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# Age and Sex-Related Chromogranin A Gene Polymorphisms and its Association with Metabolic Syndrome Components

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**Abstract**

Introduction. The purpose of this study was to determine the possible differences in genetic polymorphisms and serum levels of chromogranin A (CgA), according to age and sex, in subjects with and without metabolic syndrome (MetS).

Methodology. The genotyping and serum level of CgA and biochemical parameters were measured by the T-ARMS-PCR and PCR-RFLP and ELISA and spectrophotometer methods, respectively.

Results. A comparison of males with and without MetS showed significantly lower high-density lipoprotein-cholesterol (HDL-C) levels than those of females.

At ages 30-70 years, both sexes showed significant differences in triglycerides (TG), fasting blood sugar (FBS), CgA levels and waist circumference (WC) when compared to the two groups. Both sexes with MetS indicated significant differences in systolic blood pressure (SBP) at ages 40-70 years, while at ages 40-59 years, there was a significant difference in HDL-C level in males.

There was a significant correlation between serum levels of FBS, TG, SBP and WC (in both sexes), and CgA in subjects with MetS. Significant correlation was found between HDL-C level and diastolic blood pressure (DBP), and CgA level in males and females, respectively. CgA genotype frequency (T-415C and C+87T polymorphisms) showed no significant differences between males and females with and without MetS, while there was only a significant difference in frequency of the genotypes T-415C when compared to males with and without MetS.

Conclusion. The CgA appears to be strongly associated with MetS components in both sexes. Variation in CgA gene expression may affect the T–415C polymorphism in males. This may mean that the structure of CgA genetics differs in different ethnic groups. Differences in the serum level and expression of CgA gene may show valuable study results that it may be expected a relationship between these variables and the MetS.

*Key words: Age, Sex, Chromogranin A, genotype, metabolic syndrome*

## INTRODUCTION

Metabolic syndrome (MetS) is known as a significant factor of cardiovascular disease in the general population.[1] Many studies have indicated the relationship between MetS and coronary artery diseases in different ethnic groups, sex, age and countries.[2-7] Some findings have shown that MetS prevalence changes between 10 to 84% worldwide,[8] while some other studies revealed the MetS prevalence between 8 to 24% and 7 to 46.5% among males and females worldwide, respectively.[9,10] MetS is increasing from 20% to 30% among males and females in Europe[11,12] and increasing in Asian countries.[13] It has been reported that subjects with MetS are more at risk of developing diabetes and coronary heart disease.[14] Metabolic syndrome is a complicated disease.

Banks and Helle reported an adrenal medulla protein release in September 1965.[15] Blaschko et al.,[16] showed soluble protein release and called it chromogranin in July 1967. In September 1967, they named the protein chromogranin A (CgA) as the major component of these proteins.[17]

Chromogranin A (CgA) is a 48-52 kDa soluble acid glycoprotein that is widely secreted in the secretory vesicles

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of endocrine, neuronal and neuroendocrine cells.[18] Some studies have shown that plasma CgA levels are increased in hypertension[19] and many other diseases such as myocardial infarction[20] and acute coronary syndrome.[21] A study has demonstrated that there is an important association between CgA and increased systolic and diastolic blood pressure, insulin resistance, high plasma triglycerides and high plasma total cholesterol.[22] These are defined as a part of the criteria for MetS. Genetic variation at CgA may influence the expression of genes in different populations. Thus, CgA may act on the inhibition of glucose-stimulated insulin release from pancreatic islet β- cells[23] and the inhibition of glucose uptake by adipocytes and hepatocytes.[24] A study recognized many single-nucleotide polymorphisms (SNPs) in the CgA locus.[25] Age and sex-related changes in CgA levels in patients with MetS are not exactly determined.[26,27] The CgA gene contains many polymorphisms in the promoter and coding regions. Functional polymorphisms C+87T (rs7610) and T-415C (rs9658635) may have an important role in hypertension and the pathogenesis of diabetes mellitus and regulating blood sugar, respectively.[28-31]

A study has shown that CgA is over-expressed in hypertensive humans and rodents.[32] It is also reported that CgA knockout (CgA-KO) mice are hypertensive.[33] Studies on humans and rodents reveal that aging correlates with insulin resistance and hypertension.[32] Thus, we decided to determine the possible differences of genetic polymorphisms T-415C (rs9658635) and C+87T (rs7610) and serum level of CgA that it may be affected by age and sex in the Fars ethnic group with and without MetS.

