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Association Among HOMA-IR with Endothelin and Several Interleukins in Diabetic Mellitus Type 2 Patients

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Abstract : Diabetes is the most common form of DM characterized by hyperglycemia, insulin resistance, and relative insulin deficiency.Diabetes is inflammatory disease related with several cytokines such as endothelin, IL1B,IL18, and IL37.HOMA IR is characterized as the decrease in the effectiveness of insulin in glucose utilization or over-secreting of insulin to maintain the stability of blood glucose levels related with inflammation stress .Insulin is a hormone that facilitates the transport of glucose from blood into cells, thereby reducing blood glucose (blood sugar). Insulin is released by the pancreas in response to carbohydrates consumed in the diet. In states of insulin resistance, the same amount of insulin does not have the same effect on glucose transport and blood sugar levels. Aim of this studyies to evaluate the HOMAIR level withrelation expression of Endothelin and interleukins IL1B,IL18,and IL37. The pathogenesis of diabetes is significantly influenced by interleukins. This study including more than one type of groups according toHOMA and without HOMA so the patients divided into sub group ,and assessed the link between the gene expression of endothelin, IL1β, IL-18, and IL-37 in patients with type II diabetes. Samples were taken from type II diabetes patients and control at the Specialized Center for Endocrine Diseases and Diabetes in Baghdad between March and June 2023. For the groups under study, laboratory profiles were completed. Interluken-1β, IL-18, and IL-37 genes expression was measured by qRT-PCR.With a p-value ≤0.01, laboratory profile data revealed significant differences between patients and control in terms of HbA1c, FBS, insulin, and HOMA-IR, with out HOMA-IR. The studyresult emphasize relation aamong between HOMA IR and cytokines in which the upregulation of endothelin and IL18 in patients with increasing HOMAIR while there downregulation in IL1B with HOMAIR.that revealed an association among study factor .

Keywords: Endothelin , IL-1β ,IL-18, IL-37,HOMA-IR , Diabetes Type II

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Introduction

Diabetes Mellitus type II (DMII) is a long-term illness that results in elevated blood glucose levels with increasing Inflammation. (1)Environmental factors (for example, obesity, an unhealthy diet and physical inactivity) and genetic factors contribute to the multiple pathophysiological disturbances that are responsible for impaired glucose homeostasis in T2DM. (2) (3).

HOMA-IR is a synonym for impaired insulin action, such as inhibition of hepatic glucose production and insulin-mediated glucose disposal.(4) IR increases the incidence of metabolic syndrome, which has

emerged as a major pathophysiological factor in the development and progression of many common non-communicable diseases, including type 2 diabetes mellitus (T2DM), polycystic ovary syndrome, dyslipidaemia, hypertension, cardiovascular disease, obesity and cancer(5).IR is an early marker of the development of these diseases; primary prevention requires the identification of high-risk individuals at an early stage. (6)Insulin resistance and concomitant metabolic abnormalities, including type II diabetes, are linked to the chronic inflammatory response (8). Cytokines have a major role in the immune-mediated disease known as diabetes type II, which results in a reduction in insulin signaling and the death of β-cells that produce insulin (9).Among the immune cells that generate cytokines include mast cells, T cells, B cells, and macrophages. Both acute and chronic inflammation are influenced by cytokines, which are thought to be the primary regulators of inflammation. They can cause type II diabetes and insulin resistance (10).

IL-1β and IL-18 are proinflammatory cytokines (IL-1β and IL-18) and anti-inflammatory cytokines (IL-37), two of the eleven members of the IL-1 family. These are linked to inflammation and immunological reactions (11). Type II diabetes is caused by IL1β, a proinflammatory cytokine that affects the pancreatic β cells involved in insulin generation and increases their disorganization and dysfunction (12).By strengthening Th1 and Th2 cells and promoting the synthesis of inflammatory cytokines including IL-1β, TNF, and IFN gamma, IL-18 regulates inflammation, claim Zhang et al. (13).

