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POLYMORPHISM AT THE ANGIOTENSINOGEN GENE (AGT) AS A RISK FACTOR FOR DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE II DIABETES MELLITUS

INTRODUCTION:

Diabetes mellitus (DM) is a metabolic disorder which causes chronic complications such as atherosclerosis, diabetic nephropathy, blindness and terminal kidney failure or end stage renal disease (ESRD). There are several types of DM, which are DM type 1, type 2 and gestational DM1[1]. DM type 2 covers up to 80-90% of all DM type diseases. At this point and time Diabetes Mellitus remains the most occurring disease among people worldwide with a prevalence rate of 4%. Its prevalence rate continues to increase and it is estimated it will reach 5.4% by 2025.Most of its patients are above 40 and has diabetic symptoms[2]. 15 million people suffer from DM in the United States, of which 10% suffer from DM type 1 and 90% suffer from DM type 2[3]. Even though DM type 1 dan type 2 could cause ESRD DM type 2 remains the biggest contributor to ESRD. Only DM type 2 could develop to overt nephropathy. Abot 40% of DM develops to diabetic nephropathy4. Research shows that in DM type 1 and 2, genetic factors could increase the risk of contracting DN5.

RAS (*Renin Angiotensin System)* has an important role in patophysiologic diabetic nephropathy (DN)6. One of the hormones involved in RAS (*Renin Angiotensin System)* is angiotensin II. Angiotensin II is a strong vasoconstrictor and acts as an intermediary in cellular profileration to extracelular protein synthesis. Research shows that angiotensin II is an active metabolic hormone which initiates insulin resistance, an increase in the number of free radicals, a decrease in leptin and adiponectin production as well as an increase in oxidative stress8. Angiotensin II acts as a pro-mitosis, pro-proliferative and has an angiogenic effect. Angiotensin II intermediates a complex physiological effect by the bonding of 2 different receptors, AGTR1 dan AGTR26.

M235T Polymorphism (metionin digantikan treonin pada kodon 235) has been intensively researched in cardiovascular diseases and in kidneys. There is a correlation between M235T gene AGT polymorphism and progressive kidney failure in primary kidney disease patients. This polymorphism has a high risk of penyakit gagal ginjal konis9. Several researchers report the relation between the T allele in this polymorphism with the development of kidney disease

MATERIALS AND METHODS:

Following informed consent the demographic and laboratory variables of the patients including age, gender, BMI, diagnostic period, systolic and diastolic (hypertension/ non hypertension), total colesterol, HDL and triglyceride were noted. Furthermore, peripheral blood lymphocytes were isolated by the standard phenol extraction method and used as DNA samples in genotype analysis in this study. The M235T variant of the AGT gene was detected using primers: 5' CCGTTTGTGCAGGGCCTGGCTCTCT-3' as the forward and 5'-CAGGGTGCTGTCCACACTGGACCCC-3" as the reverse primers. The PCR product was digested with the *PsyI* restriction enzyme (Thermo Fisher Scientific Inc.). The data were statistically analyzed using chi square, t-test, odds ratio test.

RESULTS:

There were 60 patients with Type 2 diabetes mellitus, 30 subjects with nephropathy and 30 subjects without diabetic nephropathy, were included in this research. The demographic and laboratory variables of patients participated in this are presented in Table 1. The results of RFLP analysis with *PsyI 1*of PCR on AGT gene are shown in Fig 1. Genotypes MM, MT and TT were found in case and control subjects.

Table 1
Demographic and laboratory characteristics of the studied patients

Variables	DN (n=30)	Non-DN (n=30)	p<0.05
Age (yr)	59.63 ± 8.15	58.17 ± 7.96	ns
Gender (F/M)	14/16	13/17	ns
Total Cholesterol (mg/dl)	199.41 ± 39.94	191.40 ± 53.49	ns
Triglyceride (mg/dl)	159.85 ± 69.45	145.21 ± 74.96	ns
HDL (mg/dl)	42.64 ± 14.37	45.48 ± 13.87	ns
BMI (kg/m^2)	24.62 ± 4.46	23.79 ± 2.94	ns
Systolic (mmHg)	134.67 ± 22.70	122.83 ± 14.00	S
Diastolic (mmHg)	84.67 ± 13.06	79.83 ± 7.71	ns

DN: Type 2 diabetes patients with nephropathy; Non-ND: Type 2 diabetes patients without nephropathy

