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Assessment of Resolvin E1 in Relation to Hormonal Profiles and Semen Parameters in Male Infertility

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Abstract

Background: Oxidative stress, as well as inflamed tissues and damaged sperm DNA, tend to be linked to the fertility problems in men, over half of all global cases can be linked to these causes. The molecules of lipid origin, such as Resolvin E1 (RvE1), aid in alleviating the swelling and restoring the balance of body tissues. Nevertheless, researchers have not studied the potential impact of RvE1 on male reproduction fully.

Objective: This study was conducted to determine Resolvin E1 in the blood and semen of infertile males, and then compare the results with healthy ones. Correlation between hormone levels, including testosterone, FSH, and LH, and outcomes in the two groups was also studied by the researchers.

Methods: Individuals who participated provided blood and semen. Blood levels of hormones such as FSH, LH and testosterone were also monitored and RvE1 was also monitored in blood and at the same time also in semen fluid. The practical aspect of the research will occur in the period between October 2024 and December 2024. Sampling was done in two locations: the High Institute of Infertility Diagnosis - Al-Nahrain University and the IVF AL-Abayechi clinic at Baghdad, Iraq.

Results: The 44 males were separated into three groups, including the normal sperm, reduced-motility (asthenozoospermic), and astheno-oligo-teratozoospermic (AOT). High concentrations of RvE1 were found in semen in the AOT cohort ($p = 0.006$), and the concentration of RvE1 in blood remained fairly stable across groups ($p = 0.127$). AOT men were found to have low sperm count, low sperm motility, and high percentages of abnormal morphology. After assessment of hormones, there was little difference in the measurements between groups. Finally, the hormonal markers also seemed to be very close across the analyzed groups.

Conclusion: The seminal levels of higher RvE1 might be due to localized inflammation or irritation but not a better fertility. This implies that RvE1 can be the indication of inflammation of the reproductive area, but it is not the evidence of healthier sperm. Further studies that involve larger samples are needed to support this assertion.

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Keywords: *Resolvin E1, Male infertility, Hormone levels*

1. Introduction

Infertility is the failure of one couple to conceive after 12 months of regular sex without the use of a condom. It is an issue that faces a couple about 10 percent to 20 percent of couples all over the world when trying to conceive [1]. The problem is initiated by men in half of the cases and the trend is growing at a very high rate. Some of the factors that can reduce the chances of a man include performance problems, varicoceles, congenital abnormalities, hormonal problems, disease of the immune system and sexually transmitted diseases. In more than half of the infertile males, the etiology is not known and termed idiopathic infertility, consisting merely of oligospermia, asthenospermia, teratozoospermia or other sperm defects [2].

Hormonal testing is a critical component of male fertility screening, as endocrine pathological conditions are highly reversible male infertility causes. Proper hormonal control is necessary to maintain normal fertility parameters of males. The basic male reproductive process, sporadogenesis, necessitates adequate testosterone levels, which is produced via steroidogenesis at the Leydig cells. Both forms of gonadotropins are needed in physiological levels to ensure normal testicular activity [3]. The gonadotropin-releasing hormone (GnRH) produced by the hypothalamus is considered the main stimulator of gonadotropins, and hence the subsequent endocrine reproductive functions. The thyroidal or adrenal axis and a number of reproductive and non-reproductive hormones may have an impact on the hypothalamic-pituitary-gonadal (HPG) axis. A disruption of this delicate hormonal equilibrium and its interactions causes a range of endocrinopathies, which can cause subfertility or infertility in males [4]. All phases of spermatogenesis are initiated by Follicle- Stimulating Hormone, as well as testosterone. However, the exact separate task of FSH in the actions of the testicles should be thoroughly clarified.

Follicle-Stimulating Hormone (FSH) interacts with Sertoli cell FSH receptors to generate spermatogonial cells. The dissociation of the α-subunit-linked Gs protein activates FSH receptors. This activates adenylyl cyclase and increases intracellular cAMP. The catalytic subunit of protein kinase is released by cAMP, triggering a phosphorylation cascade of intracellular proteins. This includes transcription factors, cAMP response element-binding protein, and others. FSH's mode of action has many alternative possibilities, although in vivo details are lacking [5].

Lutropin or lutrophin is produced by gonadotropic cells of the anterior pituitary. In males, LH is also known as interstitial cell-stimulating hormone due to its role in stimulating the interstitial Leydig cells to facilitate steroidogenesis and testosterone synthesis. Its actions synergistically complement those of FSH on Sertoli cells, hence indirectly contributing to the precise regulation of spermatogenesis and the consistency of semen quality [5].