Several studies reported an increase in IL-18, a proinflammatory cytokine produced by the IL-18 gene. IL-18 is produced by endothelial cells, vascular smooth muscle cells, dendritic cells, macrophages, and adipocytes (14). Local research in Iraq has demonstrated the importance of IL-18 in the management of numerous ailments in Iraqi patients (15,16).Furthermore, IL-1 β levels were higher in patients with type II diabetes, according to another study (17). One member of the IL-1 family, IL-37, is essential for preserving the equilibrium of the immune system and plays a part in the development of autoimmunity and inflammation. It was linked to diabetes because of aberrant expression of IL-37 (18).The long peptides made up of 21 amino acids make up endothelin (ET), which has proliferative, profibrotic, proinflammatory, and prooxidative properties in addition to acting as a vasoconstrictor and maintaining the tone of vascular smooth muscle cells produced by endothelial cells, vascular smooth muscle cells, kidney medulla, and macrophages. ET is regarded as a cytokine that promotes inflammation. Its synthesis is linked to endothelial stress, and cytokines are released following inflammation (19). The result study emphasize relationaamong between HOMA IR and cytokines in which the upregulation of endothelin and IL18 in patients with increasing HOMAIR wheal there downregulation in IL1B with HOMAIR .

Material and method

Sample collection

Fifty patients with type II diabetes and fifty healthy samples each had five milliliters of blood drawn.According to the level of HOMA-IR current Patients divided into groups patients with HOMA, patiens without HOMA-IR.IR ranges from 0 to 1.95 mu/mI . Whole blood samples were separated into two milliliter EDTA tubes and two milliliter

gel tubes for separated serum. To extract RNA, 250 µl was placed to an Eppendorf tube that contained 750 µl of GENzol, and the tubes were then kept at -20 degrees.
Every sample was taken at the Specialized Center for Endocrine Diseases and Diabetes in Al-Rusafa, Baghdad, between March 2023 and August 2023. All of the samples were between the ages of 28 and 65. The American Diabetic Mellitus Type II Association's 2016 guideline for diabetes type II criteria, which include fast blood glucose (FBG) ≥125 mg/dL (7.0 mmol/L) and HBA1c ≥ 6.5% (48 mmol/mol), were used to select the patients. Furthermore, doctors have only been diagnosing patients with type II diabetes for less than two years. Those without diabetes who have FB levels below 95 mg/dL are represented as the control group. In the groups under study, anthropometric measurements were height (meter), weight (kg), hip circumference (cm), and abdominal circumference (cm). Insulin ranges from 1.1 to 17.0 mu/mI, HbA1c ranges from 4.2 to 6.5 mg/dI, and fasting blood glucose ranges from 75 to 130 mg/dI. The HOMA-IR score was used to calculate the concentration measurement test for insulin resistance.

Biochamicalsfactore measurement

Special reagents were placed into the Cobas C 311 analyzer (Cobas-Roche, Germany) and used to measure biochemical variables.HOMOIR= (fasting insulin [Mu/ml])×(fasting gluocose[mg/dL]) / 405.

RNA Extraction and cDNA synthesis

GENzol (TriRNA Pure Kit, Geneaid, Taiwan) was used to extract the RNA. Primers from Bioneer Company/Korea and the AccuPowerRocketScript RT PreMix kit were used to create complementary DNA (cDNA). With the exception of the GAPDH gene, the second author used the primer building tools on the NCBI website to design primers for gene studies (Table 1).

(Table 2)displays the reaction conditions for the cDNA synthesis, which was carried out with a final volume reaction of 20 µl. AccuPower Green Star qPCR premix was used to perform qRT-PCR, and 25 µl was the final reaction volume. Additionally, the housekeeping gene was GAPDH (glyceraldehyde 3-phosphate dehydrogenase). Under the reaction conditions listed in Table (3), samples were placed in an Exicycler 96 apparatus. By measuring the threshold cycle (Ct value) and computing folding target gene expression using equation (2^the-CT) (20), the gene expression levels were ascertained.

Table (1): Program of cDNA synthesis.

