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Impact of Catalase Gene Polymorphisms on Metabolic Disorders

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ABSTRACT

The metabolic syndrome (MetS) concept gathers in a single entity a set of metabolic abnormalities that have in common a close relationship with ectopic deposit of lipids, insulin resistance, and chronic low-grade inflammation. This study aimed to investigate whether patients with metabolic disorder have to find weather catalase gene polymorphism have an impact on disease susceptibility when compared with different disease groups in addition to control group from the people whose apparent healthy. A case-control study was conducted on the study to identify catalase genes polymorphism by PCR-RFLP and to detect association of its susceptibility to Mets. The comparison was made between central obesity group and control group. The heterozygous C/T genotype was significantly (p = 0.041) less frequent in central obesity group than in control group, 5 (16.7 %) versus 20 (41.7 %), respectively. Thus, the heterozygous C/T genotype acted as protective factor against central obesity with an odds ratio of 0.34 and a preventive fraction of 0.30. While, homozygous TT genotype was limited to central obesity group; however, the difference carried borderline significance level (between 0.05 and 0.1) of 0.098 and it acted as a risk factor for obesity with an approximate odds ratio of 8.87. The comparison was made between central obesity and hypertensive group with the control group. The heterozygous C/T genotype was highly significantly (p = 0.002) less frequent in central obesity and hypertensive group than in control group, 2 (6.7 %) versus 20 (41.7 %), respectively. Thus, the heterozygous C/T genotype acted as protective factor against obesity and hypertension with an odds ratio of 0.11 and a preventive fraction of 0.42.

The homozygous TT genotype was limited to central obesity and hypertensive group; however, the difference carried borderline significance level (between 0.05 and 0.1) of 0.098 and it acted as a risk factor for obesity and hypertension with an approximate odds ratio of 7.82 and the comparison was made between central obesity, hypertensive and diabetes group and control group. The heterozygous C/T genotype showed no significant variation between groups (p = 0.477). Thus, the heterozygous C/T genotype cannot be regarded as protective or preventive factor. The homozygous TT genotype was limited to obese, hypertensive and diabetes group; however, the difference carried borderline significance level (between 0.05 and 0.1) of 0.098 and it acted as a risk factor for obesity, hypertension and diabetes with an approximate odds ratio of 10.78. Regarding correlation catalase gene with metabolic syndrome, there was an increased risk for metabolic syndrome with genotype TT versus TC, which may represent a factor of risk to Mets. This study concluded that TT genotype was limited to all patients (obese, hypertensive and diabetes) groups; however, it acted as a risk factor for obesity, hypertension and diabetes.

KEYWORDS: Catalase, Insulin resistance, Metabolic disease, Polymorphisms, Iraq

INTRODUCTION

Modifications in lifestyle among the recently years participate greatly in an increasing the incidence of metabolic diseases globally [1, 2]. Each metabolic disease consider as an important public health because it can act as a risk factor to development cardiovascular and, probably, neurodegenerative diseases [3, 4].

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Extensively performed studies regarding the physiopathology of metabolic diseases identify the cardinal related features like oxidative stress processes, inflammation and aging [5, 6]. Concerned to oxidative stress, researchers found a particular association to catalase (CAT), glutathione peroxidase (GPX), and superoxide dismutase (SOD). CAT has an activity in converting H_2O_2 to oxygen and water, which prevents the accumulation of H_2O_2 that fuels cancer, inflammation and aging [7].

Other reports carried out in animals demonstrate that the over expression of CAT can increase the lifespan, decrease the blood pressure (BP), and delay the onset of atherosclerosis [8, 9, 10]. However, clinical trials revealed conflicting findings regarding relationship between activity of CAT and pathology due to the divergent outcomes [11]. Usually, the activity of CAT can be evaluated through estimation of blood compartment rather than tissues, in which, oxidative stress can involve throughout each disorder. Nonetheless, widespread limitations in many performed studies were reported including difficulties in evaluation the complete sets of parameter which influencing the activity of CAT like dietary and environmental factors [12, 13]. Cases of hypocatalasemia and acatalasemia were described in many areas of developed countries such as Japan, the Switzerland and Hungary. This study aimed for investigating the patients with metabolic disorder, whether CAT gene polymorphism having impact on disease susceptibility using the PCR-RFLP and association of its susceptibility to Mets.

