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Changes in plasma levels of endocrine hormones in lepromatous leprosy patients

Yosef Tsegaye Dabi[1,2,*], Sisay Teka Degechisa[3], Kidist Bobosha[2], Liya Wassie[2]

[1] Department of Medical Laboratory Science, Institute of Health Sciences, Wollega University, Nekemte, Ethiopia
[2] Armauer Hansen Research Institute, Addis Ababa, Ethiopia
[3] Department of Medical Biochemistry, School of Medicine, College of Health Sciences, Addis Ababa University, Addis Ababa, Ethiopia

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ABSTRACT

Background: Leprosy affects various endocrine glands and causes disorders in internal organs in addition to the skin and peripheral nerves. These disorders are often silent and remain undiagnosed or underreported. In particular, patterns of hormone changes during leprosy, especially in lepromatous leprosy (LL) patients, are often associated with dysregulation of different endocrine and sex hormones. The aim of this study was to assess changes in four endocrine hormones — namely cortisol, dehydroepiandrosterone (DHEA), growth hormone (GH), and leptin — among LL patients compared with apparently healthy controls.

Method: In total, 80 plasma samples were systematically retrieved from a biorepository at the Armauer Hansen Research Institute (AHRI), based on quality, adequacy of sample volume, and appropriateness of linked clinical and sociodemographic data. Forty of the samples were obtained from LL patients (cases) and the remaining 40 from apparently healthy controls. Enzyme-linked immunosorbant assay (ELISA) was used to quantify levels of DHEA, cortisol, GH, and leptin hormones in the plasma samples. Data were analyzed using non-parametric statistics and the Mann–Whitney U-test (GraphPad Prism version 7.01). A p-value < 0.05 was considered statistically significant.

Results: Plasma levels of cortisol concentration were significantly higher in LL cases (median = 111.4 ng/ml, range = 20.54–525.7) compared with healthy controls (median = 51.98 ng/ml, range = 3.805–328.4) ($p = 0.003$). Levels of GH and leptin were significantly lower in LL cases compared with healthy controls (median values for GH = 1.01 μIU/ml, range = 0.4625–86.82 and 2 μIU/ml, range = 0.5838–63.36, respectively ($p = 0.022$); median values for leptin = 891 pg/ml, range = 728.4–21816 and 5147 pg/ml, range = 730.4–52747, respectively ($p < 0.0001$)). There was an apparent reduction in the plasma levels of DHEA among LL cases compared with healthy controls ($p = 0.297$), although this difference was not statistically significant.

Conclusion: Alterations in levels of endocrine hormones seen in LL patients reflect clinical and immunological conditions during lepromatous leprosy. However, large-scale studies are warranted to determine how leprosy causes such alterations in hormones and the interplay between endocrine hormones and the immune system during leprosy disease.

Introduction

Leprosy, a chronic infectious disease caused by an intracellular acid-fast bacillus, *Mycobacterium leprae* (*M. leprae*) [1], remains a major public health issue in developing countries, causing damage to peripheral nerves, anesthetic skin lesions, and loss of muscle function, in some cases leading to permanent disability in various body parts [2]. Ridley and Jopling classified leprosy using a five-point spectrum of clinical images, namely: tuberculoid leprosy (TT), borderline tuberculoid leprosy (BT), mid-borderline leprosy (BB), borderline lepromatous leprosy (BL), and lepromatous leprosy (LL), with TT and LL forming the two poles of the spectrum [3].

A characteristic set of pathological and clinical signs specific to leprosy is associated with the host immune system's response to the infection. TT is distinguished by significant immunological resistance to *M. leprae* and a cell-mediated immune response with a Th1 pattern that limits the pathogen's proliferation. In hosts with low levels of resistance, however, the disease is characterized by widespread presence of the bacilli and a primarily humoral immune response in a Th2 pattern.

