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Research Article

Influence of Genetic Polymorphism of IFN-Gamma on the Occurrence of Cardiovascular Events in Patients with Hypertension

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Abstract

Introduction: The chronic inflammatory state in atherosclerosis is an important risk factor for cardiovascular (CV) outcomes. The influence of the genetic polymorphism of interferon (IFN)-gamma on such outcomes needs to be evaluated.

Objective: The aim of this study is to investigate the association between genetic polymorphism of IFN-gamma and the risk of CV event and/or death.

Patients and Methods: A prospective study was conducted including 208 hypertensive patients, where the polymorphism of IFN-gamma (+874 A → T) was analyzed. We evaluated as outcomes the occurrence of a CV event with (combined endpoint) or without death and the association between IFN-gamma polymorphism and the outcomes was analyzed.

Results: The patients had a mean age of 59.7 ± 9.3 years, with 57.2% being white, 37% having type 2 diabetes mellitus (DM) and 59.1% having metabolic syndrome (MS). Regarding IFN-gamma polymorphism, 17.7% had a TT genotype, 37.5% a TA genotype and 44.8% an AA genotype. After the follow-up, there were 7 deaths and 8 CV events. The frequency of the TT genotype was higher in patients who had a CV event (60 versus 15% in those who did not) and combined endpoint (55.6% versus 15%). Even after adjusting for age, gender, DM, total cholesterol, uric acid and MS, the presence of the TT genotype was an independent predictor for the occurrence of a CV event (RR: 10.12, CI: 1.16 – 87.79, $p < 0.05$) and combined outcome (RR: 10.74, CI: 1.909 – 60.47, $p < 0.05$).

Conclusion: In individuals with hypertension, the presence of the TT genotype of the IFN-gamma polymorphism resulted in a higher incidence of CV event and death.

ABBREVIATIONS

BMI – Body Mass Index; CAD - Coronary Artery Disease; CKD – Chronic Kidney Disease; CKDEPI - Chronic Kidney Disease Epidemiology Collaboration; CRP – C Reactive Protein; CV – Cardiovascular; CVD – Cardiovascular Disease; DBP – Diastolic Blood Pressure; DM – Diabetes Mellitus; eGFR – estimated Glomerular Filtration Rate ESRD – End Stage Renal Disease; FRS – Framingham Risk Score; HDL – High Density Lipoprotein; IDF - International Diabetes Federation; IFN – Interferon; IL – Interleukin; LDL – Low Density Lipoprotein; MHC – Main Histocompatibility Complex; MS – Metabolic Syndrome; NFKB – Nuclear Factor kappa B; PAD – Peripheral Arterial Disease; ROS – Reactive Oxygen Species; SAH – Systemic Arterial Hypertension; SBP – Systolic Blood Pressure; SNP – Single Nucleotide Polymorphism; TGD – Triglycerides; TGF – Transforming Growth Factor; TNF – Tumor Necrosis Factor

INTRODUCTION

Recognized as an important risk factor for cardiovascular disease (CVD), systemic arterial hypertension (SAH) interacts with various risk factors in the development of atherosclerosis in the coronary and cerebral arteries and the association between hypertension and inflammation results in considerable increase in coronary artery disease (CAD) risk [1]. Accordingly, chronic inflammation, involved in the genesis and perpetuation of atherosclerotic disease, is associated with increased cardiovascular risk [2-4], and serum levels of several inflammatory cytokines (IL-6, TNF, IL-10, TGF, IFN-gamma)

have been shown to be elevated in individuals with established atherosclerotic cardiovascular disease [5-6]. The serum levels of C-reactive protein (CRP), a systemic marker of inflammation, predicts risk of coronary events adding predictive power to the isolated measurement of lipid profile, blood glucose and other risk factors [7].

