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IL-6 levels do not cause insulin resistance in newly diagnosed type 2 diabetic Sudanese patients

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ABSTRACT

Objective: Insulin resistance is a key feature of type 2 diabetes, characterized by the body's reduced ability to respond to the action ofthe hormone insulin. The exact mechanism behind the development of type II diabetes mellitus is not fully understood, although risk factors like obesity, inflammation, aging, and genetics are acknowledged. This study seeks to evaluate the association between IL6, an inflammatory mediator, and the onset of insulin resistance. Understanding this relationship could enhance our comprehension of the pathogenesis of type II diabetes mellitus and aid in advancing treatment and prevention strategies.

Methods: The study comprised 115 recently diagnosed diabetic patients and 65 non-diabetic controls selected at random. Fasting blood samples were taken to measure plasma levels of IL-6, fasting insulin, and fasting plasma glucose. Subsequently, the homeostasis model assessment (HOMA-IR) was calculated to evaluate insulin resistance. Hierarchical regression analysis explored the relationship between IL-6 and insulin resistance. Additionally, all participants had their weight and height measured to calculate their Body Mass Index (BMI), which classified them into underweight, normal weight, overweight, and obese categories, while their age was noted for age subgroup classification.

Results: The mean plasma concentrations of FBS, fasting insulin, and IL-6 were significantly higher in newly diagnosed diabetics (195.4 ± 59.0, 19.7 ± 6.,2 and 18.0 ± 12.7 respectively) compared to controls (82.3 ± 7.3, 9.5 ± 2.4 and 4.4 ± 2.4 respectively) ($P < 0.001$ for all parameters) irrespective to their gender and BMI group. The overall hierarchical regression model including gender, log age, log BMI, and log IL-6 concentration was statistically significant ($P = 0.003$) with adjusted $R^2 = 0.065$. IL6 showed a significant positive correlation with fasting blood glucose (($\beta = 0.209$) (P value =0.005). Conversely, its correlation with plasma fasting insulin and insulin resistance was insignificant$\beta = 0.003$ and $\beta = 0.078$, and the P value was 0.965 and 0.305 respectively for fasting insulin and insulin resistance.

Conclusion:IL6 has not been associated with insulin resistance in newly diagnosed type 2 diabetic patients from Sudan.
Keywords: IL-6; Insulin resistance; Type 2 diabetic.

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is the predominant form of diabetes, constituting at least 90% of all diabetes mellitus (DM) cases[1]. It is a metabolic disorderconstituting a group of conditions that stem from a deficiency of insulin or an insufficient response of the body to insulin, potentially leading to severe complications. This issue is on the rise, contributing to an increase in disease and health complications[2]. It is among the most serious worldwide health emergencies of the twenty-first century [3]. Insulin resistance (IR) plays a significant role in type 2 diabetes. It is characterized by a diminished response to insulin in the body's cells, which can also be described as requiring 200 or more units of insulin daily to prevent ketosis and maintain blood sugar control[4].Numerous etiological factors contribute to the pathogenesis of insulin resistance, such as the accumulation of lipid metabolites, the activation of the unfolded protein response pathway, and the innate immune pathway. These factors collectively lead to the build-up of specific lipid metabolites in the liver and skeletal muscle, which ultimately results in insulin resistance [5].Interleukins serve as regulatory mediators that are secreted by various cells such as monocytes, macrophages, T-lymphocytes, and adipocytes. They possess the capability to either amplify or inhibit the inflammatory process[6].Inflammation frequently accompanies type 2 diabetes, playing a significant role in its development and progression[7]. Some studies found a relation between IL6, TNF, and C-reactive protein with T2DM [2]. IL-6 is a cytokine with a wide range of physiological and pathological roles. Research indicates that it may have an insulin-sensitizing effect. Elevated levels of IL-6 are associated with insulin-resistant states, but it also appears to promote insulin-mediated glucose utilization. This dual role makes IL-6 a complex but critical component in the regulation of glucose metabolism and insulin sensitivity[8]. The role of interleukin-6 (IL-6) in insulin action and glucose metabolism is subject to debate due to conflicting evidence. While some studies suggest that IL-6 positively influences glucose metabolism, particularly in skeletal muscle, it may also contribute adversely in certain pathological states such as obesity and insulin resistance (IR)[9]. Establishing the involvement of IL6 in the development of insulin resistance is pivotal for the early detection of diabetes, potentially leading to better outcomes in terms of disease mortality and morbidity.