Testosterone (T) is the androgen produced in the testis that is essential for the initiation and maintenance of spermatogenesis, with the development of mature sperm being closely reliant on

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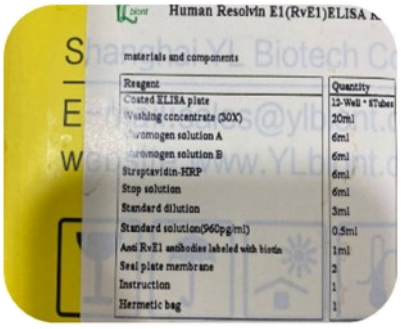
androgen activity inside the testis. Consequently, in the absence of T or its receptor, spermatogenesis fails to advance beyond the meiosis stage, leading to male sterility [6].

Resolvin E1, specifically 5, 12, 18R-trihydroxy-eicosapentaenoic acid, mediates anti-inflammatory and pro-resolving activities. Humans produce RvE1 via aspirin-dependent and aspirin-independent mechanisms. Aspirin-acetylated COX-2 and lipoxygenase interact with each other in cells to make RvE1 in inflammatory exudates. Endogenous synthesis occurs via cytochrome P450 conversion of eicosapentaenoic acid, derived from omega-3 fatty acids [7]. Oxidative stress and inflammation create a self-perpetuating cycle that diminishes sperm quality and male fertility [8]. Resolvin E1, which has anti-inflammatory and pro-resolving effects, was found in higher levels in the semen of men with leukocytospermia, varicocele, and idiopathic infertility compared to fertile men. Consequently, RvE1 may serve as a promising biological marker for a panel of seminal inflammatory indicators to enhance the diagnosis and treatment of inflammatory male infertility [9].

2. Methods

2.1 Patients and Study Details

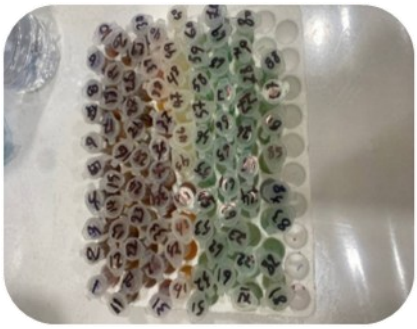
It was a cross-sectional and comparative study. The case group comprises infertile men with idiopathic and/or unexplained infertility, whereas the control group is represented by fertile men. Samples of blood and semen were collected among the study participants. Informed consent was obtained for the collection of the samples of all the patients, and the objectives of the research were explained to the participants, as well as the purpose of the questionnaire. The empirical section of the research was conducted between October 2024 and December 2024. Sample collection and the following treatment were done at the High Institute of Infertility Diagnosis and Assisted Reproductive Technologies, Al-Nahrain University, and the IVF Al-Abayechi Center in Baghdad, Iraq. The levels of resolvin E1 in blood and semen were measured with the help of an enzymatic analyzer (Cobas E411, Roche / Germany). ELISA kit, Shanghai YL Biotech Co., Ltd / China, which appears in Fig. 1, conformed to the specifications of its manufacturer in order to obtain the right results. To detect hormones, the blood samples were kept at -4degC, and then swirled to be homogenized.


Human Resolvin E1(RvE1)ELISA

materials and components

Reagent	Quantity
Coated ELISA plate	12-Well * 8Tubes
Washing concentrate (30X)	20ml
Chromogen solution A	6ml
Chromogen solution B	6ml
Streptavidin-HRP	6ml
Stop solution	6ml
Standard dilution	3ml
Standard solution(960pg/ml)	0.5ml
Anti RvE1 antibodies labeled with biotin	1ml
Seal plate membrane	2
Instruction	1
Hermetic bag	1

A) Chemical components list of RvE1 kit


B) serum and seminal plasma samples

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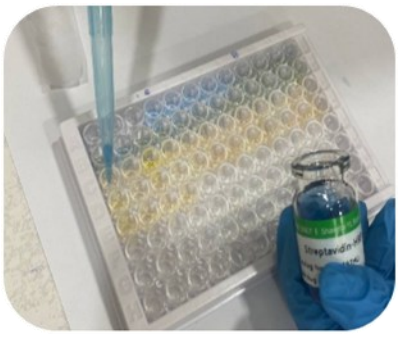
C) Stop solution adding step

D) ELISA kit solutions

Fig. 1 Steps of Resolvin E1 examination using the ELISA technique (Photos were taken in Genes Gate Lab)

Study Ethical Code: 0702-MM-2025159

2.2 Sample Size

The size of the sample was determined by the time constraints related to the completion of the research, which was affected by the challenges of the study in terms of collecting the sample within this very period, which coincided with the selection criteria set forth in the research. We therefore designed the study to contain a sample of between 40 and 60 specimens. Poor outcomes and unexpected complications led to the total exclusion of 16 samples in the analysis.

