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Original Article

Serum insulin and leptin in patients with end stage renal disease on regular hemodialysis treatment (RDT)

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Abstract

This work aimed to study serum insulin and serum leptin in patients with end stage renal disease on regular hemodialysis therapy. The study included two groups:
Group I: 20 non diabetic, end stage renal disease male patients on regular hemodialysis therapy.
Group II: 12 volunteers non-diabetic males as a control group, they were age and height matched, and of the same socioeconomic class as patients group.
The results concluded that, patients with ESRD on RDT shawed decrease in mean body mass index (BMI), significant reduction in mean serum insulin level and non significant increase in mean serum leptin level compared to the control group.

Introduction

Patients with end stage renal disease (ESRD) on regular dialysis have negative nitrogen balance due to the removal of amino acid and peptides by the dialysis procedure, and because hemodialysis appears to stimulate protein catabolism, [1].
Insulin (MW 5.8 KD) is secreted from the pancreatic islet ß cell. It acts through binding to high affinity Tyrosine Kinase receptors that are widely distributed in tissue. One of the major functions of insulin is the regulation of glucose uptake into cell, although it has a week mitogenic effect on cells and tissue through activation of transcription factors and transcription of several genes [2]. The half-life of insulin in the circulation in humans is about five minutes, 80% of secreted insulin is normally degraded in the liver and kidney [3].

Leptin – from the Greek word "Leptos" (Thin) - MW 16 KD, is almost exclusively produced by adipocytes. A strong positive correlation exists between the body fat mass and serum leptin level. In lean subject, the majority of leptin circulates in the bound form, while in obese subject the majority of leptin is present in free form. Leptin reaches the brain by a saturable transport mechanism via the blood brain barrier. The weight reducing effect of leptin may be mediated by signal transudation through leptin-receptor in hypothalamus that modulate the activity of neuromodulators known to affect feeding behavior such as neuropeptide Y (NPY) and melanocortin [4]. Leptin also modulates other physiologic action such as hematopoiesis, pancreatic α-cell function [5], thermogenesis [6], ovarian function and angiogenesis [4]. The kidney is the main organ responsible for leptin clearance [7].

Aim of the study

This work aimed to study the relation between serum leptin and serum insulin levels in patient with end stage renal disease on regular hemodialysis therapy.

Materials and methods

This study included two groups:
Group I: 20 non diabetic end stage renal disease male patients on regular hemodialysis therapy, 12 hour / week, schedule on three settings.
Group II: 12 volunteers non-diabetic males as a control group. They were age and height matched, and of the same socioeconomic class as patients group (from patients relatives or friends).

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Methods: All subjects were subjected to the following:

- Clinical examination
- Measurement of height & weight
- Biochemical assessment of serum creatinine, HBA1C.
- Measurement of serum leptin [8]
- Measurement of serum insulin [9]

Result:

Table 1 shows the laboratory & clinical data of patients group (Group I).

Table 1. Group I (patients) laboratory data & BMI

Pt.No.	*S. leptin ng/ml*	*S. Insulin ng/ml*	*S.creatinin mg/dl*	*BMI*
1	14.90	6.831	13.5	20.6
2	18.35	7.134	12.6	27.8
3	0.913	6.549	9.8	26.4
4	1.166	6.775	10.2	21.4
5	14.29	33	14.2	26.3
6	1.564	12.4	11.9	20.3
7	1.365	6.606	12.1	23.9
8	2.368	12.77	13.4	21.2
9	1.544	65.10	9.8	24.0
10	3.586	6.549	8.2	24.2
11	1.604	12.17	12.3	24.0
12	1.974	7.134	14.1	17.2
13	3.086	6.718	14.0	22.9
14	4.191	7.335	13.2	21.1
15	12.89	8.371	11.9	21.8
16	1.723	7.223	10.8	21.2
17	3.694	7.0	10.0	24.0
18	1.604	7.61	12.1	23.3
19	8.879	26.93	9.9	23.0
20	3.889	16.35	12.3	20.8
Mean	5.17	13.212	11.815	22.77
SD	5.46	14.28	1.716	2.46

Table 2 shows the laboratory and clinical data of the control group (Group II).

