Original Research Article

Leptin, Insulin resistance and Dyslipidemia in Acanthosis Nigricans

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Abstract

Background: Leptin is a adipocytokine hormone, with 167 amino acids. It acts via hypothalamic neuronal pathway, signalling satiety centre and controlling body weight. Acanthosis nigricans is associated with Leptin, obesity, metabolic syndrome, hyperinsulinemia. **Methodology:** 35 cases with Acanthosis nigricans and 35 controls without Acanthosis nigricans were included for the study. Height, weight, BMI, hip and waist circumference was measured. Serum was estimated for Leptin, Glucose, insulin, insulin resistance, Total cholesterol, Triglyceride, HDL, LDL, and VLDL and compared between both groups. **Results and conclusion:** BMI, waist/hip ratio was high compared to controls. Leptin, Glucose, insulin, insulin resistance, Total cholesterol, LDL was increased in cases compared to controls. Triglyceride, HDL and VLDL didn't show significant changes. Hyperleptinemia, hyperglycemia, hyperinsulinemia, insulin resistance and dyslipidemia is associated with Acanthosis nigricans.

Keywords: Leptin, HOMA-IR, hyperinsulinemia, acanthosis nigricans, Cholesterol, triglyceride.

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INTRODUCTION

Leptin is a adipocytokine hormone, known as OB gene, located in chromosome no 7. It consists of three exons and two introns that span 20 kb of DNA. It is produced by white adipose tissue consisting of 167 aminoacids. It is 16 KD hormone regulates energy homeostasis via hypothalamic neuronal pathway expressing leptin receptor. Leptin signals satiety and controls body weight. It is unregulated by insulin and cortisol and downregulated by catecholamines.[1] Leptin secretion increases with increase in adipocyte and directly proportional to fat mass. Leptin suppresses appetite and increase energy expenditure. Hyperleptinemia and leptin resistance is strongly associated with metabolic syndrome. Leptin receptor deficiency is similar to leptin deficiency features like early infancy obesity, hyperphagia, hyperinsulinemia.[2] Acanthosis Nigricans (AN) is dark, coarse thickened skin with velvety texture being symmetrically distributed on the neck, axillae, antecubital, popliteal fossae and groin folds. Histopathologically, characterised by papillomatosis and hyperkeratosis of skin. Acanthosis nigricans is usually found with skinfolds, obesity, dyslipidemia and insulin resistance.[3, 4, 5] Grading of Acanthosis Nigricans is from 0 to 4. Grade 0- not visible on close inspection. Grade 1- Clearly present on close visual inspection, extent not measurable. Grade 2- limited to base of skull, doesn't extent to lateral margins of the neck. Grade 3- extending to the lateral margin of the neck, but not visible from front. Grade 4- extending anteriorly.[6]

METHODOLOGY

Study group consists of 70 participants with age group between 20 to 40 years of both sex. 35 cases was diagnosed with Acanthosis nigricans by dermatologists and all the grades of AN was included for the study. 35 participants without any features of AN was considered for control group. Height, weight, waist circumference and hip circumference were measured. BMI was

calculated using weight in kg/square of height in meters. Waist /hip ratio was calculated.

Fasting serum sample was collected from the study group. Fasting Glucose, Total cholesterol, HDL, TGL was estimated using commercially available kits in Seimens dimension Xpand analyser. VLDL was calculated using formula TGL/5. LDL-cholesterol was estimated using Freidewalds formula, LDL=Total chol – (HDL chol + VLDL chol). Fasting Insulin was determined in Advia Centaur Immunoassay system using commercially available kit. Leptin was estimated by Elisa method using Raybiotech kit in Alere Elisa instrument. HOMA-IR (Homeostatic model assessment- insulin resistance) was calculated based on the formula insulin (µIU/ml) X glucose (mmol/L) / 22.5. Or Insulin (µIU/ml) x glucose (mg/dl) / 405. Patients with other endocrine disorders like diabetes mellitus, cushing syndrome, acromegaly, pheochromocytoma, autoimmune disorders, liver or kidney disease or on Oral contraceptives drugs were all excluded. Statistical analysis was done using SPSS software. Student t test (two tailed, independent) was used to find the significance of study parameters.

