Journal of **R**eproduction & **I**nfertility
Volume 26, Issue no. 2
https://doi.org/10.18502/jri.v26i2.19435

Original Article

Check for updates

Serum Levels of CCN3 Protein in Iranian Women with Polycystic Ovary Syndrome

Akram Vatannejad [1*], Fatima Zahraa Fouani [2], Reza Fadaei [3], Asma Kheirollahi [1], Soheila Ansaripour [4], Maryam Shabani Nashtaei [5, 6], Nariman Moradi [7], Hossein Montakhab-Yeganeh [8, 9*], Faezeh Fattahi [10], Farah Jadidizadeh [1]

1- Department of Comparative Biosciences, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran
2- Department of Cellular and Molecular Nutrition, School of Nutritional Sciences and Dietetics, Tehran University of Medical Sciences, Tehran, Iran
3- Sleep Disorders Research Center, Kermanshah University of Medical Sciences, Kermanshah, Iran
4- Reproductive Biotechnology Research Center, Avicenna Research Institute, ACECR, Tehran, Iran
5- Department of Infertility, Shariati Hospital, Tehran University of Medical Sciences, Tehran, Iran
6- Department of Anatomy, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran
7- Liver and Digestive Research Center, Research Institute for Health Development, Kurdistan University of Medical Sciences, Sanandaj, Iran
8- Department of Biochemistry, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
9- Molecular Medicine Research Center, Hormozgan Health Institute, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
10- Emergency Department, Shahid Fayazbakhsh Hospital, Tehran, Iran

** Corresponding Authors:*
Akram Vatannejad, Department of Comparative Biosciences, Faculty of Veterinary Medicine, University of Tehran, Tehran, Iran

Hossein Montakhab-Yeganeh, Department of Biochemistry, Faculty of Medicine, Hormozgan University of Medical Sciences, Bandar Abbas, Iran
E-mail: vatannejad@ut.ac.ir

Received: 9, Oct. 2024
Accepted: 19, Jan. 2025

Abstract

Background: Polycystic ovary syndrome (PCOS) is a heterogeneous condition that encompasses several cardiometabolic and endocrinological disorders. Studies have shown that its pathogenesis aligns with several underlying mechanisms associated with recurrent pregnancy loss (RPL). Cellular communication network (CCN)-3 protein is a well-studied adipokine involved in tumorigenesis, organogenesis, inflammation, fibrosis, and glucose metabolism. The purpose of the current study was to determine the association of CCN3 levels with a number of parameters involved in PCOS pathogenesis.

Methods: This is a case-control study including 120 PCOS patients (60 cases with RPL; PCOS-RPL and 60 cases with infertility; PCOS-Inf and 60 healthy controls). Circulating levels of homocysteine and high-sensitivity C-reactive protein (hs-CRP), homocysteine, and CCN3 were measured using ELISA kits.

Results: Circulating levels of CCN3 were significantly elevated in PCOS-RPL and PCOS-Inf subgroups when compared to the control group (7.61±3.03 and 6.85±2.54 *vs*. 3.12±0.82, $p<0.001$). Serum CCN3 positively correlated with fasting insulin and homeostatic model assessment of insulin resistance (HOMA-IR) in the control group ($p<0.05$) and PCOS group ($p<0.001$). Moreover, CCN3 was significantly associated with PCOS (OR 4.808, 95%CI [2.744-8.423], $p<0.001$).

Conclusion: According the results of this study CCN3 may be involved in the pathogenesis of PCOS. However, future studies are needed to evaluate the possibility of utilizing CCN3 in the diagnosis and treatment of the disease.

Keywords: Abortion, C-reactive protein, CCN3, Homocysteine, Metabolic syndrome, Nephroblastoma overexpressed protein, Polycystic ovary syndrome.
To cite this article: Vatannejad A, Fouani FZ, Fadaei R, Kheirollahi A, Ansaripour S, Shabani Nashtaei M, et al. Serum Levels of CCN3 Protein in Iranian Women with Polycystic Ovary Syndrome. J Reprod Infertil. 2025;26(2):98-108. https://doi.org/10.18502/jri.v26i2.19435.

Introduction

Polycystic ovary syndrome is a complex endocrine-metabolic syndrome affecting approximately 20% of women of reproductive age (1). It is characterized by polycystic ovaries on ultrasound, clinical and/or biochemical hyperandrogenism, and/or oligo- or anovulation. PCOS

is often associated with visceral adiposity, cardiometabolic diseases, and impaired fecundity such as Recurrent Pregnancy Loss (RPL) and infertility (2, 3). In fact, adiposity, insulin resistance, chronic low-grade inflammation, and hyperandrogenism create a vicious cycle, where each factor amplifies and exacerbates the severity of the others (4).

Adipose tissue is a crucial endocrine organ, releasing adipokines that modulate appetite and energy expenditure, along with insulin sensitivity. The aberrant release of these adipokines contributes to the development of insulin resistance and other metabolic disorders. For instance, PCOS patients exhibit such aberrations with reduced levels of adiponectin, C1q/tumor necrosis factor α-related protein (CTRP)-3, -5, -12, -13, and meteorin-like protein (Metrnl) and elevated levels of leptin, and CTRP6 (5-11). In cases of recurrent implantation failure, an impaired balance between adiponectin and leptin is evident, characterized by abrogated endometrial leptin expression and downregulation of adiponectin receptor (AdipoR) expression (12).

Nephroblastoma overexpresses NOV (also known as CCN3 or IGFBP9), a proto-oncogene that encodes a 48-*kDa* protein associated with the extracellular matrix (ECM) (13-15). CCN3 is a member of the CCN family of proteins, which also includes Cyr61/CCN1 (cysteine-rich protein 61), CTGF/CCN2 (connective tissue growth factor), Nov/CCN3, WISP-1/CCN4 (WNT1inducible signaling pathway protein 1), and other related proteins (16). These regulatory proteins play diverse biological roles in cell proliferation, chemotaxis, angiogenesis, adhesion, and ECM (17).

While most of the research on CCN3 has focused on its role in tumorigenesis, fibrosis, and inflammation, its specific function in PCOS remains unclear (15, 18-31). However, CCN3 has been linked to metabolic disorders such as insulin resistance, obesity, dyslipidemia, and inflammatory conditions (32, 33), all of which have been identified as hallmarks of PCOS. Also, the association of CCN3 with a number of disorders including diabetes mellitus (DM), non-alcoholic steatohepatitis (NASH), cardiomyopathy, multiple and systemic sclerosis, rheumatoid arthritis (RA), and obstructive sleep apnea (OSA) has been reported (32, 34-41). Notably, studies have shown that CCN3 plays a role in placental angiogenesis during pregnancy (42, 43). Intriguingly, cumulus cells of infertile PCOS women show downregulation in ECM proteins and cell adhesion molecules (44).

