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Original Article

FNDC5 genetic polymorphism in patients with peripartum cardiomyopathy

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Abstract

Background: Late in pregnancy or soon after delivery, peripartum cardiomyopathy (PPCM) which is an uncommon type of cardiomyopathy, can develop. To assess the association between the level of irisin expression and (FNDC5) (rs3480) gene polymorphism with peripartum cardiomyopathy.

Methods: This is a case control study included a thirty female patients with new-onset PPCM and sixty healthy females at the at the peripartum period in same time window for PPCM as a control. For each patient, comprehensive medical history was taken, full clinical assessment was done, ECHO., FNDC5 (rs3480) & Irisin assay.

Results: The left ventricle end diastolic dimensions &left atrium diameters were statistically significant higher in patients' group than controls' group (P=0.000 for all), Also left ventricular ejection fraction (%) was statistically significant lower in patients than controls and as regards irisin, its Mean ±SD was lower in patient group than control group (8.44±1.1 vs 10.65±2.31) with (p <0.001) which is considered a significant difference statistically.

Conclusion: Irisin level was lower in peripartum cardiomyopathic patients when compared with normal individuals and regarding its genotype, the homotype A/A was higher than homotype G/G.

Keywords: FNDC5 Polymorphism, Peripartum cardiomyopathy, Irisin.

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Peripartum cardiomyopathy (PPCM) is an uncommon kind of cardiomyocyte dysfunction that develops in the third trimester or shortly after delivery which is characterized by left ventricular systolic dysfunction & cardiac failure (HF) (1, 2).

The European Society of Cardiology described PPCM as an idiopathic type of cardiomyopathy manifested by HF at late gestation or in the postnatal period, the lack of extra detectable reason of cardiac failure & left ventricular (LV) systolic dysfunction with (LV) ejection fraction(EF) of <45%. PPCM's cause is still unknown. There is a link between PPCM and eclampsia during pregnancy. The fundamental process is yet unknown. African ancestry, age, pregnancy-related hypertension problems, multiparity, obesity and long-term use of tocolytics are all risk factors for PPCM. Several researches have suggested a variety of possible pathways for the development of PPCM (3, 4).

New features of the illness have emerged as a result of recent genetic studies. PPCM and dilated cardiomyopathy (DCM) have a hereditary predisposition. Genetic alterations linked with DCM were identified in 15% of PPCM patients, and they had a poorer recovery rate. Genetic predisposition linked to both hypertension and cardiac diseases through angiogenic imbalance may explain shared aspects of hypertensive disorders and PPCM (5). The secretion of irisin is triggered by the subsequent molecular pathway.Exercise enhances the expression of the PPAR-coactivator (PGC)-1, which triggers the production of fibronectin type III domain-containing (FNDC5) (6).

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A membrane protein called FNDC5 is released in the skeletal muscles and the brain. It is a category of transmembrane protein that is encoded by the FNDC5 gene and serves as the precursor to irisin, which is created when an unidentified proteolytic enzyme (s) cleaves FNCD5 at the cell membrane stage to produce white adipocytes and other cells, such as hepatocytes &myocytes, have unidentified receptors that irisin binds to (7).

Irisin is secreted by the heart, one of the biggest muscles in the human body, and it has a crucial role in controlling the amount of irisin in the blood, at least in animals. Irisin secretion is impacted by ischemic heart disease and its severe form, myocardial infarction (MI) (8). It is not yet known if the change in serum level of irisin serves as the "trigger" for the onset of cardiac failure or merely as a "consequence" of cardiac failure. Given that the heart may be both the source and the recipient of irisin, the answer may even be both. To provide the extra energy needed in cases of obesity or to make up for the lack of energy in cases of diabetes, the body increases the levels of circulating irisin. Increased generation of reactive oxygen species accompanied enhanced cardiac function at higher levels of irisin stimulation.

