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ORIGINAL ARTICLE

Decreased Sirtuin 1 Gene Expression in Human Ejaculated Sperm is Associated with Unexplained Infertility

İnsan Ejaküle Spermlerinde Azalmış Sirtuin 1 Gen Ekspresyonu Açıklanamayan İnfertilite ile Ilişkilidir

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ABSTRACT

Aim: The potential mechanisms underlying unexplained infertility, which is a condition in which couples experience infertility without an identifiable cause in both men and women, have not yet been clarified. The present study aimed to investigate the role of Sirtuin 1 (SIRT1) gene in male infertility and unexplained infertility.
Methods: A total of 50 couples who applied for infertility evaluation and treatment were included. Medical histories were obtained, and fertility status was assessed. Semen analysis results, evaluated according to World Health Organization (WHO, 2010) criteria, were categorized into low and normal semen parameter groups based on sperm count and motility. Couples were further classified into three groups based on fertility status: Non-infertility group (n = 13), comprising couples without clinical infertility. Male infertility group (n = 19), comprising couples with infertility attributed to a male factor. Unexplained infertility group (n = 18), comprising couples with infertility for which no identifiable cause could be determined in either partner. Changes in SIRT1 gene expression among the groups were analyzed using qPCR.
Results: SIRT1 gene expression was not associated with sperm count or motility parameters. However, expression of SIRT1 was significantly reduced in the male infertility group and, more notably, in the unexplained infertility group compared to the non-infertility group.
Conclusions: Our study is the first to demonstrate that decreased SIRT1 expression in human mature spermatozoa may play a significant role in fertilization potential by influencing functions of sperm other than count and motility, highlighting a novel potential mechanism underlying unexplained infertility.

Keywords: Male infertility, Semen parameters, Sirtuin 1 gene, unexplained infertility.

ÖZ

Amaç: Kadın ve erkekte tanımlanabilir bir neden olmaksızın çiftlerin infertilite yaşaması durumu olan açıklanamayan infertilitenin altında yatan olası mekanizmalar henüz tam olarak aydınlatılamamıştır. Bu çalışmada, Sirtuin 1 (SIRT1) geninin erkek infertilitesi ve açıklanamayan infertilitedeki rollerinin araştırılması amaçlanmıştır.
Gereç ve yöntemler: Çalışmaya infertilite değerlendirmesi ve tedavisi için başvuran toplam 50 çift dâhil edildi. Çiftlerin tıbbi öyküleri alındı ve fertilite durumları değerlendirildi. Dünya Sağlık Örgütü (WHO, 2010) kriterine göre değerlendirilen semen analizi sonuçları, spermin sayı ve motilite parametreleri açısından düşük ve normal semen parametre gruplarına ayrıldı. Çiftler ayrıca fertilite durumlarına göre üç gruba ayrıldı: İnfertilite olmayan grup; klinik infertilite sorunu yaşamayan çiftlerden oluştu (n = 13). Erkek infertilite grubu; erkek faktörüne bağlı infertilite sorunu yaşayan çiftlerden oluştu (n = 19). Açıklanamayan infertilite grubu; her iki partnerde de tanımlanabilir bir neden olmaksızın infertilite sorunu yaşayan çiftlerden oluştu (n = 18). Gruplar arasında SIRT1 gen ekspresyonundaki değişimler qPCR kullanılarak analiz edildi.
Bulgular: SIRT1 gen ekspresyonu sperm sayı ve motilite parametreleriyle ilişkili değildi. Bununla birlikte, SIRT1 ekspresyonunun erkek infertilite grubunda ve özellikle de açıklanamayan infertilite grubunda, infertilite olmayan gruba kıyasla önemli ölçüde azaldığı gözlendi.
Sonuçlar: Çalışmamız, insan olgun spermatozoasında azalmış SIRT1 ekspresyonunun, spermin sayı ve motilite parametreleri dışında farklı fonksiyonlarını etkileyerek fertilizasyon potansiyelinde önemli bir rol oynayabileceğini gösteren ilk çalışmadır ve açıklanamayan infertilitenin altında yatan yeni bir potansiyel mekanizmayı vurgulamaktadır.

Anahtar Kelimeler: Erkek infertilitesi, Açıklanamayan infertilite, Semen parametreleri, Sirtuin 1 geni.

