Journal of Biology, Agriculture and Healthcare
ISSN 2224-3208 (Paper) ISSN 2225-093X (Online)
Vol.3, No.3, 2013

Role of Interleukin 1, IL-18 and Tumor Necrosis Factor Alpha Levels in Seminal Plasma of Infertile Males in Hillah Patients

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Abstract:

Objective: Evaluation the role of tumor necrosis factor alpha (TNFα) and interleukin-18 (IL- 18) in male infertility.

Intervention: Interleukin 1, IL-18 and Tumor Necrosis Factor Alpha levels were measured in seminal plasma of in different groups of infertile males as well as in control men.

Results: The mean of the cytokines for **Normospermia IL-1** 24.11, **IL-18** 327.50, **TNF-α** 7.05. While the mean of the cytokines for **Oligospermia IL-1** 48.25, **IL-18** 584.60, **and TNF-α** 32.50. For the **Azoospermia** The mean of the cytokines **IL-1** 55.03, **IL-18** 741.30, **TNF-α** 35.73.

There was significantly elevated in the levels of TNFα and Interleukin 1 in seminal fluid correlate with leukocyte counts and ratios in the same ejaculates, also there was significantly elevated in the levels of IL-18 in seminal levels among infertile groups compared to normal control subjects.

Conclusions: Cytokines and especially IL-18 and TNFα may play a role in pathogenesis of male factor infertility and may be a part of infertility workup in near future.

Introduction:

Male infertility is a serious diagnostic problem and in many cases the exact cause of failure to reproduce remains unknown. New diagnostic methods are being evaluated in search of more precise diagnosis and possibility of causal treatment. Measuring the levels of cytokines, in seminal plasma, does not only expand the diagnostic option, but also, through the growing knowledge of immune process, can give rise to new therapeutic methods of improving the quality of semen and increasing the chance to reproduce[1].

Cytokines, important intra-cellular communicators, are involved in numerous physiological and pathological processes, which include mediation of inflammatory responses, reproductive physiology and regulation of gonadal steroid production and release [2].

Human sperm contains a wide spectrum of cytokines such as tumor necrosis Factor alpha (TNFα) and interleukin 18 (IL-18) [3].

There is clear evidence indicating the effects of cytokines on spermatozoa functions. It has been found that TNFα decreases the sperm motility [4]. And stimulate sperm membrane lipid peroxidation by increasing reactive oxygen species generation [5].

Different cytokines, such as interleukin-2 (IL-2), interleukin- 10 (IL-10), and tumor necrosis factor alpha (TNFα) have been found in prostate secretion fluids of CP patients and presumably play an important role in the process of CP [6, 7].

Interleukin 1 also is an important mediator of immunologic and pathologic responses to stress, infection, and antigenic challenge. It acts synergistically with other factors in the

activation and differentiation of B- cells to immunoglobulin secreting cells, and it stimulates the activation and differentiation of natural killer (NK) cells, fibroblasts, and

Thymocytes. It acts antiproliferatively, increases the tumor cytotoxicity of macrophages, and induces tumor regression. In synergy with TNFα, IL-1 plays an important role in bone metabolism. It has a variety of effects in the brain, such as induction of fever as an endogenous pyrogen, alteration of slow-wave sleep, and an important role in modulating reproductive functions through stimulation of corticotropin-releasing factor and ACTH secretion and further influence on the hypothalamic-pituitary-gonadal axis [8].

In the present study we measured the levels of representative cytokines: TNFα, proinflammatory; IL-10

anti-inflammatory; IL-2 immunoregulatory; Interleukin 1 and Interleukin 18.

Materials and Methods

Patients

This prospective study included 175 men from sub fertile couples with and without symptoms of genital tract infections. Semen samples were collected from out clinic from May/2011 to April/2012. The medium duration of infertility was 2 years. The age of the male patients ranged from 25 to 55 years. Couples presented for primary infertility in 65% and for secondary infertility in 35% of the cases.