Table 2. Group II (control) laboratory data & BMI

Pt.No.	*S. leptin ng/ml*	*S. insulin ng/ml*	*S. creatinin mg/dl*	*BMI*
1	2.826	67.8	0.9	33.7
2	8.037	79.07	0.8	33.6
3	3.26	68.09	1.0	29.4
4	4.191	69.88	1.1	30.7
5	3.694	70.57	0.9	28
6	3.086	70.64	0.9	26.4
7	2.93	67.7	0.8	27.6
8	8.06	79.9	0.7	26.8

9	3.19	68.88	0.9	30.4
10	4.49	69.75	0.8	31.4
11	3.49	70.46	1.0	31.5
12	2.93	70.8	1.1	32.3
Mean	4.182	71.12	0.908	30.15
SD	1.87	4.06	0.12	2.51

Analysis of result

Body mass index has been calculated using the following equation:
BMI = weight in Kg/ (height in mater)^2.
The mean BMI of group I (22.77±2.46) was significantly lower than the mean BMI of group II (30.15±2.51) "P< 0.001".

Serum leptin

The mean serum leptin level of group I (5.17 ± 5.46 ng/ml) was higher than that of group II (4.182 ± 1.87 ng/ml), but this difference was statistically insignificant.

Serum insulin

There is a significant difference in the mean serum insulin level in patients groups (Group I) compared to control group (Group II) (13.21±14.28 VS 71.12±4.06 ng/ml, P<0.001).

Discussion

Proinsulin (86 amino acid residues) is syntheized in pancreatic islet ß cells and gives rise to insulin (MW 5.8 kD) and C-peptide after proteolytic cleavage. Insulin acts through specific high-affinity tyrosine kinase receptors that are widely distributed in tissue. Binding of insulin to receptors cause autophosphorylation of α-subunit of the receptor, and activation of the receptor tyrosine kinase which leads to activation of a series of tyrosine kinase signaling molecules in effector cells. Activation of transcription factor is associated with cell growth and transcription of several other genes [2]. Patients on maintenance hemodialysis have increased dietary protein requirement, probably because of the removal of amino acid and peptides by the dialysis procedure, and because hemodialysis appears to stimulate protein catabolism, particularly when it is conducted with less biocompatible dialysis membranes. Most patients on regular hemodialysis probably require about 1.0 to 1.2 gram protein / kg body weight /day. 1.2g/kg/day protein is recommended. To ensure adequate intake of essential amino acids at least half of the dietary protein should be of high biologic value [1].
In our study, there is a significant difference between the mean serum insulin levels in patient group (Group I) 13.212±14.28 ng/ml compared to control group (Group II) 11.12±4.06 ng/ml (P<0.001). This could be attributed to the following:

a) In group II the mean BMI was 30.15 ± 2.51 which is considered elevated (i.e. obese subject) and obesity is commonly associated with hyper-insulinemia and insulin resistance [10]. Hyperinsulinemia in obesity may be attributed to increase in body fat and mobilization of excess free fatty acid in the portal circulation which reduce hepatic clearance of insulin [11].
b) In group I (patients group) restriction of protein intake in diet will result in mild transient increase in plasma amino acid after a protein meal compared to marked increase in plasma amino acid in control group after a protein-rich meal, which is accompanied by, increased secretion of insulin [12].
c) Decrease appetite of patients with end stage renal disease may decrease the neuronal factors which stimulate insulin secretion in response to presence of food in the intestine. Also the stress condition which is faced by patients group leads to an increased serum level of epinephrine and norepinephrine that may shut off insulin secretion through α2 receptor on the surface of beta cells [11].

