THE RELATIONSHIP OF HIGH SENSITIVITY C-REACTIVE PROTEIN, SIALIC ACID AND LIPID PROFILE WITH HYPERTENSION

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ABSTRACT

BACKGROUND

Hypertension is the most common cardiovascular risk factor. An association between hypertension and inflammation has now been clearly demonstrated. Serum sialic acid and C-reactive protein are markers for inflammation.

The aim of our study was to evaluate the serum concentration of high-sensitivity C-reactive protein (hs-CRP) and total sialic acid and the cardiovascular risk factors, lipid parameters in hypertensive patients and the possible correlations between these factors with blood pressure in such patients.

MATERIALS AND METHODS

We studied 40 hypertensive patients and 40 controls with normal blood pressure between the age group of 30 years and 60 years. Lipid profile, hs-CRP, total sialic acid, fasting blood sugar and body mass index were estimated in the two groups. Quantitative data of the two groups were expressed as mean and standard deviation and compared by unpaired "t" test. Association between hs-CRP, total sialic acid and lipid parameters with systolic and diastolic BP was assessed by Pearson correlation. Multiple regression analysis was done with systolic and diastolic BP as dependent variables and hs-CRP, total sialic acid and lipid parameters as independent variables. A p value less than 0.05 is considered significant.

RESULTS

Serum total sialic acid, hs-CRP levels and lipid levels were significantly elevated in the hypertensive group than the normotensive group. There was significant correlation between hs-CRP and total sialic acid with systolic and diastolic blood pressure. Multiple regression analysis demonstrated that total sialic acid, fasting blood sugar, Low Density Lipoprotein (LDL) and High Density Lipoprotein (HDL) were independently associated with systolic blood pressure and total sialic acid and LDL were independently associated with diastolic blood pressure ($p < 0.05$).

CONCLUSION

Our findings suggest that in hypertension, there is an association between serum sialic acid and hs-CRP levels with blood pressure. Hs-CRP and total sialic acid were positively correlated with dyslipidaemia, thus contributing to cardiovascular risk.

KEYWORDS

C-reactive Protein (CRP), Serum Total Sialic Acid, Inflammatory Markers, Hypertension.

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BACKGROUND

Cardiovascular diseases are the most important cause of mortality and morbidity globally.¹ Hypertension is the most common cardiovascular risk factor² and is an independent predictor of cardiovascular disease, cerebrovascular accidents and death.³ About 90% of cases of hypertension are classified as essential hypertension, where the precise cause is unknown.⁴ The seventh report of Joint National Committee (JNC 7) on prevention, detection, evaluation and treatment of high BP defines hypertension with the exception of people who take antihypertensive drugs, as BP greater than 140/90 mmHg.⁵

Essential hypertension is characterised by peripheral vascular resistance to blood flow, the major cause of which is vascular remodelling. Vascular changes found in hypertension are associated with mechanical and humoral factors that modulate signalling events. Prior studies in animal models suggest that inflammation is present in the vasculature and inflammatory markers, such as C-reactive protein are associated with vascular lesions in humans.⁶ During the past few years large amount of information has been collected on vascular inflammation, which indicates that inflammation may involve in the initiation as well as development of hypertension.⁷

Inflammation is a protective response to injury and infection. Excessive inflammation can have detrimental effects and contribute to the progression of chronic and/or prolonged disease such as atherosclerosis.⁸ Earlier, high levels of traditional risk factors such as low density lipoprotein cholesterol and triglyceride were believed to be predictive factors for atherosclerotic cardiovascular disease and mortality. Nowadays, high sensitivity C-reactive protein (hs-CRP), which is a marker of low-grade inflammation has been used as a predictor of cardiovascular mortality and morbidity in healthy people.⁹

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CRP is a plasma protein, present in trace amounts in healthy subjects whose concentration increases 100 fold in response to injury, infection or inflammation. CRP is so named because of its ability to precipitate the somatic C polysaccharides of *Streptococcus pneumoniae*.¹⁰ C-reactive protein (CRP) is involved in innate immune response and has roles that include activating the complement system and enhancing phagocytosis. CRP can stimulate monocytes to release pro-inflammatory cytokines such as interleukin-6 (IL-6) Interleukin-1 beta (IL-1 β) and Tumour Necrosis Factor (TNF), which will promote inflammation. It also stimulates endothelial cells to express intracellular adhesion molecule (ICAM)-1 and Vascular Cell Adhesion Molecule (VCAM)-1, which will promote further inflammation.¹¹ Nevertheless, elevation of hs-CRP may suggest acute involvement of inflammation in the development of hypertension.

