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# Serum Adropin level in females with and without metabolic syndrome and its association with metabolic syndrome criteria in Gorgan

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Metabolic syndrome (MetS), a global public health issue that has become an epidemic over the past several years. Our study assessed to estimate the adropin level in females with and without MetS and its association with MetS criteria in Gorgan. The study enrolled 64 females with MetS and 64 females without MetS. The MetS was defined using Adult Treatment Panel-III (ATP-III) guidelines. There are significant differences in the WC, SBP, DBP, FBG, TG, HDL-C and adropin levels ($P<0.05$). The percentage of females with one, two, three, more equal and more than four criteria of MetS was 16.40%, 33.60%, 25.78% and 24.22%, respectively. There were significant differences between the groups with one or more MetS criteria. As the number of MetS criteria increased, there were more significant increases in all parameters except HDL-C and adropin. Adropin correlated significantly negatively and positively with FBG and TG and HDL-C of the females with MetS, respectively. Adropin correlated significantly negatively and positively with FBG and TG and HDL-C in females with 3 and ≥4 MetS criteria, respectively. It can be concluded that adropin is significantly decreased in females with MetS and an increasing number of MetS criteria. Based on its role in metabolic disorders, it may be considered as a risk factor for the development of MetS. Adropin may be suggested as a target treatment for MetS. However, further research is needed to fully understand the relationship between adropin and MetS complications and treatment

**Keywords: MetS, Adropin, Females, Gorgan**

## INTRODUCTION

Metabolic syndrome (MetS), a global public health issue that has become an epidemic over the past several years (Gurka et al. 2018). In 1988, *Reaven* addressed the possibility that insulin resistance (IR) could play a role in etiology of type 2 diabetes mellitus (T2DM) and cardiovascular disease (CVD) (Cheng, 2007). A person with MetS is 5 times more likely to develop type 2 diabetes mellitus (T2DM), 2 times more likely to develop CVD in the next 5 to 10 years, 2- to 4-fold more likely to suffer from stroke, 3- to 4-fold more likely to suffer a myocardial infarction (MI), and 2 times more likely to die from it (Lopez-Candales et al. 2017).World-wide, the prevalence of MetS varies widely depending on age, gender, race/ethnicity, and diagnosis criteria. Approximately a fifth of the American population is affected by MetS and about a quarter of the population of Europe is affected by it. It has a lower prevalence in south-east Asia, but it is rapidly increasing its rates to those seen in western countries (Beltrán-Sánchez et al. 2013; Marjani et al. 2012a; Shahini et al. 2013; Marjani et al. 2012b). Adropin is 76 amino acids making it a short peptide. It was found out in 2008 by *Kumar et al. (2008)*. Their study demonstrated that adropin may play a role in the metabolism of glucose and lipids as well as in energy homeostasis (Zang et al. 2018). In metabolic disorders such as type 2 diabetes mellitus (T2DM) and its complications, adropin may be a therapeutic target. A study on mice showed that adropin inhibited the production of glucose in the liver and thus reduced its level in the blood (Thapa et al. 2019). Adropin can also enhance lipid metabolism, decrease insulin resistance and inhibit inflammation in hepatocytes. Due to the probably positive metabolic effect of adropin, it could be used in the treatment of diabetic patients (Butler et al. 2012). Adropin levels are likely directly associated with type 2 diabetes. It has been indicated that the serum level of adropin in type 2 diabetes patients is lower than in non-diabetic subjects. Some studies have been shown that adropin is significantly associated with type 2

diabetes after removing confounding factors including age, sex, smoking, and adiposity, BMI, DBP, and SBP (Kumar et al. 2008). In addition, several studies showed an inverse correlation between the plasma adropin level and body mass index (BMI) (Zang et al. 2018; Gao et al. 2019; Yu et al. 2014). The studies on the role of adropin in the development of gestational diabetes showed that its level in hyperglycemic patients was lower than in healthy pregnant women (Adamczak et al. 2023; Vivek et al. 2022). According to some studies, low levels of adropin have been linked to MetS and it has been suggested that adropin may serve as a potential protective agent against MetS development (Yosaee et al. 2017). Adropin levels have been found to be correlated with changes in the metabolism of carbohydrates and lipids, metabolic diseases and glucose homeostasis (Kolben et al. 2021; Li et al. 2021). One study found that subjects with MetS had lower levels of adropin than healthy subjects who were overweight, obese or lean (Yosaee et al. 2017). In another study, the researchers hypothesized that low adropin levels could be associated with the development of insulin resistance and other criteria of MetS, such as dyslipidemia associated with obesity (Butler et al. 2012). Studies have shown that adropin deficiency is related to metabolic disorders such as type 2 diabetes mellitus (T2DM). It has shown that adropin levels are decreasing in healthy obese people and MetS patients when compared to healthy people (Zhang et al. 2022). Several clinical studies suggest that serum adropin levels are reduced in conditions such as type 2 diabetes and hypertension (Li et al. 2021). According to, the different study results on metabolic risk factors of adropin in subjects with MetS and without MetS, the effectiveness of adropin in improving the MetS components is, therefore, controversial. Thus, our study designed to estimate the adropin level in females with and without MetS and its association with MetS criteria's in Gorgan.