The purpose of the current research was to investigate the serum levels of CCN3 in women with PCOS, specifically examining its relationship with metabolic disturbances, such as insulin resistance, lipid metabolism, and reproductive complications including RPL and infertility. The findings from this study could provide valuable insights into the role of CCN3 in PCOS pathogenesis and its potential as a diagnostic marker or therapeutic target.

Methods

Study design, setting, and participants: This study adhered to the Declaration of Helsinki and was approved by the Ethics Committee of Hormozgan University of Medical Sciences (IR.HUMS.REC.1398.415). Subjects were selected from the Obstetrics and Gynecology Department of Avicenna Fertility Center, Tehran, Iran, with healthy controls also recruited from the same center. An informed written consent form was obtained from all subjects. It is important to note that this study is in line with our previous reports on PCOS and adipokines; therefore, some data have been utilized for the second time in the current study (10, 45, 46).

This is a case-control study consisting of 60 women with polycystic ovary syndrome and recurrent pregnancy loss (PCOS-RPL), 60 infertile women with PCOS (PCOS-Inf), and 60 healthy controls, all aged between 20 and 40 years (10, 45, 46). PCOS patients were those diagnosed according to the 2003 Rotterdam Criteria, after the exclusion of conditions such as hyperprolactinemia, thyroid diseases, premature ovarian failure, congenital adrenal hyperplasia, Cushing's syndrome, and adrenal tumors (47). Patients assigned to the PCOS-RPL subgroup were those who experienced more than two consecutive miscarriages earlier than the 20th week of gestation (48). Infertile patients were defined as those unable to conceive following one year of unprotected ntercourse as a result of PCOS pathogenesis. The control group included fertile females with regular menstrual cycles and the absence of clinical or biochemical hyperandrogenism. Subjects who were smokers, pregnant, lactating, diagnosed with gynecological or obstetric disorders, taking hormonal therapy, or receiving medications for the past six months including glucocorticoids, prescription weight loss drugs, estrogens and anti-

androgens were excluded. Subjects diagnosed with viral, bacterial, or inflammatory diseases as well as those with cardiovascular disorders, thyroid disorders, or diabetes mellitus were also excluded.

Anthropometric and biochemical measurements: Anthropometric data and medical histories were obtained from all subjects. Body mass index was calculated as weight divided by height squared (Kg/m^2). Blood samples were obtained from all subjects following overnight fasting at the follicular phase of their menstrual cycle. Serum samples were aliquoted in batches and frozen at -70°*C*. Fasting blood glucose (FBG), lipid profile (including serum triglyceride (TG), total cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C)), fasting insulin, free testosterone, follicle-stimulating hormone (FSH), luteinizing hormone (LH), and hs-CRP were measured as previously described (10, 45, 46). Insulin resistance was measured using the HOMA-IR, defined as [(FBG (*mg/dl*)]×[fasting insulin (*μU/ml*)]/405 (49).

Adipokine measurement: Serum levels of CCN3 protein were measured using a commercial ELISA kit (MyBioSource, USA). The intra- and inter-assay coefficients of variations (CV) of CCN3 were 6.2% and 6.7%, respectively. Circulating levels of adiponectin were assessed using the ELISA technique, as previously described (10, 45, 46).

Statistical methods: Statistical analyses were conducted using SPSS Statistics software 20.0 (IBM, USA). Kolmogorov-Smirnov test was used to check for normality. Continuous variables were presented in mean and standard deviation (SD). Statistical difference between PCOS and control group was assessed using Student's t-test. The statistical differences among the PCOS group, PCOS-Inf subgroup, PCOS-RPL subgroup, and control group were assessed using a one-way ANOVA, followed by Bonferroni correction for post hoc tests. The logarithms of nonparametric variables were calculated to approximate normal distribution. The correlation between circulating CCN3 with other variables was assessed using Pearson's correlation test. Multinomial logistic regression was performed to assess the association of serum CCN3 with PCOS risk. Finally, receiver operating characteristic (ROC) curve analysis was performed to determine the optimal cut-off level of circulating levels of CCN3 that differentiate PCOS from controls. All tests were conducted as two-tailed, with statistical significance determined by a p-value of less than 0.05.

Results

Characteristics of the study population: The characteristics of the study population are presented in table 1. There was no significant difference between the control group and the PCOS group in terms of age, BMI, FBG, TG, LDL-C, and HDL-C. Regarding the glucose profile, the PCOS subgroups had significantly higher levels of fasting insulin and HOMA-IR when compared to the healthy controls ($p<0.05$). Moreover, the PCOS subgroups had significantly elevated levels of TG when compared to the control group ($p<0.05$). Regarding the hormonal profile, the PCOS-Inf subgroup exhibited significantly higher levels of LH and lower levels of FSH ($p<0.05$) when compared to the healthy non-PCOS subjects. These results were similar in the PCOS-RPL subgroup but did not reach statistical significance. However, both subgroups showed significantly higher levels of free testosterone ($p<0.001$) when compared to the control group. These findings were reported in our previous publications (10, 45, 46).

Serum levels of cardiovascular biomarkers and adipokines: The serum levels of homocysteine and hs-CRP were significantly higher in the PCOS group, PCOS-Inf, and PCOS-RPL subgroups when compared to the control group ($p<0.001$ and $p=0.0048$, respectively) (Table 1). On the other hand, circulating levels of adiponectin were considerably reduced in the PCOS group and subgroups when compared to their respective controls ($p<0.001$). These findings were also reported in our previous publications (10, 45, 46). Nevertheless, serum levels of CCN3 were significantly elevated in PCOS group, PCOS-Inf, and PCOS-RPL subgroups (7.23±2.80 *pg/ml*, 6.85±2.54 *pg/ml*, and 7.61±3.03 *pg/ml*, respectively, $p<0.001$) (Figure 1).

Association of serum CCN3 with clinical parameters: The associations between serum CCN3 levels and the clinical and biochemical parameters of the control and PCOS groups are outlined in table 2. In the control group, serum levels of CCN3 significantly correlated with fasting insulin levels ($r=0.268$, $p<0.05$) and HOMA-IR ($r=0.262$, $p<0.05$); similarly, it directly correlated with fasting insulin levels ($r=0.496$, $p<0.001$) and HOMA-IR ($r=0.493$, $p<0.001$) in the PCOS group.