At the same time, it was demonstrated that elevated serum sialic acid is associated with increased cardiovascular mortality.^{12,13} Increased sialic acid levels have been reported during inflammatory process, probably resulting from increased levels of richly sialylated acute-phase glycoproteins. Sialic acid is a generic term for a family of acetylated derivatives of neuraminic acid, which is an essential component of glycoproteins and glycolipids. In human plasma, large quantity of sialic acid is found as a component of orosomucoid, alpha-1, antitrypsin, haptoglobin, ceruloplasmin, fibrinogen complement proteins and transferrin.¹⁴

The purpose of this study was to evaluate and compare the serum levels of inflammatory markers, hs-CRP and total sialic acid and cardiovascular risk factors like lipid parameters among hypertensive and normal subjects. We also aimed to explore the possible relationship between these inflammatory markers and lipid parameters with blood pressure and thus find their contribution to the cardiovascular risk.

MATERIALS AND METHODS

A case control study was conducted during June 2012 to September 2013. The study group was selected from the patients attending the Medical OP, Government Medical College Hospital, Thiruvananthapuram. The study group consisted of 80 subjects, 40 hypertensives and 40 normotensive controls between age group of 30 and 60 years. The classification of subjects to hypertensives and normotensives was done as per JNC 7 criteria. Normotensives had a systolic blood pressure of less than 120 mmHg and diastolic blood pressure of less than 80 mmHg. Except for those on medication, hypertensives had blood pressure more than 140/90 mmHg. Subjects with diabetes mellitus, pregnant ladies, history of any acute illness, previous vascular events such as myocardial infarction, vasculitis, alcohol and tobacco users were excluded from the study.

This study was undertaken after approval by the Institutional Ethical Committee. A written informed consent was obtained from all participants. History was taken from all subjects. Height and weight were recorded for all subjects. Body Mass Index (BMI) was calculated using the formula. BMI = weight in kilograms divided by the square of height in metres (kg/m²).

Blood pressure was measured twice using a sphygmomanometer from the right arm of the seated participant after 10 minutes rest. The mean of the two readings was taken.

Collection of Blood Samples

10 mL of venous blood was drawn in a fasting condition, under strict aseptic precautions and collected in two tubes. Blood for plasma glucose estimation was collected in tube

containing sodium fluoride and potassium oxalate. The other tube was a plain tube for serum separation. Plasma glucose was measured using a commercial kit by GOD-POD method on a fully auto analyser by Transasia Biomed. The blood in the plain tube was allowed to clot to separate serum, which was used to measure fasting lipid profile, total sialic acid and hs-CRP. Total cholesterol, triglycerides and HDL cholesterol were measured using commercially procured kits in the fully auto analyser by Transasia Biomed. LDL-Cholesterol was calculated by Fredrickson-Friedewald formula.

LDL cholesterol = Total cholesterol - (HDL cholesterol + Triglycerides/5).

Serum hs-CRP levels were measured using a commercial kit from Transasia. Biomedicals Ltd., Erba Diagnostics, Mannheim, Germany. Hs-CRP was quantified by particle-enhanced turbidimetric immunoassay.

Sialic acid was analysed by thiobarbituric acid assay of Warren.¹⁵

Statistical Analysis

Statistical analysis was performed using SPSS version 22.0. Quantitative data were expressed as mean and standard deviation. Qualitative data were expressed as proportion. Quantitative data for the two groups were compared with unpaired 't' test. Association between two quantitative variables was analysed by Pearson correlation. A p value of < 0.05 was considered to be statistically significant. Variables which are found to be significantly associated with SBP and DBP during univariate analysis were subjected to stepwise multiple linear regression analysis to evaluate the relationship between hs-CRP and serum sialic acid with blood pressure.