## METHODOLOGY

### Study subjects

The samples were collected from members of the native Iranian Fars ethnic group who were referred to the health center in Gorgan, Golestan province, Iran, and fulfilled the MetS criteria.[8] This study was done as an analytical case-control study. The sample size was conducted according to the 2008 Chen study[34] and frequency of polymorphism genotype C+^vT (p1= 0.59 and p2= 0.41) with a statistical confidence of 0.95 and power of 80 percent. The sample size was calculated at 117 in each group, and we also considered 5 percent missing. Finally, the sample size was considered 123 in each group and 246 in total.

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 (p_1q_1 + p_2q_2)}{(p_1 - p_2)^2}$$

Fifty-nine males and sixty-four females with MetS and sixty males and sixty-three females without MetS from the Fars ethnic group were included in this study. The study was carried out in the Metabolic Disorders Research Centre, Gorgan Faculty of Medicine, Golestan University of Medical Sciences. The Golestan University of Medical Sciences ethics committee approved our study (Ethic number: IR.GOUMS.REC.1400.096). Written consent was provided for all participants. Participants were excluded if they had liver disease, renal failure, lung disease, cardiovascular disease, acute and chronic infection, and inflammatory disease.

### Ethics and consent statement

The Ethics Committee of the Research Deputy of Golestan University of Medical Sciences has approved the study (Ethics number: IR.GOUMS.REC.1400.096).

### Experimental protocol

#### *Anthropometric and laboratory measurements*

Blood samples were extracted from all participants after a 12-hour fast and separated into two different tubes. Ethylenediaminetetraacetic acid (EDTA) was utilized as the anticoagulant to determine DNA extraction. Another part of the blood sample was used to measure serum fasting blood sugar (FBS), high-density lipoprotein-cholesterol (HDL-C) and triglycerides (TG) with commercial kits and spectrophotometric method. Waist circumference (WC) was determined in centimeters using a tape measure. Body mass index (BMI) was calculated by the formula weight (kg)/height (m)$^2$. Systolic and diastolic blood pressure (SBP and DBP) were determined by a digital blood pressure instrument. The definition of the subjects with MetS was done by Adult Treatment and the National Cholesterol Education Program Panel III (NCEP, ATP III).[8] According to this definition, five criteria were used for the diagnosis of MetS. The presence of three or more criteria was used for the diagnosis of MetS. The criteria are:

1-WC >102 cm (male), >88 cm (female)
2-TG >150 mg/dl
3- HDL-C <40 mg/dl (male), <50 mg/dl (female)
4- SBP and DBP >130/>85 mm Hg
5- FBS >110mg/dl

#### *Single nucleotide polymorphism (SNP) assays*

Whole blood was used to extract genomic DNA according to the salting-out method.[35] Two microtubes were utilized to separate the extracted DNA sample and stored at -20oC. Genotyping of the C+87T and T-415C was carried out by the T-ARMS-PCR (Tetra-primer Amplification Refractory Mutation System-Polymerase Chain Reaction) and PCR-RFLP (Polymerase Chain Reaction-Restriction Fragment Length Polymorphism) methods. The specific primer for T-415C and C+87T (the CgA gene) and their PCR product sizes are indicated as follows:

1-For +87 C>T:
1a-Forward inner primer (G allele):
481-GCCTCCCTACCGGAAGCATCG-501 with PCR product size 193 bp
1b-Control primer forward (5' - 3'):
382-GCCCTGCAAAGGATGTTCCAGG-403 with PCR product size 291 bp
1c-Reverse inner primer (A allele):
521-TCCTGGCCAGATGGCCCGTAT-501 with PCR product size 140 bp

1d-Control primer Reverse (5' - 3'): 672-GACCAGGAGCTGGAGAGCCTG-651 with PCR product size 291 bp
2-For -415 T>C:
2a- Common forward primer (5'-3'): CCTAGATATTGGAGAGAGCCATGAGTG
2b- Reverse (5'-3'): CCATGTGTACTGAGGTCCCTGGCAG with PCR product size 135 bp.

The total amount of mixture was 20 µl for T-ARMS PCR and RFLP PCR. The mixture consisted of forward and reverse primers with an inner to outer ratio of 1 to 1 and 2 to 1, 10 µl of PCR-master mix2X (sinaClon, Iran), 3 µl of DNAse free water and 2 µl of DNA template. The reaction condition consisted of initial denaturation at 95°C for 2 min, denaturation at 92°C for 30 sec, annealing at 64.5°C for 30 sec, and extension at 72°C for 50 sec followed by 32 cycles repeat steps 2-4 and a final extension at 72°C for 5 min. The scoring was done by running the PCR products on a 2% agarose gel electrophoresis over 40 min at 90 volts.