A high irisin level in this situation may cause cardiac failure. But on the other hand, the drop in muscle-derived irisin is unavoidable in cases of advanced heart failure where the motor functions have been severely compromised. To enhance energy production, the heart therefore secretes more irisin, which may also worsen cardiac fibrosis and death in cardiomyocytes. A more thorough cohort research with strata at various ages & etiology levels should be conducted to elucidate the significance of irisin in the cardiac failure population in light of the heterogeneity in the etiology of cardiac failure and the previously described effect of age on circulating level of irisin (9).

Treatment, prognosis, and family management may all benefit from a deeper comprehension of the genetics underlying PPCM. Though the role of FNDC5 genetic polymorphism and irisin expression in peripartum cardiomyopathy is not fully examined. This work aimed at judging the link between the level of irisin expression and (FNDC5) gene polymorphism with peripartum cardiomyopathy.

Methods

This was a case control, observational, single center research carried out at Sohag University Hospitals where we included all patients diagnosed with PPCM came to the hospital during the period from 1 March 2019 till 1 May 2021. Thirty female patients with new-onset PPCM and sixty healthy females at the peripartum period in the same time window for PPCM as control have been enrolled in this research.

The Sohag Medical Faculty Ethics Committee of Sohag University gave its approval to the study protocol. This approval carries the IRB registration number (Soh-Med-21-02-26) & registered on ClinicalTrials.gov (ID:NCT04927715). And informed written consents had been obtained from all subjects enrolled in the study.

Inclusion criteria: Included patients with new-onset PPCM who met the requirements for the research eligibility criteria and had peripartum cardiomyopathy were identified and treated clinically at Sohag university hospitals during the study period with the traits listed below:

- Cardiac failure develops towards the end of gestation or shortly after labor.
- There is no other known etiology of cardiac failure.
- LV systolic dysfunction with an LVEF of less than 45%.
- No detected ECG abnormalities or abnormal signs in clinical assessment at the antenatal period.
- The development of abnormality ranged from the final month before labor up to five months after delivery and fulfilling the required criteria for diagnosing PPCM according to the European Society of Cardiology (10).

Exclusion criteria: Other identifiable etiologies of cardiac failure such as preexisting hypertension, coronary artery disease, valvular and systemic disease had been excluded.

Method: Each patient has undergone a thorough medical history and clinical assessment. The demographic data of patients and controls include: age, weight, height, parity, blood pressure, onset of presentation, single fetus or multiple, previous PPCM, complete echocardiographic evaluation.

Echocardiography: The diagnosis of patients was done by cardiologists at Sohag university hospital. Targeted M-mode & two-dimensional echocardiography with color Doppler flow mapping was done with (Nemio SSA-550,Toshiba instrument, Japan 2.5MHZ transducer and harmonic imaging echocardiogram device). LV Systolic & diastolic dimensions were assessed according to the guidelines of the American Society of Echocardiography (11). The LV dimensions & functions were measured using an average of 3 cycles (11).

FDNC5 (rs3480) and Irisin assay: Blood sample: 3 mL of blood had been withdrawn by venipuncture in EDTA tube. DNA extraction (using Qiagen DNA extraction kit catalog no.51304) had been done after centrifugation and used for

genotyping assay of (FNDC5) gene (rs3480) with one step real time PCR technique.

Primer was purchased from (Applied BioSystem): rs3480 AGACCGGAAGGAAGGAA (F-primer), TGGTCCCCAAGGGGCGGTCATT**(A/G)**GGTGATGGC TTCTGGCTCTCTGGCT.