RESULTS

Table 1 represents the comparison of demographic and biochemical parameters in cases and controls. The mean age of the hypertensive subjects was 45.9 $\pm$ 6.6 years and that of the control group was 48.4 $\pm$ 4.6 years. Mean Body Mass Index (BMI) of cases was 25.2 $\pm$ 2.4 kg/m² and that of controls were 24.6 $\pm$ 2.7 kg/m². There was no significant difference of these two parameters between the two groups. Serum total sialic acid in hypertensive subjects was 66.9 $\pm$ 7.4 mg% and that of controls was 55.0 $\pm$ 4.5 mg%. Increase in total sialic acid was found to be highly significant (p < 0.001). Serum hs-CRP levels were 1.93 $\pm$ 0.92 mg/L in hypertensive group compared to 1.12 $\pm$ 0.57 among control group (p < 0.001) Figure 1. There was also a significant difference in the fasting blood sugar, total cholesterol and Low Density Lipoprotein (LDL) (p < 0.001), serum triglycerides and High Density Lipoprotein (HDL) levels (p < 0.05) between the two groups. The mean systolic blood pressure among cases was 137.9 $\pm$ 11.8 mmHg and that of the controls was 116.8 $\pm$ 11.8 mmHg (p < 0.001). The mean diastolic blood pressure among cases was 91.6 $\pm$ 5.1 mmHg and that of the cases was 77.8 $\pm$ 5.9 mmHg (p < 0.001).

There was a significant correlation between systolic and diastolic BP with hs-CRP and total sialic acid (p < 0.001) and with total cholesterol, LDL (p < 0.001), HDL and triglycerides (p < 0.05) (Table 2, Figures 2 and 3). Total sialic acid hs-CRP were also significantly correlated with Body Mass Index (BMI) and Triglycerides (p < 0.05) and total cholesterol and LDL cholesterol (p < 0.001) (Table 3). Total sialic acid was also significantly correlated with hs-CRP (Table 3). We used multiple linear regression analysis to evaluate the relationship between serum sialic acid and hs-CRP and lipid parameters with blood pressure in the two groups. Using Systolic BP (SBP) and Diastolic BP (DBP) as dependent variables and Total Cholesterol (TC), High Density Lipoprotein (HDL), Low Density Lipoprotein (LDL),

Triglycerides (TG), Fasting Blood Sugar (FBS), Body Mass Index (BMI), total sialic acid and hs-CRP as independent variables, we found that total sialic acid, FBS, LDL and HDL were independently associated with systolic BP ($p < 0.001$, <

0.001, 0.01, 0.033 respectively) (Table 4) and total sialic acid and LDL were independently associated with Diastolic BP ($p < 0.001$) (Table 5).

Variable	Case (N = 40)		Control (N = 40)		t	p
	Mean	SD	Mean	SD		
Age in years	45.9	6.6	48.4	4.6	-1.920	.059
Body Mass Index (kg/m ²)	25.2	2.4	24.6	2.7	1.168	.246
Total Sialic acid (mg%)	66.9	7.4	55.0	4.5	8.654	< 0.001
Fasting Blood sugar (mg%)	97.0	22.6	82.4	10.4	3.696	< 0.001
Total Cholesterol (mg%)	229.3	33.2	179.9	27.0	7.294	< 0.001
HDL Cholesterol (mg%)	45.0	8.6	49.5	8.7	-2.362	.021
Triglycerides (mg%)	117.9	40.7	99.2	26.4	2.429	.017
LDL cholesterol (mg%)	160.3	32.5	110.9	29.0	7.176	< 0.001
Systolic BP (mmHg)	137.9	11.8	116.8	11.8	7.990	< 0.001
Diastolic BP (mmHg)	91.6	5.1	77.8	5.9	11.201	< 0.001
Hs-CRP (mg/L)	1.93	0.92	1.12	0.57	4.838	< 0.001

Table 1. Demographic and Biochemical Parameters in Cases and Controls

Variable	SBP		DBP	
	Correlation Coefficient r	p	Correlation Coefficient r	p
TSA	.699	< 0.001	.673	< 0.001
TC	.662	< 0.001	.581	< 0.001
HDL	-.389	< 0.001	-.252	.024
TG	.510	< 0.001	.380	.001
LDL	.670	< 0.001	.591	< 0.001
Hs-CRP	.572	< 0.001	.505	< 0.001

Table 2. Correlation of Systolic BP and Diastolic BP with TSA, Hs-CRP and Lipid Profile

TSA - Total Sialic Acid, SBP- Systolic Blood Pressure, DBP- Diastolic Blood Pressure, TC - Total Cholesterol, TG - Triglyceride, LDL - Low Density Lipoprotein, HDL - High Density Lipoprotein.

