Original Article

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Correlation between IL-6, Insulin Resistance (HOMA-IR) and Atherogenic Index of Plasma (AIP) in Type 2 Diabetes Mellitus

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Abstract

Background: In type 2 diabetes, Interleukin-6 (IL-6) facilitates atherosclerosis through the promotion of chronic inflammation and endothelial dysfunction. Increased IL-6 levels in insulin-resistant conditions exacerbate lipid irregularities and vascular inflammation, hastening plaque development. The inflammatory milieu elevates cardiovascular risk in type 2 diabetes individuals. To see the correlation betweenIL-6, Insulin resistance (HOMA-IR) and Atherogenic Index of Plasma (AIP) in type 2 Diabetes mellitus.

Materials and methods: A hospital-based cross-sectional observational study was carried out in the Department of Biochemistry Chittagong Medical College, Department of Endocrinology of Chittagong Medical College Hospital and Chattogram Diabetic Hospital. One hundred (100) type 2 diabetes mellitus patient was included in the study by nonprobability consecutive sampling. Important variables in this study were serum IL-6, HOMA-IR and AIP (Atherogenic Index of Plasma).

Results: Serum IL-6 concentration is significantly positively correlated with waist circumference, Atherogenic Index of Plasma, LDL/HDL ratio in type II diabetes mellitus. The IL6 value is positively correlated with AIP in type II Diabetes Mellitus patients having increased waist circumference. There is a significant association of Atherogenic Index of Plasma (AIP) by Interleukin-6 (IL-6) HOMA-IR (Homeosttaic Model Assessment-Insulin Resistance) waist circumference.

Conclusion: Adipose tissue macrophage infiltration is a major inflammatory mechanism promoting insulin resistance and diabetes. Scavenger receptors on vessel wall macrophages recognise and internalise oxidatively changed lipids such oxidised LDL, forming foam cells. IL-6 secretion may vary by macrophage polarization in type 2 diabetes mellitus.

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Introduction

Over the course of the past several years, a number of studies have demonstrated that individuals who are obese and have type 2 diabetes mellitus have higher levels of various humoral markers that signal inflammation.[1] According to that has been put up on the basis of these and other studies,

long-term activation of the innate immune system has been associated with the development of insulin resistance and type 2 diabetes mellitus.[1] The development of microvascular and macrovascular complications, which significantly increase the risk of morbidity and mortality, is a consequence of high blood glucose levels. For people with Type II diabetes (T2DM) the most significant contributors to morbidity and mortality are atherosclerotic Coronary Artery Disease (CAD) and other types of Cardiovascular Disease (CVD).[2] The adult treatment panel III has acknowledged the significant responsibilities that HDL-C and TGs play in the connection between lipids and Coronary Heart Disease (CHD) and they have referred to this combination as an atherogenic dyslipidaemia. This is despite the fact that the primary focus on the connection between lipids and CHD is on LDL-cholesterol (LDL-c).[2] An increasing number of researchers have demonstrated that dyslipidaemia, which is characterised by an increase in Low-Density Lipoprotein Cholesterol (LDL-C) Total Cholesterol (TC) and Triglyceride (TG) as well as a reduction in High-Density Lipoprotein Cholesterol (HDL-C) does, in fact, lead to atherosclerosis.[3,4]

Among these, LDL-C was considered to be the primary therapeutic goal in the past. However, after decreasing LDL-C to the prescribed levels, approximately fifty percent of the residual cardiovascular risk remained. This prompted researchers to look for additional cardiovascular disease predictors.[5] Recent studies indicate that the Atherogenic Index of Plasma (AIP) calculated

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using the formula log (TG/HDL-C) reflects the relationship between protective and atherogenic lipoproteins and serves as a strong predictor of atherosclerosis and coronary heart disease.[6,7] There are a significant number of cardiovascular risk factors that can be modified and although a lot of work has been done up to this point, there is still a lot more that has to be needed.[8] Hartopo et al. established a correlation between significant adverse cardiovascular events and the AIP value (AIP ≥ 0.24 classified as high AIP group, AIP < 0.24 classified as low AIP group) in patients experiencing acute myocardial infarction during intense hospitalisation in a prospective cohort analysis.[9]

Recently, it has come to light that the progression of atherosclerosis progresses primarily due to inflammation, beginning with fatty streaks composed of macrophages. Inflammatory cells like T-cells and mast cells promote smooth muscle cell replication and extracellular matrix formation, enlarging the lesion. Studies show that Interleukin-6 (IL-6) plays a key role in driving the inflammatory response behind atherosclerosis.[10] Atherosclerosis, the leading cause of morbidity and mortality worldwide, is both a chronic inflammatory condition and a disorder of lipid metabolism.[11] High IL-6 levels are associated with low HDL, independent of multiple potential confounding variables.[12] This study discusses multiple aspects of IL-6 effects on parameters related to development of atherosclerosis.