Step	Temperature	Time
Primer annealing (oligo dT)	37ºC	10min
cDNA synthesis	42ºC	60min
Heat inactivation	95ºC	5 min

Table (2): cDNA Synthesis

step	condition	cycle
preDenaturation	95C,3 min	**1**
denaturation	95C,3 sec	**40**
annealing extension detection scan	55C,20sec	
melting		**1**

Table (3) : Real Time PCR

Genes	5'-3'	Tm c°	Product Sizepb
IL-37	TACATACGCCCAGGTGACTC	57	96
	ATAGCATGGAGTTGAGCCCAC	57	
IL-1β	CCTTGCTGTAGTGGTGGTCG	56	144
	TGATGTCAAAGCATGGTTCCTG	56	
IL-18	TTGTCTCCCAGTGCATTTTGC	55	163
	GCAGCCATCTTTATTCCTGCG	55	
Endothelin	CATTTGGGTCAACACTCCCG	59	70
	AGTGGAGCCAGCGCTAATGA	60	
GAPDH Housekeeping Gene	GAAATCCCATCACCATCTTCCAGG	60	160
	GAGCCCCAGCCTTCTCCATG	60	

Statistical Analysis

The Statistical Packages of Social Sciences-SPSS (2018) program was used to detect the effect of difference groups (patients and control) in study parameters. Least significant difference-LSD was used to significant compare between means in this study.(21) gene expression folding calculated according to levak.

Result

The result (Table 4) Significant variations in HbA1c, FBS, Insulin, and HOMO IR between study group. There were no discernible variations (body mass, waist circumference, hip circumference, and age at diagnosis).fold gene expression for patients without homo IR(1.65 ±0.07) compared with patients homo IR(7.16 ±0.38)and control (1.33 ±0.05) with significant differences(P≤0.05)

Table (4) : Comparison between difference groups in parameters study

Groups	Body Mass Index	Waist hip ratio	the Age when persion diagnose with diabetic	HbA1C (4-5.6) mg/dl	FBS 70-110 mg/dl	Insulin 1.1-17.0 Mu/Ml	HOMO IR
Patients with homo IR	49.43 ±2.74	0.81±0.64	45.00 ±2.76	7.30 ±0.38 a	145.04 ±8.91 a	19.20 ±0.89 a	7.16 ±0.38 a
Patients with out homo IR	45.63 ±2.17	0.79±0.8	47.69 ±2.24	6.08 ±0.29 ab	120.30 ±6.45 b	5.60 ±0.32 b	1.65 ±0.07 b
Control	46.23 ±2.08	0.86±0.95	48.83 ±3.10	4.96 ±0.22 b	115.02 ±6.02 b	4.55 ±0.28	1.33 ±0.05 b
L.S.D. (P-value)	5.02 NS (0.071)	1.11NS (0.61)	3.97 NS (0.088)	1.359 * (0.0277)	22.673 * (0.0351)	5.481 ** (0.0001)	1.547 ** (0.0001)
	Means having with the different letters in same column differed significantly. * (P≤0.05), ** (P≤0.01).						

The result table5 the extracted data provide a comparison of gene expression levels between different patients groups based on homo status for insulin resistance (IR). The following is a summary of the main results:Patients without homo IR .fold Endothelin: 1.30 ± 0.16 Patients with homo IR Endothelin: Fold change: 0.198 ± 0.07 Control group Endothelin: Fold change: 1.0 ± 0.00. Differences between groups are significant (P ≤ 0.05).

Patients without homo IR show significantly higher gene expression of Endothelin compared to those with homo IR, while it non-significant differ comparing to control. suggesting a possible association between homo IR and decreased expression of this gene. The control group shows an intermediate level of expression, which serves as a baseline for comparison (Table 5).