* Corresponding author: Yosef Tsegaye Dabi, Department of Medical Laboratory Science, Institute of Health Sciences, Wollega University, Nekemte, Ethiopia, Tel: +251 911 364 465.
E-mail address: yoseftsegaye01@gmail.com (Y.T. Dabi).

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The immune response at leprosy pathological sites is highly complex and harbors other T cell subsets, including immune-suppressing CD4+CD25+Foxp3+ regulatory T cells (Treg cells) and proinflammatory Th17 cells. Interestingly, Treg cells are abundantly found in LL, whereas in the TT clinical form of the disease Th17 cells are more plentiful. Treg cells are characterized by suppressing effector T cell (Th1 and Th17) function [4–7]. Notably, LL represents the severe forms of the disease manifestations, causing permanent disfigurement and loss of sensational feelings [2,3,8,9].

Endocrine disorders of leprosy have long been recognized [4]. These disorders result from the direct involvement of the tissue or are due to the alteration in immune response [10]. Some studies have reported that leprosy, especially the LL form, affects various endocrine glands, including the testis [11,12], adrenal glands [10,13], pituitary gland, and thyroid gland [14]. However, disorders in these glands are often silent, unreported, or remain undiagnosed in these patients. A few studies have reported reduced levels of adrenal androgen dehydroepiandrosterone sulfate (DHEA-S) in leprosy patients compared with sex-matched healthy controls [15], or relative adrenocortical hypofunction [13] or lower levels of cortisol in multibacillary leprosy patients [16]. Nevertheless, little has been reported on how hormone levels change during lepromatous leprosy. Our study therefore aimed to determine levels of selected endocrine hormones (cortisol, DHEA, growth hormone, and leptin) among LL patients compared with age-matched healthy controls.

Materials and methods

Study setting

As previously described [17], 80 plasma samples, collected between 2005 and 2013, were systematically retrieved (based on quality, adequate sample availability, and linked clinical and sociodemographic data) from a biorepository facility at the Armauer Hansen Research Institute (AHRI) laboratory for analyses. These plasma samples were retrieved from 40 lepromatous leprosy (LL) patients and 40 age-matched, apparently healthy controls. The mean age of LL patients was 27.3 ± 8.6 years (mean ± SD), whereas for the apparently healthy control group it was 21 ± 7.8 years (mean ± SD). Of the total cases included in this study, 80% (n = 32) of the LL cases had a bacterial index (BI) ≥ 2. All samples were obtained from a cohort of consenting, adult, HIV-negative adults. According to the repository database, samples from individuals with a clinical history of severe malnourishment, anemia, or other debilitating conditions were not included during the initial screening and registration of participants. This study did not include samples with icteric or turbid plasma.

Plasma sample preparation and quantification of hormone using enzyme-linked immunosorbent assay (ELISA)

Plasma concentrations of DHEA, cortisol, growth hormone, and leptin were measured using commercially available ELISA kits. Briefly, plasma samples were thawed and assayed using commercially available ELISA kits for the specified hormones, as described earlier [17]. Data generated were entered into Excel, cleaned, and imported to GraphPad Prism version 7.01 for Windows (GraphPad Software, San Diego, California, USA; www.graphpad.com) for statistical analyses. Comparisons between groups were performed using non-parametric statistics and the Mann-Whitney U-test, and a p-value less than 0.05 was considered statistically significant.

Results

Plasma levels of hormones among LL patients and apparently healthy controls

The median plasma concentration of cortisol was significantly higher in LL patients compared with healthy controls (median = 111.4 ng/ml, range = 20.54–525.7 vs 51.98 ng/ml, range = 3.805–328.4, respectively; p = 0.0003) (Figure 1A). On the other hand, plasma concentrations of GH and leptin were significantly lower in LL patients compared with healthy controls — median concentration of GH = 1.01 μIU/ml (range = 0.4625–86.82) vs 2 μIU/ml (range = 0.5838–63.36), respectively (p = 0.022); median concentration of leptin = 891 pg/ml (range = 728.4–21 816) vs 5147 pg/ml (range = 730.4–52 747), respectively (p < 0.0001) (Figures 1B and 1C). In addition, there was an apparent decline in plasma concentrations of DHEA in LL patients compared with controls; however, this was not statistically significant — median = 2.995 ng/ml (range = 2.008–5.87) vs 3.992 ng/ml (range = 1.725–5.477), respectively (p = 0.297) (Figure 1D).

