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Research Article

Interleukin-6 in obese type II diabetes with hypertension

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ABSTRACT

Background: Type II diabetes mellitus (T2DM) and obesity are found to be associated with increased incidence of hypertension, although the mechanisms facilitating hypertension in T2DM or nondiabetic individuals are not clear.
Methods: We compared the levels of fasting plasma glucose, HbA1c, lipid subfractions and inflammatory cytokine interleukin 6 (IL-6), being risk factors previously found to be associated with hypertension, in T2DM patients showing increased body weight (obese and overweight with body mass index, BMI ≥25 kg/m^2) with hypertension (group A, n=30), or without hypertension (group B, n=30), and in non-obese (BMI <25 kg/m^2), normotensive controls (group C, n=40).
Results: BMI, HbA1c, fasting plasma glucose, total cholesterol, triglycerides, HDL cholesterol and LDL cholesterol were found to be significantly higher in group A, B Vs C ($p < 0.05$). Also, IL-6 levels were significantly higher both in group A and B compared to group C. The highest level of IL-6 was found in group A, being significantly higher than in group B (A: 14.34 ± 4.98 pg/ml; B: 10.66 ± 1.16 pg/ml; C: 7.41 ± 0.54 pg/ml, A vs. B $p<0.001$; A, B vs. C $p<0.001$).
Conclusions: Our results have shown that appearance of hypertension in T2DM patients with increased body weight was dependent on rise in inflammatory marker IL-6 cytokine.

Keywords: Type II diabetes mellitus, Hypertension, Obesity, Interleukin-6

INTRODUCTION

In recent years, a number of studies have indicated that several humoral markers of inflammation are elevated in people with obesity and Type II diabetes mellitus (T2DM). Based on these and other findings, it has been proposed that long-term activation of the innate immune system may be involved in the development of insulin resistance and T2DM. One possible explanation for elevated inflammatory markers in obesity is that adipose tissue secretes a number of inflammatory cytokines, like interleukin-6 (IL-6).[1] Circulating IL-6 levels have been reported to be elevated in obese people[2] and in people with type 2 diabetes[3] and to correlate with indirect measures of adiposity and insulin resistance, such as body mass index (BMI), waist-to-hip ratio[2,4] and fasting insulin concentrations.[2] However, to our knowledge, no study has examined the relationship between circulating IL-6 levels and direct measures of adiposity, insulin action, and insulin secretion. Thus, it is unclear whether the association between insulin resistance and markers of inflammation is independent of obesity.

Experimental studies indicate that vascular endothelial and smooth muscle cells from normal and aneurysmal arteries produce IL-6,[5-7] that IL-6 gene transcripts are expressed in human atherosclerotic lesions[8,9] and that IL-6 may have procoagulant effects.[10-12]

It has been shown that more than 80% of patients with type II diabetes mellitus (T2DM) will become hypertensive and it has been postulated that both T2DM and Hypertension (HTN) represent potent risk factors for the development of different forms of ischemic cardiovascular disorders.[13] However, the relationship between these important risk factors in the pathogenesis of cardiovascular disease (CVD), as well as the possibilities of the modulation of their influences, has not yet been clarified. The mechanisms underlying pathogenesis of CVD in T2DM patients with hypertension are found to involve numerous factors but recent evidences have suggested that activation of low-grade inflammation might be a possible trigger of this process.[14] On the other hand; obesity has been identified as a facilitating factor for the development of both T2DM and hypertension. In addition, adipose tissue is now recognized as an endocrine organ that is a strong amplifier of insulin resistance in humans.[15] Interleukin-6 (IL-6) are cytokines with metabolic and/or weight-regulating effects. The role IL-6 plays in obesity and insulin resistance remains controversial even after many years of research. Circulating levels of IL-6 are increased in obesity[15,16] and it has been proposed that IL-6 contributes to the pathogenesis of insulin resistance in different disease states.[17]

Aim of the study

The aim of the present study was to analyze the role of inflammatory cytokine plasma IL-6 concentrations in the development of hypertension in T2DM patients with increased body weight (obese and overweight, body mass index, BMI ≥ 25 kg/m^2) in Manipuri population.

METHODS

Study setting

The study was carried out in the department of Biochemistry in collaboration with the department of Medicine, Regional Institute of Medical Sciences, Imphal, Manipur.