## MATERIALS AND METHODS

The present study was performed at the Metabolic Disorder Research Center of Gorgan, Golestan province (Southeast of Caspian Sea). The ethical committee of Golestan University for medical sciences approved the study (IR.GOUMS.REC.1401.557). Oral consent was obtained from all participants. Sixty four females with MetS were compared with sixty four age-matched females who did not have MetS. A five ml of blood was collected from each subject at Gorgan non-governmental laboratory and serum provided from each subject. We used a commercially available ELISA kit to measure the levels of adropin (Catalog No: YLA0019HU, LOT: YL7448909800).

The MetS criteria such as fasting blood glucose (FBG), high density lipoprotein-cholesterol (HDL-C) and triglycerides (TG) (all measured using commercial kits). A digital blood pressure monitor was used to measure systolic and diastolic blood pressures (Omron 70JCP; Omron Maussaka, Mie-Ken, Japan). A tape in centimeters was used to measure waist circumference (WC). Waist circumference (WC) was assessed midway between the iliac crest and the lower rib. Body mass index (BMI) (units of kg/m2) was determined using the formula: Weight (in kilograms, kg) / body height (in meters, m) exponent of 2. In order to identify those subjects with and without MetS, we applied NCEP's ATP III method to identify the MetS status of participants (Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults,Adult Treatment Panel III, 2001).The criteria of the National Cholesterol Education Program, Adult Treatment Panel III (NCEP, ATP III) were used to include subjects with MetS. Metabolic syndrome was determined if the subjects had any three or more of the following criteria:

1- WC: >102 cm (male), >88 cm (female)
2- TG levels: >150 mg / dl
3- HDL-cholesterol levels: <40 mg / dl (male), <50 mg / dl (female)
4- Blood pressure: >130/85 mmHg
5- Fasting blood glucose levels: >110 mg / dl

### Statically analysis

The data of this study analyzed using SPSS 22 software (Version 23.0, Chicago for Windows). The results were shown as mean ± standard deviation. A Kruskal-Wallis test was used to check the normality of quantitative variables. Due to the non-normality of the studied variables, the Mann-Whitney test was used to compare the means of the quantitative variables between the groups. The correlation between groups was determined using the Spearman test. P-values less than 0.05 were considered statistically significant.

## RESULTS

Table 1 shows demographic and biochemical characteristics of females with and without MetS. There are significant differences in the WC, SBP, DBP, FBG, TG, HDL-C and adropin levels ($P<0.05$). The levels of these parameters were significantly higher and; HDL-C and adropin levels were significantly lower in the females with MetS than those without MetS.

Table 2 shows the distribution of the percentage of MetS and its criteria's in all study females. The percentage of females with one, two, three, more equal and more than four criteria's of MetS was 16.40%, 33.60%, 25.78% and 24.22%, respectively.The highest percentage was in females with two criteria's of MetS (33.60%).

Table 3 shows demographic and biochemical characteristics of females, according to the numbers of criteria's of MetS. There were significant differences between the groups with one or more MetS criteria's. As the number of MetS criteria's increased, there were more significant increases in all parameters except HDL-

C and adropin.

Table 4 shows correlations of adropin with MetS criteria's in the females with MetS. Adropin correlated significantly negatively and positively with FBG and TG and; HDL-C of the females with MetS, respectively.

Table 5 shows correlations of adropin with MetS criteria in the females according to the numbers of criteria's of MetS. Adropin correlated significantly negatively and positively with FBG and TG and; HDL-C in females with 3 and ≥4 MetS criteria's, respectively.