Discussion

Hormonal changes in leprosy are induced by either direct tissue involvement or a shift in the immune response [10]. Our study examined the plasma levels of hormones in LL patients compared with apparently health controls. Endocrine dysfunction is related to the severity of the disease and is more common in lepromatous forms of the disease [14]. Patients with LL were shown to have elevated Th2-type responses, high anti-*M. leprae* antibody titers, a significant reduction in cell-mediated immunity against the bacterium, a negative lepromin skin test, and decreased lymphocyte proliferation [18–20].

The mechanism underlying the *M. leprae*-specific T-cell anergy in LL patients is still not fully clear [7]. One possible explanation is that the bacilli can modulate cellular metabolism to support their survival [21], and these changes directly influence immune responses. Among the metabolic changes, the upregulation of cholesterol, phospholipids, and fatty acid biosynthesis is particularly important [22], because it leads to lipid accumulation in macrophages and Schwann cells, which modulate the inflammatory and immune responses [23]. Tregs may also contribute to this phenomenon by suppressing the Th1 response, since they are abundantly found in LL patients [7,23]. In leprosy, the production of CD4+CD25+Foxp3+ Treg cells may facilitate progressive reduction of the host pathogen-specific IFN-y response and resistance to infection, which may allow the bacillary load to increase and lead to the onset of active disease in some individuals, as in LL patients [23,24].

Interestingly, our study demonstrated that plasma leptin level was significantly reduced in LL patients compared with healthy controls. Studies have shown that an increase in leptin promotes T cell activation and shifts the T-cell cytokine production towards a Th1 response [7,18]. However, a decrease in leptin level may cause *M. leprae*-specific anergy in the Th1 response in LL patients, and thus favors the presence of a high bacillus load. This may be due to the fact that leptin action is a negative signal for the proliferation of naturally occurring human CD4+CD25+Foxp3+ Treg cells [24]. In other words, an increase in plasma leptin concentration limits the proliferation of Treg cells, whereas a decrease enhances the proliferation of these cells, as in LL patients. Previous studies have reported that leptin deficiency is responsible for immunosuppression and a reduced T cell response to microorganisms [17,25]. Whether leprosy causes leptin deficiency or leptin deficiency predisposes to the disease is not clear, and needs further investigation.

Our findings suggest that LL patients have altered adrenocortical hormone responses, with plasma cortisol levels considerably greater in LL patients than in controls. Cortisol has anti-inflammatory properties, and its levels in the circulation and peripheral tissues affect a range of proinflammatory cytokines, which in turn influence localized inflammation [26]. In contrast to our study, no significant differences in the levels of cortisol in leprosy cases and controls have previously been observed [14]. The findings of our study also indicate that LL patients have reduced DHEA levels; however, this was not statistically significant. DHEA is an antagonist hormone to cortisol that has been demonstrated to boost Th1 cytokine production, while inhibiting Th2 cytokine synthesis [27,28].

