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Article *in* International Journal of Bioscience and Biochemistry · September 2025

ISSN Print: 2664-6536
ISSN Online: 2664-6544
Impact Factor: RJIF **5.4**
IJBB 2025; 7(1): 41-45
www.biosciencejournal.net
Received: 15-11-2024
Accepted: 18-12-2024

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Correlation of soluble endoglin with glycemic control among Iraqi type2 diabetic patients

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DOI: https://dx.doi.org/10.33545/26646536.2025.v7.i1a.96

Abstract
Background: More than 90% of all diabetic patients have type 2 diabetes mellitus, a heterogenic, complex metabolic condition that has reached epidemic frequency globally and is characterised by persistent hyperglycemia followed by a period of asymptomatic metabolic alterations that primarily lead to significant complications. In Iraq, there is an insufficiency of epidemiological studies about diabetes. Glycemic control is the process that adjusted glucose level within target range to reduce negative impact of diabetes. Endoglin is a homodimer transmembrane glycoprotein belong to transforming growth factor (TGF) receptor expressed mainly in endothelial cell and playing a crucial role in endothelium functioning and angiogenesis process. In this research, we sought to determine the prevalence of glycaemic control and sENG levels in Iraqi patients with type 2 diabetes, as well as if there was a relationship between the two and whether it was linked to diabetic complications.
Methods: A cross-sectional study was included 89 type 2 diabetes mellitus patients and 89 apparently healthy individuals as control groups as the same age and sex with cases, sociodemographic feature and anthropometric measurements for each participant were obtained, overnight fasting samples were collected for biochemical analysis (FBG, HbA1c and sENG).
Results: Patients sENG, FBG and HbA1c were significantly higher compared to controls, whereas age, BMI, WHR, diabetic family history were showed insignificant differences. Males were slightly higher than females in this study and three quarter of them with positive diabetic family history. A significant higher level of sENG in patients with disease duration greater than 5 years and among patients regarded to diabetic complication, the majority of patients were showed poor glycemic control with a significant higher level of sENG compared to those with good glycemic control. Endoglin showed a positive correlation with age, BMI, WHR, FBG, and HbA1c. The purpose of this research was to estimate the sENG levels of type 2 diabetes patients and compare them to control in order to assess the impact of glycaemic management on these levels.

Keywords: Type 2 diabetes mellitus, glycemic control, endoglin (seng) levels, diabetic complications, biochemical analysis

Introduction

The prevalence of diabetes mellitus (DM) increases in epidemic level is a globally serious health issue, the worldwide incidence in 2021 was approximately 537 million, and this number is expected to rise to 780 million by 2045 [1], in Basrah, southern Iraq, a study found that out of the 5,445 individuals screened, the diabetes prevalence was 19.7%. Remarkably, 55.7% of people diagnosed as diabetic patients had no prior diagnosis. Furthermore, the examination revealed that nearly 29.1% of the individuals had prediabetes, leading to a high dysglycemia prevalence at 48.8%. Surprisingly, only 51.2% of the individuals tested had normal blood sugar levels [2]. Type2 diabetes mellitus (T2DM) is the most common type accounting for more than 90% of diabetes which is a silent form of diabetes that preceded by a periods of asymptomatic prediabetes stage. Metabolic disturbance of carbohydrate, lipid and protein because of impaired insulin secretion, insulin resistance or both leading to decrease in utilization and overproduction of glucose, consequence, a gradual and chronic hyperglycemia leading to serious diabetic angiopathy complication [3].
Glycemic control is the process that target maintain blood glucose level at optimal concentration nearest to euglycemic concentration, which is necessary and essential for diabetes care and management to delay occurrence of diabetic complication, reduce

morbidity and enhance patients' quality of life and life expectancy [4]. The high poor glycemic control prevalence was a major public health matter ranged between 45.2% and 93% among type 2 diabetic patients [5]. Endothelial dysfunction (ED), the first stage of T_2-DM complications, is a result of hyperglycemia, insulin resistance (IR), hypertension, oxidative stress, and aberrant fat levels [6]. Microvascular complication includes retinopathy, nephropathy and neuropathy while cardiovascular diseases, atherosclerosis disorder and cerebrovascular diseases represent macrovascular diabetic angiopathy [7]. The first marker elevated in diabetic vascular changes and arising before subclinical structural vascular alterations onset are soluble endoglin (sENG) [8]. Which is the proteolytic cleavage product of extracellular domain of ENG by matrix metalloproteinase enzymes (mainly; MMP12 and MMP14) as a result of endothelial cells damage, inflammation, tumor necrosis factor α and other factors [9].