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Introduction

Infertility remains a significant reproductive health problem worldwide. Clinical infertility is when couples are unable to conceive after 12 months of trying. Infertility affects approximately 15% of reproductive-age couples (1). Male and female factors are estimated to contribute approximately equally to infertility. The male factor alone contributes to approximately 25-30% of infertility cases (2). While there is an identifiable cause in a significant proportion of couples experiencing an infertility problem, in 30% of cases, an identifiable cause cannot be determined, which is defined as unexplained infertility (3). It is known that anomalies in the number, motility, and vitality, structural and functional properties of sperm cause male infertility. Currently, the diagnosis of male infertility is based on the assessment of sperm count, motility, vitality, and normal morphology parameters, based on the criteria of the World Health Organization (WHO) guideline (4). However, increasing evidence suggests that conventional semen parameters alone are insufficient to predict male infertility. These parameters fail to reflect sperm functions that play a crucial role in fertilization capacity, such as sperm DNA integrity and acrosome function. Moreover, no significant decrease in standard semen parameters is observed in cases of unexplained infertility. The underlying causes of unexplained infertility are still unknown, and further research is needed on this topic.

Sirtuins (SIRTs), highly conserved nicotinamide adenine dinucleotide (NAD+)-dependent deacetylases, catalyze post-translational modifications of proteins. Seven types of sirtuins (SIRT1-7) have been identified in mammals. Sirtuin types have different structural properties and tissue expressions, and are found in different localizations within the cell: the nucleus, cytoplasm, and mitochondria (5, 6). In recent years, there has been evidence that Sirtuins have important roles in the maintenance of spermatogenesis such as maturation of Sertoli and Leydig cells, regulation of spermatogenesis, acrosome biogenesis, and improvement of mitochondrial function (7). SIRT1, which is predominantly localized in the nucleus but is also found in the cytoplasm, is expressed in many tissues. McBurney et al (8) first demonstrated that SIRT1 has been found in the nucleus of spermatogonia, spermatocytes and round spermatids, suggesting an intrinsic direct activity of SIRT1 in developing male germ cells during spermatogenesis. Also, this study in Sirt1-null mice provided the first evidence for a possible role of SIRT1 in male fertility control. In this study, it was observed that the few surviving mice that reached maturity had decreased testes size and the rare sperm obtained from the epididymis were non-motile and had abnormal morphology. Kolthur-Seetharam et al (9) found that knockout of the Sirt1 gene in mouse testes led to germ cell apoptosis, spermatogenesis arrest, and impaired Leydig and Sertoli cell maturation, along with reduced testosterone levels.

SIRT1 appears to play a significant role in male reproductive processes. Furthermore, the induction or absence of SIRT1 has been shown to significantly affect male reproduction in various ways. However, most studies appear to have been conducted in animal models, and data on its role in male infertility are quite limited. Moreover, no study has been found regarding the association of SIRT1 with unexplained infertility. Therefore, our study aimed to investigate SIRT1 gene expression in male infertility and unexplained infertility.

Materials and Methods

Patient Selection and Semen Analysis

A total of 50 couples who applied to the Selçuk University Hospital IVF Center for infertility evaluation and treatment were included in the study. Patients were evaluated after approval was obtained from Ethics Committee of Selcuk University, Faculty of Medicine (Decision No: 2022/57). The study was conducted under the principles of the Declaration of Helsinki. Medical histories were obtained, and fertility status was assessed. Semen parameters, evaluated according to WHO 2010 criteria (4), included semen volume, sperm concentration, total sperm count, total motility, and progressive motility. Semen parameters were categorized based on WHO reference values for male infertility: Normozoospermia group (n = 30): Sperm concentration ≥15 million/mL, total sperm count ≥39 million, total sperm motility ≥40%, and progressive motility ≥32%. Isolated oligozoospermia group (n = 13): Sperm concentration <15 million/mL, total sperm count <39 million, with normal motility parameters. Oligoasthenozoospermia group (n = 7): Sperm concentration <15 million/mL, total sperm count <39 million, total sperm motility <40%, and progressive motility <32%.