Validation of the genotyping results was done by the published method of PCR– RFLP which utilizes a BCCI enzyme (Ipswich, Massachusetts, United States, Cat. No. R0704S). The used reaction mixture was the same volume for forward and reverse primers with a ratio of 1 to 1. There were only differences in DNAse free water volume (2.5 µl). Two cycles of denaturation at 95°C for 2 min and then 30 sec, annealing at 65.8°C for 30 sec and cycles of extension at 72°C for 20 sec then repeat steps 2-4 to 38 times and the final step of extension for 72°C for 5 min were the initial program temperature. In the final step, 0.32 µl of enzyme, 2 µl buffer10x, 10.7 µl DNAse free water and 7 µl PCR products were mixed and given the temperature program mentioned above. 2.5% agarose gel electrophoresis stained by safe stain (Sina Clon, Iran) was done to determine PCR products.

### *Serum level of chromogranin A analysis*

The enzyme-linked immunosorbent assay (ELISA) technique was used to measure chromogranin A using the Human CgA kit (Zell Bio GmbH, Cat.NO: ZB-11730C-H9648 Lot. No: ZB-OEH563210812-91, Germany).

### Statistical analysis

The data was analyzed with the SPSS Statistical software (Version 23.0, Chicago for Windows) and was indicated as mean ± standard deviation and percentages. The Shapiro and Wilk test was used to determine the normality of quantitative variables. The Spearman and Mann-Whitney U tests were carried out to determine the correlation and the means of the quantitative variables between groups that did not have normal distributions, respectively. The chi-square test was used to compare qualitative variables. P-values less than 0.05 were considered significant.

## RESULTS

Table 1 shows the demographic and biochemical variables of the males and females with and without MetS. The mean ages were 55.18 ± 3.34 and 57.27 ± 8.25; and 53.68 ± 3.25 and 56.43 ± 4.75 years in males and females with and without MetS, respectively. WC, SBP, TG, FBS and CgA levels were higher and HDL-C levels were lower when compared to females and males with MetS with those without MetS ($P$ <0.001).

Table 2 shows the comparison of biochemical variables among the males and females with and without MetS. Males with and without MetS exhibited significantly lower HDL-C levels than those of females ($P$ <0.001). Males without MetS showed significantly lower HDL-C in males with and without MetS when compared to females ($P$ <0.001).

**Table 1.** Demographic and biochemical variables of the males and females with and without metabolic syndrome

| Variable | Groups | Males | | Females | |
|---|---|---|---|---|---|
| | MetS | Mean ± SD | *p* | Mean ± SD | *p* |
| Age (n) | MetS+ | 55.18 ± 3.34 (59) | 0.435 | 57.27 ± 8.25 (64) | 0.544 |
| | MetS- | 53.68 ± 3.25 (60) | | 56.43 ± 4.75 (63) | |
| FBS | MetS+ | 145.15 ± 45.63 | **<0.001** | 141.47 ± 43.84 | **<0.001** |
| | MetS- | 89.61 ± 5.21 | | 89.79 ± 5.92 | |
| TG | MetS+ | 208.03 ± 137.76 | **<0.001** | 158.47 ± 87.15 | **<0.001** |
| | MetS- | 82.33 ± 20.61 | | 78.93 ± 21.16 | |
| WC | MetS+ | 114.22 ± 9.65 | **<0.001** | 110.84 ± 12.32 | **<0.001** |
| | MetS- | 90.15 ± 11.15 | | 84.85 ± 8.33 | |
| SBP | MetS+ | 134.68 ± 1.83 | **<0.001** | 134.93 ± 1.85 | **<0.001** |
| | MetS- | 108.33 ± 1.05 | | 108.34 ± 1.05 | |
| DBP | MetS+ | 80.54 ± 1.14 | 0.056 | 82.45 ± 0.98 | 0.137 |
| | MetS- | 77.63 ± 1.07 | | 75.12 ± 1.43 | |
| HDL-C | MetS+ | 35.42 ± 6.35 | **<0.001** | 43.54 ± 7.54 | **<0.001** |
| | MetS- | 43.89 ± 6.66 | | 51.35 ± 8.34 | |
| CgA | MetS+ | 771.28 ± 158.48 | **<0.001** | 841.01 ± 612.23 | **<0.001** |
| | MetS- | 387.95 ± 98.60 | | 384.82 ± 119.53 | |

WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBS: fasting blood sugar; TG: triglyceride; HDL-C: high-density lipoprotein-cholesterol; CgA: chromogranin A; Metabolic syndrome: MetS; MetS+ and MetS-: with MetS and without MetS

Tables 3 and 4 show age-related serum CgA and MetS components in males and females with and without MetS according to age distribution. For ages 30-39, 40-49, 50-59 and 60-70 years, females and males with MetS showed significant differences in FBS, TG and CgA levels and WC when compared to those without MetS ($P$ <0.001). Females and males with MetS indicated significant differences in SBP at ages 40-49, 50-59 and 60-70 years, while at ages 40-49 and 50-59 years, there was a significant difference in HDL-C levels in males ($P$ <0.001).

Table 5 shows the Spearman correlation between MetS components and serum CgA levels in the Fars ethnic groups with MetS according to sex. There was a statistically significant correlation between serum levels of FBS, TG, SBP and WC (in both sexes); and CgA in subjects with MetS ($P$ <0.05). There was no significant correlation between DBP and HDL-C level; and CgA level in males and females, while there was a significant correlation between HDL-C level and DBP; and CgA level in males and females; respectively ($P$ <0.001).

Table 6 shows CgA genotype frequency (T-415C and C+87T polymorphisms) in males and females with and without MetS. The frequencies of the CC, CT, and TT genotypes of C+87T were 3.4%, 32.2%, 64.6% and 0%, 23.3%, 76.6% in males and 3.1%, 31.2%, 65.6% and 0%, 27%, 73% in females with and without MetS, respectively ($P$ >0.05). The

**Table 2.** Comparison of different variables among males and females with and without metabolic syndrome

| Variable | Group | MetS- | | MetS+ | |
|---|---|---|---|---|---|
| | | Mean ± SD | *p* | Mean ± SD | *p* |
| FBS | M | 89.62 ± 5.21 | 0.834 | 145.15 ± 45.63 | 0.998 |
| | F | 89.79 ± 5.92 | | 141.47 ± 43.84 | |
| TG | M | 82.23 ± 20.61 | 0.310 | 208.03 ± 137.76 | 0.095 |
| | F | 78.93 ± 21.6 | | 158.47 ± 87.15 | |
| WC | M | 90.15 ± 11.15 | 0.055 | 114.22 ± 9.65 | 0.220 |
| | F | 84.85 ± 8.33 | | 110.84 ± 12.32 | |
| SBP | M | 108.33 ± 1.05 | 0.202 | 134.68 ± 1.83 | 0.237 |
| | F | 108.34 ± 1.05 | | 134.93 ± 1.85 | |
| DBP | M | 77.63 ± 1.07 | 0.823 | 80.54 ± 1.14 | 0.473 |
| | F | 75.12 ± 1.43 | | 82.45 ± 0.98 | |
| HDL-C | M | 43.89 ± 6.66 | **<0.001** | 35.42 ± 6.36 | **<0.001** |
| | F | 51.35 ± 8.34 | | 43.45 ± 7.55 | |
| CgA | M | 387.95 ± 98.60 | 0.958 | 771.28 ± 158.48 | 0.939 |
| | F | 384.82 ± 119.53 | | 841.01 ± 612.23 | |

WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBS: fasting blood sugar; TG: triglyceride; HDL-C: high-density lipoprotein-cholesterol; CgA: chromogranin A; Metabolic syndrome: MetS; MetS+ and MetS-: with MetS and without MetS; M: Males and F: Females

**Table 3.** Age-related serum chromogranin A and metabolic syndrome components in males with and without metabolic syndrome