Endoglin is a type 1 transmembrane homodimers glycoprotein, type III transforming growth factor (TGF) receptor, 180 kDa molecular weight that linked together by a disulfide bond composed of large extracellular, hydrophobic transmembrane and short cytoplasmic domain that is express predominantly in endothelial cells, monocyte and macrophages [10]. Endoglin acts as a regulator, modulating signal transduction for various cellular processes such as cell proliferation, migration and angiogenesis by interacting with TGF-β receptors [11]. Soluble ENG level elevated in condition like preeclampsia, hypertension, diabetes mellitus, hypercholesterolemia and in the conditions related to cardiovascular diseases [12]. This study's goals were to compare the blood levels of sENG in T2DM and control patients to determine if sENG is associated with diabetes control and complications, as well as to examine the impact of antidiabetic medication and illness duration on sENG levels.

Materials and Methods

From January to October 2024, a case-control research was conducted in the Department of Biochemistry at Basrah College of Medicine in the Basrah Governorate in southern Iraq. 89 type 2 diabetes patients were enrolled in the research as cases, while 89 people who seemed healthy and were matched for age and sex were included as controls. Every participant went to the TDEMC in the southern Iraqi province of Thi-Qar, either for routine checkups or medical consultations. T2DM was diagnosed using the American Diabetes Association's criteria [13]. Every study participant signed an informed written consent form, and the questionnaire asks about the study population's sociodemographics, including age, gender, history of other illnesses and medications, family medical history of diabetes, length of disease, type of antidiabetic medication, and diabetic complications. In the morning, while wearing loose clothing and no shoes, each research participant had their height, weight, hip circumference (H.C.), and waist circumference (WC) measured. The waist to hip ratio (WHR) was determined by calculating the body mass index (BMI) as (kg/m2) [14].

Samples collection

Following an overnight fast of at least eight hours, each participant had their blood drawn while seated using a disposable syringe. Five millilitres of blood were drawn from each participant, and the blood was divided into two portions. Two millilitres were put in an anticoagulant tube that contained 1.5 milligrammes of tri-potassium ethylene-diamine tetra acetic acid (K3EDTA) per millilitre, which was used to measure HbA1c levels. The other portion was put in a serum separator tube (SST) that contained gel and clot activator. Following that, the serum samples were gathered and kept in brand-new, disposable plastic tubes, some of which were used to rapidly estimate the results of standard biochemical procedures like fasting blood sugar (FBS). The leftover serum was frozen in a tightly sealed 2.5 ml Eppendorf tube (EP) and stored at -20 C° for less than a month in preparation for the subsequent endoglin analysis.

Biochemical measurements

The level of endoglin was determined by Enzyme-linked immunosorbent assay (ELISA) technique using a kit provided by Elabscience Biotechnology Co., Ltd, China, HbA1c levels was measured by ion exchange high performance liquid chromatography (HPLC) using the Bio-Rad D-10TM Dual Program HbA1c Kit provided from Bio-Rad USA (Variant™ hemoglobin testing system; Bio-Rad Laboratories Inc., Hercules, CA, USA). The level of serum glucose was determined by enzymatic method with hexokinase (HK)/glucose-6-phosphate dehydrogenase (G-6-PDH) using Glucose kit to run glucose assay on the ARCHITECT C System (Abbott Architect C4000), supplied from Abbott GmbH & Co. KG, Germany.

Statistical Analysis

The data from this study was analysed using the Statistical Package for Social Science (SPSS) software version 28, and the findings were presented as percentages, Mean±Standard Deviation (SD), and numbers. For continuous data, Independent t-test was used to compare two different groups, while one-way analysis of variance (ANOVA) was used to find the significance of variables among three or more groups. For categorical data, Chi-square (χ^2 test) has been used to analyze difference proportion between two or more groups. The correlation coefficient (r-value) between ENG and biochemical parameters as well as other factors in the research population was determined using Pearson correlation. The lowest threshold for significance was a P-value of less than 0.05.

Results

Participants' age, gender, BMI, WHR, and diabetic family history did not significantly differ from controls, according to the participant sociodemographic, biochemical, and clinical data shown in table (1). However, patients' levels of sENG, FBG, and HbA1c were significantly higher than controls'. Also, the males were appeared slightly higher than females, the patients mean value of BMI and WHR were nearest to the obese and more than three quarter of patients with positive diabetic family history.

