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Original Article

SIRT1 modulation and lipid profile alterations in the cellular regulation of blood lipids in renal disorders among extremely obese individuals

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Abstract

The global epidemic of overweight and obesity is closely linked to the development of chronic kidney disease (CKD), with extremely obese individuals facing a particularly high risk. This study aimed to assess the relationship between lipid profile levels, SIRT1 expression, and RNA-34a-5P in the regulation of blood lipid levels among severely obese individuals with renal diseases. Conducted over six months in three specialized hospitals, the study included 100 participants divided into two groups: 50 obese individuals with renal diseases and 50 obese controls without renal problems. Ethical standards, including confidentiality and informed consent, were strictly observed. Biochemical assessments included measurements of total cholesterol, LDL, HDL, triglycerides, creatinine, GFR, SIRT1 protein (via Western blotting), and RNA-34a-5P expression (via qPCR). Statistical analysis was performed using SPSS v26 and Pearson's correlation. The results revealed a negative association between RNA-34a-5P expression and total cholesterol, LDL, triglycerides, and SIRT1 expression, while a positive but non-significant association was found with HDL and GFR. Notably, SIRT1 expression was significantly downregulated in the patient group compared to controls. These findings provide compelling evidence that SIRT1 expression is markedly reduced in extremely obese individuals with renal diseases, suggesting a potential molecular link between SIRT1, lipid metabolism, and renal dysfunction in severe obesity.

Keywords: SIRT1, Lipid profile, Obesity, Renal disease, Gene expression.

1. Introduction

Lipids in living organisms are organic compounds composed of non-polar hydrocarbons and, unlike water, are classified into two main groups: neutral lipids and polar lipids. Polar lipids include phospholipids, glycolipids, and polyprenols [1]. Steroid lipids and lipid-soluble vitamins are referred to as a third group derived from lipids. Blood lipid profiles, which include total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol and low-density lipoprotein (LDL) cholesterol levels, are important laboratory tests that can measure all lipids in the blood [2]. Although all lipids are necessary for cells, they need to be effectively balanced in terms of quantity to prevent the occurrence of health problems related to the individual. For the ongoing assessment and management of metabolic health in a population, lipid profile balance is an essential data set [3,4].

Elevated low-density lipoprotein cholesterol (LDL-c) levels and low-HDL-c levels are the primary lipid fraction disturbances that should be taken into account in the context of cardiovascular risk [5]. Subgroup IIa/IIb of lipoproteins is made up of LDL cholesterol. A disturbance in LDL-c levels in individuals is extremely vulnerable to coronary artery diseases (CAD) [6]. HDL-c is another lipid fraction, called the “good” cholesterol, due to its protective cardiovascular roles. There are several indications that some dysmetabolic circumstances are linked with HDL-c lowering [7]. The functions of HDLs should be viewed from multiple perspectives to better describe their antiatherogenic role. Certain practical recommendations should be put into effect to assess lipid levels, namely fasting state. A lot of studies suggest that the cytokines, produced from FAT loss, are useful for enhancing insulin sensitivity and they lead to a rise in the HDL-c [8].

SIRT1, a member of the Sirtuin family of proteins, is an NAD+-dependent deacetylase that plays a pivotal role in the regulation of lipid metabolism and energy homeostasis [9]. SIRT1 influences a range of tissues, including liver, pancreas, muscle and adipose tissue, that contribute to whole body lipid profiles [10]. Observations of SIRT1 transcription have led to a detailed description of the molecular mechanisms by which SIRT1 influences the modulation of lipid profiles [11].

SIRT1 promotes fatty acid oxidation, or the breakdown of fatty acids into energy. SIRT1 enhances enzyme activity and modulates the expression of genes involved in

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fatty acid oxidation [12]. For example, SIRT1 enhances the activity of PPARα, causing increased expression of genes involved in fatty acid import, β-oxidation, and ketogenesis [12]. These effects on lipid metabolism contribute to SIRT1's protective effects against metabolic stress in obesity and the pathogenesis of diabetes [13]. Conversely, SIRT1 inhibits lipogenesis, or the synthesis of fatty acids, cholesterol and triglycerides. SRSF1, SREBP-1, and ChREBP are RNA-binding proteins that mediate this effect [14]. Insulin-stimulated SIRT1 deacetylates these proteins, causing their degradation through the proteasomal pathway. The cumulative impact of these activities is to diminish their ability to promote increased rates of fatty acid synthesis [15].