| Ages | 30-39 (years) | | 40-49 (years) | | 50-59 (years) | | 60-70 (years) | |
|---|---|---|---|---|---|---|---|---|
| Variables | MetS- | MetS+ | MetS- | MetS+ | MetS- | MetS+ | MetS- | MetS+ |
| HDL-C | 44.50 ± 10.75 | 36.00 ± 6.05 | 43.28 ± 6.19 | 33.35 ± 5.43* | 44.82 ± 7.04 | 35.48 ± 6.95* | 41.35 ± 3.55 | 38.76 ± 5.47 |
| FBS | 59.25 ± 6.24 | 148.5 ± 43.86* | 88.00 ± 6.54 | 165.94 ± 58.13** | 90.31 ± 4.75 | 131.72 ± 26.09** | 90.00 ± 4.03 | 142.84 ± 52.17** |
| TG | 80.50 ± 14.38 | 227.25 ± 85.69* | 81.06 ± 54.25 | 283.52 ± 193.03** | 82.25 ± 20.08 | 191.12 ± 107.04** | 85.55 ± 21.16 | 135.92 ± 53.54** |
| WC | 91.25 ± 8.42 | 114.50 ± 3.87* | 89.67 ± 13.49 | 111.35 ± 8.97* | 90.78 ± 10.96 | 115.16 ± 11.45* | 88.22 ± 9.93 | 116.08 ± 7.69* |
| DBP | 78.70 ± 0.76 | 73.10 ± 1.19 | 79.30 ± 0.92 | 82.40 ± 1.44 | 76.30 ± 1.27 | 80.20 ± 1.02 | 79.10 ± 0.55 | 80.90 ± 0.89 |
| SBP | 122.25 ± 0.25 | 107.30 ± 1.19 | 108.70 ± 1.04 | 133.10 ± 2.17* | 106.10 ± 1.00 | 134.70 ± 1.32* | 109.40 ± 1.05 | 144.90 ± 1.327* |
| CgA | 437.37 ± 50.84 | 838.48 ± 167.97* | 352.73 ± 111.18 | 801.36 ± 208.72* | 369.84 ± 103.48 | 757.37 ± 131.13* | 393.02 ± 60.87 | 738.06 ± 132.23* |

Mann-Whitney U tests were applied.
WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBS: fasting blood sugar; TG: triglyceride; HDL-C: high-density lipoprotein-cholesterol; CgA: chromogranin A; Metabolic syndrome: MetS; MetS+ and MetS-: with MetS and without MetS.
*$P$ <0.05; **$P$ <0.001

**Table 4.** Age-related serum chromogranin A and metabolic syndrome components in females with and without metabolic syndrome

| Ages | 30-39 (years) | | 40-49 (years) | | 50-59 (years) | | 60-70 (years) | |
|---|---|---|---|---|---|---|---|---|
| Variables | MetS- | MetS+ | MetS- | MetS+ | MetS- | MetS+ | MetS- | MetS+ |
| HDL-C | 50.10 ± 0.11 | 44.50 ± 7.78 | 55.39 ± 9.84 | 42.67 ± 8.94 | 50.69 ± 7.78 | 42.78 ± 7.05 | 48.51 ± 6.77 | 46.54 ± 7.28 |
| FBS | 93.00 ± 2.84 | 143.00 ± 4.24* | 88.75 ± 5.93 | 127.27 ± 16.16* | 89.51 ± 6.19 | 143.06 ± 38.54* | 91.27 ± 5.59 | 155.36 ± 77.59* |
| TG | 48.00 ± 20.15 | 170.50 ± 57.27** | 80.75 ± 28.18 | 168.13 ± 97.17** | 75.58 ± 17.42 | 158.50 ± 60.86* | 86.00 ± 18.24 | 143.00 ± 144.64* |
| WC | 92.00 ± 1.08 | 114.50 ± 2.12* | 83.19 ± 9.39 | 106.46 ± 13.04* | 85.36 ± 7.01 | 112.08 ± 12.46* | 85.13 ± 9.99 | 112.09 ± 11.62* |
| DBP | 80.14 ± 0.98 | 79.01 ± 1.27 | 76.80 ± 1.28 | 81.20 ± 1.18 | 73.90 ± 1.68 | 82.50 ± 0.98 | 75.70 ± 1.27 | 84.60 ± 0.75 |
| SBP | 124.03 ± 1.35 | 125.50 ± 2.45 | 108.80 ± 1.15 | 129.10 ± 2.03* | 107.70 ± 0.96 | 134.60 ± 1.69* | 108.10 ± 1.13 | 143.90 ± 1.54* |
| CgA | 518.19 ± 88.25 | 852.04 ± 107.71* | 382.63 ± 138.41 | 795.85 ± 159.62* | 375.52 ± 118.38 | 914.07 ± 803.59** | 397.47 ± 105.25 | 661.45 ± 81.99* |

Mann-Whitney U tests were applied.
WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBS: fasting blood sugar; TG: triglyceride; HDL-C: high-density lipoprotein-cholesterol; CgA: chromogranin A; Metabolic syndrome: MetS; MetS+ and MetS-: with MetS and without MetS.
*$P$ <0.05; **$P$ <0.001

frequencies of the TT, TC, and CC genotypes of T-415C were 52.5%, 42.4%, 5.1% and 76.7%, 21.7%, 1.7% in males ($P$ = 0.021) and 65.6%, 34.4%, 0% and 52.5%, 25.4%, 0% in females with and without MetS, respectively ($P$ >0.05).

