HYPERHOMOCYST(E)INEMIA IN CHRONIC STABLE RENAL TRANSPLANT PATIENTS

David José de Barros Machado, Flávio Jota de Paula, Emil Sabbaga and Luiz Estevan Ianhez


Purpose: Hyperhomocyst(e)inemia is an important risk factor for atherosclerosis, which is currently a major cause of death in renal transplant patients. The aim of this study was to assess the influence of immunosuppressive therapy on homocyst(e)inemia in renal transplant recipients.

Methods: Total serum homocysteine (by high performance liquid chromatography), creatinine, lipid profile, folic acid (by radioimmunoassay—RIA) and vitamin B12 (by RIA) concentrations were measured in 3 groups. Group I patients (n=20) were under treatment with cyclosporine, azathioprine, and prednisone; group II (n=9) were under treatment with azathioprine and prednisone; and group III (n=7) were composed of renal graft donors for groups I and II. Creatinine, estimated creatinine clearance, cyclosporine trough level, lipid profile, folic acid, and vitamin B12 concentrations and clinical characteristics of patients were assessed with the aim of ascertaining determinants of hyperhomocyst(e)inemia.

Results: Patient ages were 48.8 ± 15.1 yr (group I), 43.3 ± 11.3 yr (group II); and 46.5 ± 14.8 yr (group III). Mean serum homocyst(e)ine (tHcy) concentrations were 18.07 ± 8.29 mmol/l in renal transplant recipients; 16.55 ± 5.6 mmol/l and 21.44 ± 12.1 mmol/l respectively for group I (with cyclosporine) and group II (without cyclosporine) (NS). In renal donors, tHcy was significantly lower (9.07 ± 3.06 mmol/l; group I + group II vs. group III, p<0.008). There was an unadjusted correlation (p<0.10) between age (r=0.427; p<0.005) body weight (r=0.412; p<0.05), serum creatinine (r=0.427; p<0.05), estimated creatinine clearance (r=0.316; p<0.10), and tHcy in renal recipients (group I +II). Independent regressors (r²=0.46) identified in the multiple regression model were age (coefficient= 0.253; p=0.009) and serum creatinine (coefficient=8.07; p=0.045). We found no cases of hyperhomocyst(e)inemia in the control group. In contrast, 38% of renal recipients had hyperhomocyst(e)inemia: 7 cases (35%) on cyclosporine and 4 (45%) without cyclosporine, based on serum normal levels.

Conclusions: Renal transplant recipients frequently have hyperhomocyst(e)inemia. Hyperhomocyst(e)inemia in renal transplant patients is independent of the scheme of immunosuppression they are taking. The older the patients are and the higher are their serum creatinine levels, the more susceptible they are to hyperhomocyst(e)inemia following renal transplantation.

cyst(e)inemia – in a cross-sectional study on three groups of patients divided according to presence or absence of cyclosporine in the treatment regimen. We have also assessed the factors known to influence homocysteine metabolism in this population.

SUBJECTS AND METHODS

Fasting blood samples were collected for analysis of total homocysteine (tHcy) by high-performance liquid chromatography with fluorescence detection. Normal serum total homocysteine concentration values ranged from 5.5 to 17 mmol/l.

Plasma folate and vitamin B12 levels were measured by radioimmunoassay. Serum creatinine, total cholesterol, LDL cholesterol (low-density lipoprotein), HDL cholesterol (high-density lipoprotein), and triglycerides were determined using standard automated clinical chemistry laboratory techniques. Creatinine clearance was estimated from the Cockcroft-Gault formula. Whole blood cyclosporine through levels were analyzed with TDx Immunosuppressant Drug Assays – Cyclosporine Monoclonal Whole Blood (Abbot Laboratories).

Twenty-nine renal transplant patients were studied at least 12 months after transplantation, undergoing treatment with fixed doses of immunosuppressive drugs for 6 months and having serum creatinine levels of less than 2.0 mg/dl. Study patients were not under treatment with any vitamin supplement following the transplantation. End-stage renal disease was due to chronic glomerulonephritis (n=11), chronic pyelonephritis (n=5), nephro sclerosis (n=5), diabetic nephropathy (n=3), polycystic kidney disease (n=2) or undetermined cause (n=3).

