [5]. Hence, it would be advisable to prevent and treat anaemia in kidney transplant recipients.

However, the incidence or prevalence of anaemia in kidney transplant recipients has not been well studied. A few small studies [6–8] have shown a high prevalence of this under-recognized problem and one recent large European study confirmed these results [9].

The purpose of this study was to elucidate the prevalence and risk factors for anaemia during the first year after the kidney transplantation. We obtained data on 192 consecutive kidney transplant recipients who underwent renal transplantation between January 1995 and November 1999 from a prospectively recorded database and studied the prevalence and risk factors for anaemia.

### **Subjects and methods**

We studied 192 adult kidney transplant recipients who received allografts between January 1995 and November

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**Table 1.** Patient characteristics

Total number of patients	192	
Age at transplant (year)	16–69 (44 ± 13; mean ± SD)	
Gender	Male	116 (60.4%)
	Female	76 (39.6%)
Race	AA	112 (58.3%)
	Non-AA	80 (41.7%)
Aetiology of ESRD	SLE	13 (6.8%)
	DM	66 (34.4%)
	Others	113 (58.8%)
Type of transplant	Cadaveric	97 (50.5%)
	Living related	75 (39.1%)
	Living unrelated	20 (10.4%)
Number of patients who had	Delayed graft function	30 (15.6%)
	Acute rejection ≥1	60 (31.2%)
	CMV infection	11 (5.7%)
Use of	MMF	146 (76.0%)
	AZA	42 (21.9%)
	ACEI or ARB	32 (16.7%)
	EPO	3 (1.6%)
	Iron supplement	15 (7.8%)

DM, diabetes mellitus; HTN, hypertension; CGN, chronic glomerulonephritis; ADPKD, autosomal dominant polycystic kidney disease; DGF, delayed graft function.

1999 and had at least 1 year of post-transplant follow up data at the Henry Ford Hospital, Detroit, which is a tertiary referral centre in Michigan, USA.

### Demographics (Table 1)

Among 192 patients [age at transplant ranged between 16 and 69, 44 ± 13(mean ± SD)], 116 (60.4%) were males and 76 were females. Fifty-eight per cent ( $n=112$ ) were African Americans (AA). Thirteen (6.8%) and 66 (34.4%) patients, respectively, had systemic lupus erythematosus (SLE) and diabetes mellitus as the cause of end-stage renal disease (ESRD). Ninety-seven patients (50.5%) were cadaver transplant recipients and 95 were living donor transplant recipients [75 living related and 20 living unrelated]. Thirty-two (16.7%) patients had been on angiotensin converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB) for 1 year after transplantation. Thirty patients experienced delayed graft function and 11 had cytomegalovirus (CMV) infection. Only three out of 192 patients (1.6%) were on EPO and 15 (7.8%) were on oral iron supplementation.

Immunosuppressive regimens were as follows; steroid (methylprednisolone or prednisolone) was given to all the patients but nine. Steroid was tapered down to a maintenance dose of 10 mg/day, equivalent to prednisolone, by 6 months post-transplant unless they were treated for rejection. All patients received calcineurin inhibitors with 71 patients on tacrolimus and 121 patients on cyclosporine, 15 of whom were changed to a tacrolimus-based regimen during the study period. Target level of cyclosporine was 200–250 ng/ml during the first 3 months and 150–200 ng/ml thereafter; that of tacrolimus was 10–15 ng/ml during the first 3 months and 5–10 ng/ml thereafter. Forty-two patients (21.9%) were on an azathioprine (AZA)-based immunosuppressive regimen and 146 (76.0%) were on a mycophenolate mofetil (MMF)-based immunosuppressive regimen (four were neither on MMF nor AZA). Dose of AZA was 2 mg/kg/day

and that of MMF was 1.5–3 g/day throughout the first year post-transplant.

Iron profile was checked in only 31 patients out of 86 who had anaemia by WHO definition during the first post-transplant year and 15 out of those 31 patients had ferritin levels <100 mg/dl or transferrin saturation <20%. All patients except one of these iron deficient patients had iron supplementation. Only three out of 86 patients were treated with EPO and all of these patients had Hb <10 g/dl.

### Definition of anaemia

We adopted three different definitions for anaemia. One is the WHO criteria (Hb level <12 g/dl in females, and <13 g/dl in males). We also arbitrarily defined ‘significant’ anaemia as Hb level <11 g/dl in females and <12 g/dl in males and ‘severe’ anaemia as Hb level <10 g/dl in both genders.