Interferon (IFN)-gamma is a T cell-derived cytokine and serves as a marker for Th1 helper lymphocyte activation, which promotes and amplifies the inflammatory response, thereby playing an important role in the coordinate regulation of the immune response. IFN also has direct effects on inflammation by increasing the expression of the major Histocompatibility complex (MHC) class II and stimulates macrophages to produce inflammatory mediators of tissue damage, such as TNF alpha, proteases, reactive oxygen species (ROS) and nitric oxide [8]

In the general population, IFN-gamma is highly expressed in atherosclerotic lesions and has emerged as a significant factor in the development and progression of CVD. Studies have shown that IFN is the major trigger for the production and release of ROS also in the endothelium and that a T cell subtype involved in atherosclerosis produces large amounts of IFN-gamma [9]. Chronic ROS production leads to depletion of antioxidants such as vitamin C, vitamin E and glutathione, with consequent development of oxidative stress. This condition is the main factor responsible for atherogenesis and progression of CVD [9].

It is known that the genetic control of cytokine production is affected by various known polymorphisms, which may result in higher or lower levels of these inflammatory mediators in plasma. A single nucleotide polymorphism (SNP) at position +874 of the IFN-gamma gene (+874 T → A) may influence the secretion of IFN-gamma [10]. Studies of the biological role of this polymorphism have suggested that allele a carriers are low producers of IFN-gamma [11]. The presence of the T allele in this functional variant increases NFKB binding efficacy, leading to a high expression of IFN-gamma *in vitro* [10]. The polymorphism at position +874

(A → T) has been associated with increased expression of IFN-gamma and greater susceptibility to chronic kidney disease (CKD) for various reasons [12]. Thus, this study aimed to elucidate the potential association between the IFN-gamma polymorphism +874 T → A and the occurrence of the following outcomes:

1. Primary: cardiovascular (CV) events and death

2. Secondary: progression of CKD and albuminuria and incidence of DM and metabolic syndrome (MS).

MATERIALS AND METHODS

A total of 664 consecutive patients seen at the outpatient clinic of the Integrated Center for Hypertension and Cardiovascular Metabolism of the Oswald Ramos Foundation-UNIFESP were considered, and only patients diagnosed with SAH were included for cardiovascular risk stratification and genetic study.

We collected the following data from medical charts: age, sex, race, weight, height, body mass index (BMI), systolic (SBP) and diastolic (DBP) blood pressure, diagnosis of DM, obesity and CVD, family history, smoking history, fasting blood glucose, total cholesterol and fractions, triglycerides, waist circumference, diagnosis of metabolic syndrome (MS) by the criteria of the International Diabetes Federation (IDF) [13], creatinine, uric acid, CRP, albuminuria in a single sample, glomerular filtration rate estimated by the formula of the CKD-EPI (eGFR CKD-EPI) (14), and the Framingham Risk Score [15]. The data of IFN-gamma polymorphism (+874 T→ A) were also recorded. BMI was calculated by the formula: weight (kg)/ (height x height) (m).

CVD was defined as the presence of CAD (evidence of silent myocardial infarction or myocardial ischemia, history of unstable or stable angina, and coronary angioplasty or coronary surgery), or equivalent risk of CAD, stroke, peripheral arterial disease (PAD), abdominal aortic aneurysm, carotid artery disease or renal artery disease, according to the American Heart Association [16].

For analysis of lipid profile, blood glucose, CRP and uric acid, blood samples were drawn after a 12-hour period of fasting. Plasma concentrations of glucose, total cholesterol and triglycerides were determined by automated enzymatic methods. The measurement of HDL-cholesterol and LDL-cholesterol fractions was performed using commercial kits according to manufacturer's specifications. Plasma CRP and uric acid were determined using a commercial kit according to the manufacturer's specifications. Serum creatinine levels were measured using the alkaline picrate method traceable to isotope dilution mass spectrometry. Albuminuria was measured with immune turbidimetry and normal value was defined as < 26mg/g.

Analysis of cytokine gene polymorphisms

Genomic DNA was isolated from peripheral blood using standard techniques. The SNP 874T/A was detected by PCR (polymerase chain reaction) using the cytokine genotyping kit (One Lambda, Canoga Park, CA, USA) according to the manufacturer's instructions. The genotyping kit allowed the detection of the +874 IFN -gamma gene polymorphism (T versus A). Besides the specific primer for IFN-gamma, internal oligonucleotide sequences were added as a positive control for each reaction. The primer of internal control amplifies a region of the beta-globin gene of 750 bp. This internal control was present in each well.