Couples were further classified according to fertility status: Non-infertility group (n = 13): Couples without clinical infertility (no female or male factors; normal semen parameters). Male infertility group (n = 19): Couples with clinical infertility due to a male factor (abnormal semen parameters) and no female factor. Unexplained infertility group (n = 18): Couples with clinical infertility without an identifiable cause in either partner (normal semen parameters).

Male individuals with testicular tumors, clinical varicocele, cryptorchidism, Klinefelter syndrome, Y chromosome microdeletion, severe oligozoospermia, or azoospermia were excluded from the study. Written informed consent was obtained from all participants. The study was approved by the Selçuk University Faculty of Medicine Ethics Committee (2023/15).

Semen samples were obtained by masturbation following a 2–7 day period of sexual abstinence. The collected samples were allowed to liquefy at 37°C for 30–60 minutes, after which semen volume was measured and recorded. Sperm count and motility were assessed using a Makler counting chamber under a phase-contrast microscope at 200–400× magnification. All assessments were performed in duplicate on at least 200 spermatozoa, and the results were compared. If the difference between duplicate measurements exceeded the acceptance limits, the assessment was repeated. Total sperm count was calculated by multiplying sperm concentration by semen volume. Sperm motility was assessed in

three categories: progressive motility (spermatozoa moving forward in a straight line or in large circles), non-progressive motility (spermatozoa that show movement but without forward progression, such as small circles or only tail beating), and immotile spermatozoa (spermatozoa that show no movement at all). Total sperm motility was defined as the sum of progressive and non-progressive motility (4).

Gene expression analysis

In the study, SIRT1 gene expression levels were evaluated by qPCR method. For this purpose, RNA was obtained from sperm samples and cDNA conversion was performed for all individuals. Subsequently, gene expression levels of target genes were determined.

RNA isolation

Collected patient semen samples were taken into sterile 15 mL falcon tubes to be centrifuged at 1500 rpm for 4 minutes. After centrifugation, the supernatant was removed and PBS was added to wash the pellet. Then, it was centrifuged again at 1500 rpm for 4 minutes. The supernatant was discarded and 1 mL of Trizol was added to the pellet. Then, standard RNA isolation protocol was applied. The quantity and quality of RNA samples were measured with the Nanodrop spectrophotometer device. RNA samples were stored at -80 until use.

cDNA Synthesis

cDNA synthesis from total RNA was performed using the Bio-Rad iScript™ cDNA synthesis kit according to the manufacturer's instructions. The obtained cDNAs were used in qPCR analyses and stored at -20˚C until use.

qPCR Analysis

qPCR analysis was performed using "Fast SYBR Green Qpcr Master Mix" (Roche). The primers for the SIRT1 target gene and the β-actin gene were used, with β-actin serving as a reference gene for normalization (10). The mixture prepared was placed in 96-well plates (Roche Light Cycler 1.2) and the qPCR protocol was applied as: denaturation at 95 °C for 10 min, followed by 40 cycles consisting of denaturation at 95 °C for 30 s, annealing at 60 °C for 30 s, and extension at 72 °C for 30 s. The 2-ΔΔCt method was used to analyze the relative changes in gene expressions (11).

Statistical analysis

SIRT1 gene expression level was interpreted using Ct values, with β-actin serving as the reference gene for normalization. Expression changes were evaluated using the 2-ΔΔCt method, all decreases of expression and more than 2-fold increases were considered as significant.

RESULTS

Demographic Characteristics of the Individuals

The male participants included in the study ranged in age from 17 to 45 years, with a mean age of 32.6 years. Based on semen analysis results, 30 (60%) were classified as normozoospermic, 13 (26%) as isolated oligozoospermic, and 7 (14%) as oligoasthenozoospermic. Regarding fertility status, 13 couples (26%) had no infertility issues, 18 couples (36%) had male infertility, and 19 couples (38%) had unexplained infertility. Participants' ages, semen parameters, and fertility status are summarized in Table 1.

