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Relationship Between Trace Element Dysregulation and Lipid Profile Alterations in Male Infertility: A Case-Control Study

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ABSTRACT

Background: *Infertility is a significant international health problem with significant medical, psychological and socioeconomic consequences, and the World Health Organization estimates it to be the third most common health challenge after cancer and cardiovascular diseases.* ***Purpose***: *This study aimed to evaluate how abnormalities in lipid profiles and key trace elements such as Zinc (Zn), Copper (Cu) and Lead (Pb) associated with male infertility. In addition, the study investigates the negative influence of lipid metabolism disorders of infertile males which are usually caused by unhealthy eating habits.* ***Methods***: *The sample was 320 married men aged 20-40 years who participated in a case-control study in June 2024 to February 2025 in Fertility center of Al-Sadder Hospital in Najaf province. The men were grouped into two categories: 220 infertile men and 100 fertile men as control group. Zinc content was determined by means of spectrophotometry, lipid (Cholesterol, HDL, triglycerides) by means of Cobas c 111 and Copper and Lead by means of atomic absorption spectrophotometry.* ***Results and Conclusions:*** *The analysis showed that the total cholesterol, triglycerides, copper, and lead levels were much higher in infertile patients. These results indicate a possible connection between lipid and metal imbalances and infertility and the need to pay attention to these biomarkers to reduce the related risks.*

Keywords: Infertility, Lipid, Sperms.

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INTRODUCTION

Infertility is defined as the inability of a couple to conceive after 12 months of regular unprotected intercourse. It is among the gravest social and health issues, posing a great pressure on most family units and carrying enormous consequences to the health of individuals and the community. Globally, infertility has been estimated to occur in the range of 14-20 percent of couples of reproductive ages, and the population of individuals with infertility is estimated to be more than 186 million. The infertility rates in Iraq have been on the rise in recent years, attributable to a wide range of factors that comprise war, lifestyle, stress, smoking, occupation, food habits, and genetic predisposition [(1)]. The World Health Organization (WHO, 2018) categorizes infertility into, primary infertility when a couple has never had a pregnancy and secondary infertility when one or both previous pregnancies have already been achieved [(2,3)]. Infertility is a male as well as a female issue and it is therefore important to consider both the male and female partners when investigating its causes

The pathophysiology may be male, female, or a mix of both such as ovulatory disorders, tubal disease, endometriosis, chromosomal abnormalities, sperm related, and unexplained infertility .(4)

Idiopathic infertility is primary or secondary infertility with no discernable medical etiology and is seen to affect about 25% of couples. One of the hypothesized causes of idiopathic infertility is reactive oxygen species (ROS) and oxidative stress (OS). Oxidative stress is caused by the disequilibrium between antioxidants and ROS in the body and is one of the main causes of male infertility. Such a condition may be a result of lifestyle factors like alcohol use, smoking, unhealthy dieting and environmental pollutants. Other causes of ROS are inflammation, genetic mutations, immature spermatozoa, and hormonal imbalances [5,6].

Zinc is an essential element for male reproductive function and sperm health. Oxidative stress induced by ROS is the primary mechanism linking zinc deficiency to sperm DNA fragmentation, reduced membrane integrity, cell death, antioxidant depletion, poor sperm quality, and male infertility [7]. Zinc is a multifunctional metal, accounting for approximately 1.5–2.5 g in the human body, primarily distributed in the skin, skeletal muscles, prostate, and retina. It plays a crucial role in immune function as an antioxidant and serves as a cofactor for over 300 metalloenzymes involved in cellular signaling [8].