MATERIALS AND METHODS

Study population

The current study was performed during November 2019 to September 2020. The study patients were divided to 3 groups; 1st involving the obese, 2nd involved the obese and hypertension, and 3rd involved the obese, hypertension and diabetes mellitus patients. Each of these group include (30) patients mixed of males and females with age range 18-66 years old. This study was performed at Al-Diwaniyah Teaching Hospital. The patients were diagnosed clinically by physician with metabolic syndrome. Direct interview was performed with the study patients to report the associated data including age, sex, residence, family size, history of obese, hypertension, diabetes, heart disease and others. In addition, apparently healthy individuals were clinically considered as a study control group. This study was in agreement with the ethics Al-Diwaniyah Teaching Hospital.

Collection of Blood Samples

A total 5 ml of venous blood was drained from each one of study population into K3-EDTA anti-coagulated tube that stored at -20°C for DNA extraction.

Catalase gene polymorphism

Following the manufacturer instructions, genomic DNAs were extracted from the samples of blood using the G-spin™ Total DNA Extraction Kit. The purity and concentration of extracted genomic DNAs was evaluated using the Nanodrop (THERMO, USA) system.

RFLP-PCR technique was used to detect Catalase C-262T Gene polymorphism in metabolic diseases patients and control individuals. This method was carried out according to previously performed study [14].
The PCR mastermix was prepared following the manufacturer instructions of the Maxime PCR PreMix kit. PCR thermocycler conditions were designed specifically for each gene independent [14]. The PCR products were analyzed by agarose gel electrophoresis.
RFLP-PCR mix of Catalase C-262T Gene prepared by *SmaI* restriction enzyme (New England Biolabs, UK) and performed independently according to manufacturer instructions. RFLP-PCR products were analyzed in 3% agarose gel electrophoresis. For (CC) wild type homozygote, the products were digested using the restriction enzyme into 155 bp and invisible 30 bp band. For (TT) mutant type homozygote, the products were

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undigested by restriction enzyme and still 185bp band. For (C/T) heterozygote, the products were digested by restriction enzyme into 185 bp, 155 bp and invisible 30 bp bands.

RESULTS AND DISCUSSION

Catalase SNP and Metabolic Disease Susceptibility : The frequency of catalase genotypes and alleles in control group and patients' groups is shown in tables 1 through 3.figure1,2 The CC genotype is the most frequent genotype; therefore it is going to be regarded as the reference genotype.In table 1, the comparison was made between central obesity group and control group. The heterozygous C/T genotype was significantly (p = 0.041) less frequent in central obesity group than in control group, 5 (16.7 %) versus 20 (41.7 %), respectively. Thus, the heterozygous C/T genotype acted as protective factor against central obesity with an odds ratio of 0.34 and a preventive fraction of 0.30. While, the homozygous TT genotype was limited to central obesity group; however, the difference carried borderline significance level (between 0.05 and 0.1) of 0.098 and it acted as a risk factor for obesity with an approximate odds ratio of 8.87.

Table 1: The frequency of catalase genotypes and allele's frequency in control group and central obesity group

Catalase genotype rs1001179 (CAT-262C >T)	**Control *n* = 48**	**central obesity *n* = 30**	***P***	**OR**	**95 % CI**	**EF**	**PF**
CC	28 (58.3 %)	22 (73.3 %)	Reference				
CT	20 (41.7 %)	5 (16.7 %)	0.041 C S	0.34	0.10-0.98	---	0.30
TT	0 (0.0 %)	3 (10.0 %)	0.098 F NS	8.87*	---	---	---
Catalase allele	**Control *n* = 96**	**central obesity *n* = 60**	***P***	**OR**	**95 % CI**	**EF**	**PF**
C	76 (79.2 %)	49 (81.7 %)	0.703 C NS	1.17	0.52 - 2.66	0.06	---
T	20 (20.8 %)	11 (18.3 %)		0.85	0.38 - 1.93	---	0.06

n: number of cases; C: Chi-square test; F: Fischer exact test; OR: odds ratio; *: approximate odds ratio; S: significant at $p \leq 0.05$; CI: confidence interval ;NS: not significant at $p > 0.05$; EF: etiologic fraction; PF: preventive fraction