Table 1. Age, semen parameters and fertility status of the participants

Variables	N	Mean ± SD / %	Median (5th-95th percentile)
Age, years	50	32.6 ± 6.1	33 (22.1-42.4)
Semen volume, mL	50	3.7 ± 1.3	3.3 (2-6)
Sperm concentration, million/mL	50	23.6 ± 19.6	18.5 (2.8-67.5)
Total sperm count, million	50	82.6 ± 72.9	70 (10.2-257.7)
Total sperm motility, %	50	58.4 ± 15.8	60.5 (23.2-77.8)
Progressive sperm motility, %	50	47.2 ± 16.6	50 (10.7-68.9)
Non-infertility, %	13	26	
Male infertility, %	18	36	
Unexplained infertility, %	19	38	

Age and semen parameters are given as mean ± standard deviation (SD) and median (5th-95th percentile). Infertility status is presented as the percentage of cases.

SIRT1 Gene Expression

No significant differences in SIRT1 gene expression were observed among the normozoospermia, isolated oligozoospermia, and oligoasthenozoospermia groups. However, SIRT1 expression was significantly reduced in the male infertility and unexplained infertility groups compared to the non-infertility group, with the decrease being more pronounced in the unexplained infertility group (1.35-fold reduction) (Figure 1).

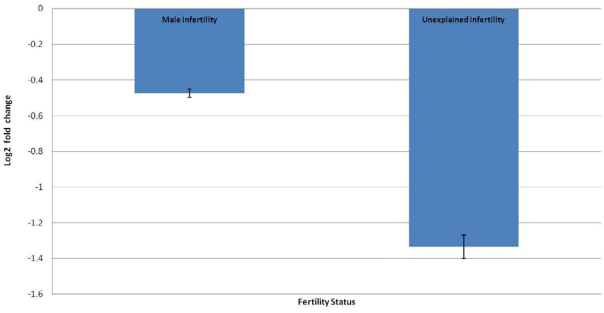

Figure 1. Sirtuin 1 gene expression levels according to fertility status

Discussion

The present study revealed that SIRT1 gene expression in human ejaculated sperm is significantly associated with clinical infertility. SIRT1 expression was observed to be decreased in male infertility and, more significantly, in unexplained infertility. Furthermore, SIRT1 gene expression was not significantly associated with oligozoospermia or oligoasthenozoospermia. This suggests that SIRT1 may be associated with different functions that play a role in sperm fertilization capacity rather than sperm count or motility parameters.

SIRT1, an NAD+-dependent class III deacetylase,

regulates numerous important physiological processes, including glucose metabolism, cell survival, mitochondrial respiration and histone modification through deacetylation of multiple substrates (12). Although SIRT1 is the most extensively studied member of the mammalian sirtuin gene family, its exact roles in regulating male reproduction have not yet been fully elucidated.

The high expression of SIRT1 in testicular tissue and critical roles in the processes of oxidative stress, metabolism, spermatogenesis and spermiogenesis, strengthens the view that SIRT1 may play a role in male infertility (13). Infertility characterized by poor spermatogenesis and abnormal sperm maturation has been detected in Sirt1-deficient male mice. It was also reported that the male reproductive gonads of these Sirt1-deficient mice were relatively smaller and sperm count and motility were significantly reduced (8, 14, 15). In addition, abnormal sperm characterized by smaller and round heads as well as spermatozoa heads with detached tails were abundant (13). McBurney et al (8) showed that Sirt1 is not essential to survival in mice; however, Sirt1-null male mice are infertile.

Increased oxidative stress is considered one of the causes of abnormal spermatogenesis. Peroxisome proliferator-activated receptor coactivator 1 alpha (PGC1α), which is activated by SIRT1-mediated deacetylation, plays a key role in antioxidant defense together with SIRT3. Therefore, it is suggested that the abnormal spermatogenesis observed in Sirt1 knockout mice may be due to SIRT1/PGC1/SIRT3 dysregulation (13, 16). Additionally, SIRT1 is implicated in the differentiation of spermatogenic stem cells and the histone-to-protamine transition during spermiogenesis (17). During the process of spermiogenesis, a tighter packing occurs by replacing histone proteins with protamines, with an unusual chromatin organization specific to sperm. This transition is essential for chromatin condensation and DNA stability in sperm (18-20). Germ cell-specific Sirt1 knockout mice exhibit abnormal histone-protamine transitions and chromatin condensation defects, which are associated with infertility (17, 21). Together, these findings indicate that SIRT1 plays a critical role in coordinating antioxidant defenses and chromatin remodeling during spermatogenesis (13).

