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Evaluation of TRAIL in Infertil Obese Individuals

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Abstract

According to the description of the World Health Organization (WHO), obesity is named as the rise in adipose tissue to the extent that it induces negative health-related results. Infertility is described as the lack of pregnancy in a reproductive age couple without using any contraceptive method for at least one year in spite of regular sexual intercourse. Even though alterations in obesity's sperm parameters and impacts on male infertility are multifactorial, they are also related with adult male infertility and are characterized by a decline in sperm and semen quality. Tumor necrosis factor (TNF-α related apoptosis-inducing ligand (TRAIL) is a member of the TNF-superfamily, combines pro-apoptotic death receptors DR4-DR5 to induces tumor selective cell death. TRAIL is one of the fas-ligand receptors. This receptor has been appointed in adult human testicles in terms of both mRNA and protein. It is also shown in the literature that TRAIL is expressed in the semen of infertile men. The knowledge about the function of this gene in men with obesity and infertility status together, and therefore whether it is owing to obesity or infertility will be explained by further studies.

Key words
Obesity, TRAIL, Gene, Infertility

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Introduction

1. Infertility

The World Health Organization (WHO) describes infertility as the lack of couples regularly having sexual intercourse to reach pregnancy within 12 months. Infertility is a serious health problem influences at least 10 % of the world's population and is conceivably higher in progressing countries (1). Moreover, in the reproductive years in most progressed countries, it has been stated that the number of women and men in the overweight and obese has rised , as well as obesity-related diseases such as hypertension, diabetes and vascular disorders (2). Weight gain is related with hormonal alterations associated with the reproductive system and testosterone hormone production (3,4,6). On the other hand, its direct impacts on semen parameters is not clear (7,8,5). The better explanation of the mechanism of infertility will be shaped by the data obtained from all these studies and the contribution of future studies to the existing ones.

1.1. The Relationship Between Infertility and Obesity

Obesity is a prevalent metabolic disease among men of reproductive age that induces male infertility due to negative impacts on spermatogenesis with endocrine abnormalities (9). Today, the rate of obesity remain in men of reproductive age. There is evidence from epidemiological studies that obesity negatively impreses male fertility (10) Epidemiological, clinical, genetic, epigenetic data and animal experiments promote these findings (11).

Recent studies in the field of epigenetics have demonstrated that paternal obesity may influence childhood metabolic and reproductive phenotypes by means of epigenetic reprogramming in spermatogonial stem cells. Understanding the impact of this reprogramming is critical to examining the relationship of obesity over generations (9).

It has been suggested that high-fat diet administration may influence the epigenetic content of the sperm and the endocrine content of the seminal fluid, and thus may lead to differences in early fetal development. Experimental and epidemiological data show that male fertility and offspring health can be improved with weight loss in obese and overweight men. Obesity is a global health problem that has reached epidemic levels not only in Western countries but also in progressing countries (10). It has been determined that there are a lots of overweight and obese infertile couples in reproductive age (3). In the other study, it is stated that obesity is associated with adult male infertility and is measured by prolonged delay before pregnancy (11,12). It is generally known that obesity impreses GnRH-FSH / LH release, disrupts the function of sertoli and leydig cells, and influences sperm maturing by release of sex hormones (13). In addition to this, the alteration in function of the sertoli cells has been defined as the major induces of spermatogenesis reduction along with an enhance in scrotal temperature and fat accumulation in the groin and pelvic (14,15). In studies performed between obese couples, it was found that obesity is also effective in decreasing secondary fertility with less sexual intercourse.

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Moreover; fertility rates have also been shown to tend to improve after weight loss (2,4,5). It is notified in the literature that the amount of testosterone in the serum, sex hormone binding globulin (SHBG) and inhibin B levels diminishes with the enhance in body mass index (BMI), while the level of estradiol augments with the enhance in BMI. Enhanced amount of estrogen from adipocytes as a result of obesity; The hypothalamus has a negative impact on the pituitary and testicular axis, leading to a decrease in testosterone levels (16). Different types of studies have been carried out the impacts of obesity on infertility in the last decade (7,8,17). In these studies (18,19) obesity in adult males has been found to induce low sperm quality. It has also been notified that obese men are three times more likely to experience a decrease in semen quality compared to men with normal weight (20). Overweight and obesity have been associated with an increased prevalence of azoospermia or oligozoospermia (21). It is the only clinical study performed by Belloc et al. In 2014 and it has the highest number of samples in terms of having more than 10000 samples. They found that there was a clear relationship between (22).

