# RELATIONSHIP BETWEEN LIPID PEROXIDATION AND ARTERIAL STIFFNESS IN RENAL TRANSPLANTED PATIENTS


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## INTRODUCTION

IN CHRONIC RENAL FAILURE AND AFTER RENAL TRANSPLANTATION LIPID PEROXIDATION IS INCREASED AND ATHEROSCLEROSIS IS ACCELERATED. WE INVESTIGATED THE SERUM PARAOXONASE ACTIVITY, ADIPONECTIN, LEPTIN CONCENTRATIONS IN RENAL FAILURE.

IN TRANSPLANTED PATIENTS PARAOXONASE ACTIVITY LOWER THAN IN CONTROLL PATIENTS. INVERSE SIGNIFICANT CORELLATION WAS FOUND BETWEEN CYSTATIN C AND HOMOCYSTEINE LEVELS.

CONCERNING ARTERIAL STIFFNESS PARAMETERS AFTER RENAL TRANSPLANTATION AUGMENTATION INDEX AND PULSE WAVE VELOCITY WERE BETTER THAN IN DIALYSED PATIENTS.

AUGMENTATION INDEX – REFERRING TO ENDOTHEL (DYS)FUNCTION - AND PULSE WAVE VELOCITY WERE BETTER WITH IMPROVED RENAL FUNCTION.

PULSE WAVE VELOCITY INCREASED PARALLEL WITH INCREASED CREATININE, UREA, CYSTATIN-C AND HOMOCYSTEINE LEVELS AND WITH RENAL FAILURE PROGRESSION.

IN OBESE RENAL TRANSPLANTED PATIENTS LOWER SERUM PARAOXONASE ACTIVITY AND INCREASED CARDIOVASCULAR RISK FACTORS FOUND: HYPERTENSION, HYPER–AND DYSLIPIDAEMIA, HYPERLEPTINAEMIA, AND ATHEROSCLEROTIC COMPLICATIONS.

## PATIENTS AND METHODS

131 RENAL TRANSPLANTED PATIENTS (46.40 ± 14.20 years) and 63 HEALTHY CONTROLS (48.20 ± 9.80 years) WERE INVOLVED IN THIS STUDY.

FASTING SERUM CREATININE, UREA, CYSTATIN–C, HOMOCYSTEINE, LIPIDS, GLUCOSE, C-REACTIVE PROTEIN (CRP), PARAOXONASE (PON1), ARYLESTERASE, ASYMMETRIC DIMETHYLARGININE (ADMA), ADIPONECTIN (ADPN) AND LEPTIN (LEP) CONCENTRATION WERE INVESTIGATED. THE PON1 and ARYLASTERASE ACTIVITY WAS DETERMINED SPECTROPHOTOMETRICALLY, AND ADMA, ADPN AND LEP CONCECTRATIONS WERE DETERMINED WITH ELISA TECHNIQUE.

THE ARTERIAL STIFFNESS PARAMETERS (AIx80 – AUGMENTATION INDEX, PWV - PULSE WAVE VELOCITY, PP - PULSE PRESSURE, SIA - SYSTOLIC AREA INDEX, DIA – DIASTOLIC AREA INDEX, MAP – MEAN ARTERIAL PRESSURE, SYSTOLIC AND DIASTOLIC BLOOD PRESSURE WERE MEASURED BY ARTERIOGRAPH (TENSIOMED).

WE INVESTIGATED THE RELATIONSHIP BETWEEN ARTERIAL STIFFNESS PARAMETERS (PWV, SAI, DAI) AND LIPID PEROXIDATION (PARAOXONASE, ARYLESTERASE ACTIVITY) AFTER RENAL TRANSPLANTATION.

## PARAOXONASE (PON I)

HIGH –DENSITY LIPOPROTEIN (HDL)– ASSOCIATED 43 kDa HYDROLASE ENZYME, REDUCING THE SUSCEPTIBILITY OF LOW–DENSITY LIPOPROTEIN (LDL) TO LIPID PEROXIDATION.

PARAOXONASE ACTIVITY, HDL – CHOLESTEROL AND APOLIPOPROTEIN (Apo ) AI LEVELS WERE FOUND SIGNIFICANTLY LOWER IN HAEMODIALYSED PATIENTS THAN IN CONTROLS.