Unexplained male infertility may also be attributed to environmental and occupational exposure to various chemical agents. Individuals exposed to significant levels of lead are more likely to experience adverse effects on gonadal development due to its impact on pituitary and thyroid hormones**.** Lead exposure disrupts spermatogenesis and negatively affects sperm function parameters, including concentration, motility, and viability. Moreover, lead significantly reduces sperm's ability to attach to the egg, impairing fertilization potential [9]. In the same spirit, copper is also a crucial trace mineral that participates in the actions of multiple metalloenzymes and metalloproteins that control energy metabolism and antioxidant defense. Nevertheless, its ionic form may easily be toxic to different types of cells, such as spermatozoa, at high levels, causing reproductive dysfunction. Poor sperm quality and low testosterone levels in infertile males have been reported to be caused by a low level of zinc in the cells. On the other hand, there is evidence that high copper may be harmful to the reproductive system, whereas zinc exerts a protective effect on semen quality. Moreover, high lipid concentration, especially cholesterol and triglycerides, could be linked to low semen quality and low motility caused by hormonal imbalances and body fat deposition in the testicular tissues [10,11]. This paper will attempt to evaluate the correlation between lipid profile abnormalities and trace element levels (zinc, copper, and lead) in male infertility and examine the possible effects they have on sperm quality and reproductive functioning.

METHODS

Patients and controls

The current case-control study was carried out on 320 men aged between 20 to 40 years from Fertility center of Al-Sadder Hospital in province of Al-Najaf, June 2024 to February 2025. Each of the participants was married and their wives had no known health problems. The main aim of the study was to investigate the connection between infertility, trace elements imbalances (zinc, copper, lead) and lipid profile deviations in infertile men, in relation to the healthy controls.

The subjects were categorized into two groups; 220 infertile men and 100 healthy fertile men as the control group. The research was endorsed by the Ethics Committee of AL-

Sadr Medical City in Najaf, and informed consent was signed by all the subjects.

Blood sample collection:

Each participant had his/her venous blood samples (3-5 mL) collected and centrifuged at 3000 xg over 15-20 minutes to get serum. The level of serum zinc was assayed by a spectrophotometric method. The parameters of lipid profiles such as total cholesterol, HDL and triglycerides, were measured using Cobas c111 analyzer (Roche Diagnostics). Atomic absorption spectrophotometry was used to determine serum copper and lead levels.

Inclusion and Exclusion Criteria:

To capture clinical heterogeneity in reality, and to assess systemic biochemical changes in relation to impaired reproductive function, males with infertility of any etiology were included in this study. To reduce the confounding factor, those with clear-cut conditions that could independently affect semen quality or biochemical parameters were excluded (genitourinary infections, endocrine disorder, malignancies, or continuous therapeutic treatment) were disqualified.

Statistical Analysis:

Data were expressed as mean ± standard deviation (SD). Comparisons between infertile patients and controls were performed using the independent samples t-test. A p-value < 0.05 was considered statistically significant [12].

RESULTS

Total cholesterol Concentration

Serum total cholesterol levels were significantly elevated in infertile men compared to healthy controls (261.0 ± 7.948 vs. 122.7 ± 3.953 mg/dL; P < 0.0001). as shown in Figure 1.

Total Triglycerides (TG) Concentration

Serum triglyceride (TG) levels were significantly higher in infertile patients compared to controls (238.8 ± 8.203 vs. 115.4 ± 3.840 mg/dL; P < 0.0001). As shown in Figure 2.

Total HDL Concentration

The comparison of serum HDL levels of study groups showed that there was a significant decrease in infertile patients (53.23 ± 1.284 mg/dL) as compared to the healthy control group (61.10 ± 2.185 mg/dL). This was significantly different (P < 0.0001*) which implies that lower HDL levels could be related to poor reproductive ability in males. As Figure 3 illustrates.