Table 1. Clinical features of the study population

Variables	Control group (n=60)	PCOS group (n=120)	PCOS-Inf subgroup (n=60)	PCOS-RPL subgroup (n=60)	p-value#
Age (years)	29.58±4.47	29.64±4.27	29.57±4.15	29.72±4.43	0.979
BMI (Kg/m^2)	25.34±3.15	25.93±3.43	25.62±3.47	26.23±3.38	0.325
FBG (*mg/dl*)	91.78±9.58	91.13±10.94	91.73±12.00	90.53±10.00	0.763
Fasting insulin (*μU/ml*)	3.37±1.85	5.22±3.48 a*	5.14±3.05 b*	5.31±3.88 c*	0.001
HOMA-IR	0.78±0.48	1.17±0.85 a*	1.15±0.81 b*	1.20±1.00 c*	0.005
TG (*mg/dl*)	124.85±35.80	136.14±59.53	126.57±58.05	145.72±59.94	0.056
TC (*mg/dl*)	161.24±40.58	176.16±36.22 a*	172.18±35.52 b*	180.14±36.78 c*	0.024
LDL-C (*mg/dl*)	95.65±30.61	102.58±29.71	102.60±28.46	102.55±31.15	0.349
HDL-C (*mg/dl*)	46.79±7.45	44.69±9.90	43.88±8.32	45.49±11.26	0.221
FSH (*IU/L*)	8.49±2.48	7.39±4.56	6.25±2.03 b*	8.53±5.94	0.001
LH (*IU/L*)	6.79±2.65	7.81±4.06	8.80±5.12 b*	6.82±2.25	0.002
Free testosterone (*pg/ml*)	1.54±0.35	3.14±1.09 a*	3.00±0.82 b*	3.27±1.29 c*	<0.001
LH to FSH ratio	0.87±0.42	1.27±0.78 a*	1.45±0.89 b*	1.09±0.60	<0.001
hs-CRP (*mg/L*)	2.46±0.91	4.04±1.26 a*	4.14±1.21 b*	3.94±1.31 c*	<0.001
Homocysteine (*μmol/L*)	10.56±3.73	12.61±5.90 a*	12.40±3.54 b*	12.82±7.59 c*	0.048
Adiponectin (*μg/ml*)	5.72±2.48	2.79±1.43 a*	2.70±1.34 b*	2.88±1.53 c*	<0.001
CCN3 (*pg/ml*)	3.12±0.82	7.23±2.80 a*	6.85±2.54 b*	7.61±3.03 c*	<0.001

Parametric data are presented as mean ± standard deviation.
a: Comparison between control group *vs.* PCOS group. b: Comparison between control group vs PCOS-Inf subgroup. c: Comparison between control group and PCOS-RPL subgroup.
* p<0.05 is of statistical significance. # p-value obtained from ANOVA analysis
PCOS: Polycystic Ovary Syndrome, RPL: Recurrent Pregnancy Loss, PCOS-Inf: Infertile PCOS, BMI: Body Mass Index, FBG: Fasting Blood Glucose, HOMA-IR: Homoeostasis Model Assessment of Insulin Resistance, TG: Triglyceride, TC: Total Cholesterol, LDL-C: Low-Density Lipoprotein Cholesterol, HDL-C: High-Density Lipoprotein Cholesterol, LH: Luteinizing Hormone, FSH: Follicle-Stimulating Hormone, hs-CRP: High Sensitivity C-reactive protein

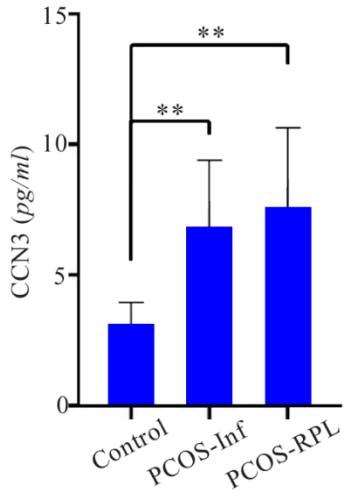

Figure 1. Serum levels of CCN3 in PCOS subgroups and control group
PCOS: Polycystic Ovary Syndrome, RPL: Recurrent Pregnancy Loss, PCOS-Inf: Infertile PCOS, CCN3: Cellular Communication Network 3

Association of serum CCN3 with PCOS risk: Logistic regression analysis was performed to determine the association between circulating levels of CCN3 and PCOS. The results indicated a sig-

Table 2. Correlation of circulating CCN3 with anthropometric, hormonal, and biochemical variables

Variables	Control group (n=60)	PCOS group (n=120)
Age (years)	-0.146	0.070
BMI (Kg/m^2)	0.061	0.003
FBG (*mg/dl*)	0.055	0.139
TG (*mg/dl*)	0.173	0.103
TC (*mg/dl*)	0.175	0.165
LDL-C (*mg/dl*)	0.166	0.151
HDL-C (*mg/dl*)	0.147	0.033
FSH (*IU/L*)	-0.083	0.036
LH (*IU/L*)	0.096	- 0.100
Free testosterone (*pg/ml*)	0.080	0.043
Fasting insulin (*μU/ml*)	0.268 *	0.496 **
HOMA-IR	0.262 *	0.493 **
Hs-CRP (*mg/L*)	0.160	0.003
Homocysteine (*μmol/L*)	0.011	-0.081
Adiponectin (*μg/ml*)	-0.142	-0.032

Pearson correlation analyses were performed to determine if an association exists between the variables. * p<0.05, ** p<0.01
PCOS: Polycystic Ovary Syndrome, BMI: Body Mass Index, FBG: Fasting Blood Glucose, TG: Triglyceride, TC: Total Cholesterol, LDL-C: Low-Density Lipoprotein Cholesterol, HDL-C: High-Density Lipoprotein Cholesterol, LH: Luteinizing Hormone, FSH: Follicle-Stimulating Hormone, HOMA-IR: Homoeostasis Model Assessment of Insulin Resistance

Table 3. Logistic regression analysis of the association between serum levels of CCN3 with PCOS

Model	Beta coefficient	Standard error	Wald statistic	Odds ratio (95%CI)	p-value
1	1.570	0.286	30.121	4.808 [2.744—8.423]	<0.001
2	1.592	0.293	29.563	4.913 [2.768—8.720]	<0.001