The global epidemic of overweight and obesity has been constantly increasing. It is associated with the development of many diseases, such as chronic kidney disease (CKD) [16]. The prevalence of overweight and obesity among extremely obese individuals is still too high. The mean global incidence of CKD is 13.4%, but many patients go undiagnosed. Due to the progressive course and a specialist therapeutic approach, patients with CKD are characterized by a higher mortality rate compared to the general population [17]. Obesity contributes to the development of CKD in many ways. Chronic kidney disease follows because obesity causes chronic systemic inflammation. This leads to oxidative stress, impaired secretion of adipokines, and lipotoxicity that results in damage to the nephrons [18]. Obese individuals contain a high amount of adipose tissue, which is an endocrine organ. It secretes many pro-inflammatory and pro-fibrotic adipokines that cause chronic inflammation and fibrosis. Obesity is a pro-inflammatory state [19,20]. Pro-inflammatory TNF-α, leptin, and visfatin significantly promote both systemic and local inflammation. On the other hand, anti-inflammatory, OMEGA-3, and adiponectin levels decrease [21]. Obese individuals are a common group at a high risk for many diseases, including renal, and are associated with the occurrence of metabolic syndrome, which can promote the development of kidney diseases [22].

RNA-34a-5P is a microRNA that is actively involved in the cellular regulatory mechanism of different metabolic pathways, affecting a range of metabolic dysregulations [23]. The upregulation of microRNA-34a-5P has been shown to boost the intracellular low-density lipoprotein cholesterol accumulation by targeting the related genes of cholesterol metabolism [24,25]. Changes have also been observed in the liver tissue in microRNA-34a-5P-overexpressing mice, as well as changes in the concentrations of hepatic cholesterol and triglycerides [26]. These observations provide clear insights into the link between microRNA-34a-5P and cellular lipid metabolism, which may be considered when predicting the potential involvement of microRNA-34a-5P in lipid disorders [25]. The potential availability of microRNA-34a-5P in the plasma for the prediction of intracellular lipid profile changes in the obese patients will be a priority [27]. In parallel, the clinical relevance of the relationship between microRNA-34a-5P and both lipid profiles and SIRT1 in the context of maintaining cellular homeostasis in the kidneys and avoiding obesity-related renal disorders is noteworthy [28]. Though SIRT1, a versatile and NAD+-dependent deacetylase, is notably susceptible to various cellular alterations in case of any microenvironmental changes and even amongst metabolic organs like the kidneys and liver—in response to the progress of metabolic disorders, there have been few studies to date on the relationship between microRNA-34a-5P and SIRT1 [29].

This study aims to elucidate the correlation between lipid profile levels, RNA-34a-5P expression level and SIRT1 modifications in the regulation of blood lipids in severely obese individuals with renal impairment.

2. Materials and Methods

2.1. Study design

This research was structured as a comparative case-control study to assess the expression levels of lipid profiles and SIRT1 in the regulation of blood lipid levels among severely obese persons with renal diseases. The research aimed to identify associations between lipid profiles (cholesterol, LDL, HDL, and triglycerides) and SIRT1 activity in individuals with renal impairment.

2.2. Study setting

The research was carried out in various hospital environments: Al-Rifai General Hospital—Renal dialysis facility. Al-Hussein Teaching Hospital — Renal dialysis center. Al Karama Hospital — Renal dialysis facility. The study spanned six months, providing considerable time for participant recruiting, sample collection, and analysis.

2.3. Study population

The research comprised 100 subjects categorized into two groups: - Group 1 (Patient Group): 50 obese individuals diagnosed with renal diseases. Group 2 (Control Group): 50 obese persons devoid of renal problems. Both groups were equivalent in age, gender, and BMI. This study enlisted participants from three principal healthcare facilities: Al-Rifai General Hospital, Al-Hussein Teaching Hospital, and Al Karama Hospital, each equipped with specialized kidney dialysis centers. Participants were evaluated according to inclusion and exclusion criteria, and informed consent was secured from all individuals. Eligibility verification included patients diagnosed with obesity and renal problems, whereas control groups were matched by age, gender, and BMI, lacking renal disorders. Participants retained the right to withdraw at any moment without repercussions to their medical treatment.

2.4. Inclusion and exclusion criteria

This study examines obese persons aged 18 and older, including individuals with and without kidney diseases. Participants granted informed consent, and blood samples were utilized for the study of lipid profiles, SIRT1. Exclusion criteria encompass autoimmune diseases, pregnant individuals, genetic disorders impacting metabolism or lipid control, active infections or severe renal disease complications, smokers, and substance addiction that may disrupt metabolic or renal function.

2.5. Biochemical assessments

2.5.1. Lipid profile

Blood samples were analyzed to quantify the following lipid components: total cholesterol (mg/dL), low-density lipoprotein cholesterol (LDL-C, mg/dL), high-density lipoprotein cholesterol (HDL-C, mg/dL), and triglycerides (mg/dL).

2.5.2. Renal function assessments

Renal function was assessed using two primary indicators: serum creatinine and glomerular filtration rate (GFR). Serum creatinine (measured in mg/dL) serves as a fundamental biomarker of kidney function and was directly measured from blood samples. GFR (expressed in mL/min/1.73 m²) is a critical measure of renal filtration capacity, estimated from serum creatinine levels using validated equations. Together, these parameters provide a comprehensive evaluation of kidney function, with GFR offering an essential index of the kidneys' ability to clear waste products from the bloodstream.