Genotyping of FDNC5 (rs3480) (A/G) polymorphism: DNA extraction was done by using Qiagen DNA extraction kit catalog no.51304). DNA was eluted & kept at -20° C for subsequent PCR assays. One step real time - PCR was used to genotype the irisin gene using an allelic discrimination assay. (TaqMan Master Mix, Applied Biosystems), the qPCR Master Mix (300×), context sequence was provided from Thermo Fisher Scientific catalog no.4351379). The context sequence for irisin rs3480 AGACCGGAAGGAAGGAA (F-primer), TGGTCCCCAAGGGGCGGTCATT**(A/G)**GGTGATGGC TTCTGGCTCTCTGGCT. 1.25 µl of the SNP genotyping assay primer mix & 3.75 µl of DNAase-free water were combined with 10 µl of the master mix. 5 µl of genomic DNA extract for each sample & 5 µl of DNAase-free water for the negative control reaction were applied. The subsequent circumstances had been applied A 10-minute initial denaturation step was followed by 40 cycles of primer annealing at 60 °C for 60 seconds, denaturation at 95 °C for 15 seconds, extension at 72 °C for 2 minutes & the final extension at 72 °C for 1 minute. Analysis of data was finished with the use of (Applied Biosystems StepOne™ Instrument, Singapore). Step 1 real time PCR using taq polymerase showing DNA plateau in patients and controls (figure 2).

Irisin had been analyzed by Sandwich enzyme immunoassay kit (ELISA) using Stat fax220012 VAC2A, Stat fax2600 &Stat fax2, 100 USA) .The linearity of successive dilutions of plasma and serum (1, 1/2, 1/4, 1/8) was examined. Additionally, the effects of a number of freeze/thaw cycles (0, 2, 4, 8) on concentration & cross-reactivity between the two assays were examined. The potential of a "hook effect" was investigated using successive dilutions (1/10, 1/100, and 1/1000) in samples with low levels of FNDC5.

Statistical analysis: Statistical program for social science (SPSS) Version 25 (Armonk, NY: IBM Corp) was used to tabulate and analyze the data gathered on an IBM compatible computer. According to the type of data, qualitative data are represented as numbers or percentages, whereas quantitative data are represented as mean or standard deviation. The chi-square test (2) was employed, as well as the independent samples student-test and the ANOVA (f) test. Hardy-Weinberg equilibrium (HWE) and Linkage Disequilibrium (LD) were examined for homotype A/A, homotype G/G and heterotype /G. Genepop software version 4.7 was used to calculate the HWE and LD. HWE was present for p-values >0.05.The deviation from Hardy Weinberg equilibrium (HWE) was verified using chi-square test. A p-value of less than 0.05 was statistically significant.

Results

In A full of 90 individuals enrolled in this study. There was no statistically significant increase found by comparison between two groups as regards age, Gravida, Para and BMI in the patients' group than controls' group (table 1).

There was no statistically major change found by comparison among two groups as regard multi-fetus, familial cardiomyopathy, peripartum stage, gestational DM and hypertension. Regarding genotype in patients and control group, among PPCM cases, the genotype frequencies of A/A, G/G and A/G were in H-W equilibrium. Among control, all of the genotype frequencies were in H-W equilibrium. There was one (3.3%) & 7 (11.7%) with homotype A/A, 9 (30.0%) & 13 (21.6%) with homotype G/G and 20 (66.7%) & 40 (66.7%) with heterotype, respectively, without significance between both groups (table 2). The allelic discrimination plot of real-time TaqMan diagnostic assay for FNDC5 (rs3480) between different genotypes in both patients and controls was shown in (figure 1).

Table 1. Comparison between patients' and controls' groups as regards demographic data

	Patients (n=30) Mean ±SD			Controls (n=60) Mean ±SD			P-value
Age	32.43	±	5.828	30.20	±	4.627	0.060
Body mass index	26.27	±	4.835	25.10	±	4.536	0.328
Gravida	4.77	±	1.695	4.20	±	1.710	0.177
Para	3.27	±	1.437	2.90	±	0.296	0.075

*significant P-value when ≤ 0.05& ** highly significant P-value when ≤ 0.001

Table 2. Comparison between patients' and controls' groups as regards clinical data