Recently, evidence for a novel function of SIRT1 in acrosome biogenesis has emerged (12). Acrosome biogenesis is a very important step in spermiogenesis. In this process, autophagic molecular marker microtubule-associated protein light chain 3 (LC3), which is present in the spermatid nucleus in acetylated form, is deacetylated by SIRT1 and exits the cytosol and combines with other autophagic elements (Atg7) to perform the acrosome process (12, 22). Liu et al (12) showed that Sirt1 suppression results in the failure of LC3 transport from the nucleus to the cytosol, which is required for the assembly of Golgi-derived vesicles into the nucleus-associated acrosome. In the study, they detected abnormal spermatozoa with irregularly shaped or rounded heads and less acrosome in germ cell-specific Sirt1 knockout mice and they reported that these were very similar to round-headed spermatozoa with malformed acrosomes, which are characteristic of human globozoospermia (23). They stated that the proportion of round-headed spermatozoa in Sirt1 deficient mice was approximately 40%, suggesting that Sirt1 is a potential pathogenic gene for globozoospermia.

Studies investigating the role of SIRT1 in male infertility are generally conducted on null mice, and human studies are quite limited. Mostafo et al (24) investigated the SIRT1 gene expression in the seminal plasma of fertile normozoospermic men (n = 23), infertile oligoasthenoteratozoospermic (OAT) men without varicocele (n = 23) and infertile OAT men with varicocele (n = 35). They suggested that seminal SIRT1 expression has a role in male infertility being significantly decreased in infertile OAT men in general and in infertile OAT men associated with varicocoele in particular. Also, Nasiri et al. (25) investigated the effects of SIRT1 and SIRT3 protein levels and antioxidants, oxidative stress biomarkers, and DNA fragmentation in semen plasma of 40 normozoospermic and 40 asthenoteratozoospermic individuals. They reported that the levels of SIRT1 and SIRT3 in semen plasma of asthenoteratozoospermic men were low and oxidative stress, DNA fragmentation, and lipid peroxidation increased, resulting in immotile and immature spermatozoa. Martin-Hidalgo et al. (26) investigated the possible role of SIRT1 activator (YK 3-237) in the capacitation process of human spermatozoa. They reported that SIRT1 activator YK 3-237 induces capacitation-related events in human spermatozoa such as increase of tyrosine phosphorylation levels and acrosome-reacted spermatozoa after the ionophore challenge. Also, their results showed that YK 3-237 affects human spermatozoa capacitation-related events by a mechanism independent of protein lysine acetylation but dependent on bicarbonate and calcium.

A limited number of previous human studies have investigated SIRT1 expression at the protein or gene level in seminal plasma and have demonstrated its association with male reproductive functions. To our knowledge, the present study is the first to assess SIRT1 gene expression in human ejaculated spermatozoa and to demonstrate that decreased SIRT1 expression is associated with male infertility, particularly unexplained infertility. Our findings suggest that SIRT1 deficiency may be linked to disruptions in sperm maturation processes, including chromatin condensation, acrosome biogenesis, and capacitation, or to impaired DNA integrity, as previously reported, rather than to defective spermatogenesis affecting sperm count or motility.

In recent years, attention has increasingly focused on the causes and treatment of unexplained infertility, which occurs in the absence of identifiable factors in both partners. Our study indicates that reduced SIRT1 expression may represent a potential underlying mechanism in unexplained infertility, even when conventional semen parameters are normal. Further research is needed to elucidate the role of SIRT1 in sperm maturation and its relationship with sperm morphological features, particularly round-head

defects. Such studies may provide new insights into the diagnosis and management of infertility, especially unexplained infertility.

CONCLUSION

The present study is the first to demonstrate SIRT1 gene expression in mature human spermatozoa. Our findings indicate that reduced SIRT1 expression is significantly associated with unexplained infertility, without causing notable impairments in sperm count or motility parameters. Previous studies in mice and limited investigations in human seminal plasma have suggested that SIRT1 deficiency may disrupt sperm maturation processes, including chromatin condensation, acrosome biogenesis, and capacitation, or compromise DNA integrity, potentially contributing to unexplained infertility. Therefore, our results suggest that decreased SIRT1 expression may represent a potential underlying mechanism of unexplained infertility.

Conflict of Interest

No conflict of interest was declared by the authors.

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