SERUM PARAOXONASE AND ARYLESTERASE ACTIVITIES CORRELATED WITH RENAL FUNCTION (DECREASED SERUM UREA, URIC ACID, CREATININE, CYSTATIN-C AND INCREASED HOMOCYSTEINE).

SEVERAL FACTORS, SUCH AS LIPID PEROXIDATION PRODUCTS AND CYTOKINES WERE SUGGESTED HAVING EFFECT ON PARAOXONASE ACTIVITY AND PON I SYNTHESIS

INVERSE ASSOCIATIONS OF PON I WITH OBESITY AND SERUM LEVELS DECREASED PON I ACTIVITY CAN BE EXPLAINED BY THE INACTIVATION OF ENZYME CAUSED BY INCREASED OXIDATIVE STRESS.

LIPID PEROXIDATION ALSO CORRELATED NEGATIVELY WITH LACT (LECITHIN CHOLESTEROL ACYLTRANSFERASE) AND POSITIVELY WITH CEPT (CHOLESTERYL ESTER TRASFER PROTEIN).

IN CHRONIC RENAL FAILURE AND CHRONIC DIALYSIS PROGRAMME DECREASED PARALLEL SERUM PARAOXONASE ACTIVITY WITH WORSENING RENAL FUNCTION HAVE BENN FOUND.

## ADIPONECTIN (ADPN)

ADIPOSE TISSUE SECRETED 29 kDa ADIPONECTIN, IS A RECENTLY DISCOVERED ADIPOCYTE-DERIVED PROTEIN HAVE PROTECTIVE ROLE AGAINST ATHEROSCLEROSIS. ADPN IN CONTROL SUBJECTS 14.00 ± 9,1 ug/ml. PLASMA CONCENTRATIONS OF ADPN ARE CORRELATED WITH LIPID LEVELS: POSITIVELY WITH HDL – CHOLESTEROL AND NEGATIVELY WITH TRIGLYCERIDE.

ADIPONECTIN IS A PROTEIN WITH INSULIN – SENSITIZING, ANTI–INFLAMMATORY AND ANTI-ATHEROGENIC PROPERTIES AND REDUCE INSULIN RESISTANCE IN HUMANS.

ADIPONECTIN EXERTS ITS VASCULOPROTECTIVE EFFECTS THROUGH ITS DIRECT ACTION IN THE VASCULAR SYSTEM, SUCH AS INCREASING ENDOTHELIAL NO PRODUCTION, INHIBITING ENDOTHELIAL CELL ACTIVATION AND ENDOTHELIUM-LEUCOCYTE INTERACTION, ENHANCING PHAGOCYTOSIS AND SUPPRESSING MACROPHAGE ACTIVATION, MACROPHAGE – TO-FOAM CELL TRANSFORMATION, PLATELET AGGREGATION.

VISCERAL FAT AREA (VFA) IS A MAJOR DETERMINANT OF PLASMA ADPN LEVEL, SUGGESTING THAT VISCERAL FAT ACCUMULATION MIGHT BE CLOSELY ASSOCIATED WITH THE PROGRESSION OF THEROSCLEROTIC VASCULAR DISEASE IN HAEMODIALYSED AND RENAL TRANSPLANTED PATIENTS.

## LEPTIN (LEP)

HORMONE, SECRETED BY ADIPOSE TISSUE (16 kDa) DECREASES FOOD INTAKE VIA NEUROENDOCRINE SYSTEM IN THE HYPOTHALAMUS.

SERUM LEPTIN CONCENTRATION IS PROPORTIONAL TO ADIPOSE TISSUE MASS, IS INCREASED IN OBESITY, IN CHRONIC RENAL FAILURE. HYPERLEPTINAEMIA INVOLVED IN THE PATHOGENESIS OF OBESITY-RELATED DISORDERS, ARTERIAL HYPERTENSION AND PROCESS OF ATHEROSCLEROSIS.

ELEVATED LEPTIN (LEP) CONCENTRATION IS RESPONSIBLE FOR LOW SERUM PARAOXONASE (PON1) ACTIVITY.