Only 18% and 20.2% of the diabetic patients, respectively, had good glycaemic control based on FBG and HbA1c, according to the study. Table (2) also demonstrates that the mean sENG levels were higher in uncontrolled diabetic patients with a statistically significant difference compared to good control patients. The study found that the mean value of disease duration was (6.328±5.294) and more than half of the studied diabetic patients suffered from the disease for less than 5 years (55.1%). The patients sENG mean with duration of disease more than 5 years was significantly higher compared to patients with less than 5 years. According to the result in this study, approximately 90% of type 2 diabetic patients depended on antidiabetic drug for treated the disease, and there was no significant difference in the mean of sENG levels with respect to diabetic treatment. In this study, more than three quarters of patients had diabetic complication and most of them (40.5%) had more than one diabetic complications. Additionally, the mean of diabetic complicated patients sENG level was significantly higher than those without complication. The Pearson correlation analysis of sENG with other variables of diabetic patients in this study was revealed that serum sENG was correlated positively and significantly with FBS, HbA1c, age, duration of DM, BMI and WHR.

Table 1: Sociodemographic, clinical and biochemical data of study population

Parameter		Cases	Control	P-Value *
Age(years)		45.044±11.283	44.640±11.269	NS *
BMI(kg/m2)		29.176±5.473	28.132±4.088	N. S *
WHR		.994±.108	.972±.116	N. S *
Endoglin (ng/ml)		2.443±.587	1.782±.715	<0.001 *
FBG (mg/dl)		216.651±78.718	96.110±7.861	<0.001 *
HbA1c (mg/dl)		9.511±2.215	5.061±.294	<0.001 *
Gender	Male	46(51.7%)	45(50.6%)	N. S#
	Female	43(48.3%)	44(49.4%)	
F.H of DM	Positive	68 (76.4%)	58 (65.2%)	N. S#
	Negative	21 (23.6%)	31 (34.8%)	

Data were presented as (number and percentage) and (Mean±SD), (*) level of significant between cases and controls, p-value < 0.05 was significant, (*) independent student T-test, (#) Chi-square test.

Table 2: Distribution of sENG according to glycaemic control in diabetic patients.

Parameter		Pt. distribution	Endoglin (ng/ml)	P-Value *
FBS (mg/dL)	≤130	16 (18.0%)	1.972±.571	< 0.001 *
	>130	73 (82.0%)	2.547±.541	
HbA1c%	Good control <7%	18 (20.2%)	2.107±.601	< 0.05 #
	Fair control 7-8%	11 (12.4%)	2.238±.626	
	Poor control >8%	60 (67.4%)	2.582±.531	

Data were presented as (number and percentage) and (Mean±SD), (*) level of significant between patients, p-value < 0.05 was significant, (*) independent student T-test, (#) one way ANOVA test.

Table 3: Distribution of sENG according to duration of disease, type of treatment and diabetic complications.

Parameters		Pt. distribution	Endoglin (ng/ml)	P-Value*
Duration of disease	≤5 years	49 (55.1)	2.304±.593	< 0.05 *
	>5 years	40 (44.9)	2.613±.540	
Type of treatment	Dietary	9 (10.1)	2.201±.661	NS#
	OAHD	40 (44.9)	2.338±.566	
	Insulin	14 (15.7)	2.470±.629	
	Mixed	26 (29.2)	2.674±.522	
Diabetic complication	no complication	20 (22.5%)	2.133±.609	<0.05#
	HT(Hypertension)	11 (12.4%)	2.471±.567	
	DPN (diabetic peripheral neuropathy)	8 (9.0%)	2.295±.498	
	DRP (diabetic retinopathy)	7 (7.9%)	2.564±.649	
	CVD (cardiovascular diseases)	7 (7.9%)	2.531±.502	
	have 2 complications	16 (18.0%)	2.370±.399	
	have more than 2 complications	20 (22.5%)	2.783±.618	

Data were presented as (number and percentage) and (Mean±SD), (*) level of significant between cases, p-value < 0.05 was significant, (*) independent student T-test, (#) one way ANOVA test.

Table 4: Pearson Correlation of sENG levels with the patient's biochemical data.

