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Study of Insulin-Like Growth Factor-1 and Insulin-Like Growth Factor Binding Protein-1 Relation to Insulin Resistance in Normal Persons and Type 2 Diabetics

Authors
Khalifa A.M.[1], Ismael A.A.,El Neily D.A.[2], Abd El Ghafour R.A.[1]
[1]Internal Medicine Department, Faculty of Medicine, University of Alexandria, Egypt
[2]Clinical Pathology Department, Faculty of Medicine, University of Alexandria, Egypt
Corresponding author
Reem Ahmed Mohammed Abd El Ghafour (Abd El Ghafour R.A.)
Specialist of Internal Medicine, Damanhour Medical Institute, Egypt
Email: *reemdoc10@yahoo.com, phone: 002 01227943121*

Abstract
Aim and Background: *IGF binding proteins predominantly control the access of IGFs to tissues and cell-surface IGF receptors. Of these, IGFBP-1 is the most likely candidate for acute regulation of IGF actions because of its acute down regulation by insulin and upregulation by other glucoregulatory hormones and cytokines and in catabolic states. This study was undertaken to to assess the relation of the IGF-1 and IGFBP-1 to insulin resistance in a group of adult Egyptian diabetics and non diabetic population.*
Subjects and Methods: *This study was conducted on 45 adult males with age between 20-50 years. They were divided into group I (n=25) type 2 diabetics and group II (n=20) non diabetics. Patient`s general information was noted, anthropometrical measurements were conducted and The eligible participants were asked to overnight fast for 8 hours. Blood was sampled for FBG, fasting Insulin, fasting IGF1, fasting IGFBP-1 And IR (HOMA-IR) was analyzed. Insulin and IGF-1 were analyzed by chemiluminescent immunoassay, FBG was analyzed by the glucose oxidase (enzymatic oxidation) method and IGFBP-1 was analyzed by IGFBP-1 ElLISA*
Results: *Diabetic group had IGF1(P=0.0001) and IGFBP-1(P=0.041) values statistically lower than non diabetic group. Diabetic group had a significant negative correlation between levels of FBG and those of IGF-1(p=0001).We noted that, diabetic group had a significant negative correlation between IGF-1 and IR(HOMA-IR) (p=.045) and a significant negative correlation between IGFBP1 and IR(HOMA-IR) (p=.046).*
Conclusion: *IGF1 and IGFBP-1 seems to be at lower levels in Type 2diabetics than in normal subjects, IGF1 seems to be negatively associated with fasting glucose in Type 2diabetics and Insulin resistance (HOMA-IR) seems to be negatively associated with IGF1 and IGFBP-1 in Type 2diabetics.*
Keywords: *IGFBP-1, IGF-1, IR(HOMA-IR), Type 2diabetics*

Introduction

This review addresses the possible role of the insulin-like growth factor (IGF)- axis in normal glucose homoeostasis and in the etiopathogenesis of type 2 diabetes. The three peptide hormones or growth factors, in the IGF family–insulin, IGF-I, and IGF-II–have approximately 50 percent of their amino acids in common. Insulin is synthesized in the beta cells of the pancreas as proinsulin, which is cleaved to form insulin and C peptide. The

IGFs, which are synthesized primarily by the liver, retain the C peptide and have an extended carboxy terminus. [1]

In several pathological states, an impairment of IGF-1 action on glucose metabolism has been recorded, along with insulin resistance; [2] however, it is not known whether IGF-1 and insulin resistance are always associated and it is not clear whether resistance, when it does occur, affects only glucose uptake and metabolism or protein metabolism as well.

IGF-I, a peptide hormone, shares amino acid sequence homology with insulin and has insulin-like activity; most notably, the promotion of glucose uptake by peripheral tissues. Although IGF-1 is structurally related to insulin, unlike insulin, it circulates bound to specific proteins called IGF binding proteins (IGFBPs) with variable affinity.[3] Insulin-like growth factor binding proteins (IGFBPs) that are present in extracellular fluids have been shown to modulate the biological activity of IGFs. [4] Both stimulatory and inhibitory effects of IGFBPs on IGF actions have been described and IGF-independent effects of several IGFBPs are emerging.