2.5.3. Analysis of SIRT1 protein

Western Blotting was employed to quantify SIRT1 protein levels. Protein Extraction: Proteins were extracted from blood samples utilizing a lysis buffer supplemented with protease inhibitors to avert breakdown. Proteins were isolated by molecular weight by polyacrylamide gel electrophoresis (SDS-PAGE). Proteins were transported to a membrane and identified by chemiluminescent techniques. Normalization: SIRT1 expression was standardized against a housekeeping protein, such as GAPDH, to ensure precise comparison among samples.

2.5.4. RNA extraction & qPCR

The research employed RNA extraction and quantitative PCR (qPCR) to assess the expression level of RNA-34a-5P in blood specimens. The extraction procedure included the addition of lysis buffer, incubation, washing stages, and evaluation of RNA purity and concentration via spectrophotometry. The RNA was subsequently combined with reverse transcriptase enzymes and appropriate primers to produce complementary DNA (cDNA). The cDNA was preserved at -20°C until it was prepared for qPCR analysis.

Quantitative PCR (qPCR) was conducted with real-time PCR equipment, combining cDNA samples with a master mix that included SYBR Green or TaqMan probes alongside particular forward and reverse primers for RNA-34a-5P. A housekeeping gene was employed to standardize RNA-34a-5P expression levels among samples. The fluorescence intensity was measured during each amplification cycle, and the cycle threshold (Ct) value was recorded to quantify RNA-34a-5P expression in each sample. The relative expression level of RNA-34a-5P was determined utilizing the ΔΔCt technique. This entails calculating the ΔCt for each sample, subtracting the mean ΔCt of the control group from the sample's ΔCt, and determining the relative expression level as 2^(-ΔΔCt), thereby quantifying the expression of RNA-34a-5P in patients relative to the control group.

2.7. Statistical analysis

The research employed SPSS v26 for statistical analysis, utilizing the Shapiro-Wilk test and histograms to assess data normality. Quantitative data were expressed as mean and standard deviation, non-parametric data as median and interquartile range, and qualitative data as frequency and percentage. Pearson's correlation was employed to assess the relationship between variables, with a two-tailed P value of 0.05 deemed statistically significant.

3. Results

3.1. Study population and demographic characteristics

A total of 100 participants were included in this study, comprising 50 obese individuals with renal diseases (patient group) and 50 obese individuals without renal problems (control group). The demographic characteristics, including age, gender, and BMI, were comparable between the two groups, with no statistically significant differences observed (Table 1). The study design and participant flow are illustrated in Figure 1.

3.2. Lipid profile analysis

Analysis of the lipid profile revealed that the patient group exhibited significantly higher levels of total cholesterol, LDL cholesterol, and triglycerides compared to the control group. In contrast, HDL cholesterol levels were significantly lower in the patient group. These findings indicate a more atherogenic lipid profile among obese individuals with renal impairment (Table 2, Figure 2).

3.3. Kidney function tests

Kidney function was assessed by measuring serum creatinine levels and glomerular filtration rate (GFR) in

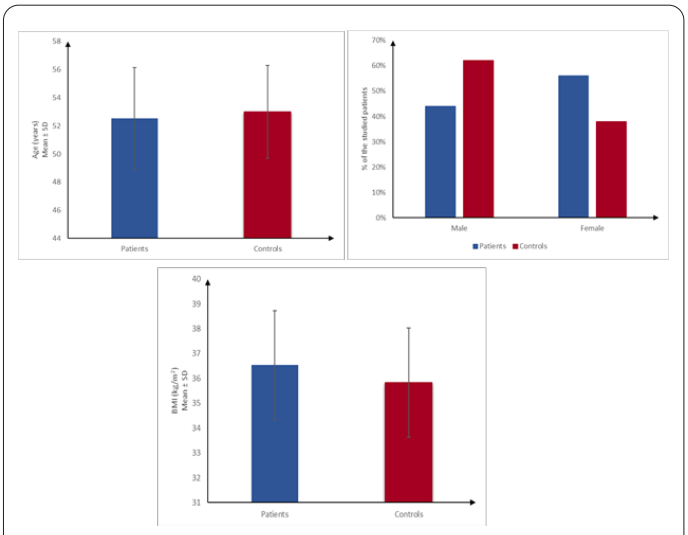

Fig. 1. Age, Gender, and BMI of the studied groups.

Table 1. Demographic data of the studied groups.

		Patients (n=50)	Controls (n=50)	P value
Age (years)	**Mean ± SD**	52.52 ± 3.63	52.98 ± 3.3	0.509
	Range	47 - 59	47 - 59	
Gender	**Male**	22 (44%)	31 (62%)	0.071
	Female	28 (56%)	19 (38%)	
BMI (kg/m²)	**Mean ± SD**	36.54 ± 2.19	35.83 ± 2.21	0.110
	Range	33.1 - 39.9	32.7 - 39.6	

BMI: body mass index.

Table 2. Lipid profile analysis of the studied groups.