Study design

Cross-sectional study

Study duration

The duration of study was of two years, October 2013 to September 2015

Study population

The study population consists of type II diabetes mellitus patients attending medicine OPD irrespective of sex, age and socioeconomic status form the study group. A group of normal healthy individuals of comparable age and sex who were free of any systemic disease were included in the control group.

We performed a cross-sectional study of 100 subjects: (a) T2DM with increased body weight (obese and overweight, BMI ≥ 25 kg/m^2) and hypertension (group A, n = 30), (b) T2DM patients with increased body weight (obese and overweight, BMI ≥25 kg/m^2) without hypertension (group B, n = 30) and (c) nonobese (BMI ≥25 kg/m^2) healthy controls (group C, n = 40). Exclusion criteria were BMI ≥35 kg/m^2, clinically significant renal or hepatic disease, anemia, diabetic retinopathy or symptomatic neuropathy, cardiac failure (New York heart association grades III and IV), angina pectoris, or recent myocardial infarction and severe uncontrolled hypertension. T2DM was diagnosed in accordance with the criteria of American Diabetes Association, the European association for the study of diabetes, and the International Diabetes Federation: symptoms of diabetes plus random blood glucose concentration 11.1 mmol/l (200 mg/dl), fasting plasma glucose 7.0 mmol/l (126 mg/dl), haemoglobin A1C >6.5% and two-hour plasma glucose 11.1 mmol/l (200 mg/dl) during an oral glucose tolerance test.[16] T2D patients were treated with oral antidiabetic agents, none of them were treated with insulin.

Hypertension was defined as (systolic/diastolic blood pressure (BP) (≥140/≥90 mmHg), according to seventh report of the joint national committee on prevention, detection, evaluation and treatment of high blood pressure (JNC-7) criteria[18] or currently receiving antihypertensive agents.

The study was approved by the ethics review committee of Institutional ethical subcommittee RIMS, Imphal.

Study design

At screening visit at the outpatients clinic, subjects were interviewed about medical conditions, current medication, alcoholic and smoking habits. Antihyperglycemic, hypolipidemic and antihypertensive agents were stopped 24-48 h before the metabolic testing.

The presence of obesity was determined by using BMI which was calculated as weight/height^2 (kg/m^2). Height was recorded to the nearest 0.5 cm, and weight was measured to the nearest 0.1 kg.

In each patient we performed the detection of (a) HbA1c, (b) fasting plasma glucose (c) IL-6 inflammatory cytokine and (d) lipid subfraction levels (total, HDL, LDL cholesterol and triglycerides).

All analyses were carried out during the same day and blood samples drawn after 12 h overnight fast and were stored at -70°C until assayed. Plasma glucose concentrations were measured using the glucose oxidase method using beckman glucose analyzer (beckman

instruments, fullerton, CA, USA). Glycosylated hemoglobin (HbA1c) levels were determinate using turbidimetric immunoassay for HbA1c (Boehringer Mannheim, Mannheim, Germany). Total cholesterol, HDL cholesterol and triglyceride concentrations were determined with enzymatic methods (Boehringer Mannheim). LDL cholesterol concentrations were calculated using Friedewald formula. IL-6 was measured by ELISA system (ALPCO, Salem, NH, USA).

Statistical analysis

Data are expressed as means ± SD. Normality of distribution of the data was tested by the Kolmogorov-Smirnov Test, a p value greater than 0.05 indicated that the observed distribution of a variable is not statistically different from the normal distribution. Chi-square test, independent sample T test and Kruskal-Wallis test were applied whenever necessary. The continuous variables were analyzed with analysis of variance (ANOVA). Data with a p value less than or equal to 0.05 were considered statistically significant. The software package SPSS version 16.0 for Windows (Chicago, IL, USA) was used for all computations.