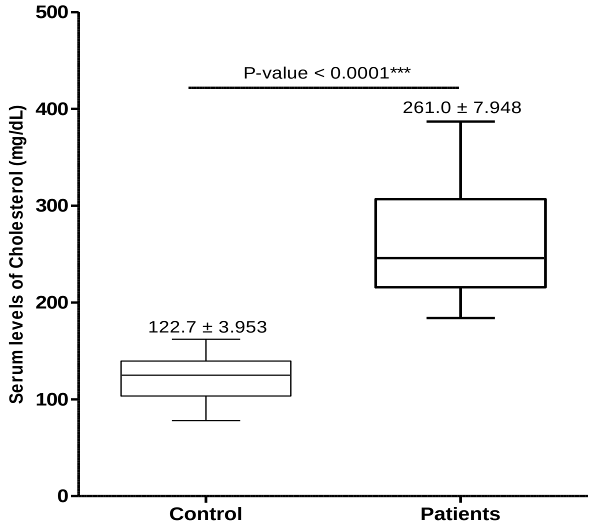

Figure (1): Serum cholesterol levels between infertile patients and healthy controls.

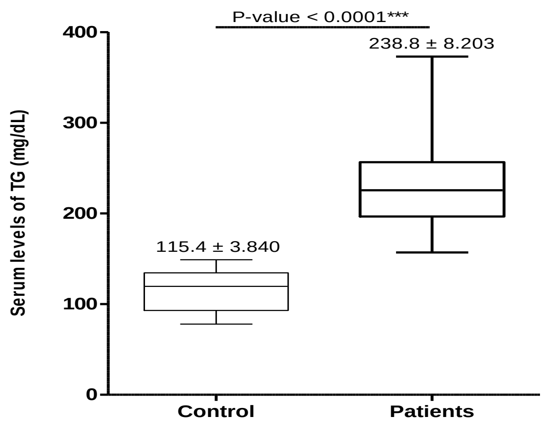

Figure (2): Serum Triglycerides (TG) levels between infertile patients and healthy controls.

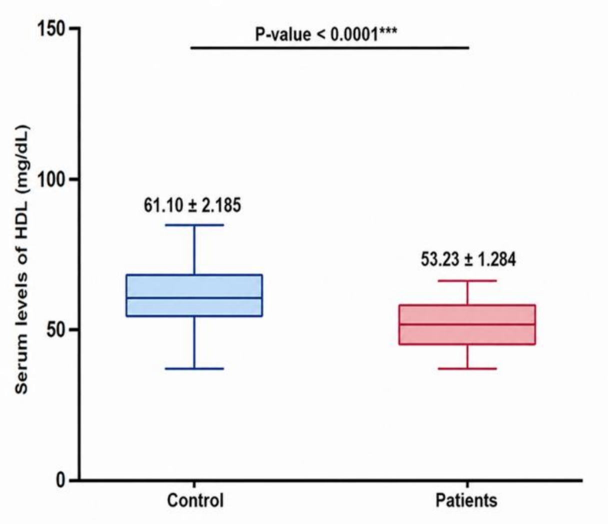

Figure (3): Serum HDL levels between infertile patients and healthy controls.

Total Zinc Concentration

The graph compares serum Zinc level in the study groups and indicates that infertile patients had significantly lower levels of serum Zinc level (59.52 ± 1.938 µg/dL) as compared to their healthy counterparts (98.40 ± 3.110 µg/dL). The findings indicate that the statistical difference is very significant (P < 0.0001*) and there might be a correlation between low Zinc and infertility. The above results highlight the need to monitor Zinc status to reduce the risks that are related to infertile patients, as shown in Figure 4.

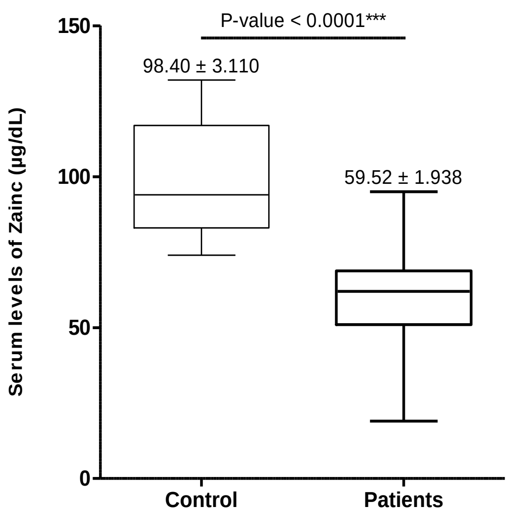

Figure (4): Serum Zinc levels between infertile patients and healthy controls.