		Patients (n=50)	Controls (n=50)	P value
Total Cholesterol (mg/dL)	**Mean ± SD**	229.3 ± 11.17	226.06 ± 11.9	0.164
	Range	210 - 248	200 - 245	
LDL (mg/dL)	**Mean ± SD**	143.48 ± 8.99	141.68 ± 7.95	0.291
	Range	130 - 160	127 - 154	
HDL (mg/dL)	**Mean ± SD**	35.76 ± 3.51	37.06 ± 3.67	0.074
	Range	30 - 41	32 - 46	
Triglycerides (mg/dL)	**Mean ± SD**	253.6 ± 15.98	248.68 ± 13.16	0.096
	Range	230 - 278	226 - 270	

LDL: low-density lipoprotein, HDL: high-density lipoprotein. Lipid profile data (Total Cholesterol, LDL, HDL, and Triglycerides) were insignificantly different between the studied groups.

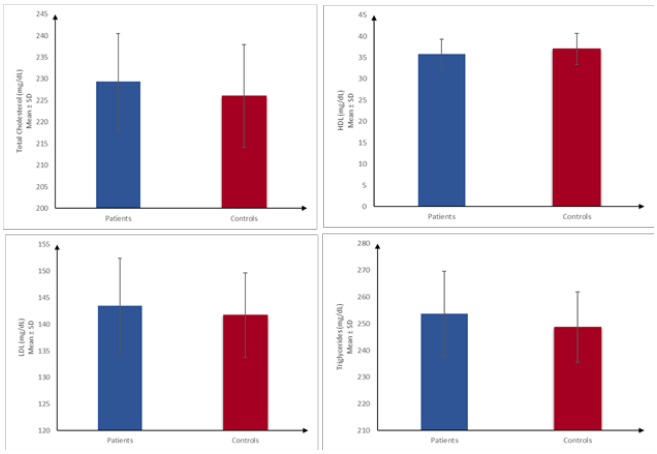

Fig. 2. Total Cholesterol, HDL, LDL, and Triglycerides of the studied groups.

both patient and control groups. As shown in Table 3 and illustrated in Figure 3, the mean serum creatinine concentration was significantly elevated in the patient group (1.97 ± 0.2 mg/dL, range 1.6–2.3) compared to controls (0.91 ± 0.2 mg/dL, range 0.6–1.2) ($P < 0.001$). Conversely, the mean GFR was significantly reduced in patients (48.84 ± 3 mL/min/1.73 m², range 45–55) relative to controls (87.1 ± 3.94 mL/min/1.73 m², range 80–94) ($P < 0.001$).

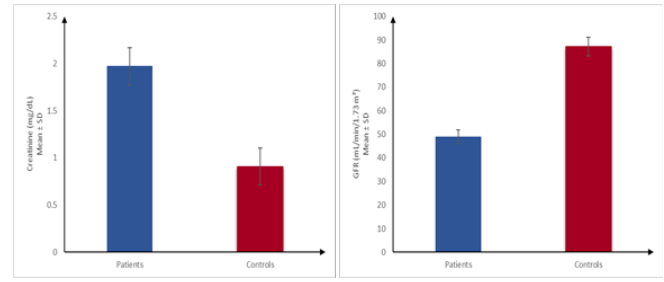

Fig. 3. Creatinine, and GFR of the studied group.

These findings indicate a marked impairment of renal function in the obese patient group with renal disease compared to obese controls without renal pathology. The significant increase in serum creatinine alongside the decrease in GFR confirms the compromised kidney function associated with renal disease in this population.

3.4. SIRT1 expression

Western blot analysis demonstrated a marked downregulation of SIRT1 protein expression in the patient group compared to controls (Table 4, Figure 4). The difference in SIRT1 levels between groups was statistically significant ($P < 0.05$), suggesting a potential association between decreased SIRT1 activity and the presence of renal disease

Table 3. Kidney function tests of the studied groups.

		Patients (n=50)	Controls (n=50)	P value
Creatinine (mg/dL)	**Mean ± SD**	1.97 ± 0.2	0.91 ± 0.2	**<0.001***
	Range	1.6 - 2.3	0.6 - 1.2	
GFR (mL/min/1.73 m²)	**Mean ± SD**	48.84 ± 3	87.1 ± 3.94	**<0.001***
	Range	45 - 55	80 - 94	

GFR: glomerular filtration rate, *: significant as P value ≤ 0.05. The Creatinine was significantly increased in patients than controls (P value <0.001), The GFR was significantly decreased in patients than controls (P value <0.001).

Table 4. SIRT1 analysis of the studied groups.