Patients were divided into 2 groups according to immunosuppression therapy:
- Group I: 20 renal transplant patients on cyclosporine, azathioprine, and prednisone;
- Group II: 9 renal transplant patients on azathioprine and prednisone;
- And the third group enrolled comprised renal donors (control group):
  - Group III: 7 renal graft donors for groups I and II.

Results were expressed as mean ± standard deviation (SD). Continuous variables were compared by t-test, and the chi-square test was applied for estimating the occurrence of categorical variables. Pearson Product Moment correlation was used for unadjusted correlation between continuous variables. Multiple regression analysis was performed to identify independent predictors of tHcy. Statistical significance was defined as tests with a probability of < 0.05. The statistical analyses were performed in SigmaStat 2.0 software.

RESULTS

Characteristics of patients and control groups are summarized in Table 1. The mean plasma homocyst(e)inemia concentration was 18.07 ± 8.29 mmol/l in renal transplant recipients: 16.55 ± 5.6 mmol/l (group I, with cyclosporine), and 21.44 ± 12.1 mmol/l (group II, without cyclosporine) (NS). In renal donors, tHcy was significantly lower (9.07 ± 3.06 mmol/l; group I + group II vs. group III, p<0.008).

Pearson correlation was tested using age, body weight, dialysis duration before transplantation, transplant duration, serum creatinine, estimated creatinine clearance, cholesterol, HDL – cholesterol and LDL – cholesterol, trig-

<table>
<thead>
<tr>
<th></th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
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</thead>
<tbody>
<tr>
<td>n</td>
<td>20</td>
<td>9</td>
<td>7</td>
</tr>
<tr>
<td>Age (yr; mean ± SD)</td>
<td>48.8 ± 15.1</td>
<td>43.3 ± 11.3</td>
<td>46.5 ± 14.8</td>
</tr>
<tr>
<td>Sex (number female)</td>
<td>7</td>
<td>2</td>
<td>6</td>
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<tr>
<td>Serum creatinine (mg/dl; mean ± SD)</td>
<td>1.18 ± 0.26</td>
<td>1.33 ± 0.44</td>
<td>0.97 ± 0.18</td>
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<tr>
<td>Body weight (Kg; mean ± SD)</td>
<td>72.5 ± 16.8</td>
<td>66.8 ± 11.9</td>
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<td>Estimated creatinine clearance (ml/min ; mean ± SD)</td>
<td>73.2 ± 25.1</td>
<td>69.5 ± 20.1</td>
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<td>Transplant duration (months; mean ± SD)</td>
<td>49.4 ± 28.2</td>
<td>58.2 ± 18.2</td>
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<td>Dialysis duration before transplantation (months; mean ± SD)</td>
<td>32.4 ± 25.5</td>
<td>39.8 ± 13.3</td>
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<tr>
<td>tHcy (micromol/l; mean ± SD)</td>
<td>16.5 ± 5.6</td>
<td>21.4 ± 12.1</td>
<td>9.1 ± 3.0 **</td>
</tr>
<tr>
<td>Folate (ng/ml; mean ± SD)</td>
<td>7.7 ± 3.5</td>
<td>7.4 ± 1.2</td>
<td>6.7 ± 1.6 **</td>
</tr>
<tr>
<td>Vitamin B12 (pg/ml; mean ± SD)</td>
<td>315.0 ± 139.1</td>
<td>418.0 ± 397.0</td>
<td>350.0 ± 176.5</td>
</tr>
<tr>
<td>Triglycerides (mg/dl; mean ± SD)</td>
<td>219.4 ± 115.3</td>
<td>154.2 ± 103.3</td>
<td>129.7 ± 64.2</td>
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<td>Cholesterol (mg/dl; mean ± SD)</td>
<td>227.8 ± 40.9</td>
<td>183.8 ± 29.3 *</td>
<td>194.4 ± 36.7</td>
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<td>HDL-cholesterol (mg/dl; mean ± SD)</td>
<td>51.5 ± 11.4</td>
<td>54.0 ± 12.0</td>
<td>50.1 ± 5.3</td>
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<tr>
<td>LDL-cholesterol (mg/dl; mean ± SD)</td>
<td>144.0 ± 43.1</td>
<td>105.7 ± 16.7 *</td>
<td>116.2 ± 34.1</td>
</tr>
</tbody>
</table>

