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RESEARCH ARTICLE

The Relationship Between Chronic Inflammation and Glucidic-Lipidic Profile Disorders in Kidney Transplant Recipients

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Introduction: Chronic inflammation has a proven role in atherogenesis, lipid profile parameters being related to cytokine production. In kidney transplant recipients, interleukin 6 (IL-6) is significantly associated with graft-related outcomes and also alterations of cholesterol and triglyceride metabolism. The aim of this study was to investigate the relationship between chronic inflammation and glucidic-lipidic metabolism disorders in a group of patients with kidney transplantation as renal replacement therapy. **Methods**: A prospective observational study which enrolled thirtysix non-diabetic kidney transplant recipients was conducted in the Nephrology and Peritoneal Dialysis Department, County Clinic Hospital of Tirgu Mures. The study group was divided as following: recipients with serum IL-6 concentration higher than 3.8 pg/ml (group A) and IL-6 within the normal range (group B). **Results**: Allograft recipients with higher serum IL-6 had significant higher erytrocyte sedimentation rate(ESR, p=0.0067). Patients with over-the-range levels of IL-6 had significant higher levels of serum cholesterol and LDL-cholesterol respectively (p=0.0242 and p=0.0081). Serum Apo-B was also significant higher in Group A than Group B. Protein excretion was significant higher in patients from group A (p=0.0013). No statistical significant relationship could be proven between elevated levels of IL-6 and hbA1c, insulin and glycosuria disturbances in the two groups. Also, we found no statistical significant association between resistivity and pulsatility indices (both hilum and intragraft) or carotid intima media thickness. **Conclusion**: Serum interleukin 6 is related to lipid profile disorders and less to glucidic metabolism anomalies in non-diabetic kidney transplant recipients.

Keywords: inflammation, kidney transplant, interleukin 6, lipid profile disorders, proteinuria

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Introduction

Chronic inflammation and the response of immune system have a proven role in atherosclerosis development [1,2]. As an example, in maintaining hemodialysis patients, lipid profile parameters were related to interleukin 6 (IL-6) [3]. Allograft recipients, by receiving a non-self organ, have an aditional mechanism of activation [4-7]. Cytokines can induce production of IL-6, a key marker in the coordination of the immune response, and also increases in acute phase inflamatory markers [8,9].

Increases in IL-6 production alters triglyceride metabolism leading to hypertriglyceridemia and elevated levels of very low density lipoprotein (VLDL) cholesterol due to excessive synthesis or decrease in VLDL clearance [10]. Moreover, the effect of cytokines on triglyceride metabolism seems not to be mediated by hormones such as insulin. A study performed by Ettinger et al, has shown that IL-6 increases cholesterol synthesis and decreases cholesterol secretion [11].

In kidney transplant recipients, IL-6 is significantly associated with graft-related outcomes [12].

The aim of this study was to investigate the relationship between chronic inflammation and glucidic-lipidic metabolism disorders in a group of patients with kidney transplantation as renal replacement therapy.

Methods

A prospective observational study which enrolled thirtysix non-diabetic kidney transplant recipients was conducted in the Nephrology and Peritoneal Dialysis Department, County Clinic Hospital of Tirgu Mures, between May 1st 2014 and August 1st 2015. Demographic, transplant related data and relevant laboratory data were collected. All of these patients have performed oral glucose tolerance test (OGTT) prior to inclusion.

Glycated haemoglobin (HbA1c), blood serum high sensitive C-reactive protein (hsCRP) and Apolipoprotein B (Apo-B) were determined using the immunoturbidimetric method (Roche Romania SRL on behalf of Roche-Diagnostics,Basel, Switzerland). Blood serum interleukin 6 and insulin were assesed using the chemiluminescence immunoassay method (IMMULITE® 1000 Immunoassay System, Siemens Healthcare GmbH, Henkestr. 127, 91052 Erlangen, Germany).

In order to compare glucidic-lipidic parameters and their relationship with chronic inflammation, the study group was divided as following: recipients with serum IL-6 concentration higher than 3.8 pg/ml (group A) and IL-6 within the normal range (group B).

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Glomerular filtration rate was estimated usind the Modified Diet in Renal Disease equation (MDRD) [13,14].

Hilum resistivity (RI) and pulsatility (PI) indices were obtained by transplanted kidney Doppler ultrasound examination. Intrarenal RI and PI were considered as an average value of the measurements performed by the same physician at three different intra-graft levels (cranial, medium and caudal).Carotid intima-media thickness (CIMT) was assesed via Doppler ultrasound by the same neurologist, as a mean value for twelve measurements (three horizontal-lateral and three vertical-anterior assessments each side).

