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Research Article

Relation of R-SPONDIN3 Gene Expression Android Obesity and Susceptibility to Cardiovascular Disease in Sudanese Patients in Khartoum State

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Abstract

Background: Obesity is a major risk factor for the development of cardiovascular disease. A growing database of clinical evidence implicates intra-abdominal adiposity as a powerful driving force for elevated cardio metabolic risk. Addressing intra-abdominal adiposity should play a central role in future strategies aimed at improving cardiovascular outcomes in patients with abdominal obesity and its associated cardiometabolic risk in Sudan. Several studies aimed to identify some factors controlling the size and function of different areas of fat. Our research is focusing on a particular gene called R-SPONDIN3, which is play a part in controlling fat distribution, cardiac growth through modulation of Wnt (Wnt/β-catenin signaling path way) signalingR-SPONDIN3 is essential for coronary artery formation in the developing heart.

Objectives: It is to find the amount of R-Spondin3 Gene expression in Abdominal obesity and Susceptibility to Cardiovascular disease in Sudanese Patients in Khartoum State

Material and Methods: The study was including 300 participants (156 males and 144 females) classified into three groups. The first group was including one hundred participants with abdominal obesity (obese), the second group was including one hundred participants already diagnosed with CVD entangled with obesity (Heart Group as positive control group), while the third group was include one hundred healthy lean volunteers (negative control group). All the participants their age group between 27 to 63 years old. BMI and WHR were taken for all subjects too. For detection the mutation in RSPO3 gene, Conventional PCR was done for control, obesity and heart subjects respectively and followed by Real Time PCR for all of them to measure the amount of gene expression. Data was analyzed using SPSS Version 22 software. P value < 0.05 was considered as statistically significant.

Results: The findings of this study showed Conventional PCR results were significantly different (P <0.001) in Heart group subjects as compared to healthy controls and obese group. Among heart group mutation was detected in some subjects (19%) and the rest without mutation (81%) but in obese group no mutation was detected. Comparison between the different studied groups according to gene expression showed significant differences (P <0.001) mean value of gene expression in healthy group subjects was 1.0 ± 0.0, Obesity group was 2.44 ± 0.50 and heart group subjects was 4.54 ± 0.87 respectively.

Conclusion: The amount of R-SPONDIN3 gene expression among the obese and CVD patients is show up significant different and the amount of gene expressing among the CVD patients is higher than obese which is suggested that the amount of gene expressed in obese patients with heart disease more than obese patients without cardiovascular complications

Keywords: R-SPONDIN3gene; Abdominal obesity; CVD; Gene expression

Introduction

Obesity is defined as a body fat content of more than 20% in average adult males and over 30% in females [1]. However, obese individuals vary in the amount of excess fat that they store, the regional distribution of that fat within the body, and the related health consequences differ noticeable amongst these obese persons. It is therefore essential to make a distinction between those at augmented risk as a result of abdominal obesity from those with general obesity. Even though most epidemiological studies have only used BMI as a predictor of disease, as assessed by measurement of waist circumference or waist-hip ratio, are at a greater risk of cardio metabolic risk.

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Abdominal obesity also known as central or visceral obesity is one of the essential characteristics of metabolic syndrome. There is a strong relationship between visceral fat (android obesity phenotype) and cardiovascular disease risk [2].Visceral fat is technically excess intra-abdominal adipose tissue accumulation. In other words, it's known as a "deep" fat that's stored further underneath the skin than "subcutaneous" belly fat. It's a form of gel-like fat that's wrapped around major organs, including the liver, pancreas and kidneys.

If you have a protruding belly and large waist, that's a clear sign you're storing dangerous visceral fat. While it's most noticeable and pronounced in obese individuals, anyone can have visceral fit, many without even knowing it.

Visceral fat is especially dangerous because, as you'll find out, these fat cells do more than just sit there and cause your pants to feel tight-they also change the way your body operates [3].

Carrying around excess visceral fat is linked with an increased risk for Coronary heart disease.

Visceral fat is considered toxic and spells double-trouble in the body because it's capable of provoking inflammatory pathways, plus signaling molecules that can interfere with the body's normal hormonal functions. In fact, it acts almost like its very own organ since it's capable of having such a large impact on the body [4].

Fat cells do more than simply store extra calories-they have proved to be much more involved in human physiology than we had previously thought. We now know that fat tissue itself acts like its own organ by pumping out hormones and inflammatory substances. Storing excess fat around the organs increases production of pro-inflammatory chemicals, also called cytokines, which leads to inflammation; at the same time, it interferes with hormones that regulate appetite, weight, mood and brain function [5].