Model 1: not adjusted, Model 2: adjusted to age and BMI

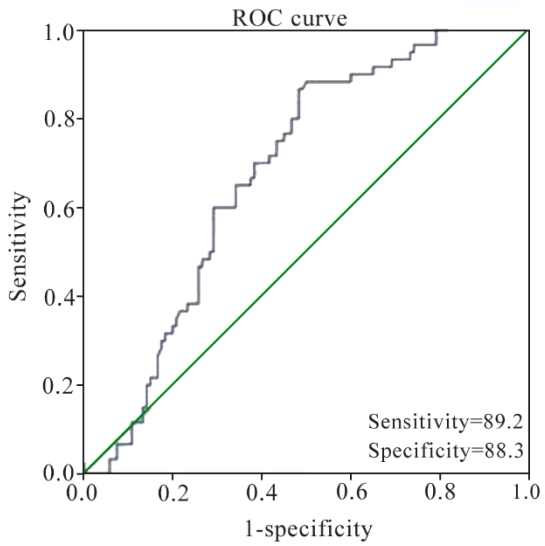

Figure 2. Receiver operating characteristic (ROC) curve analysis for predicting polycystic ovary syndrome (PCOS) using serum CCN3
AUC: Area Under the Curve

nificant association with the presence of PCOS (OR 4.808, 95%CI [2.744—8.423], p<0.001). The adjustment for the potential confounders including age and BMI did not affect the significance of the results (Table 3). Finally, ROC curve analysis was performed to evaluate the potential of CCN3 in predicting the occurrence of PCOS disease. The optimal cut-off point was 3.94 *ng/ml*, with a sensitivity of 89.2 and a specificity of 88.3. The area under the curve (AUC) was 0.680 (95%CI [0.603—0.758], p<0.001) (Figure 2).

Discussion

Metabolic inflexibility is a hallmark of the pathophysiology of PCOS, with mitochondrial dysfunction contributing to impaired fat oxidation, ectopic fat accumulation, and lipotoxicity. These processes exacerbate insulin resistance and hyperandrogenism which are the key features of the syndrome (50, 51). This study demonstrates for the first time that elevated serum concentrations of CCN3 are independently associated with PCOS, providing evidence of its potential role in the disease's metabolic and endocrine dysfunctions.

In this paper, the elevated levels of CCN3 in PCOS patients revealed an independent association with the pathogenesis of the disease, partly through insulin resistance. This was evidenced by the direct correlation between CCN3, fasting insulin levels, and HOMA-IR. Several reports highlight the role of CCN3 in glucose metabolism. *In vivo* studies showed that streptozotocin (STZ)-induced T2DM mice models exhibited reduced levels of CCN3, and an elevation occurred following insulin or anti-CCN2 antibody treatment (52, 53). Paradis et al. reported that CCN3 disrupted β-cell proliferation and insulin secretion (54). Elevated CCN3 levels in diabetic patients have been linked to glycemic parameters, including HOMA-IR and HbA1c, suggesting a broader role in insulin-resistant states (32, 55). CCN3 levels predicted the presence of T2DM at levels exceeding 5.77 *ng/ml*, highlighting its possible role in the pathogenesis of the disease (32). Quite the contrary, in a South Indian population, Smina et al. reported a significant decline in CCN3, along with remarkable elevation in transforming growth factor (TGF)-β1 and CCN2 levels, in diabetic patients suffering from diabetic foot ulcer and chronic kidney disease (CKD) when compared to those with no concurrent complications. The authors proposed that high blood glucose levels and inflammatory stimulus resulted in the elevated levels of TGF-β1, which in turn, downregulated the expression of CCN3 and increased the activity of CCN2 (56). Intriguingly, CCN3 treatment abrogated and/or reversed glomerular fibrosis in BTBR ob/ob mice model of human obesity and diabetic nephropathy progression (57). The discrepancy might be related to the different stages of DM investigated in the articles. Similar to findings in gestational diabetes mellitus (GDM), elevated CCN3 levels in PCOS might contribute to insulin resistance, possibly through pathways involving glucose transport and inflammatory sig-

naling. Conversely, in the context of GDM, Zheng and Chen reported that resveratrol improved glucose uptake and insulin sensitivity in mice model and insulin-resistant adipocytes by upregulating miR-23a-3p expression and downregulating CCN3 expression via the activation of PI3K/Akt pathway. These effects were also observed following CCN3 knockdown (58). Furthermore, in a recent study, Wang et al. investigated the levels of CCN3 in pregnant women suffering from GDM and its relation with glucose homeostasis during pregnancy. The authors found that women with GDM exhibited higher levels of CCN3 compared to healthy pregnant females, suggesting its involvement in the pathogenesis of GDM. CCN3 overexpression in GDM mice model augmented glucose intolerance by upregulating glucose transporter (GLUT)-3 and affecting mammalian target of rapamycin (mTOR) pathway (59). Therefore, elevated levels of CCN3 are associated with insulin-resistant states including T2DM, GDM, and in this context, PCOS. These findings underscore the potential of CCN3 as a biomarker for diagnosing or predicting metabolic complications in PCOS, enabling earlier interventions to mitigate insulin resistance and associated comorbidities.

Dysfunctional adipose tissue in PCOS contributes to chronic low-grade inflammation and metabolic dysregulation (4). Increased CCN3 levels, driven by hypoxia and inflammatory cytokines in adipose tissue, may exacerbate these dysfunctions by promoting mitochondrial stress and impairing adiponectin production. Excess adiposity leads to adipocyte hyperplasia and hypertrophy, resulting in tissue hypoxia and the subsequent activation of hypoxia-inducible factor (HIF)-1α, along with the release of pro-inflammatory adipokines such as tumor necrosis factor alpha (TNF-α) and CCN3. These changes contribute to major metabolic dysfunctions inducing insulin resistance, inflammation, and oxidative stress (34, 35, 60, 61). Circulating levels of CCN3 strongly correlate with BMI and fat mass. Morbidly obese patients had significantly higher levels of CCN3 when compared to lean individuals (39), and drastic weight loss resulted in a significant decline in CCN3 levels post-surgery (55). Despite the current evidence, no correlation was found between CCN3 levels and BMI, adiponectin levels, or lipid parameters. Several studies demonstrated the profound role of CCN3 in energy metabolism by promptly responding to glycolytic inhibition and glucose starvation in chondrocytes, adipocytes, and fibroblasts (62-64). Martinerie et al. reported that inhibiting CCN3 resulted in an upregulation in the expression of peroxisome proliferator-activated receptor-gamma coactivator (PGC)-1α, thereby improving adipocyte differentiation, counteracting diet-induced obesity (DIO), reducing adipose tissue inflammation, and ameliorating insulin resistance (34). Trepiana et al. suggested that the negative correlation between CCN3 levels and adipogenic genes might be the result of a protective mechanism against the obesogenic diet (65). In obesity, CCN3 expression is upregulated leading to mitochondrial dysfunction and reduced adiponectin levels (65). This suggests a link between CCN3 and metabolic dysfunction in conditions characterized by excess adiposity, such as PCOS. Reports showed that elevated levels of CCN3 significantly correlate with metabolic disorders, including NASH, cardiomyopathy, and renal dysfunction (60, 66, 67). Targeting CCN3 pathways could potentially mitigate insulin resistance and inflammation in these conditions. In a recent study, Shen et al. reported that adipose-specific overexpression of PGC-1α in DIO mice resulted in an improvement in HO-1, mitochondrial biogenesis, fasting glucose levels, blood pressure, and fibrosis. Moreover, browning of fat tissue was evident with the upregulation of UCP1, FGF21, and p-AMPK, and the downregulation of inflammatory cytokines, CCN3 expression, and TGF-β (68). Similar results were observed following the silencing of CCN3 (69). This indicates the pivotal role of CCN3 in adipogenesis and mitochondrial dysfunction, partly via the PGC-1α-HO-1 signaling pathway. Intriguingly, HO-1 levels are significantly reduced in women with PCOS (70, 71). The elevated levels of CCN3, combined with reduced levels of HO-1, may represent another factor contributing to the pathogenesis of PCOS. Future studies are needed to provide a better insight on the pharmacological induction of HO-1 to reduce CCN3 levels as a potential therapeutic approach in PCOS.