Obesity has been considered to be associated with male fertility owing to genetic factors, lifestyle, and hormonal alterations. Obesity, male reproductive potential; It influences not only by decreasing the quality of sperm, but also by changing the physical and molecular structure of germ cells in testicles, affecting the maturity and function of sperm cells (23). Despite the world health organization has named sperm number, morphology and mobility as the majör parameters used to evaluate male fertility, there may be other factors such as DNA fragmentation that may improve after weight loss (21,24) (Figure 1).

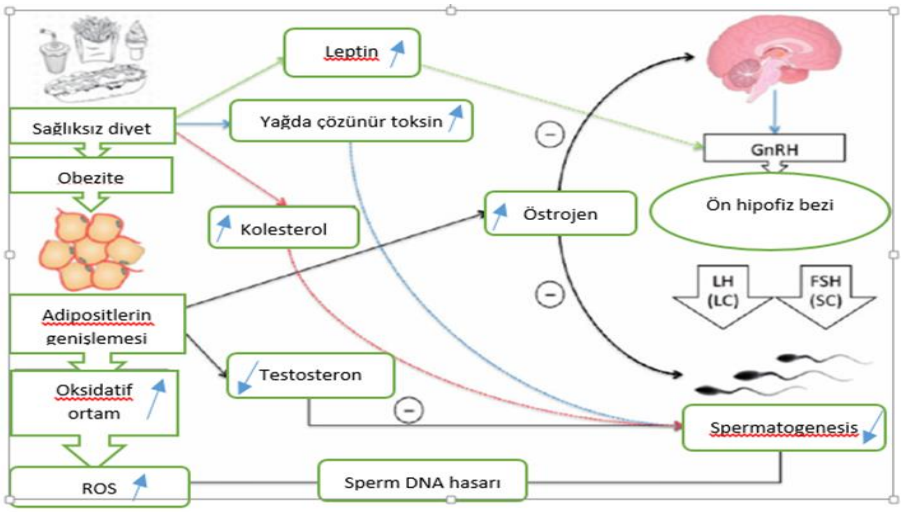

Figure 1. Overall impact of diet and nutrition on spermatogenesis. Enhanced unhealthy nutrition can lead to impaired spermatogenesis due to high cholesterol, leptin, reactive oxygen species homes and fat-soluble toxic substances. Abbreviations: FSH, follicle-stimulating hormone; GnRH, gonadotropin-releasing hormone; LC, Leydig cells; LH, luteinizing hormone; ROS, reactive oxygen types; SC, Sertoli cells (Phillips K and Tanphaichitr N, 2010)

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Along spermatogenesis, in the process of germ cell proliferation and mature sperm production of spermatogonium, a significant number of germ cells die with apoptosis. It is suggested to be a mechanism that adjusts the number of germ cells that die along spermatogenesis according to the supporting capacity of sertoli cells. In addition to physiological germ cell apoptosis that occurs continuously during life (25,26,27), testicular apoptosis of germ cells, gonadotropin (28,29), heat (30), exposure to toxins (31,32), ischemia reperfusion (33,34) and treatment with chemotherapeutic compounds or by various conditions such as irradiation (35). An augment in germ cell apoptosis has also been found in adult men infertility (36).

1. The Role of TRAIL in Infertility

Up to the present, three apoptosis-associated systems have been characterized in the testicle. These; tumor suppressor protein p53 (37,38), members of the Bcl-2 family (39,40,41,42) and the Moroccan system (43,44,29). The Fas system belongs to the tumor necrosis factor-alpha (TNF-α) gene superfamily (45) regulate several biological processes, including cell growth, differentiation, activation and apoptosis, and mostly perform the function of the immune system (46). Three of the ligands with type II transmembrane proteins; Fas ligand, TNF-α and TRAIL (TNF-α -related apoptosis-inducing ligand) have strong cytotoxic activity that induces apoptosis of sensitive cells. These cytotoxic ligands bind to cytoplasmic 'death domeins' by binding to Type I transmembrane receptors, Fas receptor, TNF-α receptor 1 (TNFR1) and TRAIL receptors, and eventually activate a protease chain that leads to apoptosis (47,48,49).