Genetic study is needed for overweight person. Discovery of genes associated with obesity are all arguments reinforcing the genetic dimension of abdominal obesity. Many studies recommended to confirm that R-SPONDIN3 should be studied further as a treatment target to manipulate the way fat is stored in the body, to help lower cardiovascular risk [6]. There is also evidence that a high level of cardiorespiratory fitness is predictive of a reduced Cardiovascular Disease (CVD) risk, independently from its association with a more favorable cardio metabolic risk profile. There is now considerable evidence supporting the notion that obesity is a heterogeneous condition. Such heterogeneity appears to be explained, to a very significant extent, by individual differences in regional body fat distribution, particularly in visceral adipose tissue accumulation. In addition to visceral adiposity as key drivers of the cardio metabolic risk associated with overweight/obesity also contribute to the risk of various cardiovascular outcomes, and further work should clarify their specific functions [7]. Studying these relationships between mutation of R-SPONDIN3 gene and cardiovascular disease lead to lose weight to understand the biology underlying body weight regulation and hope that these strategies contribute to intervene more efficiently in the development of prescription drugs are better able to reduce the weight. The researchers found the human gene may not affect the overall weight or body mass index, but also affects the distribution of fat and reduce or raise the risk of cardiovascular disease, suggesting that different types of measurements can provide insight into the process of losing weight.

Genetic determinants of total adiposity and distribution in women and men

Genome-wide Association Studies (GWAS) recently have identified genetic determinants of common polygenic obesity that interact with environmental variables in complex ways, but so far explain only a small percentage of the inter-individual variation in BMI.GWAS and meta-analyses of GWAS have also identified novel loci associated with central or peripheral fat distribution, some of which are sex-specific. Differential mRNA expression is also noted between abdominal and gluteal tissue [8,9].

R-Spondin 3 (RSPO3) is also called Cysteine-Rich and Single Thrombospondin Domain Containing-1 (CRISTIN1), Protein with TSP Type-1 Repeat (PWTSR), is a member of the R-Spondin Protein family. R-spondins (RSPO) are a recently discovered secretory protein family with four members in human and mouse. Although all four RSPO proteins activate the canonical Wnt pathway, RSPO2 and RSPO3 are more potent than RSPO1, whereas RSPO4 is relatively inactive. RSPO-3 is expressed ubiquitously and expressed at higher level in placenta, small intestine, fetal thymus and lymph node. RSPO3 is the activator of the beta-catenin signaling cascade, leading to TCF-dependent gene activation. RSPO3 acts both in the canonical Wnt/beta-catenin-dependent pathway and in non-canonical Wnt signaling pathway, probably by acting as an inhibitor of ZNRF3, an important regulator of the Wnt signaling pathway. RSPO3 also acts as a ligand for frizzled FZD8 and LRP6 and may negatively regulate the TGF-beta pathway. R-SPONDIN3 play a part in controlling fat distribution [10].

Materials and Methods

Study design

This was a case control study to find the mutation in R-SPONDIN3. The study was carried out during the period from August 2016 to March 2019.

Study area

The study was conducted in Khartoum State in Ahmed Gasim hospital Cardiac Surgery and Renal Transplant Center, Alshaab Teaching Hospital and Obesity Centers.

Study group

The study was including 300 participants (males and females) classified into three groups. The first group was include one hundred participants with abdominal obesity (obese), the second group was include one hundred participants already diagnosed with CVD entangled with obesity (positive control group), while the third group was include one hundred healthy lean volunteers (negative control group).

Inclusion criteria

Participants with abdominal obesity (obese), participants already diagnosed with CVD entangled with obesity (positive control group) and hundred lean volunteers.

Exclusion criteria

Any history of chronic hypertension, kidney disease, liver disease,

Table 1: Comparison between the different studied groups according to gene expression.