Chronic low-grade inflammation is a hallmark in the pathogenesis of PCOS. It occurs as a consequence of metabolic and inflammatory cells residing in metabolic organs, such as the liver and skeletal muscle, in response to excess energy load, resulting in metabolic dysregulation and insulin resistance (72). PCOS and RPL individuals exhibit elevated levels of inflammatory cytokines including hs-CRP and homocysteine (4, 73-75).

However, no correlation was found between CCN3 and these cytokines. Nevertheless, CCN3 is governed by several inflammatory cytokines including TNF-α, IL-1β, and TGF-β and is known to regulate the expression of other cytokines and chemokines (76). Pakradouni et al. suggested that CCN3-induced chemokine secretion might facilitate immune cell recruitment, and in turn, influence adipose tissue remodeling and systemic insulin resistance (55). The relationship between CCN3 and inflammation seems to be contradictory. On one hand, high levels of CCN3 positively correlate with CRP in patients with metabolic disorders and rheumatoid arthritis (38, 55). CCN3 knockdown attenuated inflammation and apoptosis in human alveolar epithelial cells by inhibiting TGF-β/p-Smad and NF-κB signaling pathways (77). On the other hand, CCN3 levels were drastically reduced in the atherosclerosis mouse model and individuals with abdominal aortic aneurysm (AAA). Intriguingly, the AAA phenotype of CCN3-knockout mice showed more aggressive inflammatory infiltration, ECM deterioration, smooth muscle cell loss, higher matrix metalloproteinase (MMP) activity, and heightened reactive oxygen species (ROS) production (78, 79). Moreover, Shi et al. found that CCN3 deficiency worsened atherosclerotic plaque burden by enhancing lipid accumulation within the macrophages (33). On the other hand, CCN3 overexpression abrogated inflammation and dyslipidemia in atherosclerosis and ameliorated AAA development via the ERK1/2 signaling pathway (78, 79). This discrepancy highlights the role of CCN3 in the inflammatory process. The lack of correlation of CCN3 with hs-CRP or homocysteine does not nullify the possibility of its relationship with the inflammatory aspect of PCOS. The association of CCN3 with the previously discussed inflammatory disorders indicates its potential involvement in PCOS, potentially mediated by more dominant pro-inflammatory cytokines.

Despite the novelty of the present study, there are some limitations. First, CCN proteins interact extensively with one another, exhibiting a range of overlapping or inhibitory functions. For instance, CCN2-knockout mice show an upregulation in CCN3 expression (80); CCN3-overexpression in atherosclerosis models significantly downregulates CCN1 and CCN2 expression (78); CCN3-overexpression or its administration significantly reduces CCN2 activity in mesangial cells and renal cortex, respectively (57, 81); and anti-CCN2 antibody treatment elevates an otherwise downregulated CCN3 in NASH model (53). Therefore, analyzing CCN1 and CCN2 would be of high interest to understand how these proteins interact with one another in the context of PCOS. Second, BMI was used as a tool to assess body composition in this study; however, more accurate methods such as body composition analysis and functional body composition assessment would be more beneficial. Third, the findings may be specific to the Iranian population, which limits their generalizability. Finally, the methodology employed in the current study constrains the results to correlational analysis, thereby lacking definitive evidence of causation. Additional research is warranted to establish causal relationships

Conclusion

Based on the findings of the current study, there is an independent association between CCN3 levels and PCOS, as well as a positive correlation with insulin resistance. Elevated serum CCN3 levels in PCOS patients may represent a compensatory response to underlying metabolic dysregulations, highlighting its potential as a biomarker for early detection. Additionally, CCN3 could serve as a therapeutic target for managing insulin resistance and associated metabolic dysfunctions in PCOS. However, the aforementioned potential warrants further research and clinical exploration.

Acknowledgement

This project was supported by Hormozgan University of Medical Sciences (HUMS), Bandar Abbas, Iran (grant number 980288). The authors would like to thank all the study participants.

Conflict of Interest

Authors declare no conflict of interest.

References

1. Villa J, Pratley RE. Adipose tissue dysfunction in polycystic ovary syndrome. Curr Diab Rep. 2011;11(3):179-84.
2. Ehrmann DA. Polycystic ovary syndrome. N Engl J Med. 2005;352(12):1223-36.
3. Sam S, Tasali E. Role of obstructive sleep apnea in metabolic risk in PCOS. Curr Opin Endocr Metab Res. 2021;17:46-51.
4. Nehir Aytan A, Bastu E, Demiral I, Bulut H, Dogan M, Buyru F. Relationship between hyperandrogenism, obesity, inflammation and polycystic ovary syndrome. Gynecol Endocrinol. 2016;32(9):709-13.