Table 7 shows CgA genotype frequency (T-415C and C+87T polymorphisms) between males and females with and without MetS. CgA genotype frequency (T-415C and C+87T polymorphisms) showed no significant differences between males and females with and without MetS ($P$ >0.05).

## DISCUSSION

MetS is becoming more common worldwide. MetS is a serious public health problem in people of different countries.[36] It may be occurring because of the genetic polymorphism differences among different ethnic groups worldwide. It has been reported that CgA levels are mildly increased in different diseases such as hypertension, congestive heart failure, myocardial infarction, renal failure, and liver dysfunction.[37] The findings of this study indicated

**Table 5.** The correlation of CgA with the MetS diagnostic criteria variables

| Gender | Variable | HDL | FBS | TG | SBP | DBP | WC | CgA |
|---|---|---|---|---|---|---|---|---|
| Males | HDL-C | 1.000 | -0.503 | 0.0541 | 0.300 | -0.072 | 0.432 | -0.490** |
| | P-value | - | <0.001 | <0.001 | 0.001 | 0.437 | <0.001 | <0.001 |
| | FBS | -0.503 | 1.000 | 0.643 | 0.481 | 0.127 | 0.487 | 0.869** |
| | P-value | <0.001 | - | <0.001 | <0.001 | 0.170 | <0.001 | <0.001 |
| | TG | -0.541 | 0.684 | 1.000 | 0.431 | 0.248 | 0.322 | 0.681** |
| | P-value | <0.001 | <0.001 | - | <0.001 | 0.006 | <0.001 | <0.001 |
| | SBP | 0.300 | 0.481 | 0.431 | 1.000 | 0.396 | 0.526 | 0.557** |
| | P-value | 0.001 | <0.001 | <0.001 | - | <0.001 | <0.001 | <0.001 |
| | DBP | -0.072 | 0.127 | 0.248 | 0.396 | 1.000 | 0.041 | 0.079 |
| | P-value | 0.437 | 0.170 | 0.006 | <0.001 | - | 0.657 | 0.392 |
| | WC | 0.432 | 0.487 | 0.322 | 0.526 | 0.041 | 1.000 | 0.672** |
| | P-value | <0.001 | <0.001 | <0.001 | <0.001 | 0.657 | - | <0.001 |
| Females | HDL-C | 1.000 | 0.494 | -0.532 | -0.206 | -0.011 | 0.447 | -0.467 |
| | P-value | - | <0.001 | <0.001 | 0.020 | 0.904 | <0.001 | 0.072 |
| | FBS | -0.494 | 1.000 | 0.634 | 0.463 | 0.212 | 0.598 | 0.882** |
| | P-value | <0.001 | - | <0.001 | <0.001 | 0.017 | <0.001 | <0.001 |
| | TG | -0.523 | 0.634 | 1.000 | 0.227 | 0.117 | 0.266 | 0.584** |
| | P-value | <0.001 | <0.001 | - | 0.010 | 0.190 | 0.003 | <0.001 |
| | SBP | -0.206 | 0.463 | 0.227 | 1.000 | 0.446 | 0.590 | 0.495** |
| | P-value | 0.020 | <0.001 | 0.010 | - | <0.001 | <0.001 | <0.001 |
| | DBP | -0.011 | 0.212 | 0.117 | 0.446 | 1.000 | 0.204 | 0.215** |
| | P-value | 0.904 | 0.017 | 0.190 | <0.001 | - | 0.021 | 0.015 |
| | WC | 0.447 | 0.598 | 0.266 | 0.590 | 0.204 | 1.000 | 0.664** |
| | P-value | <0.001 | <0.001 | 0.003 | <0.001 | 0.021 | - | <0.0012 |

WC: waist circumference; SBP: systolic blood pressure; DBP: diastolic blood pressure; FBS: fasting blood sugar; TG: triglyceride; HDL-C: high-density lipoprotein-cholesterol; CgA: chromogranin A; Metabolic syndrome: MetS