MATERIALS AND METHOD

Study design

Hospital-based cross-sectional study.

Materials

The ELISA reader and washing machine were acquired from Biotek Instruments in the USA. The insulin ELISA kit was sourced from Sunlong Biotech in China, while the ELISA kit for glucose estimation and the ACCENT 200 blood chemistry analyzer were both procured from Cormay in Poland. Additionally, the bench centrifuge was obtained from the Hettich Centrifuge in Japan.

Subjects

In this cross-sectional study, sixty-five seemingly healthy adults and one hundred fifteen newly diagnosed type 2 diabetic patients were recruited to form the nondiabetic control group and the diabetic group, respectively. Both the diabetic individuals and the controls were further divided into subgroups based on gender, age, and BMI. Gender was divided into two categories: male and female. Age was categorized into three groups: young (15-40 years), middle-aged (41-70 years), and elderly (71-94 years). BMI was classified into four categories: underweight, normal weight, overweight, and obese.

Methods

Individuals with fasting blood glucose levels (FBG) of 126 mg/dl or higher were identified as diabetic. Those with acute and chronic infections were not included in the study. Following an 8-hour fast, 5 ml of venous blood was drawn from both patients at the time of diabetes mellitus diagnosis and from control subjects. This blood was immediately placed into test tubes containing fluoride oxalate. After centrifugation within two hours of collection, the plasma was separated and preserved at -20°C. This stored plasma was later used to assess insulin and IL-6 levels using the enzyme-linked immunosorbent assay (ELISA) technique, adhering to the Sunlong Biotech Company's protocol. Blood glucose levels were determined using a colorimetric, enzymatic method that employs glucose oxidase. Additionally, the weight and height of all participants were measured to calculate their body mass index (BMI). Based on the BMI, participants were categorized into four groups: underweight, normal weight, overweight, and obese, following the criteria established and updated by the World Health Organization (WHO) in 1995, 2000, and 2004. The age range of the patients was also recorded.

The Statistical Package for the Social Sciences (SPSS) software, version 21, 64-bit for Windows 8, was utilized for data analysis. Techniques such as the independent t-test, one-way Analysis of Variance (ANOVA), and hierarchical regression were employed. The significance levels were established at $P < 0.05$.

Ethical consideration

The study received approval from the ethical committee of Shendi University. All participants provided written consent after being informed about the purpose and procedures of the study. They were guaranteed confidentiality concerning their data.

RESULTS

Table (1) presents the age subgroups for both diabetic and non-diabetic groups. The predominant age categories were the middle age group (41-70 years) for the diabetic group and the young age group (5-40 years) for the non-diabetic group. The male-to-female ratio was approximately 1:2 in the diabetic group and nearly 1:1 in the control group.

Table 1: Number of diabetic and control subjects in each age group by gender

Age group	Diabetic males	Diabetic female	Total	Control males	Control females	Total
15 – 40	3 (2.6%)	9 (7.8%)	12 (10.4%)	15 (30.6%)	18 (36.7%)	33 (67.3%)
41 – 70	17 (14.8%)	52 (45.2%)	69 (60%)	5 (10.2%)	9 (18.4%)	14 (28.6%)
71 – 94	14 (12.2%)	20 (17.4%)	34 (29.6%)	0	2 (4.1%)	2 (4.1%)

Table 2 represents BMI subgroups. It indicates that 57% of the individuals in the control group had a normal weight, in contrast to the diabetic group where 72% were classified as overweight or obese. The proportion of underweight individuals was lower in the diabetic group.