Gene expression	Control group (n=100)	Heart Group (n =100)	Obesity group (n=100)	F	P
Mean ± SD.	1.0 ± 0.0	4.54 ± 0.87	2.44 ± 0.50		
Sig. bet. Grps	p_1<0.001*, p_2<0.001*, p_3<0.001*				

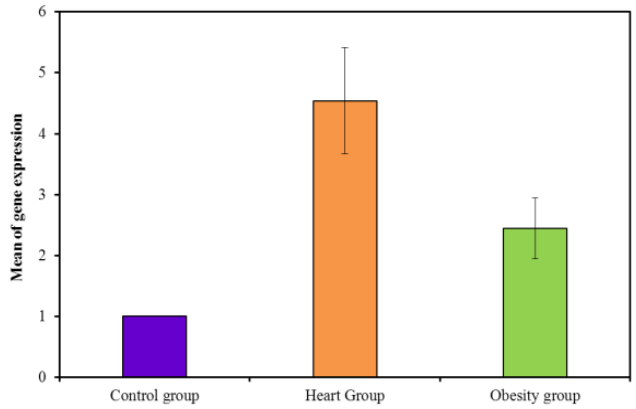

Figure 1: Comparison between the different studied groups according to gene expression.

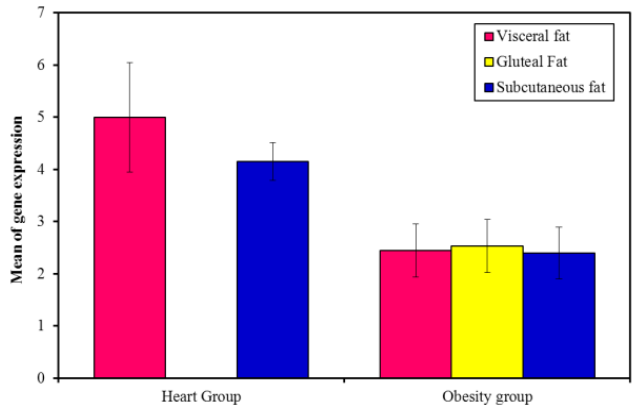

Figure 2: Relation between Fat phenotypes and gene expression in each group.

coagulation disorders. Prior informed consent was taken from all. A detailed history was taken from all subjects that include age, history of hypertension, renal disease, hepatic dysfunction or any other acute or chronic illness. Details of drug intake was also noted. Blood pressure recording along with a detailed physical examination was done.

Ethical considerations

This case control study was approved by the research committee-College of Medical Laboratory Sciences-Shendi University. Informed consent was obtained from each participant before taking the samples.

A simple random sample were taken, seven milliliters venous blood samples were withdrawn from fasting participants and was divided into 2 tubes under aseptic conditions using sterile evacuated tubes from each subject as follows:

- Three milliliters venous blood was put into Serum Separator Gel (SSG) tube for performing lipid profile.
- Four milliliters venous blood was put into a sterile Ethylene Di-Amine Tetra-Acetic Acid (EDTA) tube.

Table 2: Correlation between Gene expression and different parameters in each group.

	Gene expression			
	Heart Group		Obesity group	
	r	p	r	p
Age (years)	0.034	0.739	0.007	0.95
BMI (kg/m^2)	-0.26	0.009*	0.078	0.44
WHR	-0.06	0.525	-0.15	0.15

Quality controls and managements

Blood was collected with care and adequate safety precautions to ensure test results were reliable. Quality Assurance (QA) and standard Operating System was followed for all biological and clinical tests to achieve validity and reliability of test results.

Methods of BMI estimation

It calculates a value indicative of the fat content of the body by dividing the weight by the square of height

$$BMI=\frac{mass(kg)}{height(m^2)}$$

BMI Categories:

Categories	BMI
Underweight	Less than 18.5
Normal weight	18.5 – 24.9
Overweight	25 – 29.9
Obese	30 or higher

Statistical analysis

Data were fed to the computer and analyzed using IBM SPSS software package version 20.0. (Armonk, NY: IB was M Corp) Qualitative data were described using number and percent. The Kolmogorov-Smirnov test was used to verify the normality of distribution Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Significance of the obtained results was judged at the 5% level. Chi-square test was used for categorical variables, to compare between different groups. Student t-test. Was used for normally distributed quantitative variables, to compare between two studied groups. F-test (ANOVA) was used for normally distributed quantitative variables, to compare between more than two groups, and Post Hoc test (Tukey) (LSD) for pairwise comparisons. Pearson coefficient to correlate between two normally distributed quantitative variables. Mann Whitney test was used for abnormally distributed quantitative variables, to compare between two studied groups. Kruskal Wallis test was used for abnormally distributed quantitative variables, to compare between more than two studied groups, and Post Hoc (Dunn's multiple comparisons test) for pairwise comparisons.