POTENTIAL PROATHEROSCLEROTIC EFFECT OF LEPTIN MAY INVOLVE STIMULATION OF SYMPATHETIC ACTIVITY, ENDOTHELIAL PRODUCTION OF ENDOTHELIN-1 AND REACIVE OXYGEN SPECIES, PROINFLAMMATORY IMMUNE RESPONSE, MIGRATION AND PROLIFERATION OF VASCULAR SMOOTH MUSCLE CELLS AND METASTATIC CALCIFICATION OF VASCULAR CELLS AND VESSELS.
SERUM LEPTIN CONCENTRATION POSITIVELY CORRELATED WITH BMI, SYSTOLIC BLOOD PRESSURE, INSULIN RESISTANCE, TRIGLYCERIDE, LDL CHOLESTEROL LEVELS, AND NEGA VELY WITH HDL–CHOLESTEROL CONCENTRATION AND PARAOXONASE ACTIVITY.

THE SERUM LEPTIN AND LDL-C LEVELS WERE SIGNIFICANTLY HIGHER IN OBES HAEMODIALYSED PATIENTS.

## ARTERIAL STIFFNESS - ARTERIOGRAPH

AIx80 - AUGMENTATION INDEX - %
MEASURE OF ACTUAL DILATATION CAPACITY OF ARTERIOLES AND ENDOTHEL (DYS) FUNCTION

PWV - PULSE WAVE VELOCITY - m / s
STRONG AND INDEPENDENT PREDICTOR OF ALL – CAUSE AND CARDIOVASCULAR MORTALITY. THE SPEED BY WHICH THE PULSE WAVE TRAVELS ALONG THE AORTA, THE FIRST CAPACITIVE ELEMENT OF THE ARTERIAL TREE

PP - PULSE PRESSURE - mmHg
DIFFERENCE BETWEEN ERIPHERAL SYTOLIC AND DIASTOLIC BLOOD PRESSURE

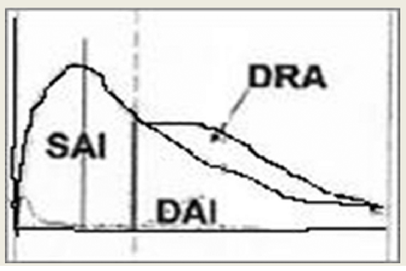
ED - EJECTION DURATION - ms
THE PERIOD OF THE MECHANICAL SYSTOLE (TO AORTIC VALVE CLOSURE )

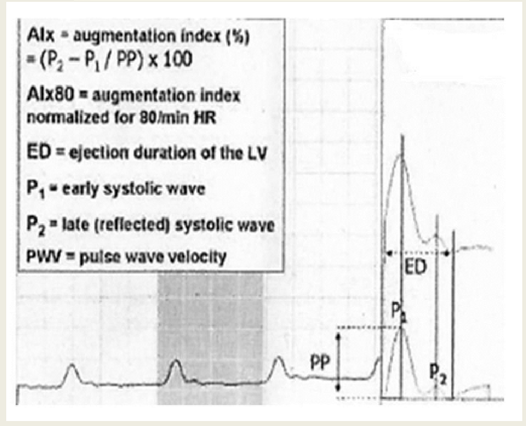
SAI - SYSTOLIC AREA INDEX - %

DAI - DIASTOLIC AREA INDEX - %

SAI/DAI - THE RATIO OF SYSTOLE AND DIASTOLE DURING A HEART CYCLE

DRA - DIASTOLIC REFLECTION AREA
THE REFLECTED WAVE RETURNS TO THE CENTRAL AORTA IN DIASTOLE AND THEREFORE ENHANCES. INDIRECTLY INDICATED BY NUMERICAL VALUES AND GRAPHICAL EVALUATION THIS VALUE INFORMS ABOUT THE ACTUAL CORONARY PERFUSION PRESSURE CONDITIONS DURING THE DIASTOLE