The PCR product was analyzed by 2% agarose gel electrophoresis, and the specific amplification bands were visualized by UV light and photographed for later analysis of the polymorphism. Quality checks to ensure the reliability of genotyping were carried out by an independent evaluation of the results by two or three investigators. Discrepancies were all resolved through consensus or redoing genotyping.

After a period of 71.2 ± 15 months (5.8 ± 1.2 years) the results of the same laboratory tests and physical examination were collected again for the assembly of a comparative database. Those patients who had incomplete data or who were lost to follow-up were excluded. The remaining 208 patients were included in the prospective study. The incidence of new CV events or death was identified through medical records of CAD, stroke, PAD or other atherosclerotic vascular events. We also evaluated progression of CKD through decrease in eGFR, increase in albuminuria, increase in cardiovascular risk through the Framingham Risk Score, and

control of blood pressure, DM and dyslipidemia, as well as the incidence of obesity and MS. IFN-gamma polymorphism was associated with the new data and outcomes obtained to establish risk association.

Statistical analysis

Data were expressed as mean and standard deviation for variables with normal distribution and median with minimum and maximum values for non-parametric variables. The Student t-test (parametric variables) and the Mann-Whitney test (nonparametric variables) were used to evaluate differences in the various variables. The chi-square test was used to compare proportions between groups with and without outcomes analyzed. A binary logistic regression model was used to confirm the associations found by adjusting them for confounding factors. We used $p<0.05$ for rejection of the null hypothesis in all tests. SPSS 20.0 software was used for statistical analysis.

RESULTS

The population was predominantly female (70.2%), while the majority (57.2%) was Caucasian, and all patients were hypertensive. The mean age of patients was 59.7 ± 9.3 years; 37% had type 2 DM, while 59.1% had MS, and the mean BMI was 30.17 ± 6.0 cm (Table 1).

With regard to IFN-gamma polymorphism, 17.7% of patients had the TT genotype, 37.5% the TA genotype and 44.8% the AA genotype (Figure 1). The observed genotype distributions were in Hardy-Weinberg equilibrium. For the presence of each allele alone, 82.3% were carriers of the A allele and 55.1% of the T allele (Figure 2). There was no significant difference in the distribution of studied IFN-gamma genotypes with respect to ethnic group (Table 2).

At the end of follow-up (after 5.8 ± 1.2 years) we observed a better control of DBP (82.0 ± 10.2 mmHg vs. 84.6 ± 10.7 mmHg), higher fasting blood glucose levels [98 (30-368) mg/dl versus 94.5 (67-381) mg/dl] and increased waist circumference (102.3 ± 13.5 versus 97.6 ± cm 13.2 cm) compared to baseline, all of them with statistical significance ($p < 0,05$) (Table 1). Patients also had lower total cholesterol levels (180.5 ± 38.9 mg/dl versus 198.8 ± 41.2 mg/dl) and HDL (47.1 ± 12.1 mg/dl versus 54.5 ± 15.5 mg/dl), both with $p < 0,05$ (Table 1). The incidence of DM in the study population was 15%, while incidence of obesity was 3% and MS was 19%, statistically significant. The frequency of patients with eGFR <60 ml/min increased to 17.4% and there was an increase in albuminuria (9.2 (0 to 2893.0) mg/g versus 4.4 (0 to 525.0) mg/g) at the end of follow-up, both with statistical significance (Table 1). The Framingham Risk Score increased to 11.3 ± 8.8% (versus 7.9 ± 7% at the beginning), consistent with the aging of the population (Table 1). The number of antihypertensive agents used by individuals increased during the follow up (2.0 ± 0.4 to 2.3 ± 1.3 – $p < 0.05$) (Table 1).

We divided population according to IFN polymorphism (A allele carriers versus TT genotype) and found no differences in groups profiles with respect to baseline characteristics (Table 3). Only a tendency toward higher prevalence of obesity and albuminuria > 26mg/g in the TT group was observed (Table 3). After follow-up, however, this trend was not evident (data not shown).