Variable	TSA		hs-CRP	
	Correlation Coefficient r	p	Correlation Coefficient r	p
SBP	.699	< 0.001	.572**	< 0.001
DBP	.673	< 0.001	.505**	< 0.001
Age in Years	-.036	.750	-.031	.784
BMI	.227	.043	.260*	.020
FBS	.531	< 0.001	.444**	< 0.001
TC	.649	< 0.001	.554**	< 0.001
HDL	-.211	.061	-.100	.377
TG	.384	< 0.001	.319**	.004
LDL	.609	< 0.001	.526**	< 0.001
CRP	.700	< 0.001		

Table 3. Correlation of TSA and Hs-CRP with other Parameters

Hs-CRP: Highly Sensitive C-reactive Protein, TSA - Total Sialic Acid, SBP - Systolic Blood Pressure, DBP - Diastolic Blood Pressure, BMI - Body Mass Index, FBS - Fasting Blood Sugar, TC - Total Cholesterol, HDL - High Density Lipoprotein, TG - Triglyceride, LDL - Low Density Lipoprotein.

Variable	Unstandardised Coefficients		Standardised Coefficients	t	p
	B	Std. Error	Beta		
Constant term	64.672	10.688		6.051	< 0.001
TSA (mg/dL)	.598	.167	.322	3.587	.001
FBS (mg/dL)	.297	.065	.356	4.601	< 0.001
LDL (mg/dL)	.101	.038	.251	2.640	.010
HDL (mg/dL)	-.299	.138	-.167	-2.174	.033

Table 4. Stepwise Multiple Linear Regression for SBP

SBP - Systolic Blood Pressure, TSA - Total Sialic Acid, FBS - Fasting Blood Sugar.

Variable	Unstandardised Coefficients		Standardised Coefficients	t	p
	B	Std. Error	Beta		
Constant term	44.482	5.184		8.581	< 0.001
TSA (mg/dL)	.516	.105	.497	4.922	< 0.001
LDL (mg/dL)	.065	.023	.288	2.852	.006

Table 5. Stepwise Multiple Linear Regression for DBP

DBP - Diastolic Blood Pressure, TSA - Total Sialic Acid, LDL - Low Density Lipoprotein.

Figure 1. Comparison of Hs-CRP between Cases and Control

Figure 2. Correlation of Total Sialic Acid, Hs-CRP, HDL and LDL with Systolic BP

Figure 3. Correlation of Diastolic BP with Other Parameters

DISCUSSION

Hypertension is a common, asymptomatic, readily detectable and treatable disease, which can lead to lethal complications if untreated.¹⁶ Elevated blood pressure is an established independent risk factor for cardiovascular diseases. Increasing prevalence of hypertension in developing countries is of significant concern.¹⁷

Increasing evidence indicates that vascular inflammation may be involved in both the initiation and development of hypertension.¹⁸ In the present study we estimated inflammatory markers, hs-CRP and total sialic acid in hypertensive and normotensive control subjects to evaluate any significant relationship between elevated serum hs-CRP levels and total sialic acid with hypertension.

Serum hs-CRP levels were significantly high in hypertensive group compared to the control group ($p < 0.001$). This is similar to other studies.^{9,19,20} This indicates that inflammation might be associated with hypertension. There was also significant increase in serum total sialic acid levels ($p < 0.001$) in the hypertensive group compared to the control group. This is also in accordance with the study done by other workers.^{9,21} Sialic acid is associated with most of the serum acute phase reactants. It is an essential component of glycoproteins and glycolipids. Some of these sialylated glycoproteins rapidly increase in concentration after the onset of an inflammatory reaction or injury.²²

In our study, hypertensive patients had an abnormal lipid profile, which is suggested by the presence of high total cholesterol and LDL-cholesterol levels ($p < 0.001$), high Triglyceride levels ($p < 0.05$) and a low HDL levels. This is comparable to other studies.^{23,24}