Total Copper Concentration

The graph compares blood Copper levels between the study groups, showing significantly higher concentrations in infertile patients (144.1 ± 4.183 µg/dL) Compared to the healthy control group (77.83 ± 3.899 µg/dL). The results demonstrate a highly significant statistical difference (P < 0.0001*), highlighting a potential link between elevated Copper levels and infertility. As shown in Figure 5.

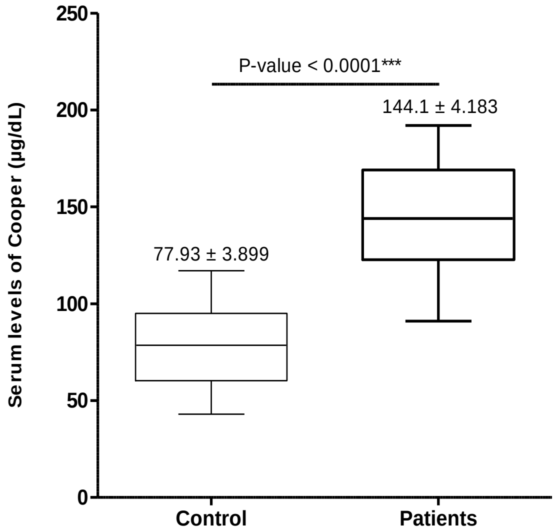

Figure (5): Serum Copper levels between infertile patients and healthy controls

Total Lead Concentration

The graph compares blood Lead levels between the study groups, showing significantly higher concentrations in infertile patients (4.175 ± 0.1392 µg/dL) Compared to the healthy control group (2.983 ± 0.1341 µg/dL). The results demonstrate a highly significant statistical difference (P < 0.0001*), highlighting a potential link between elevated Lead levels and infertility. As shown in Figure 6.

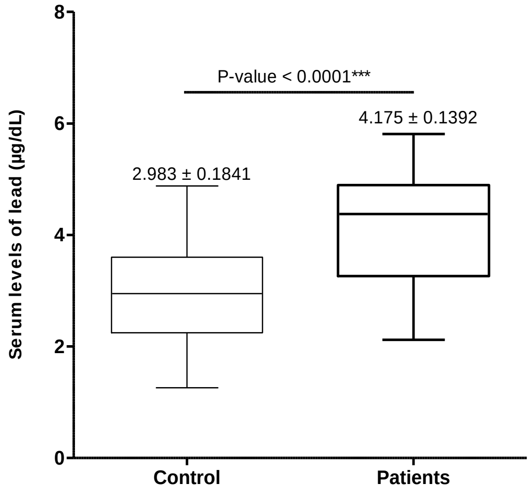

Figure (6): Serum Lead levels between infertile patients and healthy controls.

DISCUSSION

Male infertility is a significant global health concern affecting millions of individuals worldwide [5,13], which has a significant impact on the quality of life and family relationships. The knowledge of biochemical and physiological processes of infertility is the key to the further development of diagnostic and treatment methods. In this regard, the present study emphasizes the role of tracking trace elements imbalances and lipid profile alterations as the factors that contribute to male reproductive dysfunction.

Lipid and cholesterol homeostasis are essential to male reproductive functioning[14,15]. In the current research, the serum HDL level was significantly decreased in infertile patients compared with healthy controls. HDL is also known to have protective functions in lipid metabolism and antioxidant properties, which are critical in keeping sperm membrane intact and in the optimal functioning of the cell [16]. Decrease in HDL level could also play a major role in enhancing the oxidative stress and lipid peroxidation, which affect spermatogenesis and sperm motility [17].