Table (5): Fold change of *ENDO* gene expression in different groups

Groups	Means Ct of Endothelin	Means Ct of GAPDH	Mean ΔCt Target. (Ct Endothilin – GAPDH)	Calibrators	ΔΔCt	2 – ΔΔCt	Experimental result	A fold of gene expression
Patients Without homo IR	22.394	21.251	1.143	3.01	-1.86	5.37	5.371/4.0	1.30 ±0.16 a
Patients with homo IR	22.213	21.207	1.005	2.6	-1.594	5.586	0.795/4.0	0.198 ±0.07 b
Control	22.78	20.64	2.13	2.622	-0.49	4.0	4.0/4.0	1.0 ±0.00 a
L.S.D. (P-value)	--	--	--	--	--	--	--	0.588 * (0.0297)

Means having with the different letters in same column differed significantly.
* (P≤0.05).

The results table 6 of the expression analysis for the *IL-1β* gene appeared after normalization with the GAPDH gene, indicating significant down-regulation in fold gene expression for patients without homo IR(0.17 ±0.03) and patients with homo IR(0.418±0.06)compared with control (1.0 ±0.00) (Table 6).

Table (6): Fold change of *IL-1β* gene expression in difference groups

Groups	Means Ct Of IL B1	Means Ct of GAPDH	Mean ΔCt Target. (Ct ILB1 – GAPDH)	Calibrators	ΔΔCt	2 – ΔΔCt	Experimental result	A fold of gene expression
Patients With out homo IR	22.59154	21.25154	1.34	2.9	-1.56	4.879	1.5/8.5	0.17 ±0.03 b
Patients With homo IR	23.140	21.379	1.7613	3.12	-1.358	8.234	3.554/8.5	0.418 ±0.06 ab
Control	24.63	22.98	1.64	2.65	-1.63	8.5	8.5/8.5	1.0 ±0.00 a
L.S.D. (P-value)	--	--	--	--	--	--	--	0.607 * (0.0447)

Means having with the different letters in same column differed significantly.
* (P≤0.05).

IL18:

The results table 7 of the expression analysis for the *IL-18* gene appeared after normalization with the GAPDH gene, indicating up-regulation in fold gene expression for patients without homo IR(1.398 ±0.24) to patients with homo IR(0.4±0.06)and control (1.0 ±0.00) with significant differences(P≤0.05) (Table 7). Both patients group not differ from control.

Table (7): Fold change of IL-18 gene expression in difference groups

Groups	Means.. Ct Of IL18	Means Ct of GAPDH	Mean ΔCt Target. (Ct IL18 – GAPDH)	Calibrators	ΔΔCt	2 – ΔΔCt	Experimental result	A fold of gene expression
Patients With out homo IR	22.68462	21.25154	1.433077	2.45	1.01692	2.6577	2.657/1.9	1.398 ±0.24 a
Patients With homo IR	22.46	21.32	1.11	2.02	-0.907	3.30	0.76/1.9	0.40 ±0.06 b
Control	26.23	24.70	1.53	1.63	-0.18	1.9	1.9/1.9	1.0 ±0.00 ab
L.S.D. (P-value)	--	--	--	--	--	--	--	0.611 * (0.0289)

Means having with different letters in same column differed significantly.
* (P≤0.05).

IL37:

The results table8 of the expression analysis for the *IL-37*gene appeared after normalization with the GAPDH gene, indicating down regulation in fold gene expression for patients without homo IR(0.103 ±0.02) when compared to patients with homo IR(0.58 ±0.02)and while control differ significant with first group of patients but not differ from second groubs. (Table 8).

Table (8): Fold change of IL-37 gene expression in difference groups

Groups	Means Ct Of IL37	Means Ct of GAPDH	Mean ΔCt Target. (Ct IL37 – GAPDH)	Calibrators	ΔΔCt	2 – ΔΔCt	Experimental result	A fold of gene expression
Patients With out homo IR	21.938	21.25	0.686	2.7	2.013	8.398 2	8.398/8.1	0.103 ±0.02 b
Patients With homo IR	22.86	21.42	1.438	2.31	-0.87	4.701	4.701/8.1	0.58 ±0.02 ab
Control	24.16	24.18	-0.02	2.24	-2.26	8.1	8.1/8.1	1.0 ±0.00 a
L.S.D. (P-value)	--	--	--	--	--	--	--	0.593* (0.0391)

Means having with the different letters in same column differed significantly.
* (P≤0.05).

Discussion

Endothelin is a peptide with vasoconstrictive potential properties and it's involved in cell proliferation, vascular tone, and inflammation. Endothelin expression can impact with metabolic condition such as insulin resistance and cardiovascular health.In non-homo insulin resistance; family history, obesity and other risk factors are significantly enhancing the up regulation of endothelin level through influencing inflammatory mediators and endothelial function. Furthermore, IR patients exhibit significantly less endothelin expression due to alter signaling pathway in insulin resistant state and resulting down regulation. A study by MohdNor NA and proved that insulin resistance interfere with transcription pathway like p13K/AKT that regulate endothelin (24). On other hand resistance of insulin impair

endothelial function which reduce endothelin production (25).

IL-1B is a pro-inflammatory cytokine produced by activated macrophages, play major role in systemic inflammation, pancreatic beta-cell dysfunction, and insulin resistance (26). So that, the diabetes Patients with chronic low-grade inflammation significantly contributes to progress the disease, the down regulation of IL-1B subjected to several mechanisms like epigenetic modification that regulate IL-1B gene expression through altering the gene's promoter region such as DNA methylation by increased of CPG methylation islands in IL-1B promoter that reduces gene expression and transcription factor binding (27). Another study by Roy SG showed that miRNAs bind with the IL-1B mRNA and promote degradation or preventing translation (28).

Interleukins 18 and 37 are members of IL-1 family and they play an important roleas pro-inflammatory process could trigger cytokine and influence inflammation process (29). In this study gene expressions of both IL-18 and IL-37 were studied and the results showed that IL-18 gene expression was up regulated in patient without homo IR and down regulation in patient with homo IR, these results can be attributed to the ability of this cytokine to reflect insulin-resistance not only in patients with established type 2 diabetes, but also in non-diabetic controls (30). This means that non-homa IR in control may carry the genes for insulin resistant. Still the expression of IL-18 inhoma IR patient is lower than non-homa patient and control this may be due to the variation in metabolism as the diabetic patient follow a healthy diet and avoid lipid and carbohydrate, especially tat fatty acid regulate IL-18 expression (31). Regarding IL-37 results, in control group had higher expression than homa IR and non-homa IR patient as IL-37 related to high insulin sensitivity (32). Non-homa IR patient showed higher gene expression of IL-37 than homa IR patient which might be due to the insulin treatment used in homa IR patient than participate in reducing IL37 and enhancing insulin sensitivity (33). Obesity, family history, lipidemic and other risk factors of diabetes significantly enhance the up regulation of endothelin and IL-18 in non-homo insulin resistance diabetes patients by influencing inflammation, oxidative stress, and endothelial function, so it can be considered a marker for the disease progression. Concerning of IL-1B and IL-37 down regulation gene will promoting beta-cell damage, insulin resistance and exacerbates systemic and local inflammation, all these agents are critical mediator for disease progression (34). Additionally, IL-37 can attenuate the pro-inflammatory effect of IL-18 through directly or forming an IL-37/IL-18BP/IL-18Rβ complex. Thus, IL-37 capable of suppress both innate and acquired immunity of the host, and effectively control inflammatory stimulation, which was considered as a new hallmark of cancer (35). During inflammation, IL-37 suppresses the expression of several pro-inflammatory cytokines in favor to the expression of the anti-inflammatory ones by the regulation of macrophage polarization, lipid metabolism, inflammasome function, TSLP synthesis and miRNAs function. Moreover, IL-37 not only regulates the innate and acquired immunity, but also improves aging-associated immunosenescence (36). Moreover, IL-37 exerts an inhibitory effect on tumor angiogenesis and metastasis, and progression (37).

Conclusion

This study emphasizes that Homa IR effect on *Endothelin* gene expression causing downregulation while without Homa IR upregulation. Moreover, the current study emphasizes a relationship between homo IR and cytokines in which the up-regulation of endothelin and IL-18 in patients with increasing without Homa IR while there is down regulation IL-1B and IL-37 homo IR.

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