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To Evaluate the Role of Leptin in Diabetes for Male and Female Subjects

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Abstract: The leptin promotes weight loss and can reverse diabetes by improving glucose tolerance by its action on hypothalamus. Present study will be conducted to evaluate the role of leptin in obesity associated maturity onset diabetes. This study was approved by ethical committee of the institution. Study was performed as a randomized controlled trial and with parallel design separately for male and female subjects. The serum glucose, HbA1c, cholesterol, triglycerides, HDL, LDL, insulin, TNF- α, adiponectin and leptin were analyzed by using semi auto analyzer (ERBA^{TM}), ELIZA assay kit and chemiluminense assay. Study was done on 200 patients with type 2 diabetic patients to analyze the role of Leptin hormone in obesity induced type 2 diabetes. The type-II diabetes male patients were had significant higher fasting blood glucose (P<0.001), significant high significant HbA1c (P <0.001), non significant high cholesterol (P=0.332), non significant high triglycerides (P = 0.773), significantly higher high-density lipoprotein (P = 0.004), significantly higher low-density lipoprotein (P <0.001), significantly high insulin (P <0.001), significantly high TNF- α (P = <0.001), significant low adiponectin (P<0.001) and non significant low leptin (P<0.001) level were observed as compared to non diabetic subjects. The type-II diabetes female patients were had significant higher fasting blood glucose (P<0.001), significant high significant HbA1c (P <0.001), significant high cholesterol (P=0.016), significant high triglycerides (P = 0.025), non-significantly higher high-density lipoprotein (P = 0.599), significantly higher low-density lipoprotein (P <0.001), significantly high insulin (P = <0.001), significantly high TNF- α (P = <0.001), significant low adiponectin (P<0.001) and significant low leptin (P= 0.003) level were observed as compared to non diabetic subjects.
Keywords: T2DM, Glucose, Adiponectin, Leptin.

INTRODUCTION

Diabetes is a metabolic disorder that causes hyperglycemia and giving rise to various vascular complications [1].Diabetes is a forthcoming epidemic all over the globe that caused due to ineffective secretion of insulin or insulin resistance [3]. Diabetes Mellitus is classified on the basis of the pathogenic process that leads to hyperglycemia. The two mainly classified categories of DM include type 1 and type 2 DM [2].

Obesity and dyslipidemia take upper hand in the initiation, progression and complications of type 2 diabetes [4, 1]. Presently there are more than 62,000,000 people suffering from T2DM in India. Obesity and dyslipidemia are shown to play important role in its complications resulting in morbidity and mortality of T2DM [1].

Obesity and type 2 diabetes are closely associated with low plasma levels of cytokine adiponectin in different ethnic groups of the society and indicate that the degree of hypoadiponectinemia is often more closely related to the degree of insulin resistance and hyperinsulinemia than to the degree of adiposity and glucose intolerance[5].

Leptin, the 167 amino acid protein, is a cytokine-like hormone secreted from white adipose tissue. It was the first adipocytokine identified, encoded by the ob gene. Leptin receptors are expressed in a number of different tissues. Adipocytes have been identified as the primary site for leptin expression; however it is also expressed in the gastric wall, vascular wall, placenta, ovary, in skeletal muscle, and the liver [6-9]. Leptin has several roles, including growth control, metabolic control, immune regulation, insulin sensitivity regulation, and reproduction [10-12].

However, its most important role is in body weight regulation.

The mechanisms involved in leptin secretion are all quite different. The rate of insulin-stimulated glucose utilization in adipocytes is a key factor linking leptin secretion to body fat mass [13]. Although the mechanism is incompletely understood, it may involve glucose flux through the hexosamine pathway [14]. In addition, various observations indicate that leptin has a more important role than insulin in the CNS control of energy homeostasis. Insulin is secreted from the endocrine pancreas and exerts potent effects on peripheral nutrient storage. Insulin is an afferent signal to the CNS that causes long-term inhibitory effects on energy intake. Leptin receptors and insulin receptors are expressed by brain neurons involved in energy intake[15-17] and administration of either peptide directly into the brain reduces food intake whereas deficiency of either hormone does the opposite[18, 19].

Leptin is the chief regulator of the "brain gut axis", which provides a satiety signal through its action on the CNS receptors within the hypothalamus [20] Activation of hypothalamic leptin receptors suppresses food intake and promotes energy expenditure pathways [21]. Leptin levels decrease with weight reduction. The hypothesis that leptin resistance can occur in association with obesity was first suggested by the finding of elevated plasma leptin levels in obese humans [22]. This hypothesis suggests that some cases of human obesity may be due to reduced leptin action in the brain, and affected individuals are unlikely to respond to pharmacological treatment with leptin. Several mechanisms contribute to leptin resistance. Leptin uptake into the brain is facilitated by leptin receptors expressed by endothelial cells [4] in the bloodbrain barrier that function as leptin transporters. Impaired leptin transport across endothelial cells of the bloodbrain barrier is one potential mechanism leading to leptin resistance. Whether dysfunction of this transport process can lead to obesity remains to be determined, but it has been seen that in obese humans cerebrospinal fluids demonstrate low levels of leptin in comparison to plasma [23]. Upon activation of leptin receptors in the brain, a series of integrated neuronal responses required for food intake and energy balance are activated, and these neuronal effector pathways play a key role in energy homeostasis. Failure of one or more of these pathways in response to the leptin signalling will manifest as leptin resistance [24]. Reduced leptin-receptor signal transduction is another potential cause of leptin resistance. Like other cytokine receptors, activation of the leptin receptor induces expression of a protein that inhibits any further leptin signal transduction, termed 'suppressor of cytokine signalling-3' (SOCS-3) [25]. The potential contribution of SOCS-3 to acquired forms of leptin resistance and obesity is an active area of study.