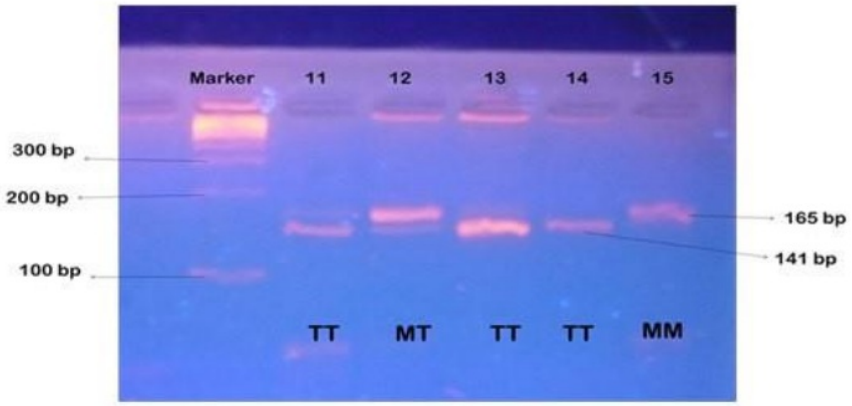

Figure 1
Polymorphism of AGT gene: pysldigestion of the PCR product. The wild type gene was 165 bp and the mutant was 141 bp.

The frequency distribution of AGT genotypes in Type 2 diabetes mellitus patients with and without nephropathy are presented in Tabel 2.

Table 2
Distribution of AGT M235T genotypes in Type 2 diabetes mellitus patients with and without nephropathy

	DN patients	Non-DN patients	P < 0.05
Genotype	(n = 30)	(n = 30)	
MM	7 (23.3%)	3 (10%)	ns
MT	8(26.7%)	16 (53.3%)	S
TT	15 (50%)	11(36.7%)	S
M allele	22(36.7%)	22 (36.7%)	ns
T allele	38 (63.3%)	38(63.3%)	ns

DN: Type 2 diabetes patients with nephropathy; Non-ND: Type 2 diabetes patients without nephropathy

Frequency distribution of AGT genotypes in the DN group are as follows, 23.3% (n=7) of the subjects with MM genotype, 26.7% (n=8) with MT genotype, and 50% (n=15) with TT genotype. Whereas in Non-DN group there were 10% (n=3) subjects with MM genotype, 53.3% (n=16) with with AC genotype and 36.7% (n=11) with MT genotype. The frequency distribution of AGT allele M and allele T in DN group are 36.7% (n=22) and 63.3% (n=38) respectively. Whereas in non-DN group the frequency of allele M and allele T consecutively are 36.7% (n= 22) and 63.3% (n=38). However, between the two groups there is no statistical difference in the both gene and allele frequency distribution at *P*=0.05

DISCUSSIONS:

Current findings suggest that among Indonesian patients, AGT gene M235T genotype TT is more prevalent in the DN group while in the non DN group genotype MT is more prevalent. When these results are compared to the data from other countries, referred to Zhang et al. as shown in **Table 3**, it seems that M235T genotype polymorphism of AGT gene in Indonesian patients are similar to that of Chinese.

Table 3

Population of AGT Gene M235T Genotype among Different Countries

Year	Population	MM	MT	TT
2009	Indonesian	16.7%	40%	43.3%
2007	Taiwan	0.5%	24.5%	75%
2003	Japan	3.8%	30.7%	65.5%
2005	Germany	34%	62.4%	3.65%
2007	Mexico	16%	58.5%	25.5%

The data showed that in Asian ethnicity (Indonesia, Taiwan and Japan), the frequency of TT genotypes have the greatest number . However in (Germany and Mexico) the number of MT genotypes is the most. The effect of intra renal RAS is kidney hemodynamic change such as the increase in intra glomeruler pressure, stimulation from mesangial cell proliferation and matrix production . The function of angiotensin II is to increase efferren arteriol pressure and afferren or preglomeruler strand that causes autoregulation response in systemic blood pressure increase causing the increase in glomerulus capillar pressure. Beside, angiotensin II also plays a role in growth stimulation, fibrogenesis induction and regulates endotel function .

CONCLUSIONS:

Frequency genotype TT polymorphism of AG2 M235T gene is more common in DN than non DN. T allele frequency of M235T AGT polymorphism in DN is as much as non-DN.

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★K Makni, F Jarraya, M Rebaï, F Mnif et al. "Risk genotypes and haplotypes of the GLUT1 gene for type 2 diabetic nephropathy in the Tunisian population", Annals of Human Biology, 2009 — 5%
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