Accumulating evidence indicates important roles for members of the IGFBP family in metabolic homeostasis. For example, IGFBP-1 concentrations fluctuate inversely in response to changes in plasma insulin levels, implicating IGFBP-1 in glucoregulation, and fasting levels of IGFBP-1 predict insulin sensitivity. IGFBP-1 has been proposed as the binding protein most likely to modulate the acute metabolic effects of IGFs, [5] because uniquely among the IGFBPs, it is acutely regulated by glucoregulatory hormones—insulin (inhibition) and cortisol and glucagon (stimulation). [6] Circulating IGFBP-1 derives from the liver, where inhibition of synthesis by changing hepatic portal insulin concentrations provides a connection between insulin levels and the hypoglycemic potential of IGF-I. [7] Insulin inhibits the hepatic synthesis and secretion of IGFBP-1[8] and increases the portal concentrations of insulin decrease serum levels of IGFBP-1 in obese subjects. [9]

Conditions characterized by insulin resistance (including obesity, metabolic syndrome, type 2 diabetes and polycystic ovarian syndrome) are associated with decreased IGFBP-1 levels. [10] IGFBP-1 concentrations correlate with insulin sensitivity in pubertal children, [11] healthy young volunteers [12], elderly adults [13] and patients with glucose intolerance or type 2 diabetes. [14]

In a prospective case-control study of Swedish men, low fasting IGFBP-1 concentrations predicted the development of diabetes over ten years,[15] when low IGFBP-1 concentrations were combined in an algorithm with glucose levels, waist measurements, height measurements and proinsulin levels, individuals in the highest quartile were found to have a 40-fold increased risk of developing diabetes. Although this study shows convincingly that, low IGFBP-1 levels predict development of diabetes, IGFBP-1 levels actually increased by almost a third in individuals who developed diabetes within the next ten years. [15]A potential explanation might be that low IGFBP-1 levels enable the development of diabetes, but as diabetes develops, IGFBP-1 concentrations rise as a consequence of hepatic insulin resistance or increased cytokine levels. The effects of emerging insulin resistance on IGFBP-1 concentrations require confirmation in other studies.

Aim and objectives

The aim of the present study was to assess the relation of the insulin-like growth factor-1 and Insulin-like growth factor binding protein-1 to insulin resistance in a group of adult Egyptian diabetics and non diabetic population.

Subjects and Methods

This study comprised 45 adult males, with age ranging from 20 to 50 years. Participants were selected at random from outpatient clinics in Alexandria Main University Hospital. A group of 25 diabetic subjects were selected from the Out-

Patient Department, along with a group of 20 healthy subjects as Controls considering the same socio-economic status. A group of patients with type 2 diabetes was matched with a control group with normal fasting glucose levels. Both groups were of comparable BMI.

The purpose of this study and the methods of investigation were explained to participants At first, the response of the people was not enthusiastic as they asked about the purpose of the study, But, explaining the purpose of the study has encourage them to participate. Written consent was taken from all the volunteers; clinical examinations were undertaken using a predesigned questionnaire. Patients with hepatic, renal, neurological, endocrinological or other systemic disease were excluded from this work by history, examination and routine laboratory investigations. The people of this study had no special life style, no special foods.

Subjects were requested to come on a prescheduled morning, after overnight fasting for 8 hours (no caloric intake for 8 hours). No special diet or restriction was recommended the day before the investigations.

2.1. Demographic and Clinical assessment

All study subjects were subjected to history taking including age, duration of diabetes and complete physical examination including anthropometric measurements. Height and body weight were measured using a digital scale, and body mass index (BMI) was calculated as follows: BMI = body weight (kg)/height squared (m^2). A body mass index <25 kg/m2 was considered to be normal. Systolic and diastolic blood pressures were measured in a sitting position after a 5-min rest. Patients were categorized as hypertensive patients if the systolic blood pressure was >140 mm Hg and / or diastolic blood pressure was >90 mm Hg.