### Methods

We recorded the Hb levels before transplantation, at 6 months and 1 year after transplantation. We performed univariate and multivariate analysis to find the risk factors for anaemia. The various variables, which are typically recognized as risk factors for anaemia were chosen for the univariate analysis. These were creatinine level (at 6 months and 1 year after transplantation), pre-transplant Hb level, female gender, cadaver renal transplantation, delayed graft function, use of ACEI or ARB, SLE as the underlying disease and CMV infection. We compared the Hb of patients who used AZA vs MMF because most of the patients were on either of these medications.

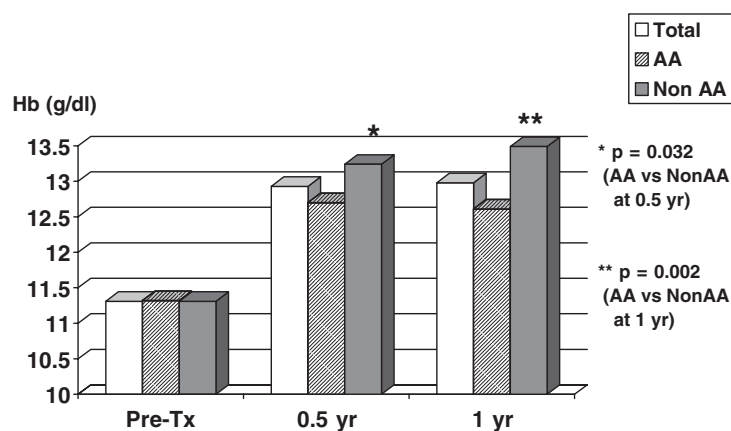
### Statistics

Data were expressed as mean ± SD unless indicated otherwise. We used SPSS® software version 10.0 (SPSS Inc., Chicago, IL, USA). We used the Mann–Whitney *U*-test in comparing the variables in two unrelated groups. Partial correlation analysis was done to determine the independent correlation of the different factors affecting anaemia/Hb levels after accounting for the different confounding factors. The continuous variables at different time points and in different groups of patients were compared using the Student’s *t*-test or binary regression models and a *P* value of <0.05 was considered significant. After we did the univariate analysis with the above variables, we selected variables that gave *P* values <0.25 to conduct multivariate analysis. For higher creatinine levels, risk ratio and *P* value were calculated for every increase of 1 mg/dl of creatinine. For lower Hb levels, risk ratio and two-tailed *P* values were calculated for every decrease of 1 g/dl of Hb.

## Results

### Prevalence of anaemia (Figure 1 and Table 2)

Pre-transplant Hb level was 11.3 ± 0.2 g/dl in both AA and non-AA patients. Hb level increased to 12.9 ± 0.1 g/dl (12.7 ± 0.2 in AA, 13.2 ± 0.2 in non-AA) at 6 months and 13.0 ± 0.1 g/dl (12.6 ± 0.2 in AA,



Hemoglobin	Total (n = 192)	AA (n = 112)	Non AA (n = 80)
Pre Transplant	11.31 ± 0.17 11.30 [10.30, 12.50]	11.32 ± 0.17 11.30 [10.00, 12.50]	11.31 ± 0.17 11.35 [10.30, 12.20]
0.5 year	12.93 ± 0.13 12.80 [11.80, 13.90]	12.70 ± 0.17 12.50 [11.53, 13.68]	13.24 ± 0.18 13.15 [12.13, 14.30]
1 year	12.98 ± 0.14 12.80 [11.70, 14.28]	12.61 ± 0.16 12.60 [11.38, 13.60]	13.49 ± 0.22 13.35 [12.20, 14.88]
P value (0.5yr vs. Pre-tx)	<0.001	<0.001	<0.001
P value (0.5yr vs. 1yr)	0.641	0.519	0.140

**Fig. 1.** Hb levels in the pre-transplant, 6-month and 1-year period after renal transplantation expressed both in bar graph and table format. The Hb level of total patients, AA and non-AA were expressed separately. Numbers are expressed as mean ± SE, median (25%, 75% percentile) and *P* values were calculated by paired *t*-test. yr, year; tx, transplantation.

\* denote *P* values of statistical significance.

**Table 2.** Prevalence of anaemia in AA and non-AA patients

		Total (n = 192)	AA (n = 112)	Non AA (n = 80)	<i>P</i> value (AA vs Non-AA)
0.5 year	WHO	41.1%	45.5%	35.0%	0.142
	'Significant'	19.3%	25.9%	10.0%	0.003*
1 year	WHO	44.8%	48.2%	40.0%	0.260
	'Significant'	19.8%	25.0%	12.5%	0.025*

Definition of WHO anaemia: Hb (g/dl) <12 g/dl in females, 13 g/dl in male. Definition of 'Significant' anaemia: Hb (g/dl) <11 g/dl in females, <12 g/dl in males. *P* values were calculated by *t*-test. Hb, haemoglobin; WHO, World Health Organization.