Table 1: Characteristics of the population before and after follow-up. Duration in months (mean ± SD): 71.2 ± 15 months

	Before (n=208)	After (n=201)	*p*value
Male (%)		29.8	
Race (%)		10.6	
Black		57.2	
White		32.2	
Others			
Age (years)	59.7 ± 9.3	65.7 ± 9.2	0
SAH (%)	100	100	0
Arterial blood pressure (mmHg)			
SBP	136.1 ± 18.0	134.9 ± 18.1	0.492
DBP	84.6 ± 10.7	82.0 ± 10.2	0.004
DM (%)	37	52.2	0
Fasting glucose (mg/dl)	94.5 (67 – 381)	98 (30 – 368)	0.005
Obesity (%)	43.3	46.3	0
BMI (kg/m^2)	30.17 ± 6.0	30.46 ± 6.2	0.166
Total cholesterol (mg/dl)	198.8 ± 41.2	180.5 ± 38.9	0
HDL-c (mg/dl)	54.5 ± 15.5	47.1 ± 12.1	0
Triglycerides (mg/dl)	134.0 (46.0 – 580.0)	134.0 (41.0 – 388.0)	0.089
Waistcircumference (cm)	97.6 ± 13.2	102.3 ± 13.5	0
MetabolicSyndrome (%)	59.1	78.1	0
Creatinine (mg/dl)	0.96 ± 0.19	0.94 ± 0.48	0.791
eGFR (ml/min)	74.4 ± 15.5	76.0 ± 17.7	0.237
eGFR< 60 (%)	14.6	17.4	0
Albuminuria (mg/g)	4.4 (0 – 525.0)	9.2 (0 – 2893.0)	0
CRP (mg/dl)	0.3 (0.02 – 3.9)	0.24 (0 – 98.0)	0.024
Uricacid (mg/dl)	5.6 ± 1.4	5.6 ± 1.5	0.45
FraminghamRisk Score (%)	7.9 ± 7	11.3 ± 8.8	0
Numberofantihypertensi-veagents	2.0 ± 0.4	2.3 ± 1.3	0.012

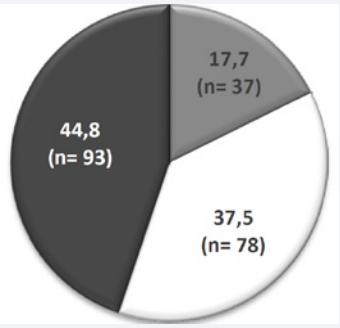

Figure 1 Frequency of IFN –gamma Genotypes (%).

Seven patients died (death from all causes), and new CV events occurred in 8 patients (4 of whom suffered a myocardial infarct and 4 of whom were diagnosed with stroke).

No significant associations were found between IFN-gamma polymorphism and decrease in eGFR, increase in albuminuria, and incidence of DM and MS (Table 3).

The frequency of the TT genotype was higher in patients with CV event (60 versus 15%, $p < 0,05$ – Table (4) and was also higher

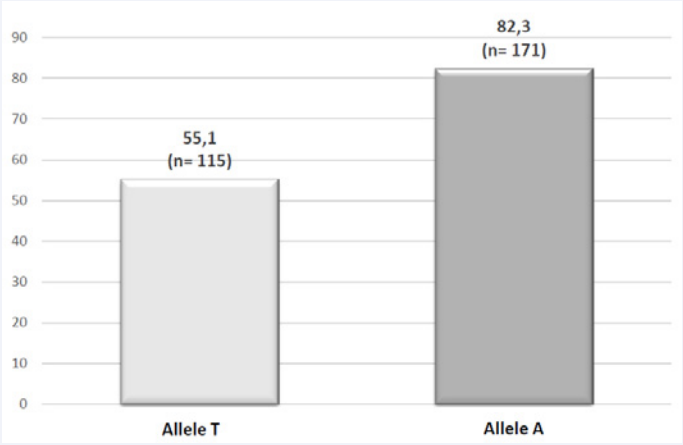

Figure 2 Frequency of T and A Alleles in the population (%).

Table 2: Distribution of IFN-gamma genotypes in the population according to race (p= NS).

