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Sexual dimorphism in physiological leptin levels as a risk factor for the male predominance of visceral leishmaniasis

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ABSTRACT

Leptin exhibits functional dimorphism since it acts as a hormone and as a cytokine (adipokine). As an adipokine, it regulates both innate and adaptive immunity. Leptin levels also exhibit sexual dimorphism in humans, since females have three-fold higher plasma leptin levels than males. However, leptin deficiency or its reduction in levels increases the risk of infectious diseases. Visceral leishmaniasis (VL) is one such fatal disease caused by a parasite infection. The VL cases are more predominant in males than females in endemic areas. This could be because of differences in socio-cultural activities and sex-related biological factors. Hence, our perspective is that the low plasma leptin levels in males are a gender-specific biological risk factor for VL prevalence. Low circulating leptin levels cause weaker immunity in males, which may increase the risk of VL. Apart from that, the male sex hormone testosterone also shows a suppressive role in leptin production and immunity. In contrast, the female sex hormone estrogen induces the production of leptin, which may cause stronger immunity and high protection against infections such as VL. Hence, the sexual dimorphism in plasma leptin levels is likely to evolve as a molecular and/or epidemiological marker in gender-based prevalence studies of VL.

Keywords - Leishmaniasis; Leptin; Gender; Prognosis

Abbreviations

VL, visceral leishmaniasis; HIV, human immunodeficiency virus; IL, interleukin; TNF-α, tumor necrosis factor-α; Th, T helper.

Introduction

Visceral leishmaniasis (VL) is the second-largest parasitic disease caused by *Leishmania donovani*, which is transmitted by the bite of infected female sandflies. Worldwide, more than 600 million people are living at risk of developing VL, and 50,000-90,000 new cases are reported every year. Among them, during 2020, 90% of the global VL burden was reported from just 10 countries (Brazil, India, China, Ethiopia, Kenya, Somalia, South Sudan, Sudan, Yemen, and Eritrea). In endemic regions of the world, VL affects the poorest of the poor population, accompanied by malnutrition and weakened immunity. In addition, Human immunodeficiency virus (HIV) infected individuals have ~100 times higher risk of developingactive VL, and such deadly co-infections are difficult to cure [1]. The manifestation of VL includes fever, weight loss, and hepatosplenomegaly. If left untreated, the majority of the VL cases(>95%) develop into fatal forms. Existing treatment procedures have serious drawbacks in terms of safety, resistance, stability, and cost [2]. All these factors make VL a global public health problem. As per the literature, men are highly susceptible to infectious diseases due to their weak immune response to invading pathogens. In contrast, women respond very strongly against pathogens causing damage at the early stages of infection, but if it persists for a long time even after the clearance of the pathogen from the body, it would lead to autoimmunity [30]. Therefore, it is required to produce a sufficiently balanced immune response, which can be regulated by hormonal, genetic, and epigenetic factors. The most common perception of high incidence and morbidity of infections in men is behavioral differences like exposure to pathogens and medical care accessibility [32]. But the difference in physiological factors (e.g. hormones, enzymes, cytokines, and immune cells, etc.) between the sexes would contribute more than the behavioral factors to the high incidence of infections in men [31].

1.1. Male predominance of VL

In terms of VL, epidemiological studies indicate that men are more likely thanwomen to contract the disease [3]. In a population-based cohort study, the sex ratio (male (M) to female (F)) among reported VLcases from India and Nepal was 1.40, and the M/F risk ratio was 1.27. Moreover, males have reported with 19% higher chance of seropositivity than females [3]. A similar pattern (male predominance) of VL distribution was also observed in other endemic countries of the world [4-6]. This trend of VL distribution is possibly due to the difference in socio-cultural activities, sex-related biological factors [3], genetic reconstitution, and levels of immunity [7] between the genders. However, there is no molecular-level data available to date to support the epidemiological findings that, men are more likely than women to contract VL. Based on our previous findings, the current perspective is that the low physiological leptin levels (a biological factor) in men may be one of the critical reasons for weaker immunity than in women, which could enhance the incidence, morbidity, and mortality of VL in males (figure. 1).

Discussion

2.1. Adipokine role of leptin

Leptin is a protein hormone produced from white adipose tissue [8]. The hormonal action of leptin regulates several metabolisms (i.e., energy, glucose, lipid, bone metabolism, etc.) [9].In addition, it acts like a cytokine (adipokine), since its structure resembles the class I family of cytokines with four alpha-helix bundles [10]. The adipokine action of leptin regulates hematopoiesis, angiogenesis, and innate and adaptive immunity [11]. Also, leptin increases macrophage phagocytic activity [12], neutrophil chemotaxis, and proinflammatory cytokines (interleukin (IL)-6, IL-12, tumor necrosis factor (TNF)-α) production [13,14]. Leptin stimulates the proliferation of T helper 1 cell (Th1) and inhibits the proliferation of regulatoryT cells and Th2 cells [11,15,16]. Moreover, deficiency of leptin signaling or low leptin levelsis reported to increase the malfunction of the immune system and the risk of infections [17].