2.3 Statistical analysis

Software used for data analysis included Microsoft Office 2010 and the Statistical Package for the Social Sciences (SPSS) version 23.0. In order to describe the data, descriptive statistics were computed. These statistics include range, standard error, frequency, and mean. When comparing more than two groups, analysis of variance (ANOVA) was used, and when comparing just two groups, the independent samples t-test was employed. Using Pearson's correlation coefficient (r), we found the degree of association between the continuous variables; a *p*-value of 0.05 or below was considered statistically significant.

3. Results

3.1 Comparison of hormonal and RvE1 levels between the studied groups

No significant differences were observed among the studied groups regarding serum FSH levels (4.72 ± 0.88 vs. 2.59 ± 0.29 vs. 4.77 ± 0.98; p=0.083), LH levels (4.52 ± 0.62 vs. 3.06 ± 0.41 vs. 4.39 ± 1.05; p=0.128), and testosterone levels (2.69 ± 0.28 vs. 2.60 ± 0.20 vs. 2.92 ± 0.31; p=0.696), as illustrated in Table 1.

Table 1: Comparison of hormonal levels between the studied groups

Parameters (Mean±SE)	Normozoo-spermia N.=16	Asthenozoo-spermia N.=15	OAT N.=13	p value
FSH (mIU/ml)	4.72 ± 0.88	2.59 ± 0.29	4.77 ± 0.98	0.083 V NS
LH (mIU/ml)	4.52 ± 0.62	3.06 ± 0.41	4.39 ± 1.05	0.128 V NS
Testosterone (ng/ml)	2.69 ± 0.28	2.60 ± 0.20	2.92 ± 0.31	0.696 V NS

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NS: Not significant (p > 0.05); V: Analysis of variance (ANOVA)

Patients with astheno-oligozoospermia had significantly higher seminal plasma Resolvin-E1 levels (63.26 ± 2.84 vs. 53.24 ± 2.22 vs. 70.08 ± 5.09; p =0.006); however, serum Resolvin-E1 levels were not significantly higher among the same patients (60.26 ± 4.87 vs. 56.80 ± 3.99 vs. 84.09 ± 17.56; p=0.127) as presented in Fig. 2.

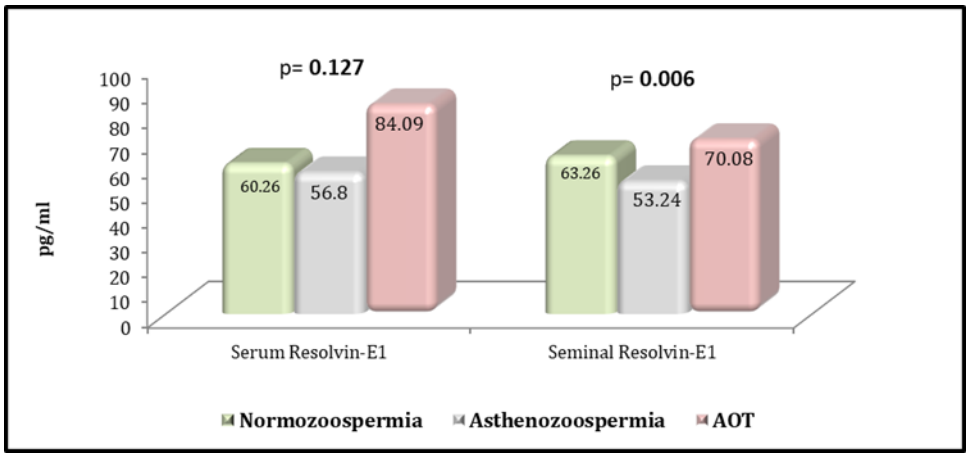

Fig. 2 Serum and seminal Resolvin-E1 comparison between the groups under investigation

Serum and seminal Resolvin-E1 correlate with patient hormones in patients with normozoospermia infertility

There was a solitary significant positive correlation between semen Resolvin-E1 with serum FSH (r=0.579 & p=0.019) as revealed in figure 3; on the other hand, there were no significant correlations between serum and semen Resolvin-E1 with serum LH and serum testosterone as presented in Table 2.