Leptin has a direct effect on hypothalamus which decreases appetite and increases metabolism. Leptin receptor (OB-R) belongs to class I cytokine receptor family and there are six alternatively spliced form of leptin receptor. OB-Ra receptor is present in all tissue; OB-Rb is expressed at a high level in the hypothalamus. The weight-reducing effect of leptin is mediated by signal transduction through leptin receptor in hypothalamus that modulates the activity of neuromodulators known to affect feeding behavior such as neuropeptide Y (NPY) and melanocortin [4].
In our study, we found that there is an increase in the mean serum leptin levels in patients group (5.17 ± 5.46 ng/ml) compared to control group (4.18 ± 1.87 ng/ml) but the difference was statistically insignificant. The lower mean BMI of patients group compared to controls (22.77 ± 2.46 vs. 30.15 ± 2.51) may explain the difference in mean serum leptin levels. The higher mean serum leptin levels may indicate a decrease in body fat, increased inflammation, or decreased elimination of leptin from our patients group.
Patient with ESRD especially males with low body mass index (BMI) and low plasma insulin level maintain a normal or even low leptin level, [4], and our patients have very low serum insulin (13.21 ± 14.28)

compared to the control group (71.12 ± 2.06) and both groups are nondiabetics. Reduced renal elimination play a major role in elevation of plasma leptin level in patient with ESRD, but other factors such as infection and inflammation that provoke cytokines release, trigger release of leptin from fat cell may have a role [12].

Leptin is partly cleared by the kidney and is not removed by hemodialysis using modified cellulose membranes [13]. Other counter regulatory mechanism(s) may become operative in ESRD and it is possible that non renal (splanchnic) organs contribute to some leptin removal [4].

Conclusion: Patients with ESRD on RDT have:

1- Decrease mean BMI compared to control.
2- Significant reduction in mean serum insulin level.
3- Increase but non significant in mean serum leptin level.

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References

1. Joel D Lopple: Chronic renal failure, in Text book of nephrology, 4th ed, P1463, Ed Massry & Classock 2001 Lippincott Williams & Wilkins NY, 2001.
2. Raimund Hirschberg: Insulin, Insulin like growth factor 1, somatostatin, & glucagons. In Text book of nephrology, 4th ed, P220-222, Ed Massry & Classock, Lippincott Williams & Wilkins NY, 2001.
3. Ganong WF: Structure, Biosynthesis & Secretion of Insulin. Review of Medical Physiology. 7th ed. Appletion & Lange publishers, 1995.
4. Peter Stenvinkel Leptin, in Text book of nephrology, 4th ed, P 1367 – 1371, Ed Massry & Classock, Lippincott Williams & Wilkins NY, 2001.
5. Widjaja A, Stratton IM, Horm R, and et al: Plasma leptin, obesity and plasma insulin in type II diabetic subjects. J. Clin. Enocrinol. Metab., 1997; 82 (2): 654-657.
6. Suslic VS, and Lowell BB: Brown adipose tissue and the regulation of body fat stores, Curr. Opim. Endo. Diabetes, 1996 3L: 44-50.
7. Haluzik M, Sulkova S, Svobodova J & et al: Serum leptin levels in diabetic patient on hemodialysis, relationship to parameters of diabetes metabolic control. Endocr, Res, 2000; 26(2): 303 – 317.
8. Schwartz MW. Baskin DG, and Buckowskitr: Specificity of leptin action on elevated blood glucose level and hypothalamic neuropeptide Y gene expression in ob/ob mice. Diabetes, 1996; 45: 531 – 535.
9. Immunoenzymetic assay for the quantitative measurement of human insulin in serum and plasma, code 40 125 00; BIOSOURCE, Europe S.A. 8, rue de I'Industrie. B01400 Nivelles, Belgium.
10. Defranzo RA & Ferrannini E: Insulin resistance: A multifaceted syndrome responsible for NIDDM, obesity, hypertension, dyslipidemia and atherosclerotic cardiovascular disease. Diabetes care, 1991; 14: 173- 194.
11. Johnson LR, Byrne JH, et al.: Physiological action of insulin. Essential Medical Physiology .2nd ed, Lippincott Raven, 1998.
12. Jonas Bergstrom: Appetite in chronic renal failure, in Text book of nephrology, 4th ed, P 1445, Ed Massry & Classock, Lippincott Williams & Wilkins NY, 2001.
13. Bernard L, Ziad M, & Tilman BD: Lipid metabolism. in Text book of nephrology, 4th ed , p 1351., Ed Massry & Classock , Lippincott Williams & Wilkins NY, 2001.