The study protocol and design were approved by the Ethics Committees of both County Clinic Hospital and University of Medicine and Pharmacy in Tirgu Mures. All patients have provided written informed consent prior to enrollment in this study.

Statistical analysis was performed using Graph Pad Prism 6.0 and statistical significance was defined as $p<0.05$.

Results

Thirtysix adult kidney allograft recipients with no active infection or neoplastic disease and negative OGTT for diabetus mellitus were included in our study. We selected only patients with at least 6 months elapsed from surgery, the number of cases and transplantation period, is shown in Figure 1.

Main characteristics of the study group are shown in Table I. Our study population was mainly male gender (69.44%) and renal allograft prelevation was from brain dead donors in 52.77% of the cases. The most frequent underlying cause for renal replacement therapy was represented by glomerular nephropathies (52.77%). Average serum creatinine at inclusion was 1.653±0.8185 mg/dl, and average weight 78.19±18.31 kg.

Comparative analysis between the two groups (group A and group B) is shown as mean±SEM (standard error of mean) in Table II.

The analysis between the two groups shows that recipients with higher serum IL-6 had significant higher erytrocyte sedimentation rate (ESR, p=0.0067), with no other statistical significant relationship between elevated IL-6 and other inflammatory markers. In the same time, although patients in group A had elevated creatinine levels, no statistical signifficant association could be established, except for estimated glomerular filtration rate using 4 variables MDRD formula, which was significant lower in recipients with higher IL-6 levels in group A.

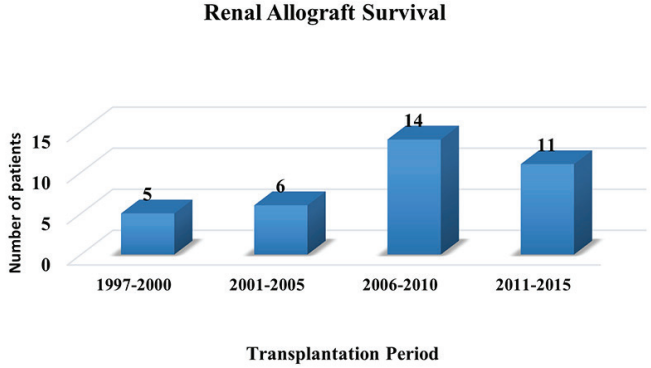

Fig. 1. Renal Allograft Survival based on transplantation period

Table I. Main characteristics of the study group

Group Characteristics at inclusion	n=36 (mean±SD, % from total)
Age (years)	43.64±10.79
Weight (kg)	78.19±18.31
Gender	
Male	25 (69.44%)
Female	11 (30.56%)
Donor Type	
Brain Dead	19 (52.77%)
Living related	16 (47.23%)
Graft positioning	
Left Iliac Fossa	12 (33.33%)
Right Iliac Fossa	24 (66.67%)
Underlying Disease that required RRT*	
Glomerular	19 (52.77%)
Tubulo-interstitial	2 (5.55%)
Cystic	5 (13.88%)
Reflux/congenital nephropathies	4 (11.15%)
LupusErythematosus	1 (2.77%)
Other	5 (13.88%)
Creatinine (mg/dl)	1.653±0.8185