Table 2: Serum and seminal Resolvin-E1 correlations with patient hormones in the normozoospermia group

Parameters		Serum Resolvin-E1	Seminal Resolvin-E1
FSH	r	- 0.214	**0.579**
	p value	0.425	**0.019 ***
LH	r	- 0.353	- 0.158
	p value	0.116	0.560
Testosterone	r	0.016	- 0.171
	p value	0.953	0.528
Note: r: Pearson's correlation coefficient, * significant.			

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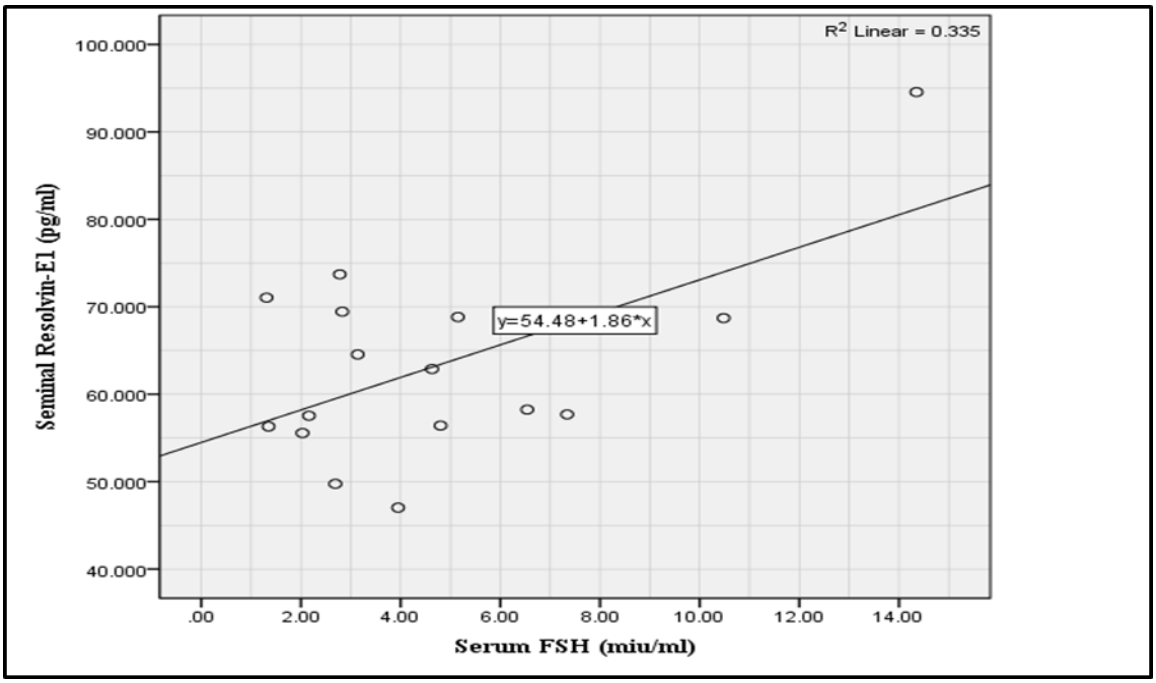

Fig. 3 Correlation between seminal Resolvin-E1 with serum FSH among normozoospermia group

Correlations between serum and seminal Resolvin-E1 and the hormones of patients with asthenozoospermia infertility

No significant relationships were seen between serum and seminal Resolvin-E1 and FSH, LH, and testosterone in patients with asthenozoospermia infertility (Table 3).

Table 3: Correlations between serum and seminal Resolvin-E1 and patient hormones in the asthenozoospermia cohort

Parameters		Serum resolvin-1	Seminal Resolvin-E1
FSH	*r*	-0.010	0.482
	p value	0.972 NS	0.069 NS
LH	*r*	-0.12	- 0.171
	p value	0.651 NS	0.542 NS
Testosterone	*r*	0.134	0.413
	p value	0.633 NS	0.126 NS

Correlations between serum and seminal Resolvin-E1 with patient's hormones among astheno-oligoteratozoospermia group

There were also no significant correlations between serum and seminal Resolvin-E1 with serum FSH, LH and testosterone among astheno-oligoteratozoospermia infertile patients (Table 4).