2.2. Laboratory investigations

Taking an aseptic precaution, 3 ml of venous blood was taken. We estimated plasma glucose by the glucose oxidase (enzymatic oxidation) method, fasting serum Insulin was analyzed by chemiluminescent immunoassay and Insulin growth factor-1 was analyzed by chemilumine-scent immunoassay. Insulin growth factor binding protein-1 was analyzed by IGFBP-1 ElLISA and Insulin resistance was measured by HOMA-IR.

All blood samples were obtained after an overnight fast, and the patients' usual medications were withheld until after venesection. Plasma was separated from the remaining blood by centrifugation at 4°C. Plasma samples were stored at _70°C until analysis.

2.3. Statistical analysis

Data were expressed as mean ± SD (standard deviation), median (range) and/or percentage (%) as appropriate using SPSS (Statistical Package for Social Science) software. The statistical significance of the differences between the values was assessed by Student's't' test. A two-tailed p value of <0.05 was considered to be statistically significant.

Results

4.1 Clinical characteristics of the study subjects

There were no statistical significant differences between the two studied groups regarding age, BMI, Systolic blood pressure and Diastolic blood pressure. Type2 diabetic group have FBG values (P=0.001) statistically higher than non diabetic group. (Table1)

4.2 Serum IGF-1, IGFBP-1, Insulin and IR (HOMA-IR) status of the study subjects.

Type2 diabetic group have IGF1 values statistically lower than control group (P=0.0001). Control group have IGFBP1 values statistically higher than Type2 diabetic group (P=0.041). Type2 diabetic group have Insulin values statistically higher than control group (P=0.001). We noted also that, Type2 diabetic group have IR (HOMA-IR) values statistically higher than control group (P=0.0001). (Table 2)

4.3 Correlation between different studied parameters among diabetics.

There was negative significant correlations between FBS and IGF1(r=-.517, p=.0001), IGF1 and IR (HOMA-IR) (r=-.300, p=.045) and also, a negative significant correlation was found between IGFBP1 and IR(HOMA-IR) (r=-.315, p=.046).There was a positive significant correlation between FBS and IR(HOMA-IR) (r=.496, p=.001), insulin level and IR(HOMA-IR) (r=.719, p=.0001). Other variables showed no significant correlations. (Table3)

4.4 Correlation between different studied parameters in control group.

No significant correlation between all studied variables in control group except the positive correlation(r=.797, p=.0001) between IR (HOMA-IR) and insulin level. (Table4)

Table (1): Clinical characteristics of the study subjects

Variable	Control	Diabetics	Sig.
Age	43.8000±9.32794	45.7600±4.93525	.370
BMI	29.3505±5.28115	30.3888±5.03672	.505
FBG	82.6000±7.55611	143.9200±57.49994	.0001
Systolic blood pressure	79.0000±6.40723	81.4000±13.74773	.858
Diastolic blood pressure	118.5000±27.39093	125.6000±11.21011	.244

Results are expressed as M ± SD. $p < 0.05$, significantly different compared to controls when using Student's 't' Test

Table (2): Serum IGF-1, IGFBP-1, Insulin and IR (HOMA-IR) status of the study subjects

Variable	Control	Diabetics	Sig.
IGF1 (ng/ml)	164.3500±72.21696	76.7600±69.00057	.0001
IGFBP1(pg/ml)	1742.5000±649.88157	1301.2000±731.93989	.041
Insulin (µIU/mL)	7.2475±8.72594	32.9540±30.69926	.001
IR(HOMA-IR)	.7300±.90269	4.4760±3.83148	.0001

IGF-1 = insulin like growth factor-1, IGFBP-1 = insulin like growth factor binding protein-1and HOMA-IR=homeostasis model assessment of insulin resistance.

$p < 0.05$, significantly different compared to controls when using Student's 't' test

Table (3): Correlation between different studied parameters among diabetics

		FBS mg/dl	IGF1 ng/ml	IGFBP-1 pg/ml	Insulin	IR	BMI
IGF1 ng/ml	r	-.517**					
	p	.0001					
IGFBP-1 pg/ml	r	-.278	.16				
	p	.064	.233				
Insulin	r	.264	-.175	-.155			
	p	.080	.250	.310			
IR	r	.496**	-.300*	-.315*	.719**		
	p	.001	.045	.046	.0001		
BMI	r	.003	-.220	.038	.083	.018	
	p	.986	.147	.803	.586	.905	
Duration of DM	r	.232	-.013	.098	-.071	.053	-.432*
	p	.264	.952	.642	.736	.803	.031