	Patients(n=30)		Controls (n=60)		X^2	P-value
	N	%	N	%		
Multifetal or single						
Single Fetus	13	43.3%	34	56.7%	2.411	0.121
Multifetus	17	56.7%	26	43.3%		
Gestational hypertension						
Normotensive	11	36.7%	23	38.3%	3.270	0.071
Hypertensive	19	63.3%	37	61.7%		
Gestational DM						
Absent	14	46.7%	16	26.7%	3.360	0.067
Present	16	53.3%	44	73.3%		
Familial cardiomyopathy						
Absent	25	83.3%	44	73.3%	2.963	0.085
Present	5	16.7%	16	26.7%		
Peripartum stage						
Prepartum	8	26.7%	21	35.0%	0.373	0.542
Postpartum	22	73.3%	39	65.0%		
Genotype						
Homotype A/A	1	3.3%	7	11.7%	1.624	0.444
Homotype G/G	9	30.0%	13	21.6%		
Heterotype	20	66.7%	40	66.7%		

*significant P-value when ≤ 0.05& ** highly significant P-value when ≤ 0.001

The left ventricular end diastolic diameter (LVEDD) & left atrial (LA) diameter were measured, which was statistically significant higher in patients' group than controls' group (P=0.000 for all), Also LV ejection fraction (EF) (%) was statistically significant lower in patients' set than controls and as regards irisin, its Mean ±SD was lower in patients group than controls group (8.44±1.1 vs 10.65±2.31) with a significant difference (p <0.001) (table 3).

Table 3. Comparison between patients' and controls' groups as regards LVEDD, LA diameter, LVEF (%), and irisin

	Patients (n=30) Mean ±SD	Controls (n=60) Mean ±SD	P-value
LVEDD	6.18 ± 0.46	3.88 ± 0.27	0.000**
LA diameter	3.91 ± 0.40	2.98 ± 0.11	0.000**
LVEF (%)	40.63 ± 4.59	65.80 ± 2.75	0.000**
IRISIN	8.44 ± 1.19	10.65 ± 2.31	<0.001**

*Significant P-value if ≤ 0.05, ** highly significant P-value if ≤ 0.001 LVEDD: left ventricular end diastolic dimensions, LA = left atrium, & LVEF =left ventricular ejection fraction

Comparing the genotypes among patient and control group showed that there was no statistically significant difference in regard to age, gravidity, parity and BMI, Gestational DM, peripartum stage, familial cardiomyopathy and number of fetuses. As regards hypertensive disorders during pregnancy in control group, there was statistically significant increase in heterotype than homotype G/G group (p=0.044) (tables 4, 5).

Comparison between genotypes regarding Echo data among patients group revealed that there was no statistically significant difference as regards LVEDD, LA diameter & LVEF (%). Regarding irisin level, homotype A/A genotype was higher than homotype G/G and heterotype without significant difference (p>0.05). While control group revealed no significant difference as regards LVEDD & LVEF (%) (p>0.05). While LA diameter was significantly lower in heterotype group than other two groups. As regards irisin, there was statistically significant increase in homotype A/A patients' group in group in comparison to heterotype group (P=0.007) (table 6). Comparing heterotype group (P=0.003) & significantly increase in homotype G/G patients'.

Table 4. Comparing patients and controls according to genotype as regards demographic data

	Homotype A/A Mean ±SD	Homotype G/G Mean ±SD	Heterotype Mean ±SD	P-value
Patient group				
Age	28.33 ± 5.77	31.33 ± 6.35	30.14 ± 4.09	0.667
Body mass index	25.67 ± 6.35	21.33 ± .82	26.10 ± 4.50	0.121
Gravida	5.33 ± 2.89	3.83 ± 1.72	4.14 ± 1.56	0.558
Para	1.33 ± 1.53	3.33 ± .52	3.00 ± 1.30	0.091
Control group				
Age	35.00 ± 0.0	31.22 ± 2.95	32.85 ± 6.80	0.721
Body mass index	32.00 ± 0.0	26.67 ± 4.36	25.80 ± 5.06	0.432
Gravida	4.00 ± 0.0	5.33 ± 1.32	4.55 ± 1.85	0.475
Para	3.00 ± 0.0	4.00 ± 1.50	2.95 ± 1.36	0.656