**Table 6.** CgA genotypes frequency (T-415C and C+87T polymorphisms) in males and females with and without MetS

| Sex | Groups | C+87T | | | $p$ | T-415C | | | $p$ |
|---|---|---|---|---|---|---|---|---|---|
| | | CC | CT | TT | | TT | TC | CC | |
| Males | MetS- | 0 | 14 | 46 | 0.18 | 46 | 13 | 1 | **0.021** |
| | n (%) | 0% | 23.3% | 76.6% | | 76.7% | 21.7% | 1.7% | |
| | MetS+ | 2 | 19 | 38 | | 31 | 25 | 3 | |
| | n (%) | 3.4% | 32.2% | 64.6% | | 52.5% | 42.4% | 5.1% | |
| Females | MetS- | 0 | 17 | 46 | 0.365 | 31 | 16 | 0 | 0.269 |
| | n (%) | 0% | 27.0% | 73.0% | | 52.5% | 25.4% | 0% | |
| | MetS+ | 2 | 20 | 42 | | 42 | 22 | 0 | |
| | n (%) | 3.1% | 31.2% | 65.6% | | 65.6% | 34.4% | 0% | |

CgA: chromogranin A

**Table 7.** CgA genotypes frequency (T-415C and C+87T polymorphisms) between males and females with and without MetS

| Groups | Sex | C+87T | | | $p$ | T-415C | | | $p$ |
|---|---|---|---|---|---|---|---|---|---|
| | | CC | CT | TT | | TT | TC | CC | |
| MetS- | Males | 46 | 14 | 0 | 0.641 | 46 | 13 | 1 | 0.536 |
| n (%) | (n = 60 ) | 76.7% | 23.3% | 0% | | 76.7% | 21.7% | 1.7% | |
| | Females | 46 | 17 | 0 | | 47 | 16 | 0 | |
| | (n = 63) | 73.0% | 27.0% | 0% | | 74.6% | 25.4% | 0% | |
| MetS+ | Males | 38 | 19 | 2 | 0.989 | 31 | 25 | 3 | 0.098 |
| n (%) | (n = 59 ) | 64.4% | 32.2% | 3.4% | | 52.5% | 42.4% | 5.1% | |
| | Females | 42 | 20 | 2 | | 42 | 22 | 0 | |
| | (n = 64) | 65.6% | 31.2% | 3.1% | | 65.6% | 34.4% | 0% | |

CgA: chromogranin A

that there were significant differences in the serum CgA level and MetS components according to age and sex in the subjects with MetS compared to those without MetS. CgA genotype frequency (T-415C polymorphism) indicated significant differences in males with MetS when compared with those without MetS. CgA genotype frequency (T-415C and C+87T polymorphisms) showed no significant differences between males and females with and without MetS. Some studies have revealed that CgA may affect blood pressure, obesity, fat levels and pancreatic beta cells.[37-40] The study of Kogawa et al., on type 2 patients with diabetes, showed that the level of CgA in the saliva and serum of these patients was significantly higher than in the control group.[29] The exact mechanisms of aging and sex and their effects on genetic polymorphisms and serum levels of CgA are not completely understood in subjects with MetS. A study on the role of CgA in aging-related MetS showed that blood pressure increases in humans and mice as they age and insulin sensitivity and glucose tolerance decrease, but there was an opposite effect with aging in CgA-KO mice. Then, age may improve insulin sensitivity which can decrease the level of blood glucose. Decreasing blood glucose levels may improve change from a high of a normal blood pressure.[41] The mechanisms of CgA's effects on insulin sensitivity throughout aging are still not exactly clear. Age is an important factor in hypertension, death and cardiovascular death.[37] CgA level may be affected by aging itself and/or other age-related different diseases.[42] Ahmed et al.,[43] reported that increasing age was associated with higher CgA levels, which does not follow our findings that the CgA was increased in all ages and sex with MetS. Manaf et al.,[44] reported that serum CgA levels were significantly lower in obese children with MetS than controls with normal BMI which was not in agreement with our findings. A different expression of CgA in some diseases such as hypertension[45,46] makes it necessary to identify the genetic variants of CgA gene polymorphism that may control its gene expression.[47,48] Different ethnic groups may show different SNP frequency.[49-52] Variations in the regulatory regions may cause differences in gene expression among different ethnic groups.[53] Thus, we focused our study on the genetic variants of CgA gene polymorphism in the Fars ethnic groups according to age and sex.