The present study was done on 200 male and female patients separately, with type 2 diabetic to analyze the role of leptin hormone. The serum glucose, HbA1c, cholesterol, triglycerides, HDL, LDL, insulin, TNF- α, adiponectin and leptin were analyzed.

MATERIALS AND METHODS

Study was performed in Goldfield Medical College, Faridabad, Haryana (India) and the project was approved by Geetanjali medical College, Geetanjali University, Udaipur [Rajasthan] INDIA, as a randomized controlled trial and with parallel design. According to ADA [21], study was done on 200 male and female patients with type 2 diabetic to analyze the role of leptin hormone of age group range from 30 to 80 years were selected. Participants will be adults having obesity with Type 2 diabetes mellitus. Blood samples would be drawn to determine biochemical markers after taking consent from the patient.

On the basis of history, physical examination and preliminary lab investigations patients of obesity induced DM will be selected. Serum glucose [21] cholesterol [17], triglycerides, HDL [26], LDL [27] and and HbA1c [28] will be performed on semi auto analyzer according to the methodology and instructions given on literature accompanying commercially available kits of ERBA company. Leptin along Adiponectin and tumor necrosis factor estimation will be done with help of ELIZA assay kit. Insulin will be done by chemiluminense assay [29].

All the markers mentioned above would be done from serum by collecting venous blood sample in the vacutainers. Blood sample would be withdrawn from anticubital vein. Subjects would be asked to have fasting of 8 to 12 hours. Results of biochemical markers would be analyzed to establish their role as predictor of obesity induced DM.

RESULTS

Based on the history, physical examination and preliminary lab investigations patients of obesity induced DM will be selected. In the past two decades there has been an explosive increase in the number of people diagnosed with DM particularly type 2 which is associated with modern lifestyle, abundant calories intake, reduced physical activity leading to obesity.

About 60-90 % cases of type2 DM now appears to be related to obesity. Numerous studies have shown that insulin resistance precedes development of hyperglycemia in subjects that eventually develops type-2 DM. It has been realized that type2 DM develops only in insulin resistant subjects with the onset of beta cell dysfunction. Although Type 2 diabetes can be treated with oral hypoglycemic drugs for long time but ultimately they require insulin to control their diabetes which has its side effects and available in inject able form only which is very cumbersome for the patient.

Therefore it is very necessary to look for other alternative therapy which has lesser side effects. The present study is urgently required to explore the role of leptin in the etiology of obesity induced DM.

Table-1: Biochemical parameters of male subjects in diabetic patients and control group

BIOCHEMICAL MARKERS	Male subjects (Mean ± SD)		t - value	P Value	Significance
	Diabetic patients	Non-Diabetic patients			
Fasting Blood Glucose [mg/dl]	183.8 ± 13.4	98.34 ± 1.94	60.89	<0.001	Significant
HbA1C [mmol/mol]	9.73 ± 0.53	6.4 ± 0.1	59.59	<0.001	Significant
Cholesterol [mg/dl]	183.56 ± 36.89	178.77 ± 30.79	0.97	0.332	Non-Significant
Triglycerides [mg/dl]	178.57 ± 80.08	175.47 ± 68.01	0.29	0.773	Non-Significant
High-density lipoprotein cholesterol [mg/dl]	39.55 ± 8.23	36.27 ± 7.25	2.92	0.004	Significant
Low-density lipoprotein cholesterol [mg/dl]	108.82 ± 33.40	91.50 ± 11.58	4.74	<0.001	Significant
Insulin [IU]	11.47 ± 8.32	6.45 ± 3.89	5.29	<0.001	Significant
TNF- α [ng/ml]	9.19 ± 8.61	2.52 ± 2.37	7.22	<0.001	Significant
Adiponectin [IU/ml]	9.96 ± 5.29	13.1 ± 4.2	-4.54	<0.001	Significant
Leptin [ng/ml]	35.26 ± 16.05	40.41 ± 23.98	-1.76	0.080	Non-significant

Values were expressed as Mean ± SD, indicates p<0.001 (unpaired‘t’ test)

Table-2: Biochemical parameters of female subjects in diabetic patients and control group