Semen Analysis

Standard semen analysis according to World Health Organization (WHO) criteria [9] included determination of sperm count, progressive motility after liquefaction, after 2 and 4 hours, pH, morphology, and viability (eosin testing). If necessary, seminal plasma was kept frozen at -80°C until further use. Semen samples were also used to screen for ASA by means of the mixed antiglobulin reaction (MAR) test [10, 11].

Examination of Cytokines

For the determination of TNFα in SP a commercial ELISA kit was used (Biotech, Germany) according to the manufacturer's instructions.

Results and Discussion

This prospective study included 175 men from sub fertile couples with and without symptoms of genital tract infections. Semen samples were collected from out clinic from May/2011 to April/2012.

The mean of the cytokines for **Normospermia IL-1** 24.11, **IL-18** 327.50, **TNF-α** 7.05. While the mean of the cytokines for **Oligospermia IL-1** 48.25, **IL-18** 584.60, **and TNF-α** 32.50. For the **Azoospermia** The mean of the cytokines **IL-1** 55.03, **IL-18** 741.30, **TNF-α** 35.73 as showed in figure 1.

Male infertility caused by impaired semen quality is an enormous problem for the infertile couple and the andrologist [12].

The present study focused, in parallel, on two cytokines which are key proteins in inflammatory reactions, TNFα and IL-18 to evaluate their potential significance in male infertility investigations. Owing to the occurrence of TNFα receptors on nearly all cells, TNFα show a wide variety of biological actions which may interfere with reproductive functions, e.g., induction of immune cascade and chemotactic activity on neutrophils, cytolytic and cytostatic effects on tumor cells, induction of fibroblastic growth, stimulation of collagenase and prostaglandin synthesis and potential

influence on sperm motility and functional capacity [13]. Furthermore, testicular macrophages can exert cytokine-guided paracrine regulatory influence on Leydig cell function as an example of immune-endocrine interactions in the male reproductive system [14].

The significant elevation of TNFα in infertile males in our study compared to normal subjects are in accordance with other studies that showed similar results and suggested that TNFα might influence sperm motility and thereby affecting its cervical mucus penetration properties with subsequent reduced male fertility[13]. On the other hand, other studies reported no statistically significant difference detected among fertile and infertile groups regarding TNFα levels [14,15].

Interleukin-18 (IL-18), previously known as interferon (IFN) -ä inducing factor, is an immunoregulatory cytokine that is produced predominantly by activated macrophages [16]. IL-18 shares functional properties with interleukin-12 and has structural similarities with IL-1 protein family but exert its effects independently of both [17]. IL-18 further exerts pro-inflammatory properties by inducing the production of IL-16, IL-6, IL-8 and TNFα [18]. A highly significant elevation of seminal plasma levels of IL-18 was detected in this study in both oligo-asthenozoopermic and azoospermic males compared to controls. Such finding is supported by other studies that found out significant elevation of IL- 18 levels in infertile patients [19].

This study is the first to report existence of IL-18 in seminal plasma, they also reported an inverse correlation of IL-18 levels and number of spermatozoa but the reason for such finding is not directly evident. Up to our knowledge no other studies about IL-18 levels in seminal plasma are available in literature. Moreover, a significant positive correlation was detected between TNFα and IL-18 in normozoospermic versus oligoasthenozoospermic and azoospermic males. This could point out that TNFα stimulates secretion of IL-18 as an example of cascade of cytokines, which have similar or complementary biological activities.

Cytokines are produced in response to microbes and other antigens; different cytokines stimulate diverse responses of cells involved in immunity and inflammation. Male infertility caused by impaired semen quality is an enormous problem for the infertile couple and the andrologist [20].

The synthesis of IL-1 can also be induced by endotoxins, viruses, mitogens, and antigens. In contrast, prostaglandin 2, corticosteroids, lipoproteins, _2-macroglobulins, and a naturally occurring antagonist called interleukin 1 receptor antagonist inhibit IL-1 synthesis. Interleukin 1 mediates a wide variety of biologic actions in the immune system and

in the central nervous system and interferes with endocrine regulation. The influence via ACTH stimulation on cortisol and via adrenal gland androgens on spermatogenesis [20].