We studied two polymorphisms (T-415C, C and C+87T). Our study showed that there is only one effect on CgA T-415C polymorphism genotype frequency in males with MetS in comparison to those without MetS. The CgA T-415C polymorphism genotype may be a risk factor for males in the development of MetS. CgA genotype frequency (T-415C and C+87T polymorphisms) showed no significant differences between males and females with and without MetS. A study of Chen et al.,[54] on hypertensive patients revealed that the CgA C+87T polymorphism expression is not only increased in hypertensive patients but also affected by the C+87T genotype. They followed the study of Zhang et al.,[30] that focused on patients with hypertension and showed that the CgA C+87T polymorphism had effects on blood pressure. Our findings showed no significant differences in CgA C+87T polymorphism genotype in both sexes with and without MetS. However, it looks like the elevation was restricted to males. A study revealed that in subjects with high blood pressure, males were significantly more effective than females.[54] Mahapatra et al., could make normal the increased blood pressure of the CgA knockout mouse and exhibit the importance of CgA in homeostasis of blood pressure in living organisms. They showed that CgA can affect biochemical systems (at the tissue level) and cause changes in whole body systems (physiological systems). They also found that severe hypertension indicates insulin sensitivity and decreased triglyceride levels, and in that connection causes MetS.[33] These findings were not in agreement with our findings, because our results did show a significant correlation between the systolic (in males), systolic and diastolic (in females) blood pressure, and CgA level in subjects with MetS. It may mean that blood pressure in females is more changeable to the variation of CgA level than in males, without consideration of genotype variations. A study has revealed that human CgA is over-expressed in hypertension, and a genetic variant in the CgA C+87T genotype is strongly associated with human essential hypertension within the population.[54] They have been shown that the sex-dependent effect of CgA genetics is different on blood pressure. They found that CgA secretion was increased in hypertension subjects. Their results revealed also that plasma CgA secretion is not only increased in hypertension but is also affected by the C+87T genotype.[54] A study on the T–415C polymorphism of the CgA gene in diabetic patients[29] indicated that diabetic patients showed higher levels of CgA in saliva than in the control group. The findings of Subramanian et al.,[55] about the CgA gene in the Indian population revealed that the T–415C polymorphism of the CgA gene significantly increases the CgA level. According to their findings, this may cause increased insulin resistance.[55] This finding is in accordance with our results in males with MetS. The molecular mechanisms of how CgA gene polymorphisms may affect the serum level of CgA in type 2 diabetic patients are not entirely clear. The effect of CgA on glucose and lipid metabolism may influence insulin secretion. Thus, CgA may have a significant role in insulin resistance in both sexes. Our study showed that CgA in males and females with MetS have a positive significant correlation with serum levels of FBS, TG, SBP and WC, while there was a negative and positive correlation between CgA and HDL-C (in males) and DBP (in females) with MetS, respectively. Our findings also indicated that CgA gene polymorphism variations are more different in the T-415C genotype in males than the C+87T genotype when compared to each sex with and without MetS. This may indicate that males with MetS may be more sensitive to the T-415C genotype variation than females. The CgA knockout mouse showed a normal blood glucose level, despite the plasma insulin levels being 4.5-fold less than the level in wild-type mice. Thus, CgA may control insulin sensitivity and the CgA knockout mouse is hypersensitive to insulin.[55] Plasma level of triglyceride is positively correlated with insulin sensitivity/resistance as one of the components of the

MetS.[22,56] The 1.3-fold decrease in plasma triglyceride level is firm with insulin sensitivity in the CgA knockout mouse.[56] The main source of triglycerides in our body is the liver, and triglyceride levels did not indicate any difference in CgA knockout and wild-type mice. This may imply that another tissue such as adipose tissue has an important role in the decrease in the level of triglyceride.[56]

## CONCLUSION

The CgA appears to be strongly associated with MetS components in both sexes. Variation in CgA gene expression may affect the T–415C polymorphism in males. This may mean that the structure of CgA genetics differs in different ethnic groups. Differences in the serum level and expression of the CgA gene may show valuable study results that it may be expected a relationship between these variables and the MetS.

**Data Availability**
The data are not publicly available due to restricted information and the privacy of participants.

**Statement of Authorship**
All authors certified fulfillment of ICMJE authorship criteria.

**CRediT Author Statement**
**AM:** Conceptualization, Investigation, Data curation, Writing – original draft preparation, Writing – review and editing, Visualization, Supervision, Project administration; **NP:** Methodology, Formal analysis, Investigation; **AS:** Methodology, Formal analysis, Investigation, Data curation, Project administration; **MT:** Methodology, Formal analysis

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