*RRT – renal replacement therapy

Table II. Comparative analysis between groups

Studied Parameter	Group A mean±SEM	Group B mean±SEM	Statistical
Age (years)	44.86 ± 4.753	43.34 ± 1.957	NS
Hemoglobin (g/dL)	13.11 ± 0.6355	13.25 ± 0.4181	NS
Hematocrit (%)	38.80 ± 1.900	38.64 ± 1.211	NS
RDW (%)*	13.52 ± 0.4971	12.82 ± 0.2025	NS
Glucose (mg/dL)	90.43 ± 3.689	90.88 ± 2.169	NS
ESR (mm/h)	32.57 ± 7.668	14.34 ± 2.521	0.0067
Urea (mg/dL)	67.43 ± 8.552	53.76 ± 5.224	NS
Creatinine (mg/dL)	2.021 ± 0.3164	1.563 ± 0.1491	NS
eGFR** (ml/min/1.73m^2)	39.20 ± 5.771	58.28 ± 3.899	0.0308
Uric acid (mg/dL)	7.400 ± 0.3066	7.347 ± 0.4037	NS
Fibrinogen (mg/dL)	317.5 ± 13.37	281.0 ± 11.03	NS
hsCRP (mg/L)	4.701 ± 0.9895	2.518 ± 1.069	NS
Iron (mcg/dL)	74.00 ± 7.662	88.20 ± 10.64	NS
Serum cholesterol (mg/dL)	223.0 ± 19.70	179.5 ± 7.766	0.0242
Triglycerides (mg/dL)	167.3 ± 46.17	130.7 ± 14.53	NS
HDL-cholesterol (mg/dL)	46.69 ± 5.013	58.24 ± 10.01	NS
LDL-cholesterol (mg/dL)	142.9 ± 11.68	104.6 ± 6.128	0.0081
VLDL-cholesterol (mg/dl)	33.46 ± 9.234	26.12 ± 2.910	NS
intact-PTH* (pg/mL)	153.6 ± 97.65	75.92 ± 12.73	NS
APO-B (g/L)	1.200 ± 0.1234	0.9107 ± 0.05962	0.0385
Serum proteins (g/dL)	7.085 ± 0.2443	6.956 ± 0.1031	NS
Albumin (g/L)	41.68 ± 1.323	42.13 ± 0.8446	NS
Proteinuria (g/day)	1.313 ± 0.4972	0.3592 ± 0.06864	0.0013
Glycosuria (g/day)	0.03243 ± 0.01610	0.06490 ± 0.03714	NS
HBA1C(%)	5.171 ± 0.1340	5.186 ± 0.07456	NS
Insulin (uUI/mL)	11.79 ± 3.322	10.20 ± 1.210	NS
Hilum-RI	0.6775 ± 0.05089	0.6757 ± 0.01574	NS
Hilum-PI	1.278 ± 0.1926	1.284 ± 0.07827	NS
Intragraft-RI	0.6525 ± 0.05735	0.6448 ± 0.01478	NS
Intragraft-PI	1.188 ± 0.1993	1.176 ± 0.05430	NS
CIMT (mm)	0.5942 ± 0.09314	0.5516 ± 0.02986	NS

* RDW – red cell distribution width, PTH – parathormone
** estimated glomerular filtration rate by 4 variables MDRD formula
NS = not significant

Patients with over-the-range levels of IL-6 had significant higher levels of serum cholesterol and LDL-cholesterol respectively (p=0.0242 and p=0.0081). Serum Apo-B was also significant higher in Group A than Group B. No association could be made between other lipid profile parameters in the upper mentioned groups.

Protein excretion was significant higher in patients from group A (p=0.0013).

In terms of glucidic metabolism, no statistical significant relationship could be proven between elevated levels of IL-6 and hbA1c, insulin and glycosuria disturbances in the two groups.

Also, we found no statistical significant association between resistivity and pulsatility indices (both hilum and intragraft) or carotid intima media thickness.

Discussions

Renal replacement therapy by kidney transplantation is currently the best choice for the treatment of end stage kidney disease, particularly because of great improvements in patient outcome and long term graft survival. Interleukin 6 is known for it's pro-inflammatory potential in renal transplant recipients, findings in several studies have shown that there might be an association between elevated IL-6 and allograft rejection [15,16] and lipid profile abnormalities, although the relationship between IL-6 and lipid metabolism is not yet fully clarified [9,10,17]. The aim of our study was to investigate the relationship between IL-6 levels and glucidic-lipidic profile disorders in a group of renal transplant recipients.

In our study, IL-6 seems to be linked to increases in acute phase reactants, patients with over-the-range serum IL-6 have higher ESR, hsCRP and fibrinogen, the relationship being statistically significant only in the case of ESR.

Furthermore, patients with elevated IL-6 had significant higher levels of serum cholesterol and LDL-cholesterol, which is in agreement with other studies performed on solid organ transplantation[17,18], a decrease in peripheral lipoprotein lipase being related to increasing serum lipids, as findings of other several studies have shown [19,20]. Serum Apo-B was also significant higher in the group of recipients with higher IL-6.

Urinary protein excretion was significant higher in patients with elevated IL-6 in our study, a statistical significant lowering in eGFR in this group being also encountered, fact that can point to a possible connection between inflammation and proteinuria, findings in a recent study showing that pro-inflammatory status can lead to higher excretion of proteinuria in hematopoietic cell transplant recipients [21].

The main limitation of our study is the number of patients, thus we consider that further studies are needed, on larger heterogenous groups of solid organ recipients, in order to clarify the relationship between pro-inflammatory cytokines and gluco-lipidic disorders.

Conclusions

Serum interleukin 6 is related to lipid profile disorders (increases in serum total cholesterol, LDL-cholesterol and apolipoprotein B) and less to glucidic metabolism anomalies in non-diabetic kidney transplant recipients. Also, elevation in serum IL-6 can lead to increasing protein excretion.

Aknowledgment

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