13.5 ± 0.2 in non-AA) at 1 year. The differences in Hb levels at both 6 months and 1 year compared with pre-transplant levels were significant (*P* < 0.001) but there was no significant difference in Hb level between 6 months and 1 year. Although there was no difference in pre-transplant Hb levels between AA and non-AA, Hb levels in AA race was significantly lower than those in the non-AA race at 6 months and 1 year after transplantation (*P* = 0.032 and *P* = 0.002, respectively).

Prevalence of anaemia defined by WHO (Hb <12 g/dl in females and <13 g/dl in males) was 41.1% at 6 months (45.5% in AA, 35% in non-AA) and 44.8% at 1 year (48.2% in AA, 40.0% in non-AA). Differences in the prevalence of WHO defined anaemia between AA and non-AA were not statistically significant either at 6 months (*P* = 0.142) or 1 year (*P* = 0.26) although there was a trend for higher prevalence of anaemia in AA race.

The prevalence of 'significant' anaemia (Hb <11 g/dl in female and <12 g/dl in male) was still high: 19.3% at 6 months (25.9% in AA, 10.0% in non-AA) and 19.8% at 1 year. 'Significant' anaemia was significantly more prevalent in AA race both at 6 months and 1 year (*P* = 0.003 and *P* = 0.025, respectively).

'Severe' anaemia (Hb <10 g/dl in both genders) at 6 months post-transplant was less common affecting seven out of 192 (3.6%) patients. Among these, all were females (100%), six were AAs (86%), and six were on MMF (86%). At 1 year, 10 out of 192 (5.2%) had 'severe' anaemia. Of these, seven were female (70%), seven were AAs (70%) and six were using MMF (60%).

Rate of acute rejection was not significantly different between AA (32.1%; 36 patients out of 112) and non-AA (30%; 24 out of 80) (*P* = 0.75). Incidence of delayed graft function was also not significantly higher in AA race (18.9%; 20/112) than in non-AA (11.3%; 9/80) (*P* = 0.21). There was no statistically significant

**Table 3.** Factors associated with 'significant' anaemia by univariate analysis

Variables	0.5 year		1 year	
	RR (95% CI)	P value	RR (95% CI)	P value
AA race	2.59 (1.25, 5.39)	0.006 <sup>a</sup>	2.00 (1.03, 3.88)	0.032 <sup>a</sup>
Female gender	1.16 (0.65, 2.08)	0.612	2.10 (1.19, 3.73)	0.010 <sup>a</sup>
Higher serum creatinine	2.09 (1.03, 4.22)	0.040 <sup>a</sup>	1.52 (0.87, 2.65)	0.139
Lower pre-Tx Hb	1.11 (0.89, 1.39)	0.343	1.22 (0.97, 1.53)	0.082
Cadaveric donor	1.03 (0.58, 1.84)	0.910	0.57 (0.32, 1.04)	0.060
Episode of DGF	1.05 (0.53, 2.29)	0.912	0.46 (0.15, 1.41)	0.143
Episode of acute rejection	1.16 (0.64, 2.35)	0.625	0.99 (0.54, 1.66)	0.977
Episode of CMV infection	0.42 (0.06, 2.78)	0.321	0.41 (0.06, 2.71)	0.304
SLE as a cause of ESRD	1.21 (0.43, 3.43)	0.719	1.62 (0.68, 3.87)	0.304
Use of AZA	0.78 (0.37, 1.66)	0.472	0.90 (0.44, 1.81)	0.927
Use of MMF	1.11 (0.49, 2.56)	0.800	0.68 (0.32, 1.49)	0.337
Use of ACEI/ARB	1.17 (0.56, 2.42)	0.682	1.33 (0.68, 2.64)	0.418

P values calculated by  $\chi^2$  test for nominal variable and binary logistic regression for numerical variables. Risk ratios for higher creatinine and lower pre-transplant Hb are odds ratio for each 1 mg/dl increase and 1 g/dl decrease, respectively. RR, risk ratio (relative risk); CI, confidence interval; Pre-Tx, pre-transplant; DGF, delayed graft function.

difference in pre-transplant Hb level ( $11.3 \pm 1.5$  vs  $11.3 \pm 1.7$  g/dl,  $P=0.889$ ), serum creatinine level at 6 months ( $1.58 \pm 0.43$  vs  $1.58 \pm 0.51$  mg/dl,  $P=0.700$ ) and at 1 year ( $1.63 \pm 0.55$  vs  $1.67 \pm 0.60$  mg/dl,  $P=0.689$ ) between AA and non-AA patients. In addition, minimum serum creatinine levels during the first 3 months was  $1.33 \pm 0.31$  mg/dl in AA and  $1.34 \pm 0.31$  mg/dl in non-AA ( $1.34 \pm 0.31$  mg/dl in total) and the difference was not significant ( $P=0.817$ ).