		Patients (n=50)	Controls (n=50)	P value
GAPDH	**Mean ± SD**	1.13 ± 0.05	1.15 ± 0.05	0.063
	Range	1.05 - 1.23	1 - 1.24	
SIRT1	**Mean ± SD**	0.59 ± 0.11	1.73 ± 0.15	**<0.001***
	Range	0.35 - 0.94	1.38 - 2.02	
Normalized SIRT1 Expression (AU)	**Mean ± SD**	0.53 ± 0.09	1.51 ± 0.12	**<0.001***
	Range	0.31 - 0.8	1.2 - 2	

SIRT1: silent information regulator 1, *: significant as P value ≤ 0.05. GAPDH was insignificantly different between the studied groups. SIRT1 and Normalized SIRT1 Expression (AU) were significantly decreased in patients than controls (P value <0.001).

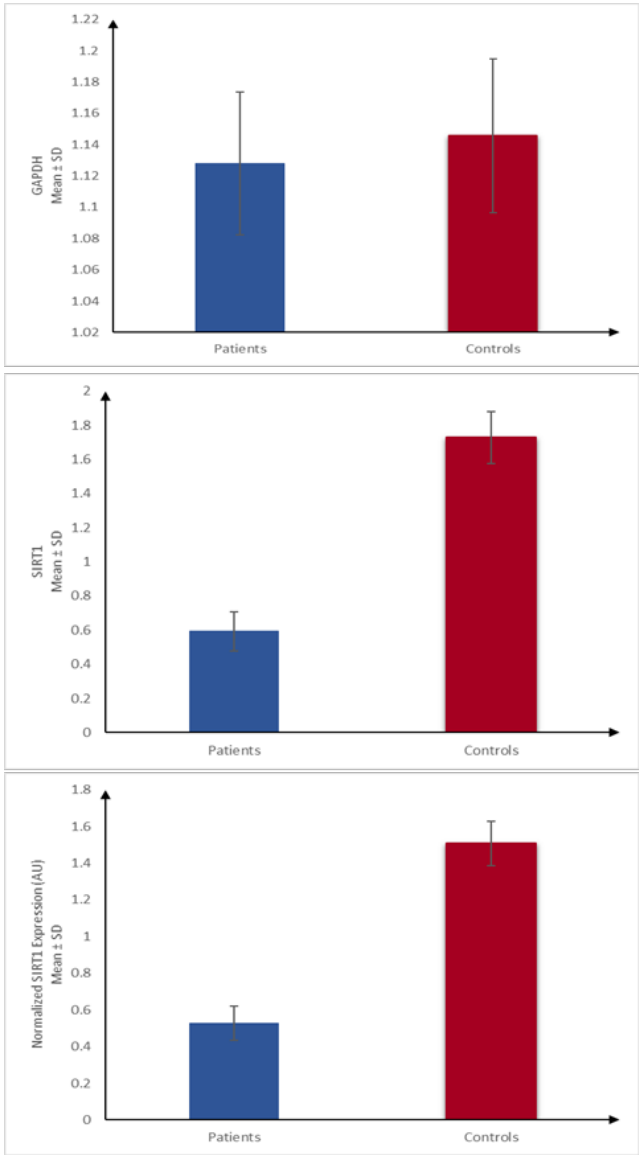

Fig. 4. GAPDH, SIRT1, Normalized SIRT1 Expression (AU) of the studied groups.

in obese individuals.

3.5. RNA-34a-5P expression analysis

The expression of RNA-34a-5P was evaluated using quantitative PCR, and the results are presented as Ct (cycle threshold), ΔCt, and ΔΔCt values. As shown in Table 5 and visualized in Figure 5, the patient group exhibited significantly lower Ct, ΔCt, and ΔΔCt values compared to the control group ($P < 0.001$ for all comparisons).

Specifically, the mean Ct value in patients was 17.86 ± 1.05 (range: 15.89–20.84), markedly lower than the control group's mean of 27.18 ± 1.72 (range: 23.66–29.6). Similarly, the mean ΔCt was -11.74 ± 1.05 (range: -13.71 to -8.76) in patients, compared to -2.42 ± 1.72 (range: -5.94 to 0) in controls. The mean ΔΔCt in the patient group was -9.32 ± 1.05 (range: -11.29 to -6.34), while the control group had a mean of 0 ± 1.72 (range: -3.51 to 2.42). All differences were statistically significant ($P < 0.001$).

These findings indicate a substantial upregulation of RNA-34a-5P expression in the patient group relative to controls, as reflected by the lower Ct, ΔCt, and ΔΔCt values. The data suggest that RNA-34a-5P may play a significant role in the pathophysiology of renal disease in obese individuals.

Quantitative PCR analysis showed that RNA-34a-5P expression was significantly higher in the patient group relative to controls (Table 6, Figure 5). This upregulation of RNA-34a-5P may contribute to the observed dysregulation of lipid metabolism and SIRT1 expression in patients with renal disease.