**Table 1: Demographic and biochemical characteristics of females with and without MetS**

| Parameters | Females with MetS (n= 64) | Females without MetS (n=64) | P-value |
|---|---|---|---|
| **Age (Year)** | 43.12 ±5.66 | 42.40 ±10.84 | 0.520 |
| **BMI (Kg/m2)** | 25.68 ± 1.24 | 24.23 ± 1.35 | 0.645 |
| **WC (cm)** | 107.84 ± 11.56 | 97.65 ± 13.14 | <0.001 |
| **SBP (mmHg)** | 130.05 ± 14.78 | 114.02 ± 10.89 | <0.001 |
| **DBP( mmHg)** | 88.71 ± 17.50 | 79.23± 8.06 | <0.001 |
| **FBG ( mg/dl)** | 170.03 ± 82.01 | 106.09 ± 47.65 | <0.001 |
| **TG (mg/dl)** | 189.36 ± 86.38 | 125.33 ± 51.72 | <0.001 |
| **HDL-C (mg/dl)** | 43.93± 7.37 | 48.92± 11.49 | 0.004 |
| **Adropin (ng/l)** | 83.78±23.15 | 125.80 ±43.78 | <0.001 |

P-value < 0.05 was significant. MetS: Metabolic syndrome, BMI: body mass index, WC: Waist circumference, SBP: Systolic blood pressure, DBP: diastolic blood pressure, FBG: fasting blood glucose, TG: Triglyceride, HDL-C: High density lipoprotein cholesterol.

**Table 2: prevalence of MetS criteria's in all study subjects**

| MetS criteria's | Females (128) |
|---|---|
| 1 Criteria (%) | 21 (16.40) |
| 2 Criteria (%) | 43 (33.60) |
| 3 Criteria (%) | 33(25.78) |
| ≥4 Criteria (%) | 31 (24.22) |
| MetS (%) | 64 (50) |

MetS: Metabolic syndrome

**Table 3: Demographic and biochemical characteristics of females according to the numbers of criteria's of MetS**

| Parameters | MetS criteria's | | | | P-value of groups |
|---|---|---|---|---|---|
| | Females with 1 criteria (N=21) | Females with 2 criteria's (N=43) | Females with 3 criteria's (N=33) | Females ≥4 criteria's (31) | |
| Age (Year) | 39.23±9.85 | 41.11±10.12 | 42.84±5.94 | 43.16±6.51 | 1-2=0.442, 1-3=0.324, 1- ≥4=0.091, 2-3=0.472, 2-≥4=0.272 and 3- ≥4=0.778 |
| BMI (Kg/m2) | 24.78 ± 1.78 | 24.45 ± 3.24 | 25.65 ± 3.75 | 25.96± 3.98 | 1-2=0.571,1-3=0.442, 1- ≥4=0.345, 2-3=0.388, 2- ≥4=0.285 and 3- ≥4=0.987 |
| WC (cm) | 94.66± 15.68 | 97.13± 12.50 | 107.55± 12.56**ac** | 108.10±10.54**bd** | 1-2=0.972,1-3=0.002, 1- ≥4=0.005, 2-3<0.001, 2-≥4<0.001and 3- ≥4=0.415 |
| SBP (mmHg) | 111.90± 9.41 | 115.05± 11.51 | 127.39± 16.54**ac** | 129.32±17.12**bd** | 1-2=0.860,1-3<0.001, 1-≥4=0.001, 2-3<0.001, 2- ≥4=0.002 and 3- ≥4=0.975 |
| DBP( mmHg) | 78.05± 9.45 | 79.31± 7.34 | 82.90± 11.01**a** | 83.83± 22.54**b** | 1,2=0.487,1,3=0.001, 1, ≥4=0.011, 2,3=0.178, 2, ≥4= 0.128 and 3, ≥4=0.336 |
| FBG ( mg/dl) | 95.01± 20.44 | 111.51± 55.82 | 135.21± 64.64**ac** | 207.10±83.12**bde** | 1-2=0.493,1-3<0.001, 1- ≥4<0.001, 2-3=0.005, 2-≥4<0.001 and 3- ≥4<0.001 |
| TG (mg/dl) | 98.85± 50.75 | 113.95± 47.64 | 139.97± 47.16**ac** | 241.94±88.07**bde** | 1-2=0.142,1-3=0.001, 1- ≥4<0.001, 2-3=0.001, 2- ≥4<0.001and 3- ≥4<0.001 |
| HDL-C (mg/dl) | 52.66± 15.86 | 50.58± 8.10 | 46.30± 8.32a | 41.87± 5.53**bde** | 1-2=0.161 ,1-3=0.011, 1-≥4<0.001, 2-3=0.512, 2-≥4<0.001 and 3-≥4=0.006 |
| Adropin (ng/l) | 132.14± 49.67 | 112.81± 24.37 | 86.51± 24.09**ac** | 81.21± 22.28**bd** | 1-2=0.154,1-3 <0.001, 1- ≥4<0.001, 2-3<0.001, 2-≥4<0.001 and 3- ≥4=0.327 |