Materials and methods

This hospital-based cross-sectional observational study was carried out in the Outpatient Department of Endocrinology, Chittagong Medical College Hospital in collaboration with the Department of Biochemistry, Chittagong Medical College, Chattogram Diabetic Hospital. The study was conducted from July 2019 to January 2023. The study was undertaken after approval by

the Ethical Review Committee of Chittagong Medical College and the concerned Departments. Informed consent was obtained from each subject.

Inclusion criteria

- Patients with Type 2 Diabetes Mellitus.

Exclusion criteria

- Chronic liver disease, Acute infection, Autoimmune disease and malignancy, Sepsis, burn, Pregnancy.

Subject were selected from the Outpatient Department (OPD) of the Department of Endocrinology, Chittagong Medical College Hospital and Chattogram Diabetic Hospital who had come for their regular checkup for diabetes.

After taking a brief history and preliminary selection eachsubject and their informed verbal consent was taken. Then they were requested to report to the Department of Biochemistry, Chittagong Medical College in the morning between 8.00 and 9.00 am following an overnight (8-12hours) fasting. When the subjects were reported, informed written consent was taken. The cut-off point of normal IL-6 was considered by ≤ 5pg/ml.[13]

Serum Interleukin-6 was measured by a commercially available IL-6 kit which is an in-vitro chemiluminescence immunoassay for quantitative determination (MAGLUMI2000). BMI and WC (Waist circumference) were measured by standard procedure. The fasting serum blood glucose was measured by glucose oxidase enzymatic kinetic method using an auto analyzer. 2HPPBS was measured by an auto-analyzer Simens dimension EXL 200.

All the data had processed and analyzed using IBM-SPSS (Statistical Package for Social Science) v 25.0 for Windows. p value < 0.05 will be considered to bestatistically significant. Variables expressed as mean ±Standard Error of Means (SEM)/SD. The normality of the distribution of the data were tested by the Kolmogorov-Smirnov Test and a p-value greater than 0.05 indicated that the observed distribution of a variable is not statistically different from the normal distribution. The Pearson correlation test has been applied whenever necessary to see the statistical significance.

Results

Table I Pearson's Correlation of serum IL-6, waist circumference, Atherogenic Index of Plasma (AIP) among study subjects

Variables	r	p-value
IL-6 & Waist Circumference	0.33	<0.01
IL-6 & Atherogenic Index of Plasma (AIP)	0.30	<0.01
IL-6 & LDL/HDL ratio	0.35	<0.05

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Serum IL-6 concentration is significantly positively correlated with waist circumference, Atherogenic Index of Plasma, LDL/HDL ratioin type II diabetes mellitus.

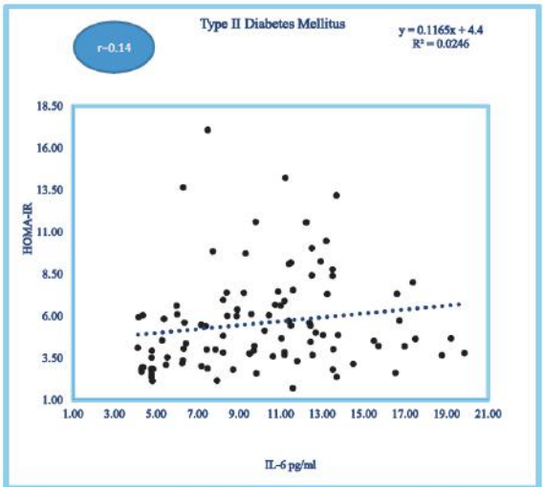

Figure 1 Correlation of serum IL-6 pg/ml & HOMA-IR in type II Diabetes Mellitus (n=100)

Figure 1 shows that Type II diabetes Mellitus patients serum IL-6 pg/ml (x-axis) & HOMA-IR (y-axis). There is a dense scatter distribution of serum IL-6 concentration between 5 pg/ml to 13 pg/ml and with HOMA-IR values ranging from 2.5 to 7 in Type II diabetes mellitus patients. The serum IL-6 concentration has a positive correlation (0.14) with HOMA-IR.

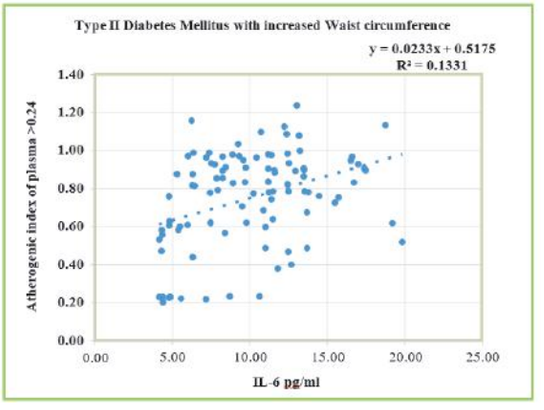

Figure 2 Correlation of IL-6 with increased waist circumferences and Atherogenic index of plasma in type II diabetes Mellitus

Figure 2 shows a Scatter diagram of increased IL-6 with increased waist circumferences and Atherogenic Index of Plasma (AIP) in type II diabetes Mellitus. The IL6 value is positively correlated with AIP in type II Diabetes Mellitus patients having increased waist circumference.