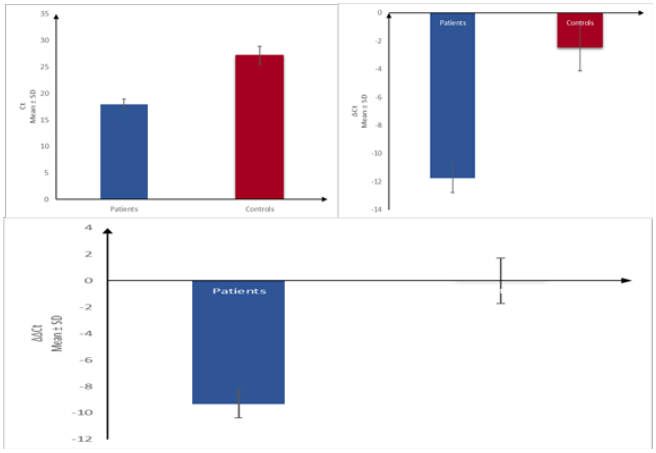

Fig. 5. Ct of the studied groups, ΔCt of the studied groups, ΔΔCt of the studied groups.

Table 5. Ct, ΔCt, and ΔΔCt of the studied groups.

		Patients (n=50)	Controls (n=50)	P value
Ct	**Mean ± SD**	17.86 ± 1.05	27.18 ± 1.72	**<0.001***
	Range	15.89 - 20.84	23.66 - 29.6	
ΔCt	**Mean ± SD**	-11.74 ± 1.05	-2.42 ± 1.72	**<0.001***
	Range	-13.71 - -8.76	-5.94 - 0	
ΔΔCt	**Mean ± SD**	-9.32 ± 1.05	0 ± 1.72	**<0.001***
	Range	-11.29 - -6.34	-3.51 - 2.42	

Ct: cycle threshold, *: significant as P value ≤ 0.05 Ct, ΔCt, and ΔΔCt were significantly decreased in patients than controls.

Table 6. RNA-34a-5p Expression of the studied groups.

		Patients (n=50)	Controls (n=50)	P value
RNA-34a-5p	**Median**	656.76	0.82	**<0.001***
	IQR	463.65 - 991.62	0.38 - 2.78	

*: significant as P value ≤ 0.05. The expression level of RNA-34a-5p was significantly increased in patients than controls (P value <0.001).

3.6. Correlation analysis

Pearson's correlation analysis revealed a significant negative correlation between RNA-34a-5P expression and SIRT1 protein levels (Table 7 and Figure 6A). Additionally, RNA-34a-5P expression was negatively correlated with total cholesterol, LDL cholesterol, and triglycerides, while a positive but non-significant correlation was observed with HDL cholesterol and glomerular filtration rate (GFR) (Figure 6B–F). These findings suggest that increased RNA-34a-5P expression may contribute to both SIRT1 downregulation and adverse lipid profile changes in obese patients with renal disease.

A notable negative association existed between the expression level of RNA-34a-5P and Total Cholesterol (r= -0.413, P= 0.003), LDL (r= -0.303, P= 0.033), and Triglycerides (r= -0.345, P= 0.014). There was a notable negative connection between the expression level of RNA-34a-5P and SIRT1 (r= -0.514, P <0.001) as well as Normalized SIRT1 Expression (AU) (r= -0.456, P= 0.001). A notable positive connection was observed between the expression level of RNA-34a-5P and HDL (r= 0.398, P= 0.004) as well as GFR (r= 0.452, P= 0.001). No significant association was observed between the expression level of RNA-34a-5P and age, BMI, creatinine, or GAPDH (Table 7).

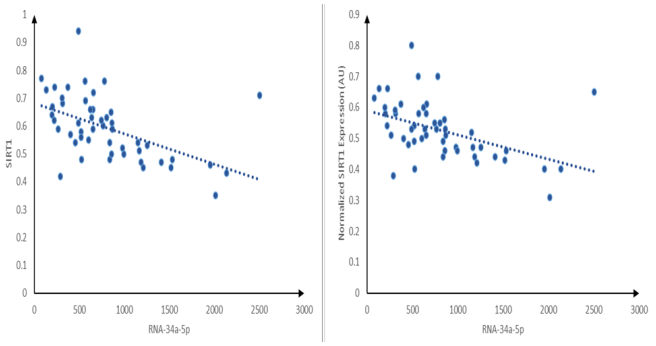

Fig. 6. Correlation between the expression level of RNA-34a-5P and SIRT1. Correlation between the expression level of RNA-34a-5P and Normalized SIRT1 Expression (AU).

4. Discussion

Chronic kidney disease (CKD) is a common condition in primary care and an important disease, affecting almost every part of the body [30]. Disorders of the kidney, especially those predominately involved with glomerulonephritis often result in varying degrees of abnormalities in lipid metabolism and hypertriglyceridemia from the result of a combination of alterations in synthesis and clearance of very low-density lipoprotein (VLDL) with a less pronounced effect on low density lipoprotein (LDL) metabolism. CKD also leads to secondary changes in plasma lipid and lipoprotein composition [31].

In a mouse model of atherosclerosis, reducing cholesterol levels increases SIRT1 protein, both by increasing the longevity of SIRT1 and increasing the affinity of the longevity–nutrition receptor [32]. Regrettably, hyperlipidemia that arises as a consequence of kidney disease cannot be effectively treated with a low-cholesterol diet, primarily because of the significant deterioration in kidney function and the resulting harm to the liver [33].