Moreover, no significant difference were detected in C and T alleles frequencies between both groups (p = 0.703); thus, they cannot be regarded as preventive or risk factors. CAT represented the most effectively antioxidant defense in body under condition of elevated oxidative stress. The main function of CAT is an intracellular antioxidant enzyme that prevents cells against ROS damage by converting hydrogen peroxide into water and oxygen to avoid cell damage [15]. The rs1001179 (CAT-262C >T) considers the most extensive gene used in polymorphism.

The current study addressed participation one SNP of principal antioxidant enzyme from nutrigenetic point of view in people living with central obesity. Specific SNP can select because its role in obesity etiology and co-morbidities. In this sense, SNPs of catalase enzymes (- 262 C >T CAT, rs1001179) were detected to code and regulate the un-translated areas of a gene that affects the net activities of each enzyme [16, 17, 18]. A s well

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as, They act as a key for avoiding the existence the oxidative stress, inactivating generation and propagation of endogenous free radicals produced due to cell metabolism [19, 20]. The case of polymorphism was -262 C > T CAT (rs1001179), and the common polymorphism of CAT gene include the substitution of T for C in position T -262 in the 5′ region [21], leading for decreasing the activity of the enzyme. The CAT TT genotype may mange reducing of antioxidant defenses, and subsequently, increasing the oxidative damage [22].
The TT genotype carriers of the central obesity group were prone to regain abdominal fat compared with those control [23].

The C allele associated with lower body weight as this found in [24, 25] studies. Current results proposed that the TT genotype act as a factor of risk to obesity. These findings were in agreement with the results of other researchers [26] who proposed that the TT genotype could increase plasma triglycerides, which may modulated by BMI and/or age [26]. The CC and TC genotype of CAT showed higher activity as compared to TT genotypes and this come in agreement with [13] and in contrast with the homozygous TT genotype that having a greater metabolic disorder prevalence [27]. Accordingly, it higher frequency of the individuals with the homozygous genotype TT in central obese group compared with control group in study sample. It can be concluded that polymorphism is a considerable risk factor for obesity and its comorbidities among the Iraqi population, and more research should be conducted in this field. Despite, these findings may come in disagreement with previous studies found different genotype correlated with central obesity that may be CC or C/T but, it is now well known that obesity is a complex disorder involving a multitude of genetic, behavioral, and environmental factors [28]. Thus, polymorphism in such gene (catalase) could pave the way for environmental factors (diet, physical activity) for development of obesity. Previous analyses of the association between the gene polymorphism and obesity or BMI are controversial among different ethnic population and geographic area.

In this study, the comparison was made between central obesity and hypertensive group with the control group. The heterozygous C/T genotype was highly significantly (p = 0.002) less frequent in central obesity and hypertensive group than in control group, 2 (6.7 %) versus 20 (41.7 %), respectively. Thus, the heterozygous C/T genotype acted as protective factor against obesity and hypertension with an odds ratio of 0.11 and a preventive fraction of 0.42. The homozygous TT genotype was limited to central obesity and hypertensive group; however, the difference carried borderline significance level (between 0.05 and 0.1) of 0.098 and it acted as a risk factor for obesity and hypertension with an approximate odds ratio of 7.82.

