SERUM LEPTIN LEVEL IN PATIENTS WITH LEPROSY

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ABSTRACT

Objective: we aim to analyze serum leptin levels of untreated leprosy patients, compare them with healthy controls, and co-relate the patterns of leptin with different parts of the spectrum of leprosy. We try to provide evidence that leptin contribute in the pathogenesis of leprosy.

Subjects and Methods: Thirty male cases of various types of untreated leprosy of different age were included in this study at Infectious Disease Hospital (IDH). In addition, fifteen healthy male individuals of comparable age, racial and BMI were taken as controls. Estimation of fasting blood sugar, fasting serum insulin, pro-inflammatory cytokine tumor necrosis factor alpha (TNFα) and interleukin 1 (IL1), estimation of morning serum leptin and calculation of **H**omeostasis **M**odel **A**ssessment for **I**nsulin **R**esistance (HOMA-IR) were done in both groups.

Result: Leptin levels were significantly higher in leprosy patients than in controls (mean serum leptin levels of 18.3 ng/mL versus 7.9 ng/mL, $p<0.001$). It has been further observed that there were significant increases as regard pro-inflammatory cytokine tumor necrosis factor alpha (TNFα) and interleukin-1 (IL1) in leprosy patients when compared with controls. Also, it has been observed that pro-inflammatory cytokines TNFα & IL1 and serum leptin levels amongst the various types of leprosy were much more in lepromatous form as compared to other clinical forms of leprosy.

Conclusion: in this article, it was noted that hyperleptinemia in leprosy patients is due to hyperinsulinemia, overproduction pro-inflammatory cytokines such as TNF-α and IL1 and through the stimulation of adipocytes with M. leprae or its dominant "lipopolysaccharide. Leptin hormone is thought to be a major factor in the pathogenesis of leprosy infection.

Key Words: Leprosy, leptin, Insulin resistance, pro-inflammatory cytokines.

INTRODUCTION

Leprosy is a chronic infectious disease caused by Mycobacterium leprae which is an obligate intracellular pathogen. It is characterised by a broad spectrum of clinical forms dictated by the patient's immune response to the organism. The tuberculoid pole has good cell mediated immunity to M.leprae, with few lesions and bacilli while the lepromatous pole has poor immunity coupled with extensive involvement and greater bacillary load. Between these two poles, there is the borderline group which can be divided into three subgroups: borderline tuberculoid (BT), mid borderline (BB) and borderline lepromatous (BL) [1].

Leptin is the 16-kDa non-glycosylated protein product of the ob gene [2]. It is a hormone synthesized mainly in adipose cells and it regulates body weight in a central manner, via its receptor in the hypothalamus [3]. Interestingly, there is increasing evidence that leptin has systemic effects apart from those related to energy homeostasis, including regulation of neuroendocrine, reproductive, haematopoietic and immune functions [4]. It is known that leptin secretion can be regulated by inflammatory mediators such as interleukin-1 (IL1) and tumor necrosis factor-α (TNFα) [5]. Furthermore, leptin exerts central effects on hypothalamic-pituitary function and these effects might affect the severity of leprosy disease.

Leptin, which is involved in a range of physiological processes, could be an important factor in the pathogenesis of leprosy. The aim of the present study is to analyze serum leptin levels of untreated leprosy patients, compare them with healthy controls, and co-relate the patterns of leptin with different parts of the spectrum of leprosy. We try to provide evidence that leptin contribute in the pathogenesis of leprosy.

PATIENTS AND METHODS

Thirty male cases of various types of untreated leprosy were included in this study as patients group. This study was conducted at the Infectious Disease Hospital (IDH), Kuwait, from April, 2010 to October, 2011. Of these, 13 patients are Indian, 7 Nepali, 4 Indonesian, 3 Egyptian, and 3 Bangladesh patients. In addition, fifteen healthy male individuals of comparable age, racial and BMI were taken as controls. All leprosy patients were diagnosed by clinical examination and their confirmation were made by histo-pathological examination of the lesions. The controls as well as leprosy cases were submitted to full history taking, thorough clinical examination, body mass index (kg/m^2), liver function test (LFT), kidney function test (KFT), complete blood count (CBC), fasting blood sugar, estimation of fasting serum insulin, estimation of pro-inflammatory cytokines tumor necrosis factor alpha (TNFα) and interleukin-1 (IL1) (Biomedix medical group, Synlab, German) and estimation of morning

serum leptin (Diagnostic Systems Laboratories, USA) using Enzyme Linked Immunosorbent Assay (ELISA). Calculation of Homeostasis Model Assessment for Insulin Resistance (HOMA-IR) is done by using the following equation= (fasting plasma insulin (μU/ml) × fasting plasma glucose (mmol/L) /22.5 and is highly correlated with insulin resistance [6].