MetS: Metabolic syndrome, BMI: body mass index, WC: Waist circumference, SBP: Systolic blood pressure, DBP: diastolic blood pressure, FBG: fasting blood glucose, TG: Triglyceride, HDL-C: High density lipoprotein cholesterol.

a: Compared group1 with 3, b: Compared group1 with 4, c: Compared group 2 with 3, d:Compared group 2 with 4, e: Compared group 3 with 4. P-value < 0.05 was significant.

**Table 4: Correlation of adropin with demographic characteristics and MetS criteria's in study groups**

| | Females with MetS (n= 64) | | Females without MetS (n=64) | |
|---|---|---|---|---|
| **Parameters** | **r** | **P-value** | **r** | **P-value** |
| **Age (Year)** | 0.008 | 0.0.94 | -0.006 | 0.662 |
| **BMI (Kg/m2)** | -0.246 | 0.452 | -0.124 | 0.653 |
| **WC (cm)** | 0.063 | 0.624 | -0.042 | 0.742 |
| **SBP (mmHg)** | 0.076 | 0.550 | -0.216 | 0.084 |
| **DBP( mmHg)** | 0.008 | 0.950 | -.0175 | 0.160 |
| **FBG ( mg/dl)** | **-0.560** | **0.003** | -0.149 | 0.241 |
| **TG (mg/dl)** | **-0.660** | **0.020** | 0.115 | 0.368 |
| **HDL-C (mg/dl)** | **0.321** | **0.007** | -0.040 | 0.753 |

P-value < 0.05 was significant. MetS: Metabolic syndrome, BMI: body mass index, WC: Waist circumference, SBP: Systolic blood pressure, DBP: diastolic blood pressure, FBG: fasting blood glucose, TG: Triglyceride, HDL-C: High density lipoprotein cholesterol.

**Table 5: Correlation of adropin with demographic characteristic and the numbers of MetS criteria's**

| | Females with 1 MetS Criteria (n= 21) | | Females with 2 MetS Criteria (n=43) | | Females with 3 MetS Criteria (n= 33) | | Females with ≥4 MetS Criteria (n=31) | |
|---|---|---|---|---|---|---|---|---|
| **Parameters** | **r** | **P-value** | **r** | **P-value** | **r** | **P-value** | **r** | **P-value** |
| **Age (Year)** | -0.118 | 0.611 | -0.234 | 0.131 | -0.009 | 0.960 | -0.005 | 0.978 |
| **BMI (Kg/m2)** | -0.362 | 0.254 | -0.222 | 0.184 | -0.273 | 0.392 | -0.225 | 0.247 |
| **WC (cm)** | -0.405 | 0.069 | -0.213 | 0.170 | 0.038 | 0.810 | 0.159 | 0.393 |
| **SBP (mmHg)** | -0.043 | 0.853 | -0.323 | 0.075 | 0.401 | 0.088 | 0.108 | 0.563 |
| **DBP( mmHg)** | 0.060 | 0.797 | -0.263 | 0.089 | 0.269 | 0.081 | 0.011 | 0.953 |
| **FBG ( mg/dl)** | 0.297 | 0.191 | -0.024 | 0.895 | -0.305 | 0.047 | -0.184 | 0.001 |
| **TG (mg/dl)** | -0.003 | 0.991 | 0.097 | 0.537 | -0.178 | 0.021 | -0.134 | 0.01 |
| **HDL-C (mg/dl)** | 0.036 | 0.877 | -0.135 | 0.388 | 0.185 | 0.008 | 0.115 | 0.005 |

P-value < 0.05 was significant. MetS: Metabolic syndrome, BMI: body mass index, WC: Waist circumference, SBP: Systolic blood pressure, DBP: diastolic blood pressure, FBG: fasting blood glucose, TG: Triglyceride, HDL-C: High density lipoprotein cholesterol.

## DISCUSSION

The present study showed that adropin decreases in females with MetS and with the increases of numbers of MetS criteria's. Some studies indicated that low levels of adropin have been linked to MetS, and it has been suggested that adropin may serve as a potential protective agent against MetS development (Yosaee et al.2017).