P1: Homotype A/A VS Homotype G/G, P2: Homotype A/A VS Heterotype, P3: Homotype G/G VS Heterotype
*Significant P-value if ≤ 0.05, ** highly significant P-value if ≤ 0.001

Table 5. Comparison between patients and controls according to genotype as regards clinical data

Genotype	Homotype A/A		Homotype G/G		Heterotype		X^2	P-value
	N	%	N	%	N	%		
Patients group								
Multifetal or single								
Single Fetus	0	0.0%	4	44.4%	9	45.0%	0.792	0.673
Multi-fetus	1	100.0%	5	55.6%	11	55.0%		
HDP								
Normotensive	0	0.0%	2	22.2%	9	45.0%	1.986	0.371
Hypertensive	1	100.0%	7	77.8%	11	55.0%		

Genotype	Homotype A/A		Homotype G/G		Heterotype		X^2	P-value
	N	%	N	%	N	%		
Gestational DM								
Absent	0	0.0%	4	44.4%	10	50.0%	0.982	0.612
Present	1	100.0%	5	55.6%	10	50.0%		
Familial cardiomyopathy								
Absent	1	100.0%	9	100.0%	15	75.0%	3.00	0.223
Present	0	0.0%	0	0.0%	5	25.0%		
Peripartum stage								
Prepartum	0	0.0%	0	0.0%	8	40.0%	5.455	0.065
Postpartum	1	100.0%	9	100.0%	12	60.0%		
Control group								
Multifetal or single								
Single Fetus	7	100.0%	9	69.2%	22	55.0%	2.112	0.348
Multi-fetus	0	0.0%	4	30.8%	18	45.0%		
HDP								
Normotensive	7	100.0%	13	100.0%	19	47.5%	8.571	P1=1.00 P2=0.217 P3=0.044*
Hypertensive	0	0.0%	0	0.0%	21	52.5%		
Gestational DM								
Absent	7	100.0%	13	100.0%	22	55.0%	5.510	0.064
Present	0	0.0%	0	0.0%	18	45.0%		
Familial cardiomyopathy								
Absent	7	100.0%	11	84.6%	40	100.0%	4.138	0.126
Present	0	0.0%	2	15.4%	0	0.0%		
Peripartum stage								
Prepartum	4	57.1%	3	23.1%	12	30.0%	4.554	0.103
Postpartum	3	42.9%	10	76.9%	28	70.0%		

P1: Homotype A/A VS Homotype G/G, P2: Homotype A/A VS Heterotype, P3: Homotype G/G VS Heterotype
*Significant P-value if ≤ 0.05, ** highly significant P-value if ≤ 0.001

Table 6. Comparison between genotypes as regards LVEDD, LA diameter, LVEF (%), and irisin in patients and control groups

	Homotype A/A Mean ±SD	Homotype G/G Mean ±SD	Heterotype Mean ±SD	P-value
Patient group				
LVEDD	5.90 ± 0.0	6.26 ± .41	6.16 ± .50	0.825
LA diameter	3.00 ± 0.0	3.87 ± .36	3.98 ± .38	0.245
LVEF (%)	43.00 ± 0.0	42.56 ± 4.33	39.65 ± 4.61	0.196
IRISIN	9.40 ± 0.0	8.24 ± .53	8.49 ± 1.41	0.332
Control group				
LVEDD	4.00 ± 0.0	3.80 ± .31	3.89 ± .29	0.695
LA diameter	3.10 ± 0.0	3.07 ± .08	2.94 ± .11	P1=0.674 P2=0.019* P3=0.013*
LVEF (%)	66.00 ± 0.0	66.00 ± 1.10	65.71 ± 3.27	0.950
IRISIN	14.30 ± 0.0	12.15 ± 2.48	9.11 ± .92	P1=0.413 P2=0.003** P3=0.007**

P1: Homotype A/A VS Homotype G/G, P2: Homotype A/A VS Heterotype, P3: Homotype G/G VS Heterotype. LVEDD left ventricular end diastolic dimensions, LA = left atrium, & LVEF =left ventricular ejection fraction. *Significant P-value <0.05 & ** highly significant P- value ≤0.001.