Variable	Endoglin (mean ±STD) (ng/ml)	
	Correlation Coefficient	P value
Fasting glucose	.223*	< 0.05
Glycated hemoglobin	.310**	0.003
Age	.341**	0.001
Duration of DM	.278**	0.008
Body mass index	.343**	0.001
Waist to hip ratio	.323**	0.002

**.Correlation is significant at the 0.01 level (2-tailed),*. Correlation is significant at the 0.05 level (2-tailed)

Discussion

Over the past 10 years, diabetes mellitus has become an epidemic in Iraq, which is in line with global trends in its incidence. Therefore, considering its high prevalence rate, rising incidence rate, and overall economic burden, diabetes is a serious public health problem for Iraqis (15). According to the data collected in this study the mean value of patients age was (45.04±11.28) years with positive correlation between sENG and age revealed by Pearson Correlation test in this study, this results were agreed with some studies (16, 17), age-related increases in oxidative stress and inflammatory cytokines may enhance endoglin expression and appears to be exacerbated due to the underlying inflammatory processes associated with insulin resistance and metabolic dysregulation [18]. Higher male diabetic prevalence than female in this study was agreed with other study [19], sex related variation of hormones, sociocultural behaviours, environmental changes and gene-environment interactions were resulted in this variation [20]. According to the Iraq STEPS survey, the prevalence of overweight and obesity in Iraq was 65.7%, making the twin epidemics of obesity and diabetes the largest public health concern of the twenty-first century [21]. The mean of patients BMI and WHR in this study were higher than normal and nearest to the obese, the casual associated risk for T2DM was 26% for BMI and 38% for WHR [22].

More than three quarter of the patients in the present study had poor glycaemic control regarded to HbA1c and majority of them respected to FBG, this result agreed with other study [23]. The risk of diabetic angiopathy incidence increases by (11%) for every (1%) increase in HbA1c levels over (6.5%) [24]. Socio-economic factors, inadequate patient education and poor healthcare, factors elucidated by Tol A *et al.* [25] as effector on glycemic control. While Shuhaida MH *et al.* [26] added psychological factors, such as depression and anxiety to the effector list, Yahaya JJ *et al.* [27] reported that irregular medication adherence, dietary mismanagement, and lack of regular monitoring diabetic state resulted in fluctuation of glycemic control. The mean of sENG levels were significantly higher in an uncontrolled diabetic patient, Pearson correlation analysis were appeared positive correlation between ENG with FBG and HbA1c, this result agreed with the results of Ali MK *et al.* [28], Antwi-Baffour S *et al.* [29] studies. Increased level of sENG in poor glycemic controlled patients attributed to chronic hyperglycemia and its results; oxidative stress, low-grade inflammation and advanced glycation end products (AGEs), Furthermore, insulin resistances related inflammatory cytokines can induce the expression of endoglin [30]. The current study was appeared that half of patients with disease duration less than 5 years which could be explained by the fact that the patients seeked medical attention as early as possible once they were diagnosed with DM before development of diabetic complications. Type2 diabetic patients with more than 5 years have sENG levels significantly higher than patients with less than 5 years duration, indeed that there was a positive correlation between sENG and duration of disease. Study Wang *et al.* [31] supported this result. Approximately 90% of type 2 diabetic patients depended on antidiabetic drug for treated the diabetes, despite that, there was no significant difference in endoglin level according to type of antidiabetic drug (no drug, oral drug, insulin and mixed drug of insulin and oral). The results were agreed with the result of Bilir B *et al.* [32].

Increased level of sENG has been identified as endothelial dysfunction biomarker [33] a common pathway for vascular complication of type2 diabetes mellitus (65). The current study exhibit that, more than three quarters of patients (77.5%) had diabetic complications, most of them experiencing more than one diabetic complication. Interestingly, all the type2 diabetic patients with complications have significantly higher endoglin levels, while the highest mean level of endoglin (ENG) was observed in patients with more than two complications of diabetes mellitus, when compared to diabetic cases who had no complications, the above result was corroborated by other studies [34]. Hsieh *et al.* has elucidated that "increased endoglin levels are linked to inflammation and oxidative stress in patients with diabetes, both of which are known mechanisms that exacerbate the development of complications" [35].

Conclusion

Patients with type 2 diabetes had a higher sENG level than those without the disease, and those with poorly managed diabetes, long-term diabetes, and diabetic complications had significantly higher levels. These findings suggest that sENG may play a role in the development of the disease and its complications, and that it may be used as a marker of metabolic disturbance in diabetes mellitus and diabetic complications.

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