Table II Linear regression analysis for prediction of Atherogenic Index of Plasma (AIP) by the effect of increased IL-6 concentrtaion, HOMA-IR and waist circumference in patients with type 2 diabetes mellitus (n=100)

	Unstandardized Coefficients		Standardized Coefficients			95.0% Confidence Interval for B	
	B	Std. Error	Beta	t	Sig.	Lower Bound	Upper Bound
IL6	0.016	0.006	0.247	2.586	0.011*	0.004	0.028
HOMA-IR	0.014	0.008	0.258	2.381	0.046*	0.006	0.012
Waist circumference	0.007	0.003	0.263	2.701	0.008*	0.002	0.012

Dependent variable: AIP.

There is asignificant association of Atherogenic Index of Plasma (AIP) by interleukin-6 (IL-6) HOMA-IR, waist circumference.

Discussion

In this study type II diabetes mellitus patients have a significant positive correlation of IL-6 with waist circumference, Atherogenic Index of Plasma, LDL/HDL ratio (Table I). A greater number of adipose tissue macrophages are held accountable for the increased plasma concentration of pro-inflammatory cytokines including IL-6 as cited by Stephens, J. W. et al.[14]

There is a dense scatter distribution of serum IL-6 concentration between 5 pg/ml to 13 pg/ml and with HOMA-IR values ranging from 2.5 to 7 in Type II diabetes mellitus patients. The serum IL-6 concentration has a positive correlation (0.14) with HOMA-IR (Figure 1).

Rehman, K. et al. conclude thatproinflammatory cytokine interleukin-6 (IL-6) controls the apoptosis, migration, proliferation, and differentiation, it also significantly increases insulin resistance and the pathophysiology of Type 2 Diabetes Mellitus (T2DM).[15] Tissue IL-6 presence is a typical outcome, nonetheless, inflammation causes insulin resistance and overt type 2 diabetes when exposed to it for an extended period of time or when its production is irregular. An interaction between insulin resistance and IL-6 activation exists on a molecular level. Insulin resistance develops when IL-6 impairs insulin receptor and insulin receptor substrate-1 phosphorylation by promoting the development of

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SOCS-3, a possible inhibitor of insulin signalling. How Interleukin-6 (IL-6) causes insulin resistance and type 2 diabetes pathogenesis has been briefly discussed in this article. A potential therapy method for insulin resistance and type 2 diabetes might be the avoidance of inflammatory diseases by the inhibition of Interleukin-6 (IL-6) and IL-6 signaling.

Increased IL-6 with increased waist circumferences and Atherogenic Index of Plasma (AIP) in type II diabetes Mellitus. The IL6 value is positively correlated with AIP in type II Diabetes Mellitus patients having increased waist circumference (Figure 2).

According to Reiss A B et al. several cells involved in lipid processing and plaque formation are affected by the effects of an increase in IL-6 in atherosclerosis.[16] In addition, IL-6 is the principal factor that determines the development of acute phase proteins. IL-6 promotes the onset of cardiovascular disease due to its many harmful characteristics. Among them, endothelial cell activation, platelet pro-thrombotic actions, smooth muscle proliferation stimulation, and macrophage lipid accumulation are included. Although IL-6 has general negative effects on cells involved in atheroma development, it does have some beneficial effects on the lipid handling system. This is due to the overexpression of ATP binding cassette transporter (ABC) A1, a protein that is involved in the efflux of lipids from macrophages. In addition, IL-6 has the ability to block the action of certain inflammatory cytokines.

In linear regression model suggests (Table II) that IL-6, HOMA-IR, increased waist circumference is a strong predictor of lipid-related cardiovascular risk. It indicates that higher IL-6 levels are associated with an increase in AIP, reinforcing the role of inflammation in lipid metabolism and cardiovascular disease. This finding supports the potential of IL-6 as a biomarker for cardiovascular risk assessment.

Limitation

Cross-sectional designs, limiting the ability to determine whether elevated IL-6 causes changes in AIP over time or if both are coexisting markers of cardiovascular risk.

Conclusion

The relationship of Interleukin-6 (IL-6) and Homeostatic Model Assessment of Insulin Resistance (HOMA-IR) with the Atherogenic Index of Plasma (AIP) emphasises the interaction among inflammation, insulin resistance and lipid metabolism in cardiovascular risk. Key pro-inflammatory cytokine IL-6 promotes inflammation, which may affect lipid anomalies and atherogenesis. Dyslipidaemia is connected to HOMA-IR, an indicator of insulin resistance, thereby increasing the risk of heart disease.

Recommendation

A prospective, multicentre study is indicated to establishthe increased serum IL-6 concentration in type 2 diabetesmellitus. The association between IL-6 and insulinresistance and between Hs-CRP and Insulin resistanceneed to be evaluated.

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Contribution of authors

SD-Design, Acquisition of data, data analysis, drafting & final approval.

MH-Conception, design, interpretation of data, critical revision & final approval.

SKB-Conception, acquisition of data, data analysis, interpretation of data, drafting & final approval.

Disclosure

The authors declared no conflict of interest.

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