Table 2: The frequency of catalase genotypes and alleles frequency in control group and central obesity and hypertension group

Catalase genotype	**Control *n* = 48**	**Central obesity and hypertension *n* = 30**	***P***	**OR**	**95 % CI**	**EF**	**PF**
CC	28 (58.3 %)	25 (83.3 %)	Reference				
CT	20 (41.7 %)	2 (6.7 %)	0.002 C HS	0.11	0.02-0.53	---	0.42
TT	0 (0.0 %)	3 (10.0 %)	0.098 F NS	7.82*	---	---	---
Catalase allele	**Control *n* = 96**	**central obesity and hypertension *n* = 60**	***P***	**OR**	**95 % CI**	**EF**	**PF**
C	76 (79.2 %)	52 (86.7 %)	0.235 C NS	1.71	0.70 - 4.18	0.17	---
T	20 (20.8 %)	8 (13.3 %)		0.58	0.24 - 1.43	---	0.17

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n: number of cases; C: Chi-square test; F: Fischer exact test; OR: odds ratio; *: approximate odds ratio; HS: highly significant at $p \leq 0.01$; NS: not significant at $p > 0.05$; CI: confidence interval; EF: etiologic fraction; PF: preventive fraction

Moreover, no significant differences were seen in C and T alleles frequencies between both groups ($p = 0.235$); thus, they cannot be regarded as preventive or risk factors.This current result is inconsistent with a study done by [29] who found that there insignificant differences within the frequency of C/T genotype. "An association between CAT and hypertension is compatible with a research in China demonstrating the association of homozygous people with CAT-844 AA and high blood pressure [30]. The CAT-262 SNP has not earlier been examined for blood pressure values, although the CAT-262 T allele is linked with the catalase gene's greater expression level [21]. The CAT enzyme is capable of controlling oxidative stress by hydrogen peroxide degradation [31]. In the promoter region of the CAT gene, polymorphism may decrease gene expression, eventually decreasing enzymatic activity and increasing oxidative stress [18]. These findings indicated that CAT gene polymorphisms were related likely to hypertension [32, 29]. The results of other study [26] suggested that TT genotype acting as a factor of risk to increasing hypertension. The findings were similar to that obtained in present study as homozygous TT genotype was limited to central obesity and hypertensive group; however, the difference carried borderline significance level (between 0.05 and 0.1) of 0.098 and it acted as a risk factor for obesity and hypertension with an approximate odds ratio of 7.82. Typically, catalase enzyme genes are susceptible to polymorphism and may lead to gene expression modification and reduce enzyme activity [33]. In one study, the findings showed that various metabolic disorders are concerned with the function of antioxidant enzymes that play an important role in the pathogenesis of many diseases like cancer, hyperlipidemia, diabetes mellitus, metabolic disorders, cardiovascular diseases (hypertension, ischemic heart disease, chronic heart failure) neurodegenerative diseases and atherosclerosis [34, 35]. Oxidized lipid contributes for many stages in developing and progressing of atherosclerotic plaque by producing the inflammatory cytokines [36]. Inflammation, oxidation as wellas genetic predisposition are the most important factors for endothelial damage followed by macrophage cell infiltration and smooth muscle cell (SMC) impaired function and cause increase blood pressure or atherosclerosis [37, 38, 39].

The present study showed that heterozygous C/T genotype has no significant variation between groups ($p = 0.477$). Thus, the heterozygous C/T genotype cannot be regarded as protective or preventive factor. The homozygous TT genotype was limited to obese, hypertensive and diabetes group; however, the difference carried borderline significance level (between 0.05 and 0.1) of 0.098 and it acted as a risk factor for obesity, hypertension and diabetes with an approximate odds ratio of 10.78.

Table 3: The frequency of catalase genotypes and allele's frequency in control group and central obesity, hypertension and diabetes group

Catalase genotype	**Control *n* = 48**	**Central obesity hypertension and diabetes *n* = 30**	***P***	**OR**	**95 % CI**	**EF**	**PF**
CC	28 (58.3 %)	18 (60.0 %)	Reference				
CT	20 (41.7 %)	9 (30.0 %)	0.477 C NS	0.70	0.26-1.87	---	0.12
TT	0 (0.0 %)	3 (10.0 %)	0.098 F NS	10.78*	---	---	---
Catalase	**Control**	**central obesity**	***P***	**OR**	**95 % CI**	**EF**	**PF**