	Black	White	Others
TT (n= 37)	8,3%	58,3%	33,3%
TA (n= 78)	5,9%	56,9%	37,3%
AA (n= 93)	16,4%	45,9%	37,7%

Table 3: Characteristics of the population in relation to IFN-gamma polymorphism.

	Allele Acarriers (n= 171)	GenotypeTT (n= 37)	*p*value
Age (years)	58.8 ± 9.43	56.42 ± 6.92	0.243
Males (%)	32.1	29.2	0.776
SBP (mmHg)	137.32 ± 16.32	142.83 ± 23.03	0.167
DBP (mmHg)	85.53 ± 11.24	87.29 ± 12.44	0.495
DM (%)	26.8	33.3	0.517
Obesity (%)	37.5	58.3	0.060
BMI (kg/m^2)	29.18 ± 5.35	30.93 ± 5.25	0.149
Waist(cm)	95.62 ± 11.47	100.21 ± 14.49	0.093
Metabolicsyndrome (%)	52.7	58.3	0.614
Creatinine(mg/dl)	1.00 ± 0.17	1.00 ± 0.22	0.972
eGFR (ml/min)	72.05 ± 13.98	74.29 ± 18.66	0.505
eGFR< 60 (%)	18	16.7	0.875
Albuminuria> 26 mg/g (%)	8.5	21.7	0.064
Prior CVD (%)	7.1	8.3	0.839
Smokers (%)	10.7	12.5	0.729
Family history of CAD (%)	28.2	22.7	0.600
Framinghamrisk score - %	8.2 ± 6.6	7.9 ± 8.2	0.852
Secondaryoutcomes			
Increase in albuminuria(%)	56.3	63.6	0.637
Decrease in eGFR (%)	39.1	18.2	0.062
Incidenceof MS (%)	30.3	26.1	0.804
Incidenceof DM (%)	18.9	12	0.566

Values as mean ± SD for parametricvariables. SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; DM = Diabetes Mellitus; BMI = Body Mass Index; eGFR = estimated Glomerular Filtration Rate; CVD = Cardiovascular Disease; CAD = Coronary Artery Disease; MS = Metabolic Syndrome. Thet-testwas usedfor quantitative parametricvariables. The chi-square test was used for the qualitative variables.

in those with combined outcome - death or CV event (55.6 versus 15%, p < 0,05 – Table (5).

After logistic regression analysis, adjusted for age, gender, DM, total cholesterol, uric acid and MS, the presence of the TT genotype was an independent predictor for the occurrence of CV event (RR: 10.12, CI: 1.16– 87.79, p < 0.05) and combined outcome - death or CV event (RR: 10.74, CI: 1.909 – 60.47, p < 0.05 – Table (6).

DISCUSSION

The influence of IFN-gamma in cardiovascular risk has

Table 4: Baseline clinical and laboratory characteristics of the population with cardiovascular event (+) and without cardiovascular event (-).

	CV event (+) (n= 8)	CV event (-) (n= 193)	*p*value
Age (years)	59.75 ± 11.27	59.64 ± 9.34	0.974
Males (%)	37.5	28.5	0.582
BMI (kg/m^2)	31.42 ± 6.31	30.13 ± 6.01	0.553
SBP (mmHg)	144.5 ± 22.03	135.59 ± 17.32	0.160
DBP (mmHg)	85.75 ± 12.84	84.68 ± 10.75	0.784
Waste(cm)	104.62 ± 14.83	97.19 ± 13.04	0.118
Cholesterol (mg/dl)	214.88 ± 44.88	197.74 ± 41.48	0.255
HDL-c(mg/dl)	44 ± 21.28	55.16 ± 15.29	0.048
LDL-c (mg/dl)	137.62 ± 38.47	112.63 ± 34.80	0.049
Triglycerides (mg/dl)	166.75 ± 74.24	152.27 ± 89.54	0.653
Glucose (mg/dl)	107.43 ± 32.93	104.16 ± 35.34	0.810
DM (%)	37.5	37.3	0.991
Metabolicsyndrome (%)	75	59.1	0.368
Prior CVD (%)	25	9.3	0.147
Family history of CAD (%)	12.5	17.6	0.708
Uric acid (mg/dl)	5.94 ± 1.97	5.53 ± 1.42	0.464
Creatinine (mg/dl)	0.91 ± 0.17	0.95 ± 0.18	0.554
CRP (mg/dl)	0.50 ± 0.55	0.58 ± 0.70	0.792
Allele A carriers (%)	40	85	0.008
Genotype TT (%)	60	15	0.011