* p< 0.05 group I vs. group II
** p< 0.05 group I + II vs. group III
lycercides, folate level, vitamin B12 level, azathioprine, and prednisone doses vs. homocyst(e)inemia. Unadjusted correlations (p<0.10) were found between age (r=0.427; p<0.005), body weight (r=0.412; p<0.05), serum creatinine (r=0.427; p<0.05), estimated creatinine clearance (r=0.316; p<0.10), and tHcy in renal recipients (group I +II). There was no statistically significant correlation between sex and tHcy. Independent regressors (r²=0.46) identified in the multiple regression model were age (coefficient= 0.253; p=0.009) and serum creatinine (coefficient=8.07; p=0.045).

Total serum homocysteine in the cyclosporine-treated group had no one independent regressor in this study, when age, body weight, dialysis duration before transplantation, transplant duration, serum creatinine, cyclosporine trough level, estimated creatinine clearance, cholesterol, HDL-cholesterol and LDL-cholesterol, triglycerides, folate level, vitamin B12 level, azathioprine dose, prednisone dose, and cyclosporine dose were included.

We found no cases of hyperhomocyst(e)inemia in the control group. In contrast, 38% of renal recipients had hyperhomocyst(e)inemia: 7 cases (35%) in the cyclosporine-treated group and 4 (45%) in the group not receiving cyclosporine, based on plasmatic normal levels. If there was a positive and direct relationship between serum and plasma homocysteine levels, we would state, based on the Kang et al. classification, that for patients receiving cyclosporine, 35% had moderate hyperhomocyst(e)inemia; for patients not receiving cyclosporine (group II), 33% had moderate and 12% had intermediate hyperhomocyst(e) inemia.

DISCUSSION

Homocysteine is a sulfur-containing non-essential amino acid that is formed as a product of methionine metabolism. Its chemical structure is 2-amin-4-mercaptobutanoic acid.

Methionine is converted to homocysteine through S-adenosyl methionine. Then homocyst(e)ine undergoes either remethylation or transsulfuration. In the remethylation pathway, homocysteine is salvaged by the acquisition of a methyl group in a reaction catalyzed by methionine synthase. Vitamin B12 (cobalamin) is the precursor of methylcobalamin, which is the cofactor for methionine synthase, and N5- methyl-tetrahydrofolate is the methyl donor in this reaction. Remethylation can also be catalyzed by betaine-homocysteine methyl transferase.

Under conditions in which an excess of methionine is present or cysteine synthesis is required, homocysteine condenses with serine to form cystathionine in a reaction catalyzed by the vitamin-B6-dependent enzyme, cystathionine ß-synthase. Cystathionase is subsequently hydrolyzed to form α-ketobutyrate and cysteine, which may in turn be incorporated into glutathione or further metabolized to sulfate and excreted in the urine.

Clinical studies involving homocysteine generally rely on the measurement of total plasma homocysteine, which includes homocysteine, mixed disulfides involving homocysteine, homocysteine thiolactone, free homocysteine, and protein-bound homocyst(e)ine. The sum of all free and protein-bound forms is referred to as total homocysteine (tHcy) or as homocyst(e)ine to emphasize the uncertain distribution of reduced sulfhydryl and oxidized disulfide moieties. This correct but cumbersome convention is frequently overlooked but needs to be acknowledged.

Normal total plasma homocysteine concentration ranges from 5 to 15 mmol per liter in the fasting state, and serum levels are known to be higher in the fasting state. Kang et al. have classified hyperhomocyst(e)inemia as moderate (from 15 to 30 mmol per liter), intermediate (>30 to 100 mmol per liter), and severe (>100 mmol per liter) on the basis of fasting plasma measured concentrations. An oral challenge (100 mg/kg) can be given to persons suspected of hyperhomocyst(e)inemia who have normal fasting homocyst(e)ine levels. Plasma homocyst(e)ine concentrations are determined before methionine challenge and 4 and 8 hours afterwards. Hyperhomocyst(e)inemia is considered to be present if the concentration of tHcy is more than 2 standard deviations above the mean. The oral methionine challenge is more useful for subjects with cystathionine-ß-synthase deficiency than for those with methylenetetrahydrofolate reductase deficiency.