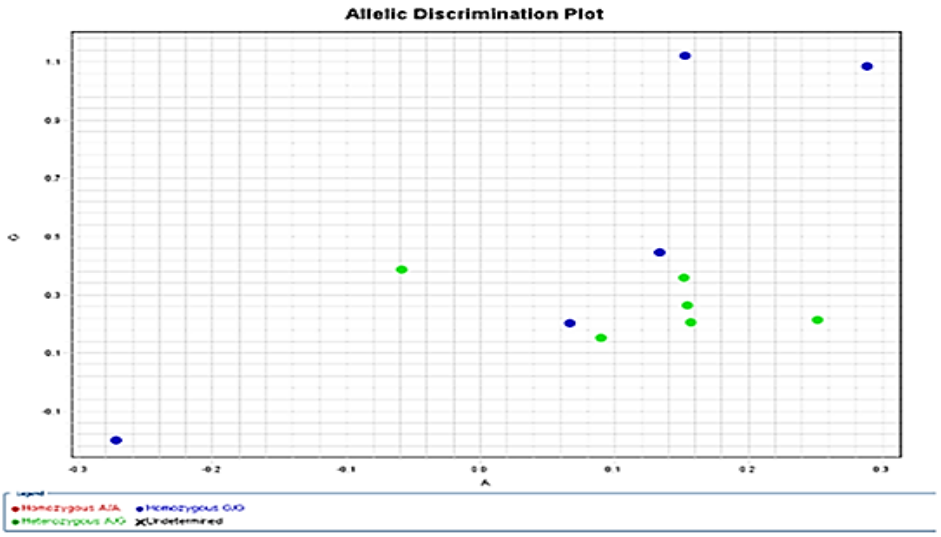

Figure 1. Step 1 real time PCR shows the allelic discrimination in patients and controls

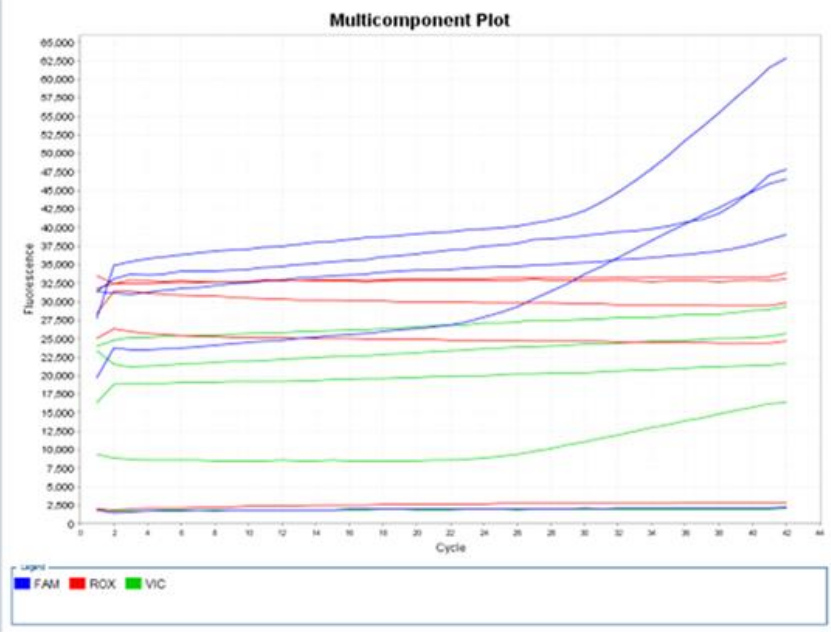

Figure 2. Step 1 real time PCR using taq polymerase showing DNA plateau in patients and controls

Discussion

To the best of our knowledge, there is insufficient data regarding level of irisin expression and (FNDC5) gene polymorphism with peripartum cardiomyopathy and this is a novel study to assess this relation.