Table 3: Relation between Fat phenotypes and gene expression in each group.

Gene expression	Fat phenotypes			Test of sig.	p
	Visceral fat	Gluteal Fat	Subcutaneous fat		
Heart Group	(n=46)	(n=0)	(n=54)		
Mean ± SD.	5.0 ± 1.05	-	4.15 ± 0.36	t=5.229*	<0.001*
Obesity group	(n=31)	(n=17)	(n=52)		
Mean ± SD.	2.45 ± 0.51	2.53 ± 0.51	2.40 ± 0.50	F=0.413	0.663

Results

Comparison between the different studied groups according to gene expression showed significant differences (P <0.001) mean value of gene expression in healthy group subjects was 1.0 ± 0.0, Obesity group was 2.44 ± 0.50 and heart group subjects was 4.54 ± 0.87 respectively (Table 1) (Figure 1).

Correlation between gene expression and age in heart and obesity group showed weak positive correlation with the r-value of age in heart group was 0.034 and obesity group was 0.007 respectively (Table 2).

Correlation between gene expression and BMI in heart and obesity group showed weak Negative correlation with the r-value of age in heart group was -0.259 and obesity group was 0.078 respectively (Table 2).

Correlation between gene expression and WHR in heart and obesity group showed weak Negative correlation with the r-value of age in heart group was -0.064 and obesity was - 0.145 respectively (Table 2).

Comparison between gene expression and fat phenotype among the heart group showed significant association (P <0.001) mean value of gene expression among heart group subjects was 5.0 ± 1.05. Visceral fat and 4.15 ± 0.36 Subcutaneous fat respectively and Comparison between gene expression and fat phenotype among the obesity group showed insignificant association (P=0.663) mean value of gene expression among obesity group subjects was 2.45 ± 0.51 Visceral fat, 2.53 ± 0.51 Gluteal Fat and 4.15 ± 0.36 Subcutaneous fat respectively (Table 3) (Figure 2).

Comparison between gene expression and sex among the heart group showed insignificant association (P=0.926) mean value of gene expression among heart group subjects was 4.53 ± 0.91 male and 4.55 ± 0.81 female respectively and respectively and Comparison between gene expression and sex among the obesity group showed insignificant association (P=0.154) mean value of gene expression among obesity group subjects was 2.52 ± 0.51 male and 2.38 ± 0.49 female respectively (Table 4).

Comparison between the heart and obesity groups according to fat phenotypes showed significant differences (P <0.001) number 46 and percent 46% Visceral fat, number 0 and percent 0% Gluteal Fat and number 54 and percent 54% Subcutaneous fat respectively among the heart group and number 31 and percent 31% Visceral fat, number 17 and percent 17% Gluteal Fat and number 52 and percent 52% Subcutaneous fat respectively among the obesity group respectively (Table 5).

Table 4: Relation between sex and gene expression in each group.

Gene expression	Sex		t	p
	Male	Female		
Heart Group	(n=60)	(n=40)		
Mean ± SD.	4.53 ± 0.91	4.55 ± 0.81		
Obesity group	(n=42)	(n=58)		
Mean ± SD.	2.52 ± 0.51	2.38 ± 0.49		

Comparison between the different studied groups according to sex showed significant differences (P=0.035) number 54 and percent 54% male and number 46 and percent 46% female among control group, number 60 and percent 60% male and number 40 and percent 40% female among heart group and number 42 and percent 42% male and number 58 and percent 58% female among obesity group respectively (Table 6).

Comparison between the different studied groups according to age showed significant differences (P <0.001) mean value of age in healthy group subjects 40.70 ± 4.81, Obesity group was 43.73 ± 8.85 and heart group subjects was 50.61 ± 8.65 respectively. Comparison between the control and heart groups according to age showed significant differences (P1 <0.001). Comparison between the control and obesity groups according to age showed significant differences (P2=0.015). Comparison between the heart and obesity groups according to age showed significant differences (P3 = <0.001*) (Table 6).

Comparison between the different studied groups according to BMI showed significant differences (P <0.001) mean value of BMI in healthy group subjects 40.70 ± 4.81,Obesity group was 43.73 ± 8.85 and heart group subjects was 50.61 ± 8.65 respectively. Comparison between the control and heart groups according to BMI showed significant differences (P1<0.001). Comparison between the control and obesity groups according to BMI showed significant differences (P2 = 0.015). Comparison between the heart and obesity groups according to BMI showed insignificant differences (P3=0.131) (Table 6).