RESULTS

The clinical and metabolic characteristics of the patients and subjects involved in the study are shown at Table 1. No significant differences were seen among groups with respect to mean age, BMI, HbA1c, total cholesterol, triglycerides, HDL cholesterol, LDL cholesterol and fasting plasma glucose, between the groups of diabetic patients. BMI, HbA1c, fasting plasma glucose, total cholesterol, triglycerides, HDL cholesterol and LDL cholesterol were found to be significantly higher in group A, B Vs C ($p<0.05$). In addition, IL-6 levels were significantly higher both in group A and B compared to group C. The highest level of IL-6 was found in group A, being significantly higher than in group B (A: 14.34 ± 4.98; B: 10.66 ± 1.16; C: 7.41 ± 0.54 pg/ml, A vs. B $p<0.001$; A, B vs. C $p<0.001$).

Values are expressed as mean ± SD. Bar graph show the value of Interleukin 6 (IL-6). IL-6 were significantly higher in T2D patients with increased body weight and hypertension compared to T2D patients with increased body weight with optimal BP and the same relationship were found in comparison to healthy subjects (A vs. Bp <0.001; A, B vs. C p <0.001).

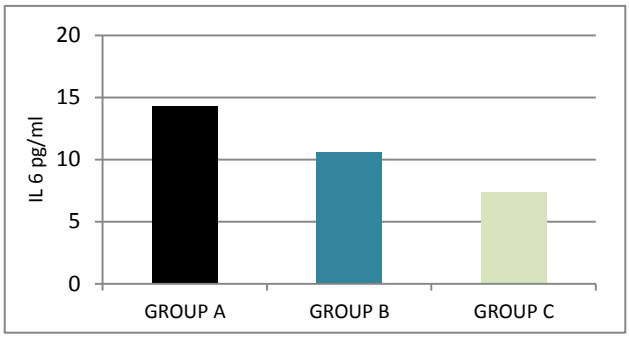

Figure 1: Levels of IL-6 in T2DM patients with increased body weight.

IL-6 levels were significantly higher both in group A and B compared to group C. The highest level of IL-6 was found in group A, being significantly higher than in group B (A: 14.34 ± 4.98; B: 10.66 ± 1.16; C: 7.41 ± 0.54 pg/mL, A vs. B $p < 0.001$; A, B vs. C $p < 0.001$) (Figure 1).

Table 1: Clinical and laboratory characteristics in T2DM patients with increased body weight and healthy subjects.

	Group A	Group B	Group C	P value
	(T2DM + HTN+)	(T2DM + HTN−)	(CONTROL)	(GROUP A vs B)
N (M/F)	30 (18/12)	30 (16/14)	40 (20/18)	NS
Age (Years)	58.37 ± 2.71	57.37 ± 5.92	57.50 ± 2.31	NS
Duration of diabetes (Years)	4.68 ± 4.43	4.34 ± 1.43	-	NS
BMI (Kg/m^2)*	31.89 ± 1.45	30.56 ± 6.74	22.45 ± 2.23	NS
SBP (mmHg) *	143.34 ± 13.25	142.76 ± 23.53	124.03 ± 6.87	NS
DBP (mmHg)*	87.78 ± 4.32	85.56 ±7.81	77.54 ± 3.23	NS
HbA1c (%)*	6.65 ± 0.86	6.54 ± 0.61	4.73 ± 0.22	NS
FPG (mmol/L)*	7.26 ± 1.32	7.36 ± 1.67	4.11 ± 0.82	NS
Total Ch (mmol/L)*	6.23 ± 0.74	6.15 ± 0.81	5.72 ± 0.62	NS
TG (mmol/L)*	2.72 ± 1.24	2.35 ± 0.72	1.25 ± 0.61	NS
HDL-Ch (mmol/L)*	0.99 ± 0.21	1.14 ± 0.20	1.56 ± 0.53	NS
LDL-Ch (mmol/L)*	3.83 ± 0.81	3.94 ± 0.56	3.51 ± 0.53	NS
IL-6 (pg/ml)**	14.34 ± 4.98	10.66 ± 1.16	7.41 ± 0.54	P<0.001
Family H/O diabetes in 1° relative (%)*	42.3	45.7	21	NS

Data are n, means ± SD. * $p \leq 0.05$ **$p< 0.001$ A, B versus C. T2DM: Type II diabetes mellitus; HTN: Hypertension; BMI: body mass index; SBP: Systolic blood pressure; DBP: diastolic blood pressure; HbA1c: glycosylated hemoglobin; FPG: fasting plasma glucose; Total Ch: total cholesterol; TG: total cholesterol; HDL-Ch: high density lipoprotein cholesterol; LDL-Ch: low density lipoprotein cholesterol.