There was a significant correlation between hs-CRP and total sialic acid ($p < 0.001$) with systolic and diastolic BP. This is similar to the work of Li Jinghua et al (2014).⁹ Furthermore, total sialic acid and hs-CRP significantly correlated with BMI and triglycerides ($p < 0.05$) and total cholesterol and LDL ($p < 0.001$). This association is similar to the association between low-grade inflammation and other components of the metabolic syndrome.⁷

Moreover, total sialic acid was significantly correlated with hs-CRP also ($p < 0.001$) Table 3. This suggests that blood CRP may be a risk factor for progression of hypertension and hypertension can activate inflammation. This may be by the following mechanisms. CRP can damage vascular endothelial cells and reduce the release of nitric oxide and prostaglandins. It can weaken the vasodilatation function. Elevation of blood pressure can damage vascular endothelial cells. There will be production of a number of pro-inflammatory cytokines, such as tumour necrosis factor α (TNF- α), Interleukin-6 (IL-6), etc. This can activate the inflammation response, which leads to an elevated CRP. Elevated CRP may cause increased endothelin release, contraction of blood vessels and promotion of vascular smooth muscle proliferation and migration and thus contribute to atherosclerosis.^{9,25} Moreover, there will be up-regulation of Angiotensin receptors by CRP. It also enhances expression of plasminogen activator inhibitor-1 by endothelial cells.¹⁸ Both these changes could raise blood pressure and promote atherogenesis.

It was shown in several studies that there is an association between serum sialic acid and cardiovascular mortality in the general population.²⁶ Serum sialic acid is also

a marker of acute phase response.^{27,28} In this study, there was a significant increase in sialic acid levels of hypertensive subjects ($p < 0.001$).

Moreover, regression analysis also demonstrates that total sialic acid was independently associated with systolic as well as diastolic BP. Sialic acid can influence blood pressure by the following mechanisms. Sialic acid can promote development of atherosclerosis by inflammatory response and promote platelet thrombus formation mechanisms. Sialic acid contributes to the vascular endothelial cell surface negative charge. It can influence vascular endothelial cell function. Sialic acid can also affect LDL metabolism. It can induce vascular smooth muscle damage. All these mechanisms can promote hypertension.^{9,29}

On regression analysis, there was no independent association of CRP with BP. Hence, compared with CRP, sialic acid may be a more stable inflammatory marker. It can reflect the overall level of acute phase reaction. There was significant association between LDL, HDL and fasting blood sugar with systolic blood pressure and LDL with diastolic blood pressure on regression analysis. Therefore, dyslipidaemia can also promote the risk of high blood pressure and cardiovascular disease.

CONCLUSION

In conclusion, our results suggest that increased serum hs-CRP and total sialic acid which are acute phase markers are increased in hypertension. Increased serum levels of both hs-CRP and sialic acid are associated with systolic and diastolic blood pressure respectively. These inflammation sensitive markers may be useful for assessment of cardiovascular risk in hypertension. A dyslipidaemia which correlated well with the inflammatory markers and blood pressure was also found in the hypertensive subjects. All these data suggests that vascular inflammation plays a role in the pathophysiology and progression of hypertension and may exacerbate the pro-atherogenic effects of hypertension, thus contributing to cardiovascular risk.

REFERENCES

- [1] Anand SS, Yusuf S. Stemming the global tsunami of cardiovascular disease. *Lancet* 2011;377(9765):529-32.
- [2] Kearney PM, Whelton M, Reynolds K, et al. Global burden of hypertension: analysis of worldwide data. *Lancet* 2005;365(9455):217-23.
- [3] Murray CJ, Lopez AD. Global mortality, disability and the contribution of risk factors: Global Burden of Disease study. *Lancet* 1997;349(9063):1436-42.
- [4] Messerli FH, Williams B, Ritz E. Essential hypertension. *Lancet* 2007;370(9587):591-603.
- [5] Chobanian AV, Bakris GL, Black HR, et al. The seventh report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure: the JNC 7 report. *JAMA* 2003;289(19):2560-72.
- [6] Savoia C, Schiffrin EL. Inflammation in hypertension. *Curr Opin Nephrol Hypertens* 2006;15(2):152-8.
- [7] Li JJ, Fang CH, Hui RT. Is Hypertension an inflammatory disease? *Med Hypotheses* 2005;64(6):236-40.