Comparison between the different studied groups according to WHR showed significant differences (P <0.001) mean value of WHR in healthy group subjects 40.70 ± 4.81, Obesity group was 43.73 ± 8.85 and heart group subjects was 50.61 ± 8.65 respectively. Comparison between the control and heart groups according to WHR showed significant differences (P1 <0.001). Comparison between the control and obesity groups according to WHR showed significant differences (P2 = 0.015). Comparison between the heart and obesity groups according to WHR showed insignificant differences (P3=0.316) (Table 6).

Discussion

Body fat distribution is a heritable trait that independently

Table 5: Comparison between the different studied groups according to fat phenotypes.

Fat phenotypes	Heart Group (n=100)		Obesity group (n=100)		χ^2	P
	No.	%	No.	%		
Visceral fat	46	46	31	31	19.960*	<0.001*
Gluteal Fat	0	0	17	17		
Subcutaneous fat	54	54	52	52		

Table 6: Comparison between the different studied groups according to demographics data.

	Control group (n=100)		Heart Group (n=100)		Obesity group (n=100)		Test of Sig.	p
	No.	%	No.	%	No.	%		
Sex								
Male	54	54	60	60	42	42	χ^2= 6.731*	0.035*
Female	46	46	40	40	58	58		
Age (years)								
Mean ± SD.	40.70 ± 4.81		50.61 ± 8.65		43.73 ± 8.85		F=43.884*	
Sig. bet. Grps	p_1<0.001*, p_2=0.015*, p_3<0.001*							
BMI (kg/m^2)								
Mean ± SD.	21.06 ± 1.41		41.01 ± 7.17		39.44 ± 6.75		F=373.477*	
Sig. bet. Grps	p_1<0.001*, p_2<0.001*, p_3=0.131							
WHR								
Mean ± SD.	0.84 ± 0.06		1.05 ± 0.16		1.07 ± 0.14		F=106.401*	
Sig. bet. Grps	p_1<0.001*, p_2<0.001*, p_3=0.316							

predicts type 2 diabetes and cardiovascular risk. Genome-Wide Association Studies (GWAS) meta-analyses have identified sexually dimorphic associations, with greater effect in women, between loci within RSPO3 (e.g. rs9491696) and BMI-adjusted Waist-to-Hip Ratio (WHR). RSPO3 is a LGR4 receptor ligand and a Wnt/β-catenin signaling agonist.

The aim of study was to investigate the possible correlation between mutation in R-SPONDIN3 gene, abdominal obesity and susceptibility to cardiovascular disease.

The study was including 300 participants (156 males and 144 females) classified into three groups. The first group was including one hundred participants with abdominal obesity (obese), the second group was include one hundred participants already diagnosed with CVD entangled with obesity (Heart Group as positive control group), while the third group was include one hundred healthy lean volunteers (negative control group). All the participants their age group between 27 to 63 years old. BMI and WHR were taken for all subjects too. For detection the mutation in RSPO3 gene, Conventional PCR was done for control, obesity and heart subjects respectively and followed by Real Time PCR for all of them. The same of the three group underwent for lipid profile. For measurement of fat distribution in clinical practice, Waist Circumference (WC) and WHR were used used to determine regional FD. Computerized Tomography (CT) and whole body MRI scan were used for evaluating the adipose tissue, which were considered as gold standard for that. To measure the visceral and subcutaneous abdominal areas in total abdominal area), a CT or MRI scan was taken at the level of L4-L5 or the umbilicus. The ratio of visceral to subcutaneous adipose tissue has been shown to be strongly correlated with RSPO3 gene in obese subjects and heart subjects respectively Abdominal sagittal diameter derived from CT or MRI images has also been used to determine abdominal FD. The CT and MRI were applied in 200 volunteers,

The conventional PCR was done to all of the three groups which showed clear variation in the mean value of conventional PCR (P <0.001) in Heart group subjects as compared to healthy controls and obese group.

Of the 200 cases (obesity &heart) 19 (19%) were positive for mutation in RSPO3 gene all of them from heart group and the rest of heart group 81 (81%) were negative for mutation as well as obesity group all 0 (0%) positive for mutation (Table 4-3). This result was leads us to do real time PCR to quantify the level of gene expressed. Comparison between the different studied groups according to gene expression showed clear variation in the mean value of gene expression with (P <0.001) in healthy group subjects was 1.0 ± 0.0, Obesity group was 2.44 ± 0.50 and heart group subjects was 4.54 ± 0.87 respectively (Table 1) (Figure 1). This result was agreed with the finding of finding of N.Y. Loh [11].