5. Tan BK, Chen J, Hu J, Amar O, Mattu HS, Adya R, et al. Metformin increases the novel adipokine cartonectin/CTRP3 in women with polycystic ovary syndrome. J Clin Endocrinol Metab. 2013;98(12): E1891-900.
6. Shanaki M, Moradi N, Fadaei R, Zandieh Z, Shabani P, Vatannejad A. Lower circulating levels of CTRP12 and CTRP13 in polycystic ovarian syndrome: irrespective of obesity. PloS One. 2018;13 (12):e0208059
7. Calan M, Alan M, Alarslan P, Unal Kocabas G, Bozkaya G, Acara AC, et al. Association of decreased C1q/tumor necrosis factor-related protein-5 levels with metabolic and hormonal disturbance in polycystic ovary syndrome. J Turk Ger Gynecol Assoc. 2019;20(2):89-96.
8. Gözüküçük M, Yarcı Gürsoy A, Destegül E, Taşkın S, Şatıroğlu H. Adiponectin and leptin levels in normal weight women with polycystic ovary syndrome. Horm Mol Biol Clin Investig. 2020;41 (4).
9. Sadeghi A, Fadaei R, Moradi N, Fouani FZ, Roozbehkia M, Zandieh Z, et al. Circulating levels of C1q/TNF-alpha-related protein 6 (CTRP6) in polycystic ovary syndrome. IUBMB Life. 2020;72(7): 1449-59.
10. Fouani FZ, Fadaei R, Moradi N, Zandieh Z, Ansaripour S, Yekaninejad MS, et al. Circulating levels of meteorin-like protein in polycystic ovary syndrome: a case-control study. PLoS One. 2020; 15(4):e0231943.
11. Serazin V, Duval F, Wainer R, Ravel C, Vialard F, Molina-Gomes D, et al. Are leptin and adiponectin involved in recurrent pregnancy loss? J Obstet Gynaecol Res. 2018;44(6):1015-22.
12. Dos Santos E, Serazin V, Morvan C, Torre A, Wainer R, de Mazancourt P, et al. Adiponectin and leptin systems in human endometrium during window of implantation. Fertil Steril. 2012;97(3):771-8.e1.
13. Kim HS, Nagalla SR, Oh Y, Wilson E, Roberts CT Jr, Rosenfeld RG. Identification of a family of low-affinity insulin-like growth factor binding proteins (IGFBPs): characterization of connective tissue growth factor as a member of the IGFBP superfamily. Proc Natl Acad Sci USA. 1997;94(24): 12981-6.
14. Perbal B. Nuclear localisation of NOVH protein: a potential role for NOV in the regulation of gene expression. Mol Pathol. 1999;52(2):84-91.
15. Perbal B. Contribution of MAV-1-induced nephroblastoma to the study of genes involved in human Wilms' tumor development. Crit Rev Oncog. 1994; 5(6):589-613.
16. Sakamoto K, Yamaguchi S, Ando R, Miyawaki A, Kabasawa Y, Takagi M, et al. The nephroblastoma overexpressed gene (NOV/ccn3) protein associates with Notch1 extracellular domain and inhibits myoblast differentiation via Notch signaling pathway. J Biol Chem. 2002;277(33):29399-405.
17. Li CL, Martinez V, He B, Lombet A, Perbal B. A role for CCN3 (NOV) in calcium signalling. Mol Pathol. 2002;55(4):250-61.
18. Su BY, Cai WQ, Zhang CG, Su HC, Perbal B. A developmental study of novH gene expression in human central nervous system. C R Acad Sci III. 1998;321(11):883-92.
19. Burren CP, Wilson EM, Hwa V, Oh Y, Rosenfeld RG. Binding properties and distribution of insulin-like growth factor binding protein-related protein 3 (IGFBP-rP3/NovH), an additional member of the IGFBP superfamily. J Clin Endocrinol Metab. 1999;84(3):1096-103.
20. Gupta N, Wang H, McLeod TL, Naus CC, Kyurkchiev S, Advani S, et al. Inhibition of glioma cell growth and tumorigenic potential by CCN3 (NOV). Mol Pathol. 2001;54(5):293-9.
21. Maillard M, Cadot B, Ball RY, Sethia K, Edwards DR, Perbal B, et al. Differential expression of the ccn3 (nov) proto-oncogene in human prostate cell lines and tissues. Mol Pathol. 2001;54(4):275-80.
22. Martinerie C, Gicquel C, Louvel A, Laurent M, Schofield PN, Le Bouc Y. Altered expression of novH is associated with human adrenocortical tumorigenesis. J Clin Endocrinol Metab. 2001;86 (8):3929-40.
23. Manara MC, Perbal B, Benini S, Strammiello R, Cerisano V, Perdichizzi S, et al. The expression of ccn3(nov) gene in musculoskeletal tumors. Am J Pathol. 2002;160(3):849-59.
24. Yu C, Le AT, Yeger H, Perbal B, Alman BA. NOV (CCN3) regulation in the growth plate and CCN family member expression in cartilage neoplasia. J Pathol. 2003;201(4):609-15.
25. Thibout H, Martinerie C, Créminon C, Godeau F, Boudou P, Le Bouc Y, et al. Characterization of human NOV in biological fluids: an enzyme immunoassay for the quantification of human NOV in sera from patients with diseases of the adrenal gland and of the nervous system. J Clin Endocrinol Metab. 2003;88(1):327-36.
26. Jiang WG, Watkins G, Fodstad O, Douglas-Jones A, Mokbel K, Mansel RE. Differential expression of the CCN family members Cyr61, CTGF and Nov in human breast cancer. Endocr Relat Cancer. 2004;11(4):781-91.
27. Lafont J, Jacques C, Le Dreau G, Calhabeu F, Thibout H, Dubois C, et al. New target genes for

NOV/CCN3 in chondrocytes: TGF-beta2 and type X collagen. J Bone Miner Res. 2005;20(12):2213-23.