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allele	***n* = 96**	**hypertension and diabetes *n* = 60**					
C	76 (79.2 %)	45 (75.0 %)	0.544 C NS	0.79	0.37 -1.70	---	0.09
T	20 (20.8 %)	15 (25.0 %)		1.27	0.59 -2.72	0.09	---

n: number of cases; C: Chi-square test; F: Fischer exact test; OR: odds ratio; *: approximate odds ratio; NS: not significant at $p > 0.05$; CI: confidence interval; EF: etiologic fraction; PF: preventive fraction

Moreover, no significant difference were reported in frequency of C and T alleles between both groups ($p = 0.544$), and thus, it cannot be regarded as preventive or risk factors. Such data could be explained by the hypothesis that catalase SNP may have no effect on DM susceptibility as mentioned by previous studied. On the other hand, the polymorphism of CAT gene may never associated with the development of cardiovascular disease type 1 and type 2 diabetic patients [40, 41]. The earliest research planned for our data to investigate the relation between a polymorphism of CAT gene as well as diabetic problems of type 2 diabetic patients as a one component of Mets in addition to others components due to DM is a most prognostic stage for Mets. Although, CAT is mostly researched, little studies were detected association of CAT polymorphisms with diseases. In one study, the findings suggested that polymorphism in CAT may connect to diabetes [42]. The TT genotype in – 262 C > T was elevated the risk for Mets because its limited to this patient group, and this agree with [43] whom explain that the TT genotype in -262 C > T may have elevated risk for diabetes complications. The distribution of the allelic polymorphisms of the CAT-262C / T gene showed no significant difference between the C and T alleles of central obesity hypertension and diabetes compared to the controls with no apparent sensitivity.

In our study, T allele was appeared to less common in central obesity hypertension and diabetes (25.0 %) compared to controls (20.8 %) but with a risk of developing disease with TT genotype. In comparison with another studies, the levels of erythrocytic CAT in patients having TT genotype were higher in comparison with findings of CC genotype [21]. In one report, the individuals carrying CC genotype were at greater risk than those having TT genotype to develop type 1 diabetes [44]. In CC individuals, the lowered CAT levels can result in oxidative stress conditions thereby promoting type 1 diabetes [44]. Other results were showed CAT polymorphism was linked to enhanced hazard and began playing an essential role in diabetes pathogenesis as its come in the study of [45]. The TT genotype was related to increase the dangerous of T2DM [46]. Central obesity characterize by chronic inflammatory process that contributed to hypercholesterolemia, hyperglycaemia, low HDL, and hypertension [47]. Therefore, central obesity can be correlated mostly with the mortalities resulted due to the cardiovascular diseases [48]. In one report, the findings detected that the normally weight subjected to central obesity having greater mortality in comparison with similar BMIs without central obesity. In similar, our findings detected that the patients of central obesity having a higher levels of TC and LDL and lower levels of HDL [49] demonstrated that homozygous CC genotype was most prevalent among patients and the healthy groups, and thus, we can consider that not correlated with disease. However, heterozygous C/T genotype was a protective factor from disease and its frequency was higher significant in control group. Whereas in the central obesity, hypertension and DM group it had no significant association with the disease, and was no consider as a protective factor at all. While, the homozygous TT genotype was limited by the disease groups and consider as a risk factor in all metabolic syndrome. The TT genotype of rs11001179 had risks to disease susceptibility because reduction of CAT. It means that the elevated level of H_2O_2 because of lowered CAT activity might be contributed for damaging the sensitive of pancreatic beta-cells