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Table 4: Correlations between serum and seminal Resolvin-E1 with patient's hormones among AOT group

Parameters		Serum Resolvin-E1	Seminal Resolvin-E1
FSH	*r*	- 0.076	0.290
	p value	0.806 NS	0.337 NS
LH	*r*	- 0.140	- 0.146
	p value	0.647 NS	0.634 NS
Testosterone	*r*	- 0.085	- 0.213
	p value	0.783 NS	0.484 NS

4. Discussion

The levels of testosterone, follicle-stimulating hormone, and luteinizing hormone in the study participants were largely within the typical ranges for adult males. A few participants had hormone levels that were either greater or lower than normal, but most of the cases had levels that were considered clinically normal. These spontaneous hormonal abnormalities could indicate subclinical hypothalamic-pituitary-gonadal (HPG) axis dysfunction or the impact of environmental and lifestyle factors such as stress, obesity, or smoking, all of which have been shown to impact the regulation of reproductive hormones [10], [11], [12].

The LH, FSH, and testosterone levels in the three groups under investigation normal, asthenozoospermic, and astheno-oligo-teratozoospermic did not differ statistically significantly, as indicated by the data in Table 1. This suggests that the hormonal profiles mostly remained within normal physiological ranges and did not differentiate among the studied subfertility phenotypes, even though there were clear differences in seminal parameters between these groups. Similar results were reported by Tournaye and his associates [13], who concluded that a significant proportion of infertile males can have normal gonadotropin and testosterone concentrations in their serum, even though they have suboptimal semen quality, particularly in cases not associated with extreme oligospermia and testicular failure. Prior to spermatogenesis being severely compromised, the endocrine profile was unable to reliably differentiate between males who were fertile and those who were not. This supports the current findings, indicating that the participants' varying sperm motility and morphology without necessarily exhibiting overt testicular insufficiency may be the cause of the absence of significant hormonal diversity [14].

Increased FSH levels are commonly associated with quantitative sperm abnormalities, including non-obstructive azoospermia and severe oligozoospermia, according to a study by [15]. FSH levels may stay normal in patients with primary motility or morphological problems, such as asthenozoospermia and AOT phenotypes, in line with the most recent findings. On the other hand, a 2024 study by [16] emphasized the importance of FSH in determining male infertility. Because FSH has a strong predictive value for both testicular function and spermatogenic state, they suggested that it be given priority as the main hormonal marker. The hormonal consistency seen across all groups in this study can be explained by the fact that men without Leydig cell impairment normally maintain their levels of testosterone and LH.

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Resolvin E1 concentrations in serum and seminal plasma were examined in Fig. 2 for each of the three study groups. While the serum level did not differ considerably across the groups, the results revealed a notable variation in Resolvin E1 levels between the seminal plasma. The increase in concentrations of Resolvin E1 in this compartment might be explained by the high concentration of bioactive substances found in seminal plasma, combined with its high sensitivity to oxidative stress and inflammatory factors [17].

Table 2 indicates that there is an evident positive relationship between FSH and seminal Resolvin E1 among men who have normal sperm counts. This shows that high FSH concentrations might be related to high levels of seminal Resolvin E1 production or storage. As noted by Signorini et al. [18], this could point to FSH influencing certain fat-based signaling molecules in male fertility organs - possibly acting on Sertoli cells or tweaking how local tissue handles inflammation and repair. A weak, slightly negative trend was seen in serum levels (Figure 3), which isn't statistically meaningful, indicating that any association remains restricted to the reproductive system without entering systemic circulation. Furthermore, no significant or statistically significant associations were found in other hormonal comparisons in the table, such as those between LH and testosterone with both seminal and serum Resolvin E1. There were no statistically significant relationships between seminal or serum Resolvin E1 levels and any of the assessed sex hormones (FSH, LH, and testosterone) in the asthenozoospermia (Table 3) or astheno-oligo-teratozoospermia (Table 4) categories.

5. Conclusions

In conclusion, the hormonal indicators that were investigated in this study did not significantly differ between the research groups. Resolvin E1 study, however, showed different patterns in biological fluids. Serum Resolvin E1 levels stayed constant but seminal Resolvin E1 levels varied significantly between the groups, indicating that local rather than systemic influences may affect its concentration.

Limitation of this study: One disadvantage of this study was its small sample size, which was caused by a time restriction.

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