Several investigations compared circulating level of maternal irisin in patients with gestational DM to healthy pregnancies in the second trimester. The findings were conflicting, with higher (12), lower (13-15), or comparable (16, 17) irisin levels in patients with gestational DM versus normal pregnancies, respectively. However, many studies & a meta-analysis (18) reported that the serum level of irisin was lower in gestational DM.

Garcés et al. (19) discovered that pre-eclampsia patients have lower irisin levels than healthy pregnant women, and the low serum levels in the 1st & 2nd trimesters may be a strong predictor of pre-eclampsia development.

We found in this study that majority of patients group have GDM (53.3%) and gestational hypertension (63.3%). Our current study also showed that the serum irisin level was lower in cardiomyopathy patients than healthy control with a significant difference ($p < 0.001$). Also, it was nonsignificant increase in homotype A/A group than other homotype G/G and heterotype groups.

Endothelial dysfunction has been linked to decreased irisin levels (20). These results suggest that, unlike CK-MB, There is no passive release of irisin as a consequence of cardiomyocyte damage, but is instead actively produced in response to blood supply and hence the cardiac muscle's functional capacity (8).

In the latter research (8), it was postulated that when blood and oxygen supplies are decreased, myocardium may produce less irisin to limit the heart's metabolic needs in an effort to compensate for the diminished energy supply. This theory is backed by research that suggests oxidative stress regulates FNDC5 expression (6, 21) and that irisin plays an important role in energy balance, cardiomyoblast development, and function (22).

Several animal investigations have demonstrated that recombinant irisin therapy has beneficial cardiovascular benefits. Irisin had anti-apoptotic effects during cardiomyocytes ischemia by protecting mitochondrial function, & it protected mice deficient in apolipoprotein E- from atherosclerosis by increasing proliferation of endothelial cell and/or suppressing oxidized LDL-induced cellular inflammation & apoptosis, while inhibiting the proliferation of vascular smooth muscle cells (23, 24).

However, only one single study reported that low-dose recombinant irisin therapy reduces cardiac fibrosis and LV functions, regarding diabetic cardiomyopathy, while high irisin dose fails to reduce LV function impairment & increased deposition of collagen. The effect of low dosage may be caused by irisin-mediated inhibition of high glucose-induced endothelial-to-mesenchymal transition; however, high dosage irisin increases high glucose-induced matrix metalloproteinase expression by inducing MAPK (p38 and ERK) signalling, proliferation & migration of cardiac fibroblast, resulting in a dose-dependent bidirectional effect (25).

Our study had some limitations, there is no comparable studies that agree or against us, we use single snip polymorphism (rs3480). Also, the sample size of the study was small & monocentric. Thus, a future studies with more enrolled patients is needed as results may be more significant when more patients are included in the study.

We can conclude that irisin level was lower in peripartum cardiomyopathic patients comparing with normal individuals and regarding its genotype ,in homotype A/A it was higher than homotype G/G and heterotype. Also, it is associated with other obstetric morbidity as GDM and gestational hypertension.

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Conflict of Interests: No potential conflict of interest was reported by the author(s).

Authors' contribution: AM: conception and design of the study, interpretation of data, final approval of the manuscript; ME: conception and design of the study;acquisition, interpretation of data, drafting and editing of the manuscript, and final approval of the manuscript; HM: contributed to the data acquisition and analysis and edited a major part of the manuscript; AH:contributed to study design and was co-responsible for laboratory work and genetic analysis. She agreed to the contents of the final manuscript; SM: contributed to the basic concept of the study and was co-responsible for the laboratory work and genetic analysis. She agreed to the contents of the final manuscript. AM contributed to study design and was co-responsible for laboratory work and genetic analysis. She agreed to the contents of the final manuscript.

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