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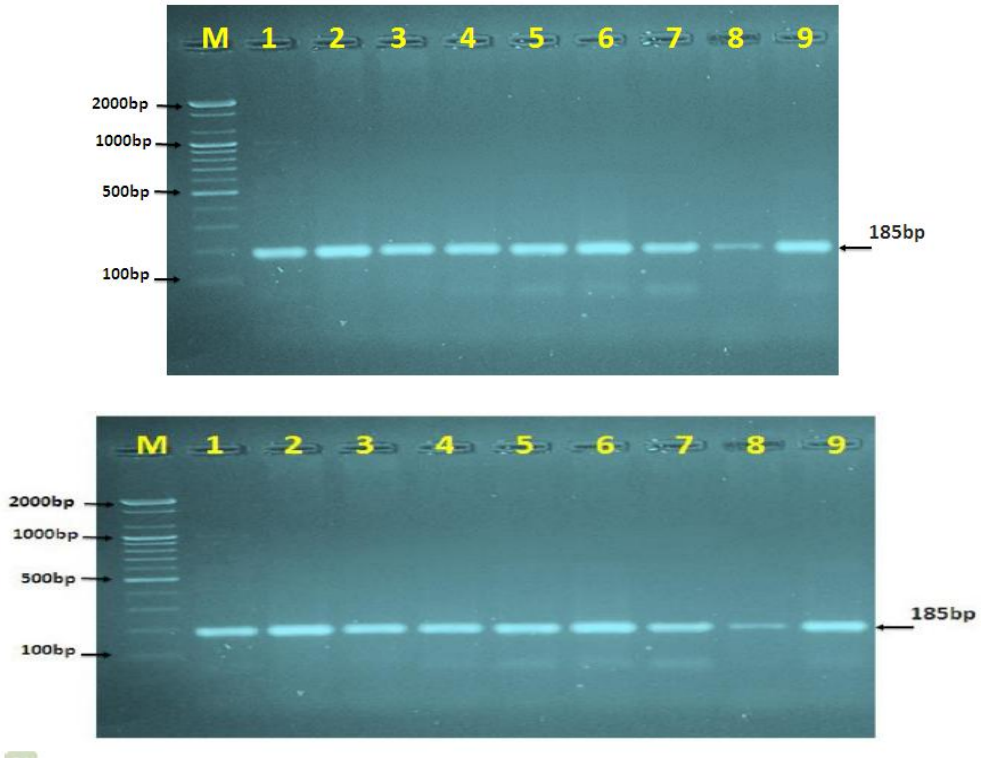

Figure (1): Agarose gel electrophoresis image of PCR product analysis of CAT gene at 1.5 % agarose

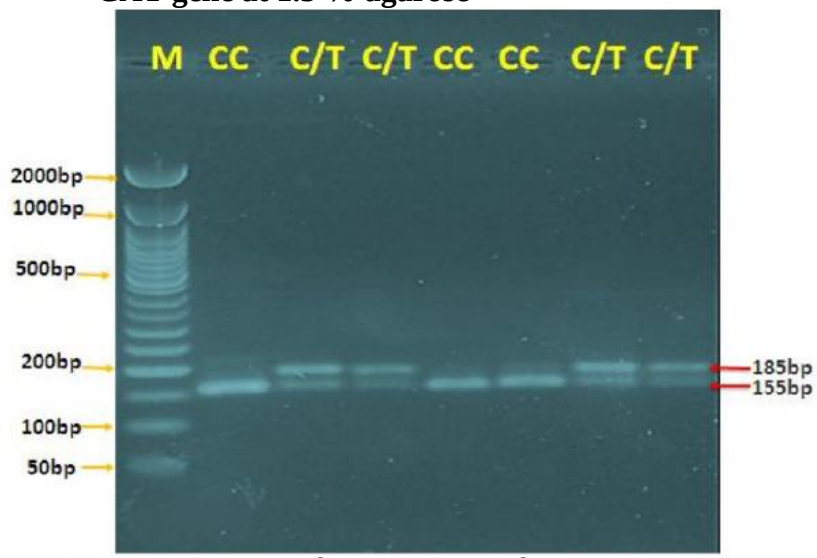

Figure (2): Agarose gel electrophoresis of RFLP-PCR of CAT C-262T Gene polymorphism using *SmaI* restriction enzyme in 2.5% agarose gel

Where M: marker (2000-50bp); Lane (CC) wild type homozygote at 155bp; Lane (TT) mutant type homozygote at 185bp; Lane (C/T) heterozygote at 158bp and 155bp

CONCLUSION

The heterozygous C/T genotype of catalase acted as protective factor in central obesity/ central obesity, hypertensive groups, while this heterozygous C/T genotype cannot be regarded as protective or preventive

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factor in central obesity, hypertension and diabetes group. The homozygous TT genotype was limited to all three patients group and it acted as a risk factor.

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