STATISTICAL ANALYSIS

The data was analyzed using the statistical package for social sciences (spss) version 8.0 software. The significance of differences between mean values of the study variables was evaluated by using t-test. The significance of differences between proportions was performed using the Chi-square test. Correlation coefficient (r) between quantitative variables was calculated. The P value less than 0.05 is considered significant.

RESULT

The age, sex and BMI of patients in both groups were compared; no statistically significant differences in the means between the groups were observed (Table 1). This was intended to exclude factors that affect serum leptin levels. Leptin levels were significantly higher in patients group than in control group (mean serum leptin levels of 18.3 ng/mL versus 7.9 ng/mL, $p<0.001$). While fasting serum insulin levels were not significantly different between the two groups, there was significant difference in HOMA-IR (Table 1). It has been further observed that there were significant increases as regard pro-inflammatory cytokine tumor necrosis factor alpha (TNFα) and interleukin-1 (IL1) in leprosy patients when compared with controls (Table 1).

Also, it has been observed that pro-inflammatory cytokines TNFα & IL1 and serum leptin levels amongst the various types of leprosy were much more in lepromatous leprosy cases as compared to other clinical forms of leprosy (Table 2). We observed a positive correlation between leptin levels and pro-inflammatory cytokines TNFα & IL1 in patients group (Table 3). Similarly, we found a positive correlation between leptin levels and insulin as well as between leptin levels and HOMA-IR (Table 3).

Table 1: HOMA-IR, Serum insulin, TNFα, IL1 and serum leptin in studied groups.

	Leprosy patients	control	P value
	Mean ±SD	Mean ±SD	
Age	31.6 ±5.3	31.3 ±5.1	0.82
BMI	22.4 ±1.9	22.0 ±2.2	0.6
HOMA-IR	4.23±2	3.11±1	0.05* S
S. insulin	14.07±6.11	11.17±3.5	0.12 NS
TNFα	14.1±4.1	6.11±1.33	0.001** S
IL1	11.9±2.38	4.8±1.3	0.001** S
S. leptin	18.3±4.9	7.9±1.9	0.001** S

Table 2: HOMA-IR, Serum insulin, TNFα, IL1 and serum leptin in clinical types of leprosy.

	TT	B	LL	P1	P2	P3
	Mean ±SD	Mean ±SD	Mean ±SD			
HOMA-IR	3.1±2.4	3.5 ±1.31	4.7±2.3	0.61	0.2	0.34
S. insulin	11.3±7.1	14.5±4.6	15.4±9.1	0.35	0.23	0.77
TNFα	8.9±3.17	11.5±1.9	15.7±4.9	0.18	0.004* S	0.05* S
IL1	7.51±1.5	10.1±1.81	15.3±2.6	0.31	0.001* S	0.001* S
S. leptin	12.3±2.1	15.45±2.8	21.6±3.4	0.23	0.001* S	0.001* S

TT: Tubercliod leprosy; **BB**: Borderline leprosy; **LL**: lepromatous leprosy
P1: TT versus BB ; **P2**: TT versus LL; **P3**: BB versus LL

Table 3: Correlation between serum leptin levels, TNFα , IL1 and other parameters in studied groups.

	Serum Leptin				TNFα				IL1			
	patient group		control group		patient group		control group		patient group		control group	
	r	p	r	p	r	p	r	P	r	p	r	p
Age	-0.02	0.944 NS	-0.01	0.96 NS	0.19	0.48 NS	0.06	0.81 NS	0.18	0.44 NS	0.07	0.8 NS
BMI	0.29	0.1 NS	0.05	0.24 NS	-0.27	0.25 NS	0.03	0.68 NS	0.21	0.1 NS	0.07	0.32 NS
S. Insulin	0.56*	<0.05 **S**	0.44	0.09 NS	-0.23	0.404 NS	0.22	0.43 NS	0.25	0.41 NS	0.28	0.45 NS
HOMA-IR	0.52*	<0.05 **S**	0.43	0.104 NS	-0.32	0.25 NS	0.11	0.68 NS	0.19	0.49 NS	0.31	0.52 NS
S.Leptin	1.000	0	1.000	0	0.55*	<0.05 **S**	0.007	0.97 NS	0.60*	<0.01 **HS**	0.02	0.94 NS
TNFα	0.55*	<0.05 **S**	0.007	0.97 NS	1.000	0	1.000	0	-.21	0.45 NS	-0.18	0.5 NS
IL1	0.60*	<0.01 **HS**	0.02	0.94 NS	-.21	0.45 NS	-0.18	0.5 NS	1.000	0	1.000	0