## LABORATORY RESULTS

| | TRANSPLANTED | CONTROLL |
|---|---|---|
| Body Mass Index - BMI | 26.40 ± 9.03 | 24.90 ± 11.58 kg/ m2 |
| CREATININE | 149.60 ± 42.60 | 79.80 ± 23.70 umol/l |
| CYSTATIN C | 1.79 ± 0.95 | 1.21 ± 0.72 mg/l |
| HOMOCYSTEINE | 17.85 ± 3.79 | 11.60 ± 4.78 umol/l |
| CHOLESTEROL | 5.80 ± 1.32 | 4.65 ± 0.98 mmol/l |
| TRIGLYCERIDE | 2.07 ± 1.29 | 1.65 ± 0.87 mmol/l |
| LDL - C | 3.26 ± 1.87 | 2.85 ± 1.05 mmol/l |
| HDL - C | 1.65 ± 0.54 | 1.85 ± 0.95 mmol/l |
| GLUCOSE | 5.38 ± 1.98 | 5.26 ± 1.65 mmol/l |
| C – Reactive Protein - CRP | 4.89 ± 1.69 | 2.79 ± 1.90 mg/l |
| PARAOXONASE - PON1 | 101.65 ± 52.30 | 148.37 ± 49.70 U/L |
| ARYLESTERASE | 100.03 ± 15.26 | 129.85 ± 30.85 U/L |
| ADMA | 175.29 ± 70.85 | 125.80 ± 49.70 ng/ml |
| LEPTIN - LEP | 37.54 ± 12.85 | 26.85 ± 12.50 ug/ml |
| ADIPONECTIN - ADPN | 23.44 ± 9.93 | 17.29 ± 5.17 ng/ml |
| ALBUMIN | 42.78 ± 3.89 | 45.36 ± 4.28 g /l |

## ASYMMETRIC – DIMETHYL – ARGININE (ADMA)

ADMA IS A RESIDUE OF PROTEOLYSIS OF ARGININE METHYLATED PROTEINS, A POTENT INHIBITOR OF NITRIC OXIDE SYNTHESIS. IN THIS REACTION, S–ADENOSYL-METHIONINE IS METHLYDONOR AND S–ADENOSYLHOMOCYS TEINE THE DEMETHYLATED PRODUCT.

PLASMA HOMOCYSTEINE (HoCy) AND ADMA CONCENTRATIONS ARE INCREASED IN RENAL DYSFUNCTION, IMPAIRMENT THE METABOLISM AND CLEARANCE.

HYPERHOMOCYSTEINAEMIA AND INCREASED ADMA CONCENTRATIONS WITH ADVERSE VASCULAR EFFECTS BY IMPAIRING ENDOTHELIAL, NITRIC OXIDE-DEPENDENT FUNCTION RESULTING IN DECREASED VASODILATATION, INCREASED SMOOTH MUSCLE CELL PROLIFERATION, PLATELET DYSFUNCTION AND INCREASED MONOCYTE ADHESION. THIS NEGATIVE VASCULAR EFFECTS OF ADMA AND HOMOCYSTEINE HAVE DIFFERENT ETIOLOGY.

HIGH ADMA AND HOMOCYSTEINE LEVELS POTENTIAL RISK FACTORS FOR CARDIOVASCULAR EVENTS THAT MIGHT BE MEDIATED IN PART BY ATHEROSCLEROSIS IN HAEMODIALYSED AND TRANSPLANTED PATIENTS.

## RESULTS

IN DYSLIPIDAEMIC TRANSPLANTED PATIENTS PON1 ACTIVITY WAS SIGNIFICANT LOWER THAN IN CONTROLL ($p < 0.01$), NEGATIVE CORRELATION WAS FOUND BETWEEN CYSTATIN C and HOMOCYSTEINE LEVELS ($p < 0.05$) and ADMA CONCENTRATIONS ($p < 0.05$).