BIOCHEMICAL MARKERS	Diabetic patients (Mean ± SD)		t - value	P Value	Significance
	Diabetic patients	Non-Diabetic patients			
Fasting Blood Glucose [mg/dl]	173.76 ± 9.28	91.32 ± 1.04	91.3	<0.001	Significant
HbA1C [mmol/mol]	7.9 ± 0.29	5.2 ± 0.02	96.08	<0.001	Significant
Cholesterol [mg/dl]	184.50 ± 40.73	172.99 ± 26.73	2.42	0.016	Significant
Triglycerides [mg/dl]	181.37 ± 76.63	158.28 ± 71.33	2.25	0.025	Significant
High-density lipoprotein cholesterol [mg/dl]	38.04 ± 8.45	37.45 ± 7.69	0.53	0.599	Non-significant
Low-density lipoprotein cholesterol [mg/dl]	110.47 ± 36.29	93.13 ± 11.51	4.69	<0.001	Significant
Insulin [IU]	12.14 ± 8.66	6.17 ± 2.95	6.73	<0.001	Significant
TNF- α [ng/ml]	8.39 ± 8.17	2.69 ± 2.65	6.85	<0.001	Significant
Adiponectin [IU/ml]	8.78 ± 4.09	12.01± 4.88	-5.16	<0.001	Significant
Leptin [ng/ml]	34.67 ± 16.77	42.60 ± 20.37	-3.06	0.003	Significant

Values were expressed as Mean ± SD, indicates p<0.001 (unpaired ‘ t’ test)

DISCUSSION

In the present study type-II diabetes male patients were had significant higher fasting blood glucose (*P*<0.001), significant high significant HbA1c (P <0.001), non significant high cholesterol (P=0.332), non significant high triglycerides (*P* = 0.773), significantly higher high-density lipoprotein (P = 0.004), significantly higher low-density lipoprotein (P <0.001), significantly high insulin (P <0.001), significantly high TNF- α (P = <0.001), significant low adiponectin (*P*<0.001) and non significant low leptin (*P*<0.001) level were observed as compared to non diabetic subjects (table 1).

In the present study type-II diabetes female patients were had significant higher fasting blood glucose (*P*<0.001), significant high significant HbA1c (P <0.001), significant high cholesterol (P=0.016), significant high triglycerides (*P* = 0.025), non-significantly higher high-density lipoprotein (P = 0.599), significantly higher low-density lipoprotein (P <0.001), significantly high insulin (P = <0.001), significantly high TNF- α (P = <0.001), significant low adiponectin (*P*<0.001) and significant low leptin (*P*= 0.003) level were observed as compared to non diabetic subjects (table 2).

In this background the adipokine-leptin could be potential and beneficial alternative treatment modality [1] Leptin promotes weight loss, regulation of appetite and can reverse diabetes by improving glucose tolerance by its action on hypothalamus. More

important leptin role in obesity energy homeostasis in relation to diabetes has received much attention. The leptin that secreted from adipose tissue does affect the insulin sensitivity and play a major role in pathogenesis of obesity related diabetes [30]. The leptin plays an important role in energy homeostasis and administration help in regulating glucose homeostasis, improves glucose tolerance by enhancing insulin sensitivity [31]. According to new findings, leptin replacement therapy is a promising and safe strategy to treat type 1 and 2 diabetes [32].

CONCLUSION

The diabetes is a metabolic disorder and forthcoming epidemic all over the globe that caused due to ineffective secretion of insulin. In the present study the type-II diabetes male patients were had significant higher fasting blood glucose (P<0.001), significant high significant HbA1c (P <0.001), non significant high cholesterol (P=0.332), non significant high triglycerides (P = 0.773), significantly higher high-density lipoprotein (P = 0.004), significantly higher low-density lipoprotein (P <0.001), significantly high insulin (P <0.001), significantly high TNF- α (P = <0.001), significant low adiponectin (P<0.001) and non significant low leptin (P<0.001) level were observed as compared to non diabetic subjects. The type-II diabetes female patients were had significant higher fasting blood glucose (P<0.001), significant high significant HbA1c (P <0.001), significant high cholesterol (P=0.016), significant high triglycerides (P = 0.025), non-significantly higher high-density lipoprotein (P = 0.599), significantly higher low-density lipoprotein (P <0.001), significantly high insulin (P = <0.001), significantly high TNF- α (P = <0.001), significant low adiponectin (P<0.001) and significant low leptin (P= 0.003) level were observed as compared to non diabetic subjects. Type 2 diabetes can be treated with oral hypoglycemic drugs but also require insulin to control diabetes which has its side effects on patient. Therefore it is necessary to look for other alternative therapy which has lesser side effects. . Leptin affect the insulin sensitivity play a major role in pathogenesis of obesity related diabetes. The leptin plays an important role in energy homeostasis and administration help in regulating glucose homeostasis, improves glucose tolerance by enhancing insulin sensitivity. The leptin replacement therapy is a promising and safe strategy to treat type 1 and 2 diabetes

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