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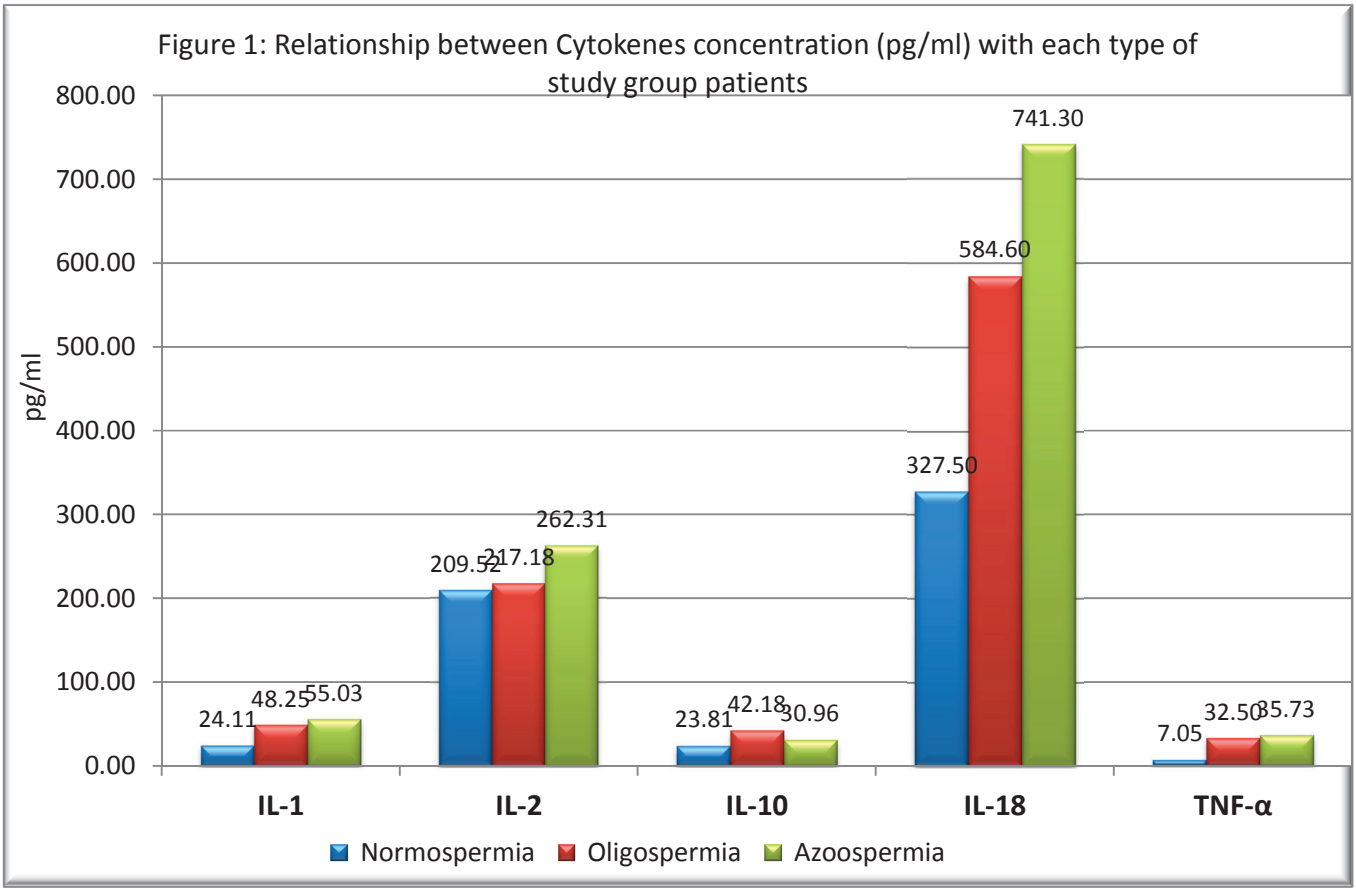
Figure 1: Relationship between Cytokenes concentration (pg/ml) with each type of study group patients



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