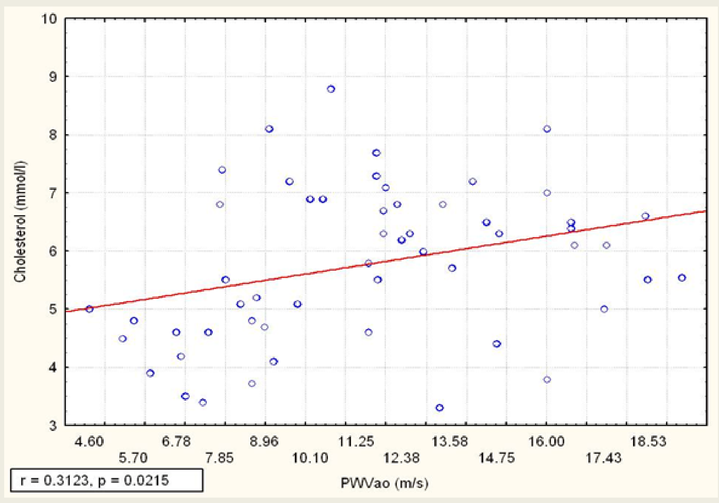
POSITIVE CORRELATION WAS FOUND BETWEEN PON1 and ADPN ($p < 0.03$) NEGATIVE SIGNIFICANT CORRELATION WAS FOUND BETWEEN PON1 ACTIVITY ($p < 0.048$), DAI BETWEEN LDL ($p < 0.0452$),TOTAL CHOLESTEROL ($p < 0.030$), and MAP ($p < 0.057$).

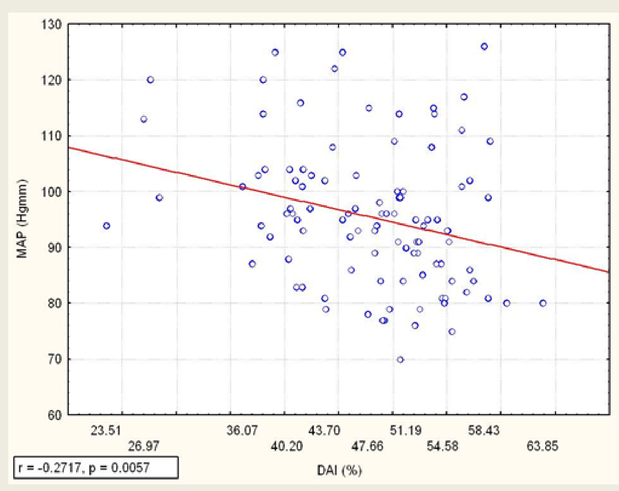
POSITIVE CORRELATION WAS FOUND BETWEEN PWV and CRP ($p < 0.03$) and TOTAL CHOLESTEROL ($p < 0.0215$), and PWV and LDL ($p < 0.0215$).

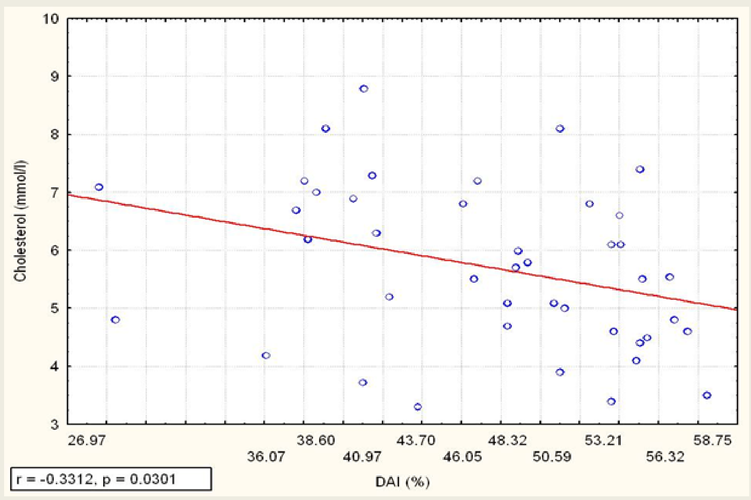
IN OBESE RENAL TRANSPLANTED PATIENTS WE CAN FOUND SIGNIFICANT HIGHER THE LDL – C and LEPTIN (LEP) CONCENTRATIONS ($p < 0.05$). POSITIVE CORRELATION WAS BETWEEN PWV and AIx , and SYSTOLIC DIASTOLIC BLOOD PRESSURE OF HYPERTENSION and MAP PARAMETERES ($p < 0.01$).

SIGNIFICANT NEGATIVE CORRELATION WAS THE ARYLESTERASE ACTIVITY BETWEEN PULSE WAVE VELOCITY (PWV), ($p < 0.05$).