- [8] Lusis AJ. Atherosclerosis. *Nature* 2000;407(6801):233-41.
- [9] Jinghua L, Tie Z, Ping W, et al. The relationship between serum sialic acid and high-sensitivity C-reactive protein with prehypertension. *Med Sci Monit* 2014;20:551-5.
- [10] Hirschfield GM, Pepys MB. C-reactive protein and cardiovascular disease: new insights from an old molecule. *Q J Med* 2003;96(11):793-807.
- [11] Pasceri V, Willerson JT, Yeh ET. Direct proinflammatory effect of C-reactive protein on human endothelial cells. *Circulation* 2000;102(18):2165-8.
- [12] Gopaul KP, Crook MA. Sialic acid: a novel marker of cardiovascular disease? *Clin Biochem* 2006;39(7):667-81.
- [13] Crook M, Haq M, Haq S, et al. Plasma sialic acid and acute-phase proteins in patients with myocardial infarction. *Angiology* 1994;45(8):709-15.
- [14] Pickup JC. Inflammation and activated innate immunity in the pathogenesis of type 2 diabetes. *Diabetes care* 2004;27(3):813-23.
- [15] Warren L. The Thiobarbituric acid assay of sialic acids. *J Biol Chem* 1959;234(8):1971-5.
- [16] Naomi DLF, Gordon HW. Hypertensive Vascular Disease. Chapter 246. *Harrison's principles of internal medicine*. 16th edn. Part Eight; Section Four. McGraw Hill Professional 2006:1463-70.
- [17] Gupta R. Trends in hypertension epidemiology in India. *J Hum Hypertens* 2004;18(2):73-8.
- [18] Li JJ. Inflammation in hypertension: primary evidence. *Chin Med J* 2006;119(14):1215-21.
- [19] Shafi DM, Pandith AA, Sameer AS, et al. hs-CRP: a potential marker for hypertension in Kashmiri population. *Indian J Clin Biochem* 2010;25(2):208-12.
- [20] Sesso HD, Buring JE, Rifai N, et al. C-reactive protein and risk of developing hypertension. *JAMA* 2003;290(22):2945-57.
- [21] Ananthasamy TS, Patel SJ, Cama HR. Significance of serum protein – bound carbohydrates in diagnosis of hypertension, myocardial infarction and liver disorders. *Ind Jour Med Res* 1967;55(2):169-73.
- [22] Crook M, Treolar A, Haq M, et al. Serum total sialic acid and acute phase proteins in Elderly Subjects. *Eur J Clin Chem* 1994;32(10):745-7.
- [23] Salam NZ. The relation of serum high-sensitive C-reactive protein to serum lipid profile, Vitamin D and other variables in a group of hypertensive patients in Erbil-Iraq. *International Journal of Science and Research (IJSR)* 2016;5(9):444-7.
- [24] de Simone G, Devereux RB, Chinali M, et al. Risk factors for arterial hypertension in adults with initial optimal blood pressure: the strong heart study. *Hypertension* 2006;47(2):162-7.
- [25] Fichtischerer S, Rosenberger G, Walter DH, et al. Elevated C-reactive protein levels and impaired endothelial vasoreactivity in patients with coronary artery disease. *Circulation* 2000;102(9):1000-6.
- [26] Pickup JC, Robert GA, Kehely A, et al. Higher serum sialic acid in women than in men with NIDDM: possible relevance to increased cardiovascular risk in NIDDM Women. *Diabetes Care* 1997;20(9):1496.
- [27] Taniuchi K, Chifu K, Hayashi N, et al. A new enzymatic method for the determination of sialic acid in serum and its application for a marker of acute phase reactants. *Kobe J med Sci* 1981;27(3):91-102.
- [28] Pickup JC, Mattock MB, Chusney GD, et al. NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. *Diabetologia* 1997;40(11):1286-92.
- [29] Bakri RS, Afzali B, Covic A, et al. Cardiovascular disease in renal allograft recipients is associated with elevated sialic acid or markers of inflammation. *Clin Transplant* 2004;18(2):201-4.