Values as mean ± SD for parametricvariables. BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HDL-C = High Density Lipoprotein-cholesterol; LDL-c = Low Density Lipoprotein-cholesterol; DM = Diabetes Mellitus; CVD = Cardiovascular Disease; CAD = Coronary Artery Disease; CRP = C-Reactive Protein. Thet-testwas usedfor quantitative parametricvariables. The chi-square test was used for qualitative variables.

Table 5: Baseline clinical and laboratory characteristics of the population with death or cardiovascular.
Cardiovascular event (+) and without death or cardiovascular event (-).

	Death or CV event (+) (n= 15)	Death or CV event (-) (n= 193)	*p*value
Age (years)	61.80 ± 9.64	59.64 ± 9.34	0.390
Males (%)	46.7	28.5	0.138
BMI (kg/m^2)	30.64 ± 6.13	30.13 ± 6.01	0.755
SBP (mmHg)	143.07 ± 25.75	135.59 ± 17.32	0.123
DBP (mmHg)	83.73 ± 11.68	84.68 ± 10.75	0.745
Waste(cm)	103.07 ± 14.57	97.19 ± 13.04	0.097
Cholesterol (mg/dl)	213.33 ± 36.22	197.74 ± 41.48	0.159
HDL-c (mg/dl)	46.80 ± 17.41	55.16 ± 15.29	0.045
LDL-c (mg/dl)	135.87 ± 30.66	112.63 ± 34.80	0.013
Triglycerides (mg/dl)	153.47 ± 71.60	152.27 ± 89.54	0.960
Glucose (mg/dl)	117.93 ± 67.20	104.16 ± 35.34	0.194
DM (%)	33.3	37.3	0.759
Metabolicsyndrome (%)	60	59.1	0.944
Prior CVD (%)	33.3	9.3	0.004
Family history of CAD (%)	13.3	17.6	0.673
Uric acid (mg/dl)	6.72 ± 1.76	5.53 ± 1.42	0.004
Creatinine (mg/dl)	1.06 ± 0.28	0.95 ± 0.18	0.035
CRP (mg/dl)	0.57 ± 0.78	0.58 ± 0.70	0.954
Allele A carriers (%)	44.4	85	0.002
Genotype TT (%)	55.6	15	0.003

Values as mean ± SD for parametricvariables. BMI = Body Mass Index; SBP = Systolic Blood Pressure; DBP = Diastolic Blood Pressure; HDL-C = High Density Lipoprotein-cholesterol; LDL-c = Low Density Lipoprotein-cholesterol; DM = Diabetes Mellitus; CVD = Cardiovascular Disease; CAD = Coronary Artery Disease; CRP = C-Reactive Protein. Thet-testwas usedfor quantitative parametricvariables. The chi-square test was used for qualitative variables.

Table 6: Association of genotype TT and risk of cardiovascular event or death.

Cardiovascular event	**RR**	**CI 95%**	***p*value**
Notadjusted	8.025	1.260 – 51.130	0.028
Adjusted for age	10.824	1.457 – 80.430	0.020
Adjusted for age and sex	11.162	1.478 – 84.288	0.019
Adjusted for age, sex and DM	10.900	1.429 – 83.133	0.021
Adjusted for age, sex, DM and total cholesterol	11.057	1.463 – 83.594	0.020
Adjusted for age, sex, DM, total cholesterol and uric acid	9.938	1.192 – 82.821	0.034
Adjusted for age, sex, DM, total cholesterol, uric acid and MS	10.120	1.166 – 87.798	0.036
Deathor cardiovascular event	RR	CI 95%	*p*value
Notadjusted	6.687	1.651 – 27.087	0.008
Adjusted for age	8.460	1.889 – 27.882	0.005
Adjusted for age and sex	9.251	1.990 – 43.010	0.005
Adjusted for age, sex and DM	9.373	1.991 – 44.132	0.005
Adjusted for age, sex, DM and total cholesterol	10.150	2.131 – 48.344	0.004
Adjusted for age, sex, DM, total cholesterol and uric acid	9.457	1.757 – 50.906	0.009
Adjusted for age, sex, DM, total cholesterol, uric acid and MS	10.744	1.909 – 60.471	0.007