Patients with primary glomerular diseases (including diabetic nephropathy) have 1.1 to 1.2 times the risk of hyperlipidemia and metabolic disorders compared with living patients with other types of nephropathies [34]. The fat-related nutritional condition of the extremely obese patient circling the glomerular disease is not well known. SIRT1 protein changes showed greater dysregulation in blood lipid metabolism in extremely borderline patients with glomerular disorders than in non-extremely obese healthy controls [15].

These medical conditions were focal segmental glomerulosclerosis, membranous nephropathy, minimal change nephrotic syndrome and IgA nephropathy, and analyzed subsequent lifestyle and blood lipid responses in these patients [35]. Hypertriglyceridemia impairs the kidney mitochondrial function-mediated production of (NO_2) from arginine, which induces glomerular hyperfiltration, early renovascular and tubular damage, CKD onset and progression, lipid alterations and abnormal glucose metabolism, consequently inducing a specific renocardiovascular risk profile [36].

Fatty fish, and omega-3 polyunsaturated fatty acids (n-3 PUFA), could exert a protective effect on kidney and cardiovascular system by contrasting subsequent concomitant pathogenic pathways, significantly reducing whether nocturnal blood pressure values and proteinuria [37].

Obesity can induce lipid abnormalities in early life,

Table 7. Correlation between the expression level of RNA-34a-5P and the patients' related data.

	RNA-34a-5p	
	r	**P value**
Age (years)	-0.045	0.757
BMI (kg/m²)	-0.049	0.738
Total Cholesterol (mg/dL)	-0.413	**0.003***
LDL (mg/dL)	-0.303	**0.033***
HDL (mg/dL)	0.398	**0.004***
Triglycerides (mg/dL)	-0.345	**0.014***
Creatinine (mg/dL)	-0.207	0.150
GFR (mL/min/1.73 m²)	0.452	**0.001***
GAPDH	-0.077	0.595
SIRT1	-0.514	**<0.001***
Normalized SIRT1 Expression (AU)	-0.456	**0.001***

BMI: body mass index, LDL: low-density lipoprotein, HDL: high-density lipoprotein, GFR: glomerular filtration rate, SIRT1: silent information regulator 1, r: correlation coefficient, *: significant as P value ≤ 0.05.

resulting in elevated LDL and triglyceride levels and diminished HDL levels in infants and adolescents [38]. The influence of obesity on lipid profiles may differ according on age, gender, and ethnicity, with white males exhibiting more pronounced connections [39]. Dyslipidemia associated with obesity can result in insulin resistance, type 2 diabetes, and heightened cardiovascular risk. Addressing obesity by lifestyle modifications or procedures such as bariatric surgery can markedly enhance lipid levels [40].

The SIRT1 protein is an essential NAD+-dependent deacetylase that plays a significant role in metabolic regulation, encompassing lipid metabolism, gluconeogenesis, and insulin secretion [41]. It functions as a sensor for nutrition availability and energy status, affecting metabolic balance. SIRT1 modulates lipid metabolism by the deacetylation of essential transcription factors such as SREBP, which play a role in lipid production and storage [15].

The activation of SIRT1 may result in reduced hepatic lipid and cholesterol concentrations, potentially aiding in obesity-related disorders. SIRT1 impedes adipogenesis by deacetylating and inhibiting the function of transcription factors including PPARγ, which is linked to heightened adiposity and metabolic dysregulation in obesity [42].

SIRT1 mitigates metabolic damage by diminishing inflammation and oxidative stress, downregulating pro-inflammatory cytokines, and enhancing antioxidant proteins. Research indicates that SIRT1 expression is diminished in obese persons, correlating with multiple metabolic and anthropometric factors, such as insulin resistance and inflammation. Activating SIRT1 or increasing its expression may provide therapeutic advantages in addressing obesity-related metabolic problems by strengthening insulin sensitivity, diminishing inflammation, and improving mitochondrial function [43].

Our results showed that the examination of SIRT1 expression in the analyzed cohorts demonstrates a markedly significant downregulation of SIRT1 in the patient group relative to the control group, even after adjusting SIRT1 expression to the housekeeping gene GAPDH. The absence of a notable differential in GAPDH expression indicates that the variation in SIRT1 is unique and not attributable to generic fluctuations in RNA levels.

In 2022, Mengozzi et al. [44] found that SIRT1 expression is diminished in obese individuals relative to non-obese individuals. This downregulation correlates with metabolic dysregulation and heightened inflammation, prevalent in obesity.

Another study by Salim et al., 2019 [45]; found that the expression of SIRT1, which is a potential biomarker for obesity, can either be upregulated or downregulated depending on the individual's level of obesity.