There are genetic and acquired causes of homocyst(e)inemia. Rare inborn errors of metabolism result in elevation of plasma and urine homocysteine. The homozygous deficiency of cystathionine-ß-synthase is the most common cause and is associated with plasma tHcy levels up to 400 mmol per liter. Atherothrombotic complications frequently develop in young adulthood and are often fatal. Heterozygotes typically have plasma levels in the range of 20 to 40 mmol per liter. A homozygous deficiency of N5-N10-methylene-tetrahydrofolate reductase (MTHFR) carries a much worse prognosis, in part due to the complete lack of effective therapy. Kang et al. reported a more common genetic defect that is phenotypically expressed as a thermolabile form of MTHFR that has a prevalence of 5% in the general population and 17% among patients with coronary disease. Deficiencies in vitamin cofactors required for homocysteine metabolism, like folate, vitamin B12, and B6, may promote...
hyperhomocyst(e)inemia, and supplementation can normalize concentrations of homocysteine. Negative correlations have been related between folate, cobalamin, and tHcy. Several drugs can interfere with the metabolism of homocysteine such as methotrexate, phenytoin, and theophylline.

In spite of in vitro studies reporting renal metabolism of homocysteine, and in vivo studies in which the concentration of homocysteine in the plasma of rats was increased due to its substantial uptake and metabolism by the kidney, van Guldener et al. showed no net renal extraction of homocysteine in fasting humans. These findings rekindle a search for “uremia-induced” extrarenal defects in homocysteine metabolism. Although it was said that urinary homocysteine excretion was minimal, hyperfiltrating diabetic subjects with supernormal glomerular filtration rates may have subnormal fasting tHcy levels. Indeed, it should be stressed that glomerular filtration rate and cystatin C are independent determinants of tHcy, and they are much better determinants than is creatinine concentration. Although there is a direct relationship between tHcy and KT/V (an index of dialysis adequacy), the dialytic amount of tHcy did not seem to contribute significantly to its removal.

In 1969, McCully described prominent arterial damage in patients with a deficiency in methionine metabolism and homocysteinemia and hypothesized that homocysteine derivatives played a role in the pathogenesis of atherosclerosis. Histopathologic hallmarks of homocysteine-induced vascular injury include intimal thickening, elastic lamina disruption, smooth muscle hypertrophy, marked platelet accumulation, and the formation of platelet-enriched occlusive thrombi. The postulated effects involve oxidative damage to vascular endothelial cells and increased proliferation of vascular smooth cells after oxidative metabolism of homocysteine to homocystine and homocysteine thiolactone. Oxidative modification of low-density lipoprotein (LDL) promotes the formation of foam cells, which in turn yields another source of reactive species. A direct endothelial cell injury can also occur. It seems that prostacyclin production is unlikely to result from homocysteine effects. Prolonged exposure of endothelial cells to homocysteine impairs production of nitric oxide and alters the normal antithrombotic phenotype of the endothelium by attenuation of endothelial cell tissue-plasminogen-activator binding sites, activation of factor V, inhibition of protein C, and heparan sulfate, and decreasing endothelial antithrombotic activity due to changes in thrombomodulin function.

There is abundant epidemiological evidence of the association between hyperhomocyst(e)inemia and atherothrombosis either in normal or end-stage renal failure population. Patient death from cardiovascular causes is an important reason for transplant failure over time. Fifty to sixty percent of deaths are directly attributable to cardiovascular disease. Future advances in long-term renal graft survival will depend largely on the success of preventing myocardial infarction and death in this patient population.

Renal transplant recipients are prone to atherosclerotic complications, and risk factors independently associated in a multivariate analysis after accounting for pretransplant vascular disease were: increasing patient age, diabetes mellitus, male gender, cigarette smoking, hypertension, and elevated serum cholesterol levels. The data had also suggested that an increased prevalence of known risk factors explains the high incidence of cardiovascular disease in the renal transplant recipient. Immunosuppressive drugs that prevent allograft rejection could exacerbate atherosclerosis. However, this possibility could not explain all cases, so efforts were made to identify other risk factors.