TRAIL, also called Apo2L, is the receptor involving death domains, DR4, and is a cytotoxic protein that induces apoptosis of several transformed cell lines (50). It is expressed as a tumor necrosis factor-related apoptosis-inducing ligand (TRAIL (TNFSF10), Type II membrane protein or a soluble cytokine (51), but also in plasma / serum, as well as in other body fluids of normal individuals (52,53,54) are in determinable amounts TRAIL interacts with any of the four transmembranes (TRAILR1, TRAILR2, TRAILR3 and TRAILR4) and one soluble (osteoprotegerin (OPG)) receptor, and also in different affinities. though, it acts as a homotrimer (55,50). The best characterized biological function of two TRAIL-receptors involving a death-domain (TRAILR1 and TRAILR2), after the binding of TRAIL It emerges as an apoptotic response where activation of intracellular signal transduction pathways such as ERK / MAPK, AKT and NF-kB is provided by the TRAILR2 connection (56, 57, 58,59, 60). TRAILR3 and TRAILR4 are admitted as membrane neutralizing or regulatory receptors. Despite OPG was initially defined as a member of the tumor necrosis factor (TNF) receptor family, despite it inhibits RANKL-mediated osteoclastogenesis, the capability to neutralize TRAIL has been notified in several in vitro studies (61,62,63).

The excess expression of TRAIL and its receptors in different tissues in human testicles is noteworthy (64). Despite TRAIL has been informed to contribute to the control of the number of spermatogonium (65), studies are still underway to fully illumine the physiopathological role of

TRAIL in the testicles. Moreover, in several studies stated by different research groups, TRAIL appears to show an anti-inflammatory activity (66,67,68,69). In a study by Grataroli et al., they demonstrated that TRAIL and its receptors are expressed in rat testicles along normal progress and TRAIL protein is found in different germ cell types, but these receptors were also notified to be detected in post-meiotic germ cells (70). In other study of the same team, the immuno-localization of TRAIL and its receptors was notified and was the first study in which their presence was defined in terms of protein and mRNA in human testicles. They have also been notified that TRAIL and its receptors such as DR4, DR5, DcR1 and DcR2 are expressed in adult human testicles. Thus, a co-localization of TRAIL ligand and TRAIL receptors was appointed in human testicular germ cells. Despite the role of the TRAIL ligand and its receptors in apoptosis or in the physiopathological context in the testicle is not yet completely known, it is thought that it may acts related with a signal transmission not associated with apoptosis (64).

Conclusion

The role of seminal fluid in the regulation of human reproductive processes has been established in several studies (71, 72). Various cytokines excreted by the seminal vesicle and prostate gland modulate the response of different cell populations, including spermatozoa and white blood cells. It has also been informed that seminal fluid influences the levels of cytokines and chemokines in the human cervix and has an immunological impact (73). In a study by Zauli et al. In 2014, soluble TRAIL was found in high levels in seminal plasma and demonstrated that TRAIL is a direct target, acting in a way that influences the viability of spermatozoa (74).

Chromatin condensation demonstrates the protamination of sperms along the development phases in the testicle. The close relationship of chromatin condensation level to male infertility is known. In addition, sperm DNA fragmentations occur in sperm development steps in maturing of the testicle or in seminal plasma.Several mechanisms, particularly ensure reactive oxygen derivatives, form DNA fragmentations (Basal semen parameters ensure the quality of being the first test to be applied in male infertility, as suggested by the World Health Organization (1). Consequently, new studies are needed to explain the mechanism that induces male infertility and to clarify the cellular size of the apoptosis mechanism that happens in a normal process at the phase of spermatogenesis in the testis. Thus, the physiopathology of testicular apoptosis can be better understood.

Conflict of Interest

The authors have any potential financial or commercial conflict of interest associated with this research manuscript (review article).

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