Table 2: Number of diabetic and control subjects in each BMI group by gender

BMI group	Diabetic males	Diabetic female	Total	Control males	Control females	Total
Underweight	0	3 (2.6%)	3 (2.6%)	2 (4.1%)	2 (4.1%)	4 (8.2%)
Nor. weight	13 (11.3%)	16 (13.9%)	29 (25.2%)	13 (26.5%)	15 (30.6%)	28 (57.1%)
Overweight	13 (11.3%)	29 (25.2%)	42 (36.5%)	5 (10.2%)	11 (22.5%)	16 (32.7%)
Obese	8 (7%)	33 (28.7%)	41 (35.7%)	0	1 (2%)	1 (2%)

Fasting blood glucose (FBG) and fasting insulin levels were significantly elevated in the diabetic group compared to the nondiabetic group, irrespective of body mass index (BMI), as shown in Tables 3 and 4. Although there is variation in FBG across different BMI subgroups, this difference is not statistically significant. Figure 1 illustrates the FBG levels among the various BMI subgroups.

Table 3: Mean plasma concentrations of fasting blood sugar (mg/dl) in control diabetic subjects by gender.

Gender	Variable	Status	N	Mean	St deviation	P value
Male	FBS	C	26	83.0	7.6	0.000
		D	34	182.0	45.0	
Female	FBS	C	39	81.9	7.1	0.000
		D	81	201.0	63.4	

Table 4: Mean sqrt plasma concentrations of (FI) (mU/L) and (FPG) (mg/dl) in control and diabetic subjects by BMI subgroups

BMI group	Variable	status	Number and percentage	Mean	STD	P value
Underweight	**FI**	C	4 (8.2%)	2.91	0.18	0.001
		D	3 (2.6%)	3.79	0.08	
	FPG	C	4 (8.2%)	9.01	0.40	0.013
		D	3 (2.6%)	14.72	3.11	
Normal weight	**FI**	C	28 (57.1%)	2.97	0.21	0.0001
		D	29 (25.2%)	4.38	0.67	
	FPG	C	28 (57.1%)	8.89	0.34	0.0001
		D	29 (25.2%)	13.67	1.68	

Overweight	**FI**	C	16 (32.7%)	2.84	0.23	0.0001
		D	42 (36.5%)	4.37	0.60	
	FPG	C	16 (32.7%)	8.99	0.38	0.0001
		D	42 (36.5%)	13.88	2.18	
Obese	**FI**	C	1 (2%)	2.83	0	0.0001
		D	41 (35.7%)	4.46	0.72	
	FPG	C	1 (2%)	9.06	0	0.0001
		D	41 (35.7%)	13.83	2.10	

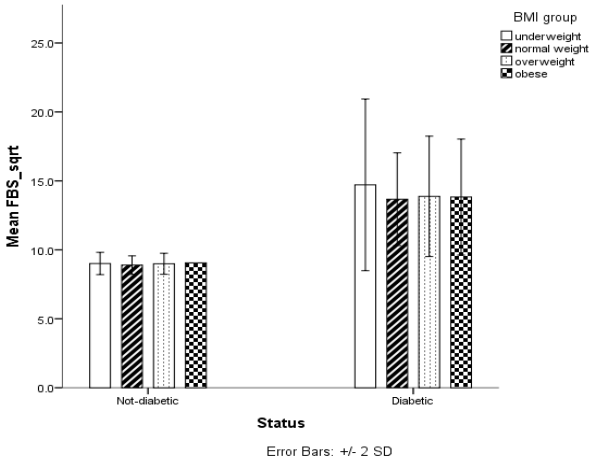

Figure 1. Mean sqrt of plasma concentrations of FPG among different BMI subgroups in diabetic and control subjects

Table 5 displays the differences in IL6 levels between diabetic and non-diabetic groups, with the diabetic group showing significantly higher IL6 levels compared to the non-diabetic group. Figure 2 depicts the variance in IL6 concentrations across different BMI subgroups, noting the highest levels in the underweight group, although this difference is not statistically significant. Refer to Figure 2 for more details.