In Correlation between gene expression and age in heart and obesity group showed weak positive correlation with the r value of age in heart group was 0.034 and obesity group was 0.007 respectively (Table 2). This result was agreed with finding of DoritSchleinitz [12]. Who was carried study on heart and obesity group respectively.

Correlation between gene expression and BMI in heart and obesity group showed weak Negative correlation with the r-value of age in heart group was -0.259 and obesity group was 0.078 respectively (Table 2). This result was agreed with finding of Michael M [13].

Correlation between gene expression and WHR in heart and obesity group showed weak Negative correlation with the r-value of age in heart group was -0.064 and obesity was - 0.145 respectively (Table 2). This result was agreed with Rajiv G, [14].

Comparison between gene expression and fat phenotype among the heart group showed significant association (P <0.001) mean value of gene expression among heart group subjects was 5.0 ± 1.05 Visceral fat and 4.15 ± 0.36 Subcutaneous fat respectively and Comparison between gene expression and fat phenotype among the obesity group showed insignificant association (P=0.663) mean value of gene expression among obesity group subjects was 2.45 ± 0.51 Visceral fat, 2.53 ± 0.51 Gluteal Fat and 4.15 ± 0.36 Subcutaneous fat respectively (Table 3) (Figure 2). This result was agreed with finding of Kalypso Karastergiou [15]. but study the obesity was diagnosed according to the Japanese obesity criteria by using CT & MRI Technologies.

In the Comparison between among heart group according to sex and gene expression showed insignificant differences (P=0.926) mean value of gene expression among heart group subject was 4.53 ± 0.91 male and 4.55 ± 0.81 female. Comparison between among obesity group according to sex and gene expression showed insignificant differences (P=0.154) mean value of gene expression among heart group subject was 2.52 ± 0.51 male and 2.38 ± 0.49 female (Table 4). This result was agreed with finding of Atzmon, G [16].

In the Comparison between the heart and obesity groups according to fat phenotypes showed significant differences (P <0.001) number 46 and percent 46% Visceral fat, number 0 and percent 0% Gluteal Fat and number 54 and percent 54% Subcutaneous fat respectively among the heart group and number 31 and percent 31% Visceral fat, number 17 and percent 17% Gluteal Fat and number 52 and percent 52% Subcutaneous fat respectively among the obesity group respectively (Table 5). This result was agreed with finding of Ian J. Neeland [17] and Tobin M. Abraham [18].

In the Comparison between the different studied groups according to age showed significant differences (P <0.001) mean value of age in healthy group subjects 40.70 ±4.81,Obesity group was 43.73 ± 8.85 and heart group subjects was 50.61 ± 8.65 respectively. Comparison between the control and heart groups according to age showed significant differences (P1<0.001). Comparison between the control and obesity groups according to age showed significant differences (P2=0.015). Comparison between the heart and obesity groups according to age showed significant differences (P3 = <0.001*) (Table 6). This result was agreed with finding of Kalypso [15].

In the Comparison between the different studied groups according to BMI showed significant differences (P <0.001) mean value of BMI in healthy group subjects 40.70 ± 4.81, Obesity group was 43.73 ± 8.85 and heart group subjects was 50.61 ± 8.65 respectively. Comparison between the control and heart groups according to BMI showed significant differences (P1<0.001). Comparison between the control and obesity groups according to BMI showed significant differences (P2=0.015). Comparison between the heart and obesity groups according to BMI showed insignificant differences (P3=0.131) (Table 6).

In the Comparison between the different studied groups according to WHR showed significant differences (P <0.001) mean value of WHR in healthy group subjects 40.70 ± 4.81,Obesity group was 43.73 ± 8.85 and heart group subjects was 50.61 ± 8.65 respectively. Comparison between the control and heart groups according to WHR showed significant differences (P1<0.001). Comparison between the control and obesity groups according to WHR showed significant differences (P2=0.015). Comparison between the heart and obesity groups according to WHR showed insignificant differences (P3=0.316) (Table 6). This result was agreed with finding of Adamska M [18,19] who concluded the obese and hearts subjects having higher WHR when compared with healthy subjects.

Conclusion

The amount of the R- SPONDIN3 gene expressed cleared different between obese and CVD subjects entangled with obesity.

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