DISCUSSION

Since leptin is involved in a range of physiological processes, it could be an important factor in leprosy infection development and outcome. Leprosy offers an attractive model for the investigations of the pathogenic correlation between the patterns of inflammation in the poles of its spectrum and leptin hormone. The exact nature of the association between leptin hormone and leprosy, up to this date; has not yet been clearly elucidated. In this study, we found a highly significant increase in serum leptin levels in patients group as compared with control group. Also, it has been established that serum leptin levels amongst the various types of leprosy were much more in lepromatous leprosy cases as compared to other clinical forms of leprosy. This might be due to several factors which may explain the elevation of serum leptin levels. First, the lepromatous leprosy is characterized by extensive involvement and greater bacillary load and it was documented that leptin levels are intensely increased by inflammatory induction such as bacterial lipopolysaccharide (LPS) stimuli [7].

Secondly, in this study, the serum leptin concentration was positively correlated with HOMA-IR which reflects the degree of insulin resistance and with the concentration of serum insulin. Our results are similar to other studies [8], which describe an important role for insulin in the state of hyperleptinemia. Compensatory hyperinsulinemia due to insulin resistance stimulates the adipocytes to produce leptin [9]. Also, hyperleptinemia can play a role in the pathogenesis of IR [10].

Thirdly, we observed that pro-inflammatory cytokines TNFα and IL1 levels were significantly higher in patients group than in control group. Similarly, pro-inflammatory cytokines TNFα and IL1 were much more in lepromatous leprosy cases than other clinical forms of leprosy. This matches what has earlier been reported by Pisa et al., (1990), who found higher levels of pro-inflammatory cytokines TNFα and IL1 in patients with leprosy and also reported that serum TNFα concentrations, as measured by an ELISA, were higher in individuals with the lepromatous form [11]. Because the total number of skin lesions and the total number of mononuclear cells exposed to M. leprae are far higher in lepromatous leprosy patients, the total TNFα secretory capacity of lepromatous leprosy patients may result in higher serum TNFα levels, although the biologic effect may be diminished by circulating inhibitors [12]. Recently, IL1 and TNFα have been implicated in leptin secretion regulation where they induce the production of leptin from adipocytes [13]. Also, Santos-Alvaraz et. al. have demonstrated that human leptin stimulates the production of cytokines such as TNFα and IL-6 [14].

These observations suggest that increased leptin production could be found as a normal component of inflammatory response in leprosy infection and also, could be linked with anorexia induced in lepromatous form of leprosy. A higher prevalence of peripheral neuropathy has been reported in subjects with leprosy, the over-expression and hyper-secretion of leptin contributes to the development of neuropathy [15].

In this context, increased leptin levels could be contribute to the pathological effects, through the influence of leptin on the wasting syndrome [16] and through its role in causing a positive feedback loop in the inflammatory process.

CONCLUSION

We can conclude that hyperleptinemia in leprosy patients is due to hyperinsulinemia, overproduction proinflammatory cytokines such as TNF-α and IL1 and through the stimulation of adipocytes with M. leprae or its dominant "lipopolysaccharide. Hyperleptinemia was much more in lepromatous form as compared to other clinical forms of leprosy. Leptin hormone is thought to be a major factor in the pathogenesis of leprosy infection.

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الملخص العربي

المقدمة :
يعتبر هرمون اللبتين من الهرمونات حديثة الاكتشاف والتي تشارك في مجموعة من العمليات الفسيولوجية و يمكن أيضا أن يكون عاملاً هاما في الآلية المرضية لمرض الجذام.

الهدف من الدراسة:
الهدف من هذه الدراسة هو تحليل مستويات اللبتين في مصل الدم لمرضى الجذام غير المعالج ومقارنتها مع مجموعة من الاصحاء كمجموعة ضابطة وتقدير مستوى اللبتين فى الاشكال المختلفة لمرض الجذام. ونحن في محاولة لتقديم أدلة على أن اللبتين تساهم في الآلية المرضية لمرض الجذام.

طريقة البحث:
اجريت هذه الدراسة فى مستشفى الامراض السارية بدولة الكويت عام ٢٠١٠ & ٢٠١٠ وقد تم تشخيص مرض الجذام عن طريق أخذ عينة من الجلد وقد تم قياس مستوى اللبتين والانسولين والانترلوكن ١وعامل النخر الورمى الفا فى مصل الدم .

الخلاصة:
قد اسفرت نتائج هذة الدراسة عن ارتفاع مستوى الليبتن فى مصل الدم لمرضى الجذم. ويعتقد هرمون اللبتين أن يكون عاملاً رئيسيا في الآلية المرضية لمرض الجذام