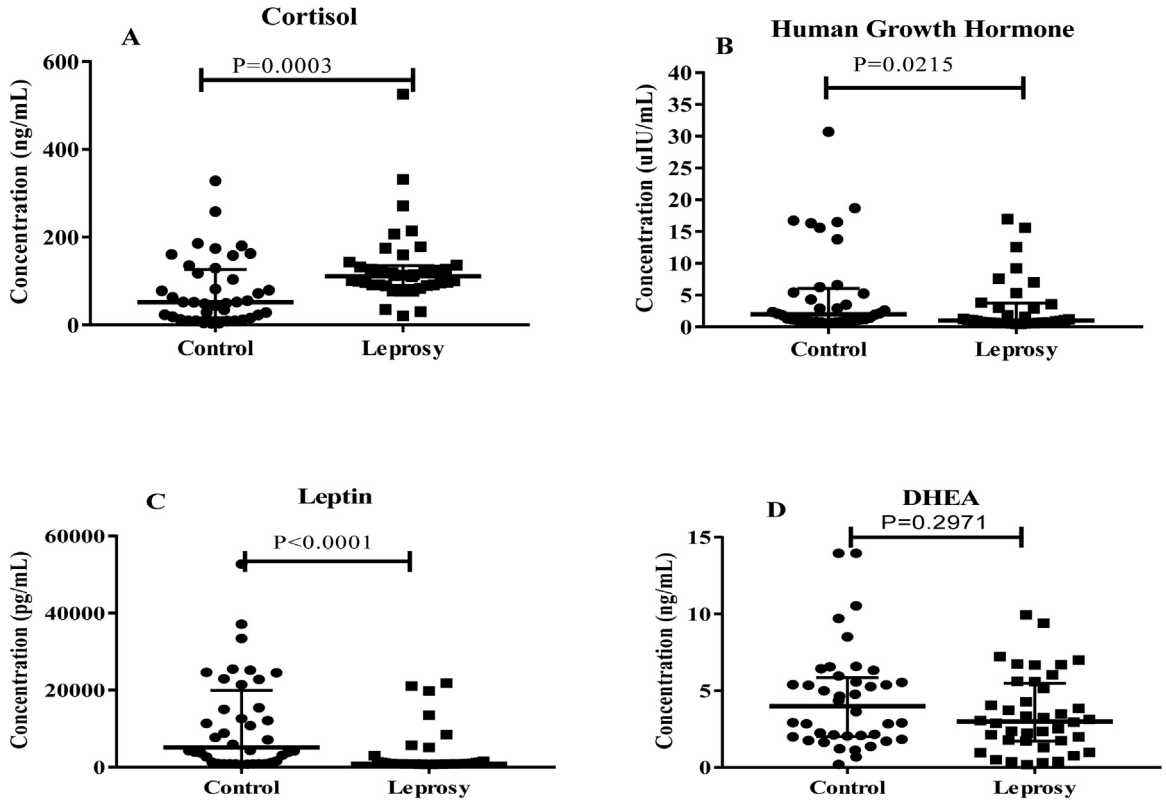

Figure 1. Dot-plots representing plasma concentrations of endocrine hormones in LL patients and apparently healthy controls. DHEA: dehydroepiandrosterone, GH: growth hormone

Evidence suggests that GH can modify the immune system, regulating both humoral and cellular immunological responses [29,30]. Some studies have also reported lower levels of circulating insulin-like growth factor 1 (IGF-I), which is generated in the liver under GH regulation, in LL patients compared with healthy controls [31]. However, other studies have reported no significant differences in the levels of GH between cases and controls [14,32], which indicates inconsistency across the literature.

In conclusion, endocrine hormone levels are altered in individuals with lepromatous leprosy, and a large-scale study is warranted to determine how leprosy causes such alterations in hormones and the interplay between endocrine hormones and the immune system during leprosy disease. Similarly, profiling these hormones across a spectrum of leprosy illness might provide insights as to how hormones affect the disease outcomes during the various clinical manifestations, and such investigations are warranted in future studies.

Conflicts of interest

The authors declare that this research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Ethical approval statement

Ethical approval was obtained from the AHRI/ALERT ethics review committee (Ref. PO07/18). To ensure the privacy and confidentiality of research participants, only anonymized samples were utilized. Institutional permission was also granted from AHRI to access biorepository samples and linked archived data.

Authors' contributions

YT carried out all the laboratory work, analyzed the data, and wrote the first draft of the manuscript. ST and KB analyzed the data, edited the manuscript, and supervised the work. LW conceived and designed the study, analyzed the data, supervised the study, and edited the manuscript. All authors contributed to the article and approved the submitted version.

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