Simultaneously, it is also stated that a significant percentage of infertile men have hypercholesterolemia and/or high triglyceride levels, which is in line with the results of the present study [18]. Despite the fact that cholesterol cannot be avoided in steroidogenesis and in the production of sperm, its imbalance can lead to negative consequences on seminal fluid composition, sperm concentration, and morphology. Lipid imbalances are especially prone to the testes as the main location in spermatogenesis, and can disrupt normal reproductive functions, leading to male infertility [13].

One of the prior studies had shown that serum triglycerides are negatively associated with the area of seminiferous tubules and diameter of Leydig cell nuclei whereas serum HDL-c is positively associated with the number of live and normal sperm, levels of testosterone, seminiferous tubule area, Leydig cell nuclei diameter, and testicular weight [19].Supporting the negative impact of hyperlipidemia on the male reproductive system, Mortazavi *et al.* [20] reported that hypercholesterolemia combined with hypertriglyceridemia not only induces pathological changes in the seminiferous tubules but also impairs sperm motility and spermatogenesis, ultimately reducing sperm viability and normal morphology.

Zinc, an essential trace element for normal spermatogenesis and steroidogenesis, is crucial for maintaining testicular function. Zinc deficiency has been implicated in decreased testicular function in infertile males**.** Males with asthenospermia / teratozoospermia have been found to have significantly lower zinc intake compared to fertile males**.** Also, research cites a positive relationship between the seminal plasma concentration of zinc and the number of sperm, motility and serum testosterone levels [21].

A very crucial aspect of zinc is the effect it has on sperm motility. Zinc helps to stiffen outer dense fibers by creating disulfide bond during sperm development in the epididymis as a requirement of attaining progressive motility. Extreme loss of zinc may cause a 50-percent decrease in zinc per ejaculation, causing pathozoospermia [22]. In addition to its effects on sperm motility, zinc plays a critical role in anatomical maturation and proper functioning of male reproductive organs. It increases spermatozoa maturation and maintains the germinal epithelium as well as promoting spermatogenesis [23]. In addition, Zinc is also involved in the synthesis and release of testosterone by Leydig cells, which is a major regulator of spermatogenesis together with follicle stimulating hormone. The antibacterial effects of zinc also help to protect the reproductive system. It is important to note that zinc deficiency has been linked to dysfunction of the gonads, reduction in testicular weight and shrinkage in seminiferous tubes [24].

The relationship between zinc and copper is a close and mainly antagonistic relationship and it is important to maintain the right levels of both to ensure the best physiological functions. Any variation of the normal levels can interfere with the Cu/Zn ratio, which may interfere with the fertility of males [25]. High concentrations of copper have also been associated with reduced sperm motility, a phenomenon that is associated with activation of free radical formation by copper ions which subsequently results in the generation of lipid peroxidation by the spermatozoa membrane. An earlier study has also established that the copper level in infertile males with subfertility was significantly greater compared to that of fertile males, which is also in accordance with our results [26].

Lead is very toxic to reproductive tissues. Lead exposure has been linked with several adverse effects on semen quality such as increase in the liquefaction time and decrease in sperm motility [27]. Moreover, lead has been found to have a negative correlation with sperm motility and sperm viability and also has been linked to a reduction in functional sperm maturation in men who had mean blood lead levels of 45 μg/dL. Inversely, there were high increases in the motile sperm counts when mean blood lead levels were lowered to 20 μg/dL compared to 42 μg/dL in the lead factory workers [28,29].

CONCLUSION

The present study demonstrated that the alterations in cholesterol and triglycerides contribute to male infertility and need to check the trace elements level and lipid profile during the assessment and diagnosis of male infertility to come up with more effective treatment frameworks to enhance male reproductive health.

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