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Table (4): Correlation between different studied parameters in control group

		FBS mg/dl	IGF1 ng/ml	IGFBP-1 pg/ml	Insulin	IR
IGF1 ng/ml	Pearson Correlation	.027				
	Sig. (2-tailed)	.910				
IGFBP-1 pg/ml	Pearson Correlation	.161	.257			
	Sig. (2-tailed)	.496	.274			
Insulin	Pearson Correlation	.062	.205	-.324		
	Sig. (2-tailed)	.796	.386	.154		
IR	Pearson Correlation	.056	.052	-.163	.797**	
	Sig. (2-tailed)	.815	.826	.441	.0001	
BMI	Pearson Correlation	.093	.186	-.161	.029	.132
	Sig. (2-tailed)	.524	.427	.497	.904	.541

Discussion

Insulin-like growth factors (IGFs) participate in the growth and function of almost every organ in the body. Because of the wide range of their biologic effects and their therapeutic potential in a variety of clinical disorders, the IGFs have become the focus of research by an increasing number of investigators. IGF-I leads to an increase in peripheral glucose uptake and a decreased production of hepatic glucose causing better insulin sensitivity. [16] In a large trial, [17] patients with type-2 diabetes who had IGF-I monotherapy had significantly lower haemoglobin A1C than those on placebo. Similarly, administration of IGF-I to patients with type-1 diabetes is associated with significant reductions in insulin requirements. [18]IGFBPs have emerged as a key regulator of insulin/IGF systems. Despite their structural homology, individual members of the IGFBP family may exert unique action. The function of IGFBP-1 on adipose tissue lipid metabolism and endocrine function may be linked with the development of obesity and insulin resistance.

In our study we found Type2 diabetic group have IGF1 values statistically lower than non diabetic group (P=0.0001). Poulos et al. [19] found low IGF-I levels in obese Type 2 diabetics. In contrast, Rajpatak et al. [13] did not find an independent association between IGF-1 and diabetes among 922 subjects 65 years of age from the Cardiovascular Health Study. Srinivas and Anoop [20] found that, lower serum IGF-1 levels were positively associated with diabetes only in subjects <65 years of age and not in those ≥65 years of age. Patients with type 2 diabetes often exhibit reduced circulating total IGF-I levels [21] One explanation is that chronic hyperinsulinemia induces GH receptor resistance. [22]Under experimental conditions, hyperinsulinemia reduces not only GH receptor expression but also GH signaling both at receptor and postreceptor levels. [22] We found that, non diabetic group have IGFBP1 values statistically higher than Type2 diabetic group (P=0.041).Sandhu et al. [23] found that, low IGFBP-I levels and an increased IGF-I:IGFBP-1 ratio were strongly associated with increased levels of insulin and glucose in men and women.

In our study we found among Type2 diabetic group, a significant negative correlation between levels of fasting blood glucose and those of IGF-1(r=-0.517 and p=.0001) and insignificant negative correlation between levels of fasting blood glucose and those of IGFBP1 (r=-.278 and p=.064) .Golam Kabir stated that, [24] IGF-1 was significantly (r =0.337, p = 0.025) associated with fasting serum glucose in simple Pearson's correlation which is also reflected in stepwise multiple regression where both free IGF-1 and IGFBP-1 showed themselves to be negatively associated with fasting serum glucose in IGT subjects.

In our study, we found insignificant negative correlation between IGF-1 and insulin (r=0.175 and p=0.250) among Type2 diabetic group, also we found insignificant negative correlation between IGFBP1 and insulin(r=-.155 and p=.310) among Type2 diabetic group. M.G. Kabir et al. [25] stated that, in stepwise multiple regression analysis, IGF-1 was inversely associated with fasting insulin and positively associated with insulin secretory capacity in type 2 DM subjects Rajpathak et al. [26] reported that, strong inverse correlation of IGFBP-1 with insulin among diabetic members of an elderly cohort.