#### Risk factors for anaemia (Tables 3 and 4)

To elucidate the risk factors for anaemia after transplantation, we conducted the univariate analysis of possible risk factors for 'significant' anaemia defined as Hb level  $<11$  g/dl in women and  $<12$  g/dl in men. Univariate analysis showed that only a higher creatinine level and AA race were significant risk factors at 6 months. No other variables gave P values  $<0.25$ . At 1 year, in addition to AA race and higher creatinine level (defined as every 1 mg/dl increase in serum creatinine), female gender also was a significant risk factor. In addition, cadaveric donor transplant, delayed graft function and lower pre-transplant Hb level had P values  $<0.25$ .

**Table 4.** Factors associated with 'significant' anaemia by multivariate analysis

Variables	Relative risk (95% CI)	P value
Risk of 'Significant' anaemia at 0.5 year post-transplant		
AA race	3.17 (1.35, 7.43)	0.008
Higher serum creatinine	2.09 (1.02, 4.28)	0.043
Risk of 'Significant' anaemia at 1 year post-transplant		
AA race	2.18 (0.94, 5.02)	0.068
Female gender	3.38 (1.46, 7.85)	0.005
Higher serum creatinine	2.30 (1.22, 4.32)	0.010
Cadaveric donor	1.56 (0.86, 2.82)	0.142
Lower pre-Tx Hb	1.18 (0.93, 1.50)	0.164

Pre-Tx, pre-transplant.

Multivariate analysis showed that at 6 months, both AA race and higher creatinine levels were significant independent risk factors for anaemia ( $P=0.008$  and  $P=0.043$ , respectively) and at 1 year, significant independent risk factors for anaemia included a higher creatinine level ( $P=0.01$ ) and female gender ( $P=0.005$ ) even with a lower cut-off level of Hb by 1 g/dl in defining anaemia compared with male gender. AA race was not a significant independent risk factor at 1 year for 'significant' anaemia but there was a strong trend ( $P=0.068$ ).

## Discussion

After successful transplantation, erythropoiesis begins and serum EPO level increases to a sustained level in a month and subsequently Hb level increases towards normal within 3 months [10]. This means that the Hb level should be completely normalized by 6 months for most patients as long as they have a good allograft function. However, in some renal allograft recipients, anaemia persists or develops following transplantation. Most of them are associated with preoperative blood loss, allograft dysfunction (delayed graft function, acute rejection, chronic allograft dysfunction) [11] although some have anaemia with normal allograft function as well [12]. The prevalence and risk factors of anaemia with or without allograft dysfunction, however, are not well studied.

In this study, we have shown that anaemia is common;  $\sim 40\%$  by WHO criteria and  $\sim 20\%$  by definition with Hb  $<11$  g/dl in females and  $<12$  g/dl in males in the first post-transplant year in our population although 'severe' anaemia (defined as Hb  $<10$  g/dl) was not so common (3.6% at 6 month and 5.2% at 1 year).

This high prevalence of anaemia in renal transplant recipients has been reported elsewhere. Yorgin *et al.* observed adult renal transplant recipients over a 5-year

period and found 30% of the patients experienced anaemia (Ht <33%) during study period [6]. In the study by Lorenz *et al.*, prevalence of anaemia (Hb <12 g/dl in females and <13 g/dl in males) was 39.7% [7]. Mix *et al.*, observed a high prevalence of anaemia (Ht <36%) at 1 year (21%) and at 4 years (36%) and found that treatment of anaemia with iron or EPO was not common even among those with severe anaemia [8]. An even larger recent study from Europe confirmed this high prevalence of anaemia (38.6% during a 5-year post-transplant enrolment period). Although it is difficult to compare each of these studies because of the different definitions of anaemia and timings of checking it, it is very important to note that all the studies including ours confirmed the high prevalence of mild anaemia after renal transplantation.

Reported causes of anaemia in transplant recipients are many; iron deficiency [7,12,13], relative or absolute EPO deficiency or resistance primarily caused by impaired allograft function including acute rejection or delayed graft function [11,14], use of ACEI or ARB [15] and autoimmune disease such as SLE, malignancy or infection including CMV or parvovirus B19 [16]. Use of immunosuppressive drugs is also well documented to be associated with post-transplant anaemia (AZA [15], MMF [17], rapamycin and calcineurin inhibitors).

Among the possible risk factors listed above, we found that a higher creatinine value (defined as each 1 mg/dl increase in serum creatinine level), female gender and AA race were the only significant independent risk factors in our study.

It is very intriguing, and a unique finding to our knowledge, that AA race had a higher prevalence of anaemia, was an independent risk for anaemia at 6 months and a strong trend for anaemia at 1 year. Yorgin *et al.* [6] found that at 5 years post-transplant, AA race was associated with a statistically higher prevalence of anaemia but the number of patients were too small to lead to a meaningful conclusion. The purpose of this study was not to elucidate the mechanism of anaemia, and the reason AA race has a higher prevalence of anaemia remains to be elucidated. In general, AA race was reported to have anaemia more frequently than non-AA race. In a national survey in the US, 47% of AA compared with 42% of non-AA on haemodialysis had a haematocrit <33% [18], although pre-transplant Hb level was similar between AA and non-AA in our patients. Besarab *et al.* reported that acute rejection completely abrogates the normal erythropoietic response until the rejection is successfully reversed and delayed graft function is associated with the delay in this response [11]. AAs are believed to be more immunogenic and to have a higher rate of acute rejection and delayed graft function [19]. In our population, however, neither the rate of acute rejection nor delayed graft function was significantly different between AA and non-AA. Although level of renal allograft function (serum creatinine level) was not different between AA and non-AA patients in our study, higher prevalence of subclinical early acute

rejection and/or delayed graft function in AA might be responsible. Interestingly, Moore *et al.* showed a higher prevalence of iron deficiency in AA renal transplant recipients compared with non-AA counterparts [13] and iron deficiency is a major cause of anaemia in transplant recipients [6]. Unfortunately, we did not have the iron parameters in many of our patients to do any meaningful statistical calculation.

Similar to our observations, other studies [6,7,9] have shown that poor renal allograft function is an independent risk factor for anaemia. It is well described that production of EPO depends on allograft function [12].

Also, more females than males had mild anaemia both at 6 months and 1 year even though we set a lower threshold for Hb level in females as a definition of anaemia. The findings are inconsistent in other studies. The large European study did not show any gender difference in prevalence of anaemia (defined as Hb  $\leq$ 13 g/dl in males and  $\leq$ 12 g/dl in females) [9]. Other studies showed higher prevalence of anaemia in males [6,7]. The negative effect of female gender on Hb level has been reported in dialysis [18] and CKD patients [20].

The European study showed use of ACEI, ARB or AZA, MMF was associated with higher prevalence of anaemia [9]. Our study did not find the association of use of ACEI or ARB with anaemia. Because most of our patients were treated either with AZA or MMF, use of those agents was not considered as independent or dependent risk factors for anaemia.

Iron profile was checked only in 36% of our anaemic transplant recipients. About half of these patients had an iron profile indicative of iron deficiency (ferritin <100  $\mu$ g/dl or transferrin saturation <20%) and all except one had iron supplementation. EPO was given only in three out of seven severely anaemic (Hb <10 g/dl) patients. Suboptimal evaluation was seen in our population and has also been reported by Mix *et al.*, who showed that among transplant recipients who had Ht <30%, only 36% had iron studies, with 46% being supplemented with iron and only 40% receiving EPO [8]. Vanrenterghem *et al.* showed only 17.8% of severely anaemic (Hb  $\leq$ 11 g/dl in males and  $\leq$ 10 g/dl in females) received EPO [9]. EPO levels tend to be low in anaemic renal transplant recipients irrespective of the allograft function [12,14] and several studies have shown the acceptable efficacy of EPO treatment in post-transplant anaemia [11,14]. So early investigation of anaemia and iron deficiency and its therapy with iron supplement or EPO should be considered in anaemic transplant recipients.

In conclusion, we found that anaemia is common during the first year after transplantation and investigation and treatment of anaemia is suboptimal. We think that the effectiveness of early recognition and treatment on the survival of these needs to be studied in prospective studies. In addition to renal allograft dysfunction and female gender, we found that AA race (is an independent risk factor for anaemia. Although the reason why AAs have higher rates of anaemia remains

to be elucidated, this finding is intriguing and warrants further studies.

*Conflict of interest statement.* None declared.

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*Received for publication: 23.08.03*

*Accepted in revised form: 10.03.04*