Table 2: Group-wise distribution of study population with respect to basic profile.

Parameters		Group A (T2D + HTA+)		B (T2D + HTA−)		C (CONTROL)		P value
		n =30	%	n =30	%	n =40	%	
Sex	Male	18	60	16	53.3	22	55	0.65
	Female	12	40	14	46.6	18	45	
Marital status	Married	25	83.3	22	73.3	12	80	0.97
	Unmarried	5	16.7	8	26.6	8	20	
Alcoholism	Alcoholic	0	0	5	16.6	7	15.5	0.02
	Non-alcoholic	20	66.7	15	50	24	60	
	Occasional alcoholic	10	33.3	10	33.3	9	22.5	
Smoking	Smoker	10	33.3	7	23.3	8	20	0.39
	Non-smoker	16	53.3	15	50	26	65	
	Occasional smoker	4	13.3	8	26.7	9	22.5	

DISCUSSION

In this study we have found increase in the levels of pro-inflammatory cytokine, IL-6 in T2DM patients with increased body weight (obese and overweight) and hypertension.

Over the past decades many studies have suggested that low-grade inflammation related to obesity might be the key regulator in pathogenesis of T2D. It has been confirmed that enlargement of adipose tissue is associated with increases of number of adipose tissue macrophages, which are responsible for increases in plasma concentration of pro-inflammatory cytokines, especially IL-6 and TNF-α expression. IL-6 is released from macrophages of adipose tissue as well as from adipocytes and skeletal muscle. In vitro and in vivo work has shown that IL-6 gene expression and circulating levels of IL-6 may be regulated by insulin and correlate well with central obesity.[19-21] These pro-inflammatory cytokines appear in early stage of T2DM and they are found to be capable to increase insulin resistance directly in adipocytes, muscle and hepatic cells leading to augmentation of the systemic insulin resistance.[22-24]

Our results have confirmed these findings of increased levels of IL-6 in T2DM patients with increased body weight (obese and overweight), but among them IL-6 was found to be significantly higher in the hypertensive patients.

In addition, some recent epidemiological studies showed that the presence of a low-grade inflammation could anticipate the future development of hypertension.[25,26] This novel observation suggests that the increase in plasma levels of pro-inflammatory cytokines observed among hypertensive patients cannot be solely attributed to the vascular damage induced by high blood pressure.[27]

Another factor that might be involved in the pathogenesis of hypertension in the settings of obesity-associated insulin resistance is increased sympathetic activity.[28] It has been recognized that obesity represents a condition of increased sympathetic activity, increase in norepinephrine concentrations and norepinephrine renal spillover, and this hyperactivity is associated with tissue insulin resistance. In pathogenesis of hypertension, some recent studies emphasize the role of arterial stiffening preceding the development of hypertension.[29] Interestingly, the impairments in pulse wave velocity, a measure of large vessels distension ability, was recently found to be associated with the increases in circulating levels of IL-628 suggesting that low-grade inflammation may contribute to arterial stiffness.

New lines of research are now investigating the possibility of a direct pathogenic effect of pro-inflammatory mediators in altering mechanisms of vascular tone regulation leading to the onset of high blood pressure[30] which might clarify the mechanisms linking hypertension and low grade inflammation.

Lifestyle modification, physical activity and nutritional interventions,[31,32] may reduce development of diabetes, but also the level of blood pressure and inflammation in patients with hypertension and T2DM, which is important for the prevention of cardiovascular diseases.[33] Our results imply that this effect might be achieved by targeting low-grade inflammation, predominantly IL-6 levels. The results of the study is based on lifestyle modification aiming to reduce the risk not only for T2DM but also to its complications and comorbidities, especially hypertension.[34] Our results imply that beneficial effect in that direction might be achieved primarily by targeting insulin resistance and low-grade inflammation, cytokine IL-6 levels.

CONCLUSION

In conclusion, we found that in obese patients with T2DM the development of hypertension depends on the increases in insulin resistance and inflammatory cytokine IL-6 levels. Our results imply that lifestyle intervention aimed to decrease insulin resistance and chronic inflammation might be beneficial in reducing the risk for hypertension in obese T2DM individuals.

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