Table 5: Comparison of mean log plasma concentrations of IL-6 (ng/L) between controls and diabetics by gender

Sex	variable	Status	N	Mean	St. D	P value
Male	**IL-6**	C	20	0.64	0.20	0.0001
		D	34	1.08	0.37	
Female	**IL-6**	C	29	0.55	0.18	0.0001
		D	81	1.14	0.37	

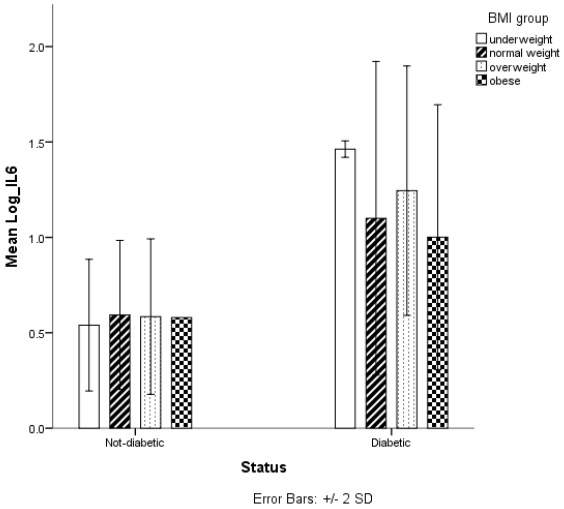

Figure 2: Distribution of mean log plasma IL-6 concentrations in control and diabetic subjects by BMI subgroups

HOMA-IR is a measure of IR[HOMA-IR = fasting insulin (mU/L) * FBS (mg/dl)/405].
IR was significantly higher in diabetic subjects (9.7 ± 4.9) compared to controls (1.9 ± 0.5) $P < 0.001$ with insignificant variation between both genders. The differences in IR between all BMI subgroups among the diabetic participants and that of all BMI subgroups among the non-diabetic participants were insignificant. There was a significant increase in IR between the BMI diabetic subgroups and their corresponding BMI non-diabetic subgroups. However, the obese subgroup showed an insignificant difference in IR ($P < 0.001$ for normal weight and overweight, $P < 0.01$ for underweight, and $P > 0.05$ for the obese subgroup). Differences in IR between different age subgroups were statistically insignificant refer to Figure 3.
Hierarchical (sequential) multiple regression was performed to assess the impact of IL6onIRexcluding the effect of gender, age, and BMI. The overall model including gender, log age, log BMI and log IL-6 concentration was statistically significant (P value = 0.022), $R^2 = 0.098$, and adjusted $R^2 = 0.065$ refer to Table (5). The addition of IL6 to the prediction of IR square root and fasting insulinsquare root led to a statistically insignificant change in R^2 ($P > 0.05$) (Refer to tables 6 and 7) respectively. Hierarchical regression for assessment of the impact of IL6 on FBG was run and the overall model including gender, age, BMI, and log IL-6was statistically highly significant (P = 0.0001), with R = 0.677, $R^2 = 0.459$, and adjusted $R^2 = 0.435$ (Refer to table 5). The addition of IL6 to the prediction of FBG led to a statistically significant change (P value = 0.005). Refer to table 8.

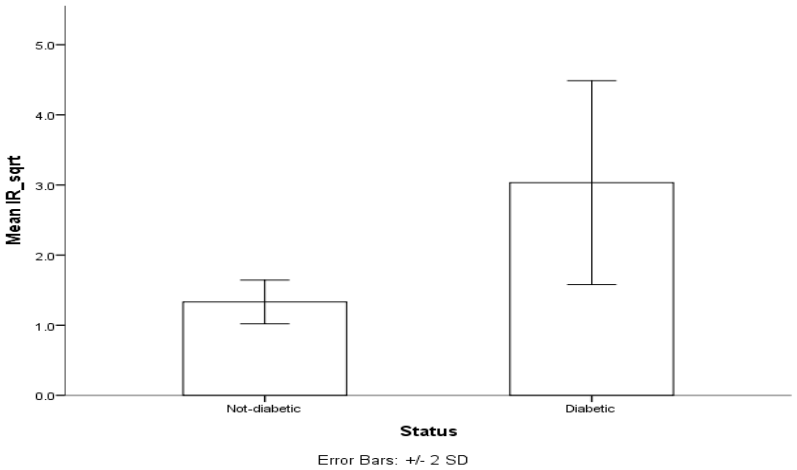

Figure 3: Mean HOMA-IR sqrtin diabetics and non-diabetic subjects

Table 5: Values of R^2, adjusted R^2,and change in R^2 in different models predicting IR.

Dependent variable	R	R^2	Adjusted R^2	P value
IR-sqr	0.659	0.434	0.409	0.0001
FBG-sqr	0.677	0.459	0.435	0.0001

Table 6: Standardized (β) and unstandardized (B) coefficients for different predictors of insulin resistance in different models.