In our study, we found a significant negative correlation between IGF-1 and insulin resistance (HOMA-IR) (r=-.300 and p=.045) among Type2 diabetic group. Also, we found a significant negative correlation between IGFBP1 and insulin resistance (HOMA-IR) among Type2 diabetic group(r=-.315 and p=.046) and insignificant negative correlation between IGFBP1 and insulin resistance(HOMA-IR) among non diabetic group (r=-.163 and p=.441). Laboratory studies have shown that in the presence of insulin resistance, there is upregulation of insulin/IGF hybrid receptor expression in muscle. [27] These receptors are largely responsive to IGF-I [27], and additional data suggest that their binding could be as potent

in stimulating peripheral glucose uptake as insulin binding with its receptor. [28]

Prior to the development of insulin resistance, however, the adverse metabolic effects of IGF-I may predominate. For example, IGF-I promotes preadipocyte differentiation and proliferation through activation of the insulin receptor substrate and mitogen-activated protein kinase pathways. [29] IGFBP-1 is a marker of declining beta cell function, just as has been observed for the incremental insulin response to glucose, [30] this is consistent with the emergence of hepatic insulin resistance .Kuppan et al. [31] stated that, Subjects with T2DM had significantly decreased levels of IGFBP-1 (21.7 ± 3.5 ng/mL) compared with NGT subjects (34.4 ± 7.6 ng/mL, P < .001). Liew et al. [32] have reported that, healthy glucose-tolerant Asian Indian subjects have an adverse combination of relative insulin resistance and low fasting IGFBP-1 levels.

In our study, we found insignificant negative correlation between IGF-1and duration of diabetes(r=.013 and p=.952) and no correlation between IGFBP1 and duration of diabetes (r=.098 and p=.642).IGFBP-1 is negatively related with insulin resistance, [14] with the development of type 2 diabetes; [14] however, IGFBP-1 concentrations rise again despite persisting hyperinsulinemia, suggesting a complex interaction between pancreatic insulin output and hepatic insulin sensitivity. Clauson PG et al. stated that, [33] levels of IGF-I decreased with diabetes duration and with increased blood glucose.

In our study, we found among Type2 diabetic group insignificant negative correlation between IGF-1 and BMI(r=-.220 and p=.147) and insignificant negative correlation between IGFBP1 and BMI among non diabetic group(r=-.161 and p=.497). Obesity may be associated with moderate elevation of free IGF-I levels, [34]this can occur despite the relation of obesity with hyposecretion of growth hormone (GH), [35] the primary regulator of IGF-I production by the liver, [36] because of IGF-I production by adipocytes, [37] the stimulation of hepatic IGF-I synthesis by insulin. [38] and insulin increases the fraction of circulating free IGF-I by down-regulating hepatic synthesis of IGFBP-1. [39] Frystyck et al. [40] have shown that the level of free IGF-1 increased in obese controls (BMI, 31.6 ±0.7) compared to lean controls (BMI, 22.8± 0.2), but in obese type 2 diabetes (BMI, 32.3±0.8) the level of free IGF-1 did not differ significantly from either lean or obese controls. M.G. Kabir et al. [25] stated that, no significant difference of IGFBP-1 level was observed between the low (BMI 6 23) and high (BMI > 23) BMI group neither in type 2 DM subjects nor in controls.

Interpretation of these findings is somewhat limited by the relatively small sample size of the study (number of diabetic cases=25, control cases=20) and the absence of data regarding additional IGFBPs, including IGFBP-2 and IGFBP-3.Prospective cohort studies of appropriate size, and with relevant data to control for other major risk factors, are needed to assess the fundamental question of whether the IGF-axis plays a significant etiopathogenic role in the development of type 2 diabetes.

Conclusion

From the results of the present study, we can conclude that our type 2 diabetes patients had IGF1and IGFBP-1 values statistically lower than non diabetic group .There was a significant negative correlation between levels of FBG and those of IGF-1 among diabetic group. Diabetic group had significant negative correlation between IGF-1 and IR and also, diabetic group had significant negative correlation between IGFBP1 and IR. All of the above data emphasized that the IGFBP-1 protein deserved attention for our understanding of its relation and the insulin-like growth factor-1 to insulin resistance.

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