28. Giusti V, Scotlandi K. CCN proteins in the musculoskeletal system: current understanding and challenges in physiology and pathology. J Cell Commun Signal. 2021;15(4):545-66.
29. Kubota S, Kawaki H, Perbal B, Kawata K, Hattori T, Nishida T. Cellular communication network factor 3 in cartilage development and maintenance. J Cell Commun Signal. 2021;15(4):533-43.
30. Son S, Kim H, Lim H, Lee JH, Lee KM, Shin I. CCN3/NOV promotes metastasis and tumor progression via GPNMB-induced EGFR activation in triple-negative breast cancer. Cell Death Dis. 2023; 14(2):81.
31. Yan X, Yan W, Fu X, Xu Y, Zhu N, Qiu C, et al. Single nucleotide mutation changes the capability of CCN3 in osteosarcoma cell invasion and differentiation. Transl Oncol. 2022;24:101485.
32. Li JY, Wang YD, Qi XY, Ran L, Hong T, Yang J, et al. Serum CCN3 levels are increased in type 2 diabetes mellitus and associated with obesity, insulin resistance and inflammation. Clin Chim Acta. 2019;494:52-7.
33. Shi H, Zhang C, Pasupuleti V, Hu X, Prosdocimo DA, Wu W, et al. CCN3 Regulates Macrophage Foam Cell Formation and Atherosclerosis. Am J Pathol. 2017;187(6):1230-7.
34. Martinerie C, Garcia M, Do TT, Antoine B, Moldes M, Dorothee G, et al. NOV/CCN3: a new adipocytokine involved in obesity-associated insulin resistance. Diabetes. 2016;65(9):2502-15.
35. Cao J, Singh SP, McClung JA, Joseph G, Vanella L, Barbagallo I, et al. EET intervention on Wnt1, NOV, and HO-1 signaling prevents obesity-induced cardiomyopathy in obese mice. Am J Physiol Heart Circ Physiol. 2017;313(2):H368-80.
36. Henrot P, Moisan F, Laurent P, Manicki P, Kaulanjan-Checkmodine P, Jolivel V, et al. Decreased CCN3 in systemic sclerosis endothelial cells contributes to impaired angiogenesis. J Invest Dermatol. 2020;140(7):1427-34.e5.
37. Naughton M, Moffat J, Eleftheriadis G, de la Vega Gallardo N, Young A, Falconer J, et al. CCN3 is dynamically regulated by treatment and disease state in multiple sclerosis. J Neuroinflammation. 2020;17(1):349.
38. Wei Y, Peng L, Li Y, Zhang N, Shang K, Duan L, et al. Higher serum CCN3 is associated with disease activity and inflammatory markers in rheumatoid arthritis. J Immunol Res. 2020;2020:3891425.
39. Weingarten JA, Bellner L, Peterson SJ, Zaw M, Chadha P, Singh SP, et al. The association of NOV/CCN3 with obstructive sleep apnea (OSA): preliminary evidence of a novel biomarker in OSA. Horm Mol Biol Clin Investig. 2017;31(2).
40. Tu P, Xu Q, Zhou X, Villa-Roel N, Kumar S, Dong N, et al. Myeloid CCN3 protects against aortic valve calcification. Cell Commun Signal. 2023;21(1):14.
41. Flinn MA, Alvarez-Argote S, Knas MC, Almeida VA, Paddock SJ, Zhou X, et al. Myofibroblast Ccn3 is regulated by Yap and Wwtr1 and contributes to adverse cardiac outcomes. Front Cardiovasc Med. 2023;10:1142612.
42. Gellhaus A, Schmidt M, Dunk C, Lye SJ, Kimmig R, Winterhager E. Decreased expression of the angiogenic regulators CYR61 (CCN1) and NOV (CCN3) in human placenta is associated with preeclampsia. Mol Hum Reprod. 2006;12(6):389-99.
43. Wagener J, Yang W, Kazuschke K, Winterhager E, Gellhaus A. CCN3 regulates proliferation and migration properties in Jeg3 trophoblast cells via ERK1/2, Akt and Notch signalling. Mol Hum Reprod. 2013;19(4):237-49.
44. Hassani F, Oryan Sh, Eftekhari-Yazdi P, Bazrgar M, Moini A, Nasiri N, et al. Downregulation of extracellular matrix and cell adhesion molecules in cumulus cells of infertile polycystic ovary syndrome women with and without insulin resistance. Cell J. 2019;21(1):35-42.
45. Sadeghi A, Fadaei R, Moradi N, Fouani FZ, Roozbehkia M, Zandieh Z, et al. Circulating levels of C1q/TNF-α-related protein 6 (CTRP6) in polycystic ovary syndrome. IUBMB Life. 2020;72(7): 1449-59.
46. Vatannejad A, Salimi F, Moradi N, Fouani FZ, Zandieh Z, Ansaripour S, et al. Evaluation of angiopoietin-like protein 3 (ANGPTL3) levels in polycystic ovary syndrome. Life Sci. 2020;263: 118595.
47. Rotterdam ESHRE/ASRM-sponsored PCOS consensus workshop group. Revised 2003 consensus on diagnostic criteria and long-term health risks related to polycystic ovary syndrome. Fertil Steril. 2004;81(1):19-25.
48. Lee RM, Silver RM. Recurrent pregnancy loss: summary and clinical recommendations. Semin Reprod Med. 2000;18(4):433-40.
49. Matthews DR, Hosker JP, Rudenski AS, Naylor BA, Treacher DF, Turner RC. Homeostasis model assessment: insulin resistance and beta-cell function from fasting plasma glucose and insulin concentrations in man. Diabetologia. 1985;28(7):412-9.