been the subject of several studies [17-25]. The role of chronic inflammation such as atherosclerotic disease predictor is what justified the present study. Some known cardiovascular risk factors can be controlled, either through changes in lifestyle or drug therapy. However, given the failure to modify the genetic risk factors, the study of IFN polymorphism appears to be extremely relevant, even to contribute to the justification of family history of early CAD as one of the classical cardiovascular risk factors.

Inflammatory response is modulated by the balance between pro- and anti-inflammatory mediators. IFN-gamma is a pro-inflammatory cytokine that plays a crucial role in host defense by directing the immune response to pro-inflammatory mediators including TNF-alpha and IL-6 [26]. Due to these functional characteristics, the bioactivity of IFN-gamma has been identified as a key mediator in several models of inflammatory diseases [21-26]. Individuals with certain genotypes are commonly referred to as low (AA), intermediate (AT) or high (TT) IFN-gamma producers, depending on their production rate *in vitro*. However, there is considerable inter-individual variation in the degree of systemic inflammatory activation, because the production of cytokines is in part genetically determined.

In a cohort of hypertensive patients, we demonstrated that patients with the TT genotype in the IFN-gamma polymorphism had a higher risk of death and CV event at the end of follow-up of 5.8 years. Similarly, Manginas and colleagues [20] showed a predominance of T allele in patients with unstable angina or myocardial infarction compared with patients with stable angina, also suggesting that T allele patients are more prone to serious CV events.

The works of Biolo [21] and Tripathi [12] showed that the genotypes (IFN-gamma +874) of intermediate (TA) and high (TT) producers were significantly associated with progression of CKD, while the low producer (AA) was associated with a protective effect.

In our population, however, there were no significant associations of IFN-gamma polymorphism (+874 T → A) with the decrease in eGFR or the increase in albuminuria.

Moreover, Adamopoulos et al. [22] found that in 80 patients with idiopathic dilated cardiomyopathy, those with the AA genotype (compared to T allele carriers) showed more deaths from cardiac causes or need for heart transplantation. Torres et al., [27] also demonstrated a higher prevalence of the AA genotype and carriers of the A allele in patients with Changes disease compared to healthy patients, suggesting a greater susceptibility to infection with *Trypanosoma cruzi*, but did not establishing a relationship with the progression of Chagas cardiomyopathy.

Notably, to date, there is a great divergence between studies with respect to which polymorphism shows higher cardiovascular risk. In a Spanish study, Garcia-Bermudez and coworkers [28] genotyped (IFN-gamma + 874 T → A) 1635 patients with rheumatoid arthritis and stratified them according to the presence or absence of CV events. No genotype or allele was associated with the presence of CV events in this population.

The present study had some limitations. Only 208 individuals were included in the prospective analysis, due to loss of information or follow-up, which resulted in a small number of outcomes (7 deaths and 8 CV events) and decreased the statistical power. Deaths were considered from all causes (not just related to CV events), because there was no record of the death cause in the medical records and because there was no access to death certificates. The method used for genetic analysis in this study (SNP) has limitation in understanding the interface genotype: phenotype, which is part of the genetic predisposition; and this method does not allow the simultaneous analysis of several genes, such as in whole genome analysis, thereby hindering the search for the genetic signature for polygenic diseases such as CVD and CKD.

Our study established a clear association of the TT genotype with increased cardiovascular risk in comparison with other genotypes, so it has to be regarded as a promising risk factor to be investigated.

New prospective studies with larger population sample are necessary to determine if the genetic polymorphism of IFN-gamma may contribute to the elucidation of the complex interactions involved in the pathogenesis of CVD and to the identification of targets for therapeutic interventions.

CONCLUSION

In individuals with hypertension, the presence of the TT genotype of the IFN-gamma polymorphism resulted in a higher incidence of CV event and death.

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