Association between VL and leptin levels

A high Th2 and low Th1 cytokine production as well as regulatory T cells producing IL-10 areassociated with VL pathogenesis [18,19]. Hence, the inverse effects of leptin might offer protection from VL. Furthermore, *L. donovani* infection in experimental animals affects the serum leptin levels and triglyceride levels [20], and lower serum leptin levels in VL patients arepositively correlated with severity parameters [21]. Likewise, the dysregulation of leptin (adipokine) production during VL may cause immune dysfunction and this could be one of thehost evasion mechanisms exhibited by *L. donovani* parasite. Also, altered lipid profiles in the host may be responsible for the drop in leptin levels during *L. donovani* infection [22]. Hence, hyperlipidemia may offer protection to the VL [23] by inducing leptin production.

Sexual dimorphism in leptin levels

Leptin exhibits sexual dimorphism with relatively higher levels in women [24-26]. The averageleptin levels in males and females are 0.17±0.01 ng/ml/kg and 0.49 ± 0.05 ng/ml/kgrespectively [24]. This is because at equal body mass index women have 10% higher body fat mass than men [27]. In contrast, independent of relative variation in total bodyfat mass, the plasma leptin levels are three-fold higher in women (19.9 ± 15.0 ng/ml) than in men (6.2 ± 3.5 ng/ml) [28]. It suggests that the gender-based difference in leptin levels is influenced by several factors. Sex steroids are one such important regulator [24] that shows the contrasting effect on leptin production. Testosterone in males [9,29] and estrogens in females [9,26] are likely to suppress and arouse leptin production, respectively. In addition, subcutaneous fat may also contribute to the higher leptin levels in women compared to men [25].

Conclusion

In conclusion, the sexual dimorphism in leptin levels is likely to evolve as a molecular and/or epidemiological marker in gender-based prevalence studies of VL. Epidemiological surveys on gender-based plasma leptin levels will contribute to understanding the relationship between leptin levels and male susceptibility to VL. The plasma leptin levels in pre- and post-treated male VL patients will help in assessing disease severity and rate of cure. Hence, leptin could be considered a prognostic marker for VL severity. In addition, strategiescould also be framed in the form of diet or medicine to improve leptin levels in males as apreventive measure. The same can be employed in the future VL elimination programs from the public health point of view.

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Conflict of Interest

The authors declared no conflicts.

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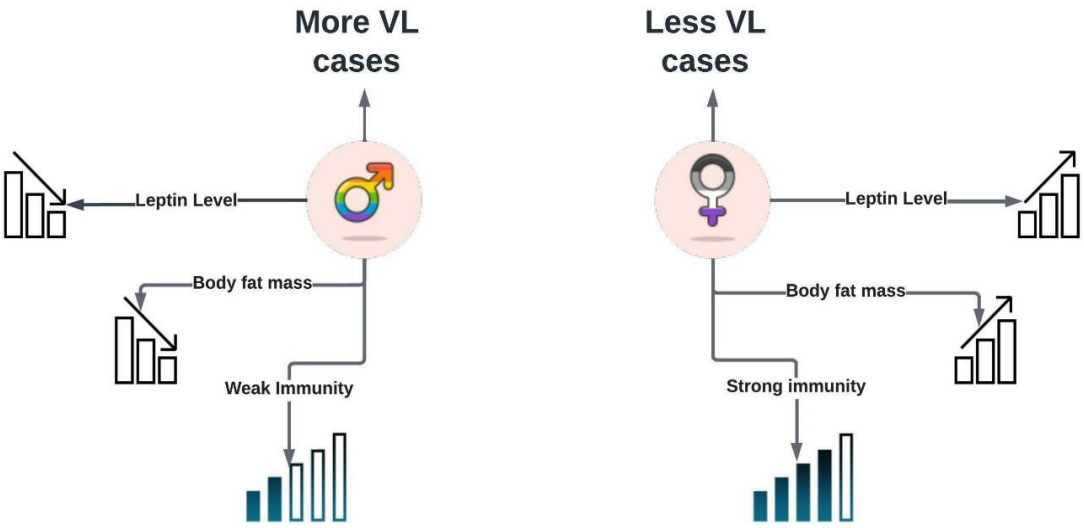

Figure 1. Possible relation between sexual dimorphism in leptin levels and risk of VL