Predictor	B	B	P value
Constant	3.312		0.002
Gender	0.113	0.062	0.323
Age	0.006	0.124	0.080
BMI	0.021	0.113	0.102
Log IL-6	0.007	0.003	0.965

Model 1: included constant and gender. Model 2: log age is added to model 1. Model 3: log BMI is added to model 2. Model 4: Log IL-6 is added to model 3. * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$.

Table 7: Standardized (β) and unstandardized (B) coefficients for different predictors of fasting insulin

Predictor	B	B	P value
Constant	0.572		0.622
Gender	0.211	0.100	0.109
Age	0.007	0.117	0.095
BMI	0.019	0.094	0.166
Log IL-6	0.188	0.078	0.305

Model 1: included constant and gender. Model 2: log age is added to model 1. Model 3: log BMI is added to model 2. Model 4: Log IL-6 is added to model 3. * P < 0.05, ** P < 0.01, *** P < 0.001.

Table 8: Standardized (β) and unstandardized (B) coefficients for different predictors of fasting blood glucose

Predictor	B	B	P value
Constant	4.430		0.171
Gender	0.612	0.102	0.094
Age	0.016	0.100	0.143
BMI	0.045	0.077	0.244
Log IL-6	1.440	0.209	0.005

Model 1: included constant and gender. Model 2: log age is added to model 1. Model 3: log BMI is added to model 2. Model 4: Log IL-6 is added to model 3. * P < 0.05, ** P < 0.01, *** P < 0.001.

DISCUSSION

Our research indicated that the predominant age group among diabetic subjects was the middle-aged group, which aligns with the understanding that Type 2 Diabetes Mellitus (T2DM) typically manifests in adulthood. The most common Body Mass Index (BMI) categories within the diabetic cohort were those classified as overweight and obese. This supports the established correlation between increased adiposity and T2DM. Our findings also revealed that levels of fasting insulin, fasting blood glucose, and IL6 were significantly elevated in diabetic individuals compared to the control group, irrespective of age, gender, or BMI. Insulin resistance (IR), as measured by the Homeostatic Model Assessment of Insulin Resistance (HOMA-IR), was higher across all diabetic subgroups when contrasted with their non-diabetic counterparts, with the exception of the obese subgroup. In this subgroup, IR levels did not differ significantly between diabetic and non-diabetic individuals, suggesting a potent link between adiposity and IR that exists independently of diabetes status. Recent research has proposed that low-grade inflammation may play a role in the development of IR and Type II Diabetes Mellitus[10]. The relationship between interleukin-6 (IL-6) and insulin resistance (IR) is complex, with studies indicating varying effects. Some research suggests that IL-6 may have a positive effect on insulin sensitivity. However, this is contrasted by other studies that associate elevated IL-6 levels with insulin-resistant states. This dichotomy highlights the need for further investigation into the role of IL-6 in glucose metabolism and its potential impact on insulin resistance [8,9]. Our research has revealed a positive correlation between interleukin 6 (IL6) levels and hyperglycemia, yet no significant effect of IL6 on insulin resistance was observed. The elevated IL6 levels in individuals with diabetes, as opposed to non-diabetic individuals, may contribute to enhancing insulin sensitivity in skeletal muscle, rather than being implicated in the development of insulin resistance (IR). This suggests that the rise in IL6 could be a compensatory mechanism in response to hyperglycemia, rather than a causative factor for IR and hyperglycemia. Pedersen and Febbraio have noted that IL6 exhibits a paradoxical role, augmenting insulin sensitivity in skeletal muscle, while concurrently diminishing it in the liver [8]. Our research suggests that IL6 could serve as a valuable marker for the early diagnosis of insulin resistance (IR).

CONCLUSION

IL6 levels are observed to be elevated in individuals with diabetes when compared to non-diabetics. The study has shown a significant positive association between IL6 levels and hyperglycemia, whereas no notable correlation was identified between IL6 levels and insulin resistance (IR). It is suggested that IL6 could serve as a biomarker for the early detection of IR.

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Conflict of interest

This statement serves as a formal declaration that there are no conflicts of interest.

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