A study on levels of adropin in fasting type 2 diabetic patients and the relationship between levels of adropin and metabolic parameters revealed that serum levels of adropin reduce in type 2 diabetic patients. There were a negative correlation between adropin and TG and FBG, while HDL-C was positively correlated with levels of adropin (Zang et al.2018; Beigi et al. 2015). Some studies have been examined on the role of adropin in glucose homeostasis in vivo. Treatment of mice with adropin showed that adropin treatment improved glucose homeostasis in mice in their study (Thapa et al. 2019). Study of *Akcilar* et al. demonstrated that treatment of rats with adropin decrease in serum TG and FBG and increase serum HDL-C and adropin levels (Akcılar et al. 2016). The findings of Kumar et al. (2008) indicated that adropin may play a role in glucose and lipid metabolism as well as energy homeostasis (Ali et al. 2022). In metabolic disorders such as T2DM and its complications, adropin may be a therapeutic target. According to a study using insulin-resistant hepatocytes, adropin can reduce liver glucose production (Chen et al. 2020). According to some other studies, adropin levels in obese and MetS patients showed a decreasing when compared with healthy people. Adropin levels are much lower in patients with MetS than in obese individuals (Oruc CU et al. 2017). Based on *Oruc CU* et al. (2017) study conducted on subjects with MetS and healthy controls, adropin levels were significantly lower in patients with MetS than the healthy control group. Study of *Hu and Chen* (2016) on patients with T2DM showed significantly lower serum adropin levels than the controls. In our study, adropin levels are decreased in subjects with MetS compared with those subjects without MetS. Our results are in line with those of similar to other findings (Yosaee et al.2017; Chen et al. 2020; Zhang et al. 2022; Oruc CU et al. 2017; Hu and Chen, 2016). They observed a negative significant correlation

of serum adropin with BMI and no significant correlation was observed between serum adropin and SBP, DBP, TG, HDL-C (Hu and Chen, 2016). It seems that the relationship between plasma adropin levels and biochemical parameters is very complex. In another study conducted on Indian patients with type 2 diabetes, researchers reported a significant reduction in adropin levels in type 2 diabetic patients compared to control subjects. Adropin was thought to be associated with glucose homeostasis (Shah et al. 2021). Hence, understanding adropin's potential role in controlling hyperglycemia and how it affects insulin-sensitive tissues is not exactly clear. According to Gao et al. (2015) adropin played an important role in modulating glucose utilization in mice with insulin resistance in skeletal muscle. Their results showed that adropin promotes glucose oxidation and diminishes fatty acid oxidation in skeletal muscle, increasing glucose uptake and enhancing mitochondrial function (Gao et al. 2015). It was shown that an adropin knockout mouse model exhibited high levels of insulin resistance, dyslipidemia, and inability to suppress endogenous glucose production hyper insulinemic conditions. They also showed increased liver adiposity (Ganesh Kumar et al. 2012). Correlation tests in our study showed that there was a negative significant correlation between adropin and FBG and TG and positive correlation with HDL-C, which was in accordance with some other studies (Zang et al.2018; Beigi et al. 2015), while our findings were not in agreement with other studies that no significant correlation was observed between serum adropin and SBP, DBP, TG, HDL-C (Hu and Chen, 2016). The interpretation of these contradictory results is not exactly clear, but it may be attributable to differences in racial differences, different area was used. This study was performed with a relatively small sample size. All of our study subjects with and without MetS were females because all referred people were females.

## CONCLUSIONS

It can be concluded that adropin is significantly decreased in females with MetS and increasing number of MetS criteria. Based on its role in metabolic disorders, it may be considered as a risk factor for development of MetS. Adropin may be suggested as a target treatment for MetS. However, further research is needed to fully understand the relationship between adropin and MetS complications and treatment.

### Supplementary materials

The supplementary material / supporting for this article can be found online and downloaded at: https://www.isisn.org/article/10.3390/antiox12081524/s1,

### Author contributions

All authors have accepted responsibility and approved its submission.

A.M: Conceived and designed the experiments;
A.M: Analyzed and interpreted the data and wrote the article;
M.A., M.A. and S.A.K.: Performed the experiments;
A.M., M.T. and H.K.: Contributed reagents, materials, and analysis data.

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### Institutional Review Board Statement

The Golestan University of Medical Sciences Ethics Committee (Ethic number: (IR.GOUMS.REC.1401.557) was approved this study, according to the Declaration of Helsinki and Good Clinical Practice guidelines.

### Informed Consent Statement

Informed consent was obtained from all individuals included in this study

### Data Availability Statement

All of the data is included in the article/Supplementary Material.

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### Conflict of interest

The authors declared that present study was performed in absence of any conflict of interest.

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