50. Connolly A, Leblanc S, Baillargeon JP. Role of lipotoxicity and contribution of the renin-angiotensin system in the development of polycystic ovary syndrome. Int J Endocrinol. 2018;2018: 4315413.
51. Di Sarra D, Tosi F, Bonin C, Fiers T, Kaufman JM, Signori C, et al. Metabolic inflexibility is a feature of women with polycystic ovary syndrome and is associated with both insulin resistance and hyperandrogenism. J Clin Endocrinol Metab. 2013;98 (6):2581-8.
52. Shimoyama T, Hiraoka S, Takemoto M, Koshizaka M, Tokuyama H, Tokuyama T, et al. CCN3 inhibits neointimal hyperplasia through modulation of smooth muscle cell growth and migration. Arterioscler Thromb Vasc Biol. 2010;30(4):675-82.
53. Ren J, Wang X, Parry SN, Yee C, Gorrell MD, McLennan SV, et al. Targeting CCN2 protects against progressive non-alcoholic steatohepatitis in a preclinical model induced by high-fat feeding and type 2 diabetes. J Cell Commun Signal. 2022; 16(3):447-60.
54. Paradis R, Lazar N, Antinozzi P, Perbal B, Buteau J. Nov/Ccn3, a novel transcriptional target of FoxO1, impairs pancreatic β-cell function. PLoS One. 2013;8(5):e64957.
55. Pakradouni J, Le Goff W, Calmel C, Antoine B, Villard E, Frisdal E, et al. Plasma NOV/CCN3 levels are closely associated with obesity in patients with metabolic disorders. PLoS One. 2013;8 (6):e66788.
56. Smina TP, Rabeka M, Viswanathan V. Diabetic foot ulcer as a cause of significant decline in the renal function among south Indian population with type 2 diabetes: role of TGF-β1 and CCN family proteins. Int J Low Extrem Wounds. 2019;18(4): 354-61.
57. Riser BL, Najmabadi F, Garchow K, Barnes JL, Peterson DR, Sukowski EJ. Treatment with the matricellular protein CCN3 blocks and/or reverses fibrosis development in obesity with diabetic nephropathy. Am J Pathol. 2014;184(11):2908-21.
58. Zheng T, Chen H. Resveratrol ameliorates the glucose uptake and lipid metabolism in gestational diabetes mellitus mice and insulin-resistant adipocytes via miR-23a-3p/ NOV axis. Mol Immunol. 2021;137:163-73.
59. Wang H, Huang B, Hou A, Xue L, Wang B, Chen J, et al. High NOV/CCN3 expression during high-fat diet pregnancy in mice affects GLUT3 expression and the mTOR pathway. Am J Physiol Endocrinol Metab. 2021;320(4):E786-96.
60. Sacerdoti D, Singh SP, Schragenheim J, Bellner L, Vanella L, Raffaele M, et al. Development of NASH in obese mice is confounded by adipose tissue increase in inflammatory NOV and oxidative stress. Int J Hepatol. 2018;2018:3484107.
61. Martinerie C, Garcia M, Do TT, Antoine B, Moldes M, Dorothee G, et al. NOV/CCN3: a new adipocytokine involved in obesity-associated insulin resistance. Diabetes. 2016;65(9):2502-15.
62. Abd El Kader T, Kubota S, Janune D, Nishida T, Hattori T, Aoyama E, et al. Anti-fibrotic effect of CCN3 accompanied by altered gene expression profile of the CCN family. J Cell Commun Signal. 2013;7(1):11-8.
63. Akashi S, Nishida T, El-Seoudi A, Takigawa M, Iida S, Kubota S. Metabolic regulation of the CCN family genes by glycolysis in chondrocytes. J Cell Commun Signal. 2018;12(1):245-52.
64. Escoté X, Gómez-Zorita S, López-Yoldi M, Milton-Laskibar I, Fernández-Quintela A, Martínez JA, et al. Role of omentin, vaspin, cardiotrophin-1, TWEAK and NOV/CCN3 in obesity and diabetes development. Int J Mol Sci. 2017;18(8): 1770.
65. Trepiana J, Gómez-Zorita S, Fernández-Quintela A, González M, Portillo MP. Effects of resveratrol and its analogue pterostilbene, on NOV/CCN3 adipokine in adipose tissue from rats fed a high-fat high-sucrose diet. J Physiol Biochem. 2019;75(3): 275-83.
66. Singh SP, McClung JA, Bellner L, Cao J, Waldman M, Schragenheim J, et al. CYP-450 epoxygenase derived epoxyeicosatrienoic acid contribute to reversal of heart failure in obesity-induced diabetic cardiomyopathy via PGC-1 α activation. Cardiovasc Pharm Open Access. 2018;7(1):233.
67. Schragenheim J, Bellner L, Cao J, Singh SP, Bamshad D, McClung JA, et al. EET enhances renal function in obese mice resulting in restoration of HO-1-Mfn1/2 signaling, and decrease in hypertension through inhibition of sodium chloride co-transporter. Prostaglandins Other Lipid Mediat. 2018;137:30-9.
68. Shen SH, Singh SP, Raffaele M, Waldman M, Hochhauser E, Ospino J, et al. Adipocyte-specific expression of PGC1α promotes adipocyte browning and alleviates obesity-induced metabolic dysfunction in an HO-1-dependent fashion. Antioxidants (Basel). 2022;11(6):1147.
69. Waldman M, Singh SP, Shen HH, Alex R, Rezzani R, Favero G, et al. Silencing the adipocytokine NOV: a novel approach to reversing oxidative stress-induced cardiometabolic dysfunction. Cells. 2022;11(19):3060.
70. Seow KM, Lin YH, Hwang JL, Wang PH, Ho LT, Lin YH, et al. Expression levels of haem oxy-

genase-1 in the omental adipose tissue and peripheral blood mononuclear cells of women with polycystic ovary syndrome. Hum Reprod. 2011;26 (2):431-7.

71. Gao H, Meng J, Xing H, Nie S, Xu M, Zhang S, et al. Association of heme oxygenase-1 with the risk of polycystic ovary syndrome in non-obese women. Hum Reprod. 2014;29(5):1058-66.
72. Gregor MF, Hotamisligil GS. Inflammatory mechanisms in obesity. Annu Rev Immunol. 2011; 29:415-45.
73. Maleedhu P, Vijayabhaskar M, Sharma SSB, Kodumuri PK. Status of homocysteine in polycystic ovary syndrome (PCOS). J Clin Diagn Res. 2014; 8(2):31-3.
74. Asanidze E, Kristesashvili J, Andguladze S. Correlation between levels of homocysteine, antimullerian hormone and insulin resistance in PCOS patients with with recurrent miscarriage. Georgian Med News. 2019(290):25-9.
75. Wagner MM, Jukema JW, Hermes W, le Cessie S, de Groot CJM, Bakker JA, et al. Assessment of novel cardiovascular biomarkers in women with a history of recurrent miscarriage. Pregnancy Hypertens. 2018;11:129-35.
76. Kular L, Pakradouni J, Kitabgi P, Laurent M, Martinerie C. The CCN family: a new class of inflammation modulators? Biochimie. 2011;93(3): 377-88.
77. Zhu HP, Huang HY, Wu DM, Dong N, Dong L, Chen CS, et al. Regulatory mechanism of NOV/ CCN3 in the inflammation and apoptosis of lung epithelial alveolar cells upon lipopolysaccharide stimulation. Mol Med Rep. 2020;21(4):1872-80.
78. Liu J, Ren Y, Kang L, Zhang L. Overexpression of CCN3 inhibits inflammation and progression of atherosclerosis in apolipoprotein E-deficient mice. PLoS One. 2014;9(4):e94912.
79. Zhang C, van der Voort D, Shi H, Zhang R, Qing Y, Hiraoka S, et al. Matricellular protein CCN3 mitigates abdominal aortic aneurysm. J Clin Investig. 2016;126(4):1282-99.
80. Bedore J, Sha W, McCann MR, Liu S, Leask A, Séguin CA. Impaired intervertebral disc development and premature disc degeneration in mice with notochord-specific deletion of CCN2. Arthritis Rheum. 2013;65(10):2634-44.
81. Riser BL, Najmabadi F, Perbal B, Rambow JA, Riser ML, Sukowski E, et al. CCN3/CCN2 regulation and the fibrosis of diabetic renal disease. J Cell Commun Signal. 2010;4(1):39-50.