RESULTS

Table 1 show that age and sex was matched between cases and controls. BMI and W/H ratio is significantly high in cases compared to controls (p value 0.035 and 0.075 respectively). Fasting Glucose and insulin is significantly high in cases compared to controls (p value <0.001 and 0.018 respectively) . Insulin resistance is high in patients with acanthuses Nigerians compared to controls (p value 0.002). Total cholesterol and LDL cholesterol is also significantly high in cases compared to controls (p value 0.082 and 0.076 respectively). HDL, TGL and VLDL don't show any changes among cases and controls. Leptin is high in acanthuses Nigerians compared to controls with P value 0.072.

Table 1: Comparison of Clinical parameters in case and controls

Variables	Cases	Control	P value
Age in years	30.46±4.74	30.69±5.52	0.853
Sex M/F	18/17	17/18	0.811
BMI (kg/m^2)	28.51±4.41	21.64±3.41	0.035*
Waist Hip Ratio	1.00±0.19	0.91±0.06	0.075+
Glucose (mg/dl)	110.49±14.03	98.17±11.99	<0.001**
Insulin (µIU/ml)	14.16±5.66	11.13±4.81	0.018*
HOMA-IR	3.84±1.67	2.67±1.30	0.002**
Total Cholesterol (mg/dl)	221.03±50.34	200.03±49.15	0.082+
HDL (mg/dl)	28.66±6.93	31.31±7.68	0.133
LDL (mg/dl)	163.03±49.96	141.66±49.33	0.076+
VLDL (mg/dl)	29.29±6.01	27.06±6.62	0.145
TGL (mg/dl)	146.63±29.64	135.03±33.47	0.129
Leptin(ng/ml)	8.12±3.88	6.39±4.03	0.072+

+ Suggestive significance (P value: 0.05<P<0.10); * Moderately significant (P value: 0.01<P ≤ 0.05); ** Strongly significant (P value: P≤0.01)

DISCUSSION

Leptin is an antiobesity and satiety signalling hormone. In obesity, when the mass of adipocyte increase, there is accumulation of triglyceride and Leptin synthesis. Leptin is a neuro transmitter expressed in hypothalamus to decrease appetite to maintain BMI. Leptin increases to decreases appetite and stimulate energy expenditure. When the mass of adipose tissue decreases, leptin decreases to favour appetite and Leptin acts on Leptin receptor in arcuate nucleus of hypothalamus and modify expression of neuropeptides. It decreases neuropeptide Y, melanin concentrating hormone, orexins and agouti related peptide. These are appetite stimulating, orexigenic neuropeptides. Leptin increases anorexigenic neuropeptides like α-melanocyte stimulating hormone, cocaine and amphetamine regulated transcripts and corticotrophin releasing hormone. These are appetite decreasing, anorexigenic neuropeptides. But Leptin with gene polymorphism prevents the functional leptin protein, thereby less leptin expression leads to obesity.[7] Macrophages infiltrate obese adipose tissue and mediate obesity induced insulin resistance (IR). They release cytokines like interleukin-1, interleukin-6 and TNG-α creating proinflammatory reaction which block adipocyte insulin action, contributing to development of IR and type 2 diabetes mellitus. So, it is hypothesised that increased leptin level in hyperinsulinemia and Insulin resistance stimulate the production of TNF- α.[8] Insulin crosses dermoepidermal junction to reach keratinocytes. Insulin also stimulates growth and replication of fibroblast. Insulin growth factor (IGF) receptors are found in fibroblasts and keratinocytes. Insulin at high concentration binds to IGF-1, and regulates insulin like growth binding proteins. Hyperinsulinemia cause AN by exerting a direct toxic effect and indirectly by increasing free IGF 1. Half life of IGF 1 is increased by insulin like growth binding protein, IGFBP 1 and IGFBP 2, which decreases in obese subjects with hyperinsulinemia, thereby increasing free IGF1, promoting cell growth and differentiation of keratinocytes and fibroblasts. Thus insulin promotes Acanthosis Nigricans.[3] High levels of insulin activate the fibroblasts of dermal cells and keratinocytes of epidermal cells via insulin- like growth factor receptors on these cell. As a result, there is increasing dermal deposition of glycosaminoglycans by fibroblasts leading to papillomatosis, hyperkeratosis and acanthosis because of keratinocyte proliferation. AN has been ascribed to increase levels of insulin that acts on insulin like growth factors (IGF-1) receptor and fibroblast proliferation. In patients with congenital partial dystrophy, hyperinsulinemia and an increase in IGF-1/IGF-1 binding protein ratio appear to contribute to an unopposed biological effect of IGF-1 on IGF-1 receptors,