AFTER RENAL TRANSPLANTATION WITH IMPROVED THE RENAL FUNCTION PARALLEL DECREASED SYSTOLIC, and DIASTOLIC BLOOD and PULSE PRESSURE, DECREASED LIPID PEROXIDATION.

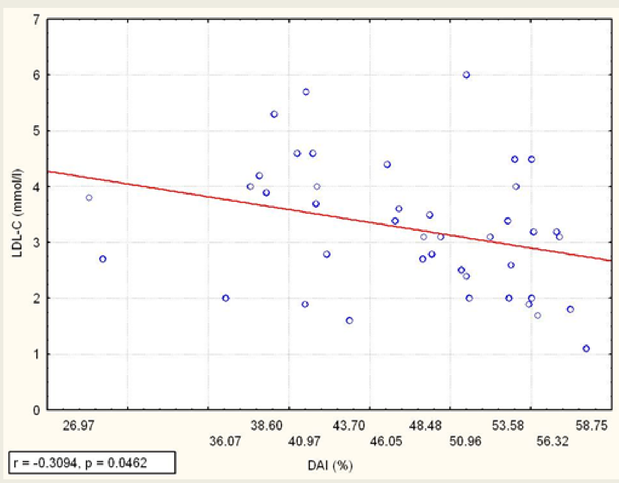



## ARTERIOGRAF RESULTS

| | TRANSPLANTED N=131 | CONTROLL N=63 |
|---|---|---|
| SYSTOLIC BLOOD PRESSURE | 127.80 ± 18.85 | 119.20 ± 20.58 mmHg |
| PRESSURE DIASTOLIC BLOOD | 76.80 ± 11.70 | 58.30 ± 14.80 mmHg |
| HEART RATE | 74,70 ± 14.60 | 68.40±16.80 beat/min |
| MAP | 94.60 ± 14.80 | 79.60 ± 12.60 mmHg |
| Pulse Pressure – PP | 53.30 ± 29.20 | 41.70 ± 15.80 mmHg |
| Augmentation Index – AIx | - 18.60 ± 8.90 | - 21.80 ± 10.40 % |
| Pulse Wave Velocity – PWV | 10.67 ± 3.56 | 6.50 ± 4.80 m/s |
| Systolic Area Index – SAI | 51.92 ± 8.04 | 58.90 ± 10.70 % |
| Diastolic Area Index - DAI | 47.90 ± 7.65 | 51.30 ± 8.65 % |




## DISCUSSION

AFTER RENAL TRANSPLANTATION SIGNIFICANTLY IMPROVED RENAL FUNCTION, DECREASED CYSTATIN C, HOMOCYSTEINE CONCENTRATION, DECREASED THE LIPID PEROXIDATION.

SERUM PARAOXONASE ACTIVITY LOWER IN TRANSPLANTED PATIENTS THAN CONTROLL PATIENTS, SIGNIFICANTLY HIGHER THAN IN DIALYSED PATIENTS.

ARTERIAL STIFFNESS PARAMETERS IMPROVED WITH PARALELL THE RENAL FUNCTION, PULSE WAVE VELOCITY DECREASED, ENDOTHEL FUNCTION IMPROVED – AUGMENTATION INDEX - THAN IN DIALYSED and RENAL FAILURE PATIENTS.

SIGNIFICANT NEGATIVE CORRELATION WAS FOUND BETWEEN SERUM PARAOXONASE, ARYLESTERASE ACTIVITY and ARTERIAL STIFFNESS PARAMETERS: PULSE WAVE VELOCITY.

SIGNIFICANT INVERS CORRELATION WAS BETWEEN DAI, SAI and LDL-C, TOTAL CHOLESTEROL, and MAP PARAMETERS.

SIGNIFICANT POSITIVE CORRELATION CAN BE FOUND BETWEEN PULSE WAVE VELOCITY and TOTAL-, LDL–C CHOLESTEROL.

SYSTOLIC (SIA) AND DIASTOLIC (DIA) AREA INDEX IMPROVED WITH BETTER RENAL FUNCTION, INCREASED PARAOXONASE ACTIVITY and BETTER LIPID METABOLISM.

THE CORONARY ARTERY CAPACITY WILL BE BETTER WITH DECREASED ARTERIAL STIFFNESS, INCREASED PARAOXONASE ACTIVITY