On the other hand, the study demonstrated that the expression of SIRT1 may fluctuate based on the particular circumstances of obesity, including the kind of fat distribution (e.g., visceral versus subcutaneous) and the existence of additional metabolic disorders. Some researchers suggest that SIRT1 may be activated under specific situations to mitigate oxidative or metabolic stress [45].

Lower levels of SIRT1 in obesity correspond to impaired metabolic functions, including insulin resistance and dyslipidemia. SIRT1 plays a crucial role in the regulation of metabolic pathways, and its reduction exacerbates metabolic disorders associated with obesity [46, 47].

Another study by Sun et al., 2024 [48] found that in response to inflammation, commonly observed in obese patients, SIRT1 levels may increase. This increase may be a defensive response that mitigates the damage inflicted by inflammation. The same findings were obtained from several studies as they found that the consumption of acute high-fat and high-calorie meals can cause a temporary decrease in SIRT1 levels; however, long-term dietary habits may affect SIRT1 expression differently. The relationship between SIRT1 and dietary elements can be intricate and may impact its function in obesity [49, 50].

The findings unequivocally indicate that RNA-34a-5P expression is markedly elevated in extremely obese patients with renal disorders relative to controls. The exceedingly low P-values (<0.001) for all three parameters (Ct, ΔCt, and ΔΔCt) signify a substantial degree of statistical significance.

The same findings were proved by Caus et al (2021) [51] as they found that miR-34a is increased in obesity-related diseases, potentially resulting in renal problems. For example, miR-34a has been associated with the pathophysiology of obesity-related kidney illness, indicating its possible involvement in renal issues linked to obesity.

miR-34a is implicated in metabolic dysregulation, encompassing insulin resistance and inflammation, prevalent in obesity and capable of aggravating renal complications. Its elevated expression in the adipose tissue of obese patients is associated with insulin resistance and metabolic inflammation [52, 53].

Our study found a notable negative association existed between the expression level of RNA-34a-5P and Total Cholesterol (r= -0.413, P= 0.003), LDL (r= -0.303, P= 0.033), and Triglycerides (r= -0.345, P= 0.014).

Although direct investigations of miR-34a-5p and lipid profiles in very obese patients with renal conditions are scarce, certain studies indicate that miR-34a may affect lipid metabolism. For example, miR-34a has been demonstrated to inhibit genes associated with lipid production and metabolism, potentially resulting in a negative correlation with lipid levels [54].

In contrast to our findings, certain research suggests that miR-34a-5p may elevate lipid levels by inhibiting genes such as ACSL1, which plays a role in lipid production. This indicates a positive correlation between miR-34a-5p expression and lipid accumulation, against the negative correlation with total cholesterol, LDL, and triglycerides [55].

There was a notable negative connection between the expression level of RNA-34a-5P and SIRT1 (r= -0.514, P <0.001) as well as Normalized SIRT1 Expression (AU) (r= -0.456, P= 0.001).

Studies demonstrated that miR-34a-5p can inhibit SIRT1, resulting in a downregulation of SIRT1 expression. Research indicates that the overexpression of miR-34a-5p can suppress SIRT1 activity, hence corroborating the identified negative association between miR-34a-5p and SIRT1 levels [52, 56].

Another study by Xiao et al 2021 [57] found that the interaction between miR-34a-5p and SIRT1 can be affected by intricate regulatory networks that encompass additional signaling pathways. Specifically, although miR-34a-5p may directly target SIRT1, various factors can modulate this relationship, potentially resulting in differing outcomes based on the particular biological context.

A notable positive connection was observed between

the expression level of RNA-34a-5P and HDL (r= 0.398, P= 0.004) as well as GFR (r= 0.452, P= 0.001).

Raucci et al 2021 [58] found that miR-34a-5p inhibits PPARA (peroxisome proliferator-activated receptor alpha), a crucial regulator of fatty acid oxidation and lipoprotein metabolism. This inhibition may indirectly affect HDL levels by modifying lipid homeostasis. Same findings were obtained by Vyas et al (2023] [59], while Zhang et al (2020) [60] found that the downregulation of miR-34a-5p is associated with hepatic lipid metabolic abnormalities, indicating that reduced levels of miR-34a-5p may aggravate lipid dysregulation instead of enhancing HDL.

This study pioneers the direct examination of exosomal microRNA-34a-5p's role in lipid control and SIRT1 modifications in renal diseases, particularly in people with severe early-onset obesity. Moreover, it aims to clarify the complex relationship between lipid profile levels and SIRT1 alterations in the regulation of blood lipids in this high-risk population with renal impairment, ultimately seeking to comprehend the molecular interactions that drive these interrelated metabolic and renal issues.

Consent for publication

All authors have reviewed and approved the final version of the manuscript and consent to its publication.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

Zain Alabdean Azeez and Elyes Chabchoub contributed to the conception and design of the study. Both authors contributed to the interpretation of data, drafting, and critical revision of the manuscript. All authors read and approved the final manuscript.

Data availability

The datasets generated and analyzed during the current study are available from the corresponding author on reasonable request.

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