leading to the development of AN.[9] Hirschler V, *et al* established that one third of obese children with insulin resistance did not show evidence of acanthosis nigricans.[10] In contrary, vines RM, *et al*. showed that there is a strong association between IR and AN. He proves that hyperinsulinemia and hence IR is the marker for Acanthosis nigricans.[11] Sharquie KE, *et al*, showed that glucose, insulin, insulin resistance and leptin is high in patients with Acanthosis nigricans than compared to control individuals.[12] High levels of total cholesterol, and LDL – cholesterol is considered atherogenic, as they are inefficiently cleared by LDL –receptors, which increase the risk of entrapment in subenthothelial matrix. Decreased levels of HDL- cholesterol limit reverse cholesterol transport.[13]

CONCLUSION

Acanthosis nigricans is associated with increased BMI, waist circumference, Hip circumference, W/H ratio, fasting blood sugar, insulin, HOMA-IR, total cholesterol, LDL and Leptin compared to controls. Triglyceride and HDL didn't show significant changes in both groups. Hyperinsulinemia promotes growth and differentiation of keratinocytes and fibroblasts favouring acathosis nigricans. Hyperleptinemia is seen in obesity to decrease appetite and stimulate energy expenditure. HOMA-IR is also found to be high in AN. Leptin gene polymorphism leads to decreased leptin expression. Hence Hyperinsulinemia, Insulin resistance, hyperleptinemia , obesity is all associated with acanthosis nigricans.

REFERANCE

1. Muhammad Wasim. Role of Leptin in Obesity. J Obes Weight loss Ther 2015, 5: 2. 1000258.
2. EI Safoury OS, Abdel Hay RM, Fawzy MM, *et al*. Skin tags, leptin, metabolic syndrome and change of the life style. Indian J Dermatol Venereol Leprol 2011; 77: 577-80.
3. Phiske MM. An approach to acanthosis nigricans. Indian Dermatol Online J 2014; 5: 239-249
4. Pires A, Paula M, AM Pereira, Patrica VS, *et al*. Insulin Resistance, Dyslipidemia and Cardiovascular changes in a Group of Obese Children. Arq Bras Cardiol. 2015; 104(4):266-273.
5. Hah Yung Ng. Acanthosis nigricans in obese adolescents : Prevalence, Impact, and management challenges. Adolescent Health , Medicine and Therapeutics 2017:8: 1-10
6. Burke JP, Hale DE, *et al*. A quantitative scale of acanthosis nigricans . Diabetes Care 1999;22:1655-9.
7. Shahid A, Rana S, Mahmood S and Saeed S. Role of Leptin G-2548A polymorphism in age-and gender-specific development of obesity. J.Biosci.40 (3) 521-530.
8. Hegazy SK and EL-Ashmawy NE. Leptin and c-reactive protein are implicated in the pathogenesis of skin tags. Journal of Diabetes Research and Clinical Metabolism 2013,2:13.
9. Janssen JA, Hoogerbrugge N, van Neck JW, Uitterlinden P, Lamberts SW. The IGF-1/IGFBP system in congenital partial lipodystrophy. Clin Endocrinol (Oxf) 1998;49:465-73.
10. Hirschler V, Aranda C, Oneta A, Gonzalez C, Jadzonsky M. Is acanthosis nigricans a marker of insulin resistance in obese children? Diabetes Care. 2002; 25(12):2353.
11. Vines RM, *et al*. (insulin resistance syndrome in obesity. Arch Dis child. 2005:90(1):10-14.
12. Sharquie, K.E., Noaimi, A.A., Mahmood, H.G. and Al-Ogaily, S.M. Clinical and Biochemical Evaluation of Facial Acanthosis Nigricans. Journal of Cosmetics, Dermatological Sciences and Applications, 2015,5, 231-237.
13. N. Gupta, T. Singh, R Choudhary, S. K. Garg, G. S Sindhu, V Mittal and S Sule. Bilirubin in coronary artery disease: Cytotoxic or protective? World Journal of Gastrointestinal Pharmacology and Therapeutics 2016, 7(4): 469-476.

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