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The amelioration effect of antidiabetic agents on cytokine expression in patients with type 2 diabetes mellitus

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ABSTRACT

Inflammation is a condition that is closely linked to diabetes mellitus type 2 (T2DM), short for T2DM several different antidiabetic medications have been produced to regulate hyperglycemia, with indications that these therapies may have anti-inflammatory effects along with their glucose-lowering efficacy. Thus, this research was planned to explore the impact of antidiabetic