Fasting hyperhomocyst(e)inemia is an independent risk factor for coronary artery disease, stroke, peripheral vascular atherosclerosis, and for arterial and venous thromboembolism. The interaction of hyperhomocyst(e)inemia with hypertension and smoking is strong, and the combined effect is more than multiplicative. The combined effect of homocysteine and cholesterol is additive.

Massy et al. were pioneers in the study of homocysteine metabolism in renal transplant patients, and they found by stepwise discriminant analysis and by logistic regression analysis in 42 patients that homocysteine was also a risk factor associated with cardiovascular disease in this population.

Total homocysteine is significantly increased in renal transplant patients as compared to healthy controls or a matched renal dysfunction group. Determinants of homocyst(e)ine concentration in renal transplant patients are listed in table 2.

In 1996, Arnaudot et al. reported that renal transplant recipients on cyclosporine had significantly higher plasma homocyst(e)inemia than those not on cyclosporine (19.7 ± 7.6 vs. 16.2 ± 4.8 mmol/l, mean ± S.D.) but in 1998, they described no correlation between plasma homocyst(e)ine and cyclosporine concentration or doses of cyclosporine, prednisone, and azathioprine. It is not known how cyclosporine could interfere in homocysteine metabolism, but cyclosporine could be a methyl donor, since during its hepatic metabolism, hydroxylation and N-demethylation are important reactions. Moreover, Ducloux et al reported that patients with or without cyclosporine...
had similar plasma homocyst(e)ine concentrations. Woodside et al found no difference in homocysteineemia between patients receiving cyclosporin (n = 39, homocysteine 11.0 ± 1.5 mmol/l), and patients receiving prednisolone + azathioprine (n = 16, 10.8 ± 1.6 mmol/l, mean ± S.D.), although there was a significant correlation between homocysteine and serum cyclosporin concentration in the sub-group of patients receiving that immunosuppressive regimen (r = 0.42, P < 0.05). Gilfix et al showed a negative correlation of tHcy to cyclosporine when using C2 levels (level of cyclosporine measured in the second hour after administration), but which was consistent with the negative correlation between creatinine concentration and C2 levels. In our previous study, although tHcy was similar under the two schemes of immunosuppressors, there was a strong negative correlation between tHcy and the cyclosporine trough level (r = -0.79 and p= 0.01). As yet, we have not found a difference between tHcy levels with or without cyclosporine or an effect of cyclosporine trough level on homocyst(e)inemia.

Azathioprine, another immunosuppressive drug, causes absolute or relative deficiency in folate and/or cobalamin, a condition also reported to increase homocyst(e)inemia. Födinger et al observed no effect of azathioprine on homocysteine metabolism. In contrast, Mazouz et al concluded that the addition of azathioprine to the standard immunosuppressive regimen further increased Hcy serum levels in renal transplant recipients, which could be mediated by absolute or relative deficiency in folate.

In adult male rats, mean plasma homocysteine concentration after treatment with cortisol was substantially lower, compared with the level of plasma homocysteine in the control group, indicating a significant protective effect of steroid on plasma homocysteine levels.

We did not observe a correlation between azathioprine or prednisone doses and homocyst(e)inemia in either of the recipient groups or between cyclosporine doses in the group taking cyclosporine.

It had been previously reported that there was no difference in homocyst(e)inemia levels between individuals treated with tacrolimus and cyclosporine, and there was no correlation between homocysteine and immunosuppressant trough levels or the development of histologically diagnosed chronic graft nephropathy.

Although vitamin B6 treatment resulted in a 22.1% reduction in geometric-mean post-methionine-loading increases in plasma total homocysteine levels, and folic acid plus vitamin B12 treatment caused a 26.2% reduction in geometric-mean fasting plasma total homocysteine levels, their effect on cardiovascular disease is not known.

We must stress that hyperhomocyst(e)inemia is an important problem in the follow-up of renal transplant recipients. Renal recipients with renal function loss and the older recipients are the most at risk population. Since hyperhomocyst(e)inemia increases cardiovascular disease risk and patient survival, efforts have to be made to search for other possible determinants of homocyst(e)inemia and to reduce it.

### Table 2 - Determinants of homocyst(e)in concentration in renal transplant patients.

<table>
<thead>
<tr>
<th>Reference</th>
<th>Hyperhomocyst(e)inemia µmol/l</th>
<th>Determinants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arnadottir et al.⁹⁰</td>
<td>27.7 ± 14.8**</td>
<td>glomerular filtration rate, creatinine concentration, plasma folate level</td>
</tr>
<tr>
<td>Ducloux et al.⁶</td>
<td>21.4 ± 10.2**</td>
<td>glomerular filtration rate, creatinine concentration, plasma folate level</td>
</tr>
<tr>
<td>Ducloux et al.⁵</td>
<td>21.3 ± 9.7**</td>
<td>glomerular filtration rate, plasma folate level</td>
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<tr>
<td>Arnadottir et al.⁴</td>
<td>19.0 ± 6.9**</td>
<td>glomerular filtration rate, cyclosporine-treated group, sex, plasma folate level</td>
</tr>
<tr>
<td>Machado et al.²⁰</td>
<td>18.4 ± 9.6⁹</td>
<td>glomerular filtration rate, creatinine concentration</td>
</tr>
<tr>
<td>Machado et al. – this paper</td>
<td>18.0 ± 8.2⁹</td>
<td>creatinine concentration, age, weight</td>
</tr>
<tr>
<td>Boston et al.²²</td>
<td>15.6**</td>
<td>creatinine concentration, age, pyridoxal 5'-phosphate level, plasma folate level, plasma vitamin B12 level</td>
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<tr>
<td>Födinger et al.¹⁵</td>
<td>17.6 ± 9.2**</td>
<td>glomerular filtration rate, plasma folate level, MTHFR genotype , sex, body index mass, age and plasma vitamin B12 level</td>
</tr>
</tbody>
</table>

* - serum level
** - plasma level

Objetivos: A hiper-homocisteinemia é um fator de risco importante para aterosclerose e, esta é uma das principais causas de óbito em transplantados renais. O objetivo deste estudo é avaliar a influência da terapêutica imunossupressora na homocisteinemia de receptores de transplante renal.

Casuística e Método: Vinte e nove pacientes foram divididos em dois grupos: grupo I (n=20) – pacientes transplantados renais em uso de ciclosporina, azatioprina e prednisona; grupo II (n=9) – pacientes transplantados renais em uso de azatioprina e prednisona; grupo III (n=7) doadores de rim para pacientes dos grupos I e II, constituíram o grupo controle. O nível sérico de creatinina e o clearance estimado de creatinina, o nível sérico de ciclosporina, o perfil de lipídeos, a concentração de ácido fólico e vitamina B12 e as características clínicas dos indivíduos foram avaliados na procura de determinantes da homocisteinemia. A concentração sérica de homocisteína foi medida através da cromatografia de alta resolução e a concentração de ácido fólico e vitamina B12 por radioimunoensaio.

Resultados: Os pacientes tinham 48.8 ± 15.1 aa e 43.3 ± 11.3 aa respectivamente, nos grupos I e II e os doadores 46.5 ± 14.8 aa. A homocisteinemia média dos pacientes transplantados renais foi de 18.07 ± 8.29 mmol/l. No grupo de pacientes em uso de ciclosporina foi de 16.55 ± 5.6 mmol/l e no grupo sem ciclosporina foi de 21.44 ± 12.1 mmol/l (NS). No grupo de doadores foi significativamente menor (9.07 ± 3.06 mmol/l; grupo I + grupo II vs. grupo III, p<0.008), não tendo sido encontrado nenhum caso de hiper-homocisteinemia. Houve correlação entre idade (r=0.427; p<0.005), peso corpóreo (r=0.412; p<0.05), creatinina sérica (r=0.427; p<0.05), clearance estimado de creatinina (r=0.316; p<0.10) e tHcy nos pacientes transplantados renais. Porém no modelo de regressão múltipla, só foram significativos idade (coeficiente = 0.253; p=0.009) e creatinina sérica (coeficiente =8.07; p=0.045). No grupo de transplantados renais encontramos 38% de casos com hiper-homocisteinemia sendo sete casos (35%) do grupo I e quatro casos (45%) do grupo II, baseado nos níveis séricos normais.

Conclusões: Os pacientes transplantados renais apresentam hiper-homocisteinemia independente do esquema de imunossupressão que estejam utilizando. A hiper-homocisteinemia após o transplante renal tem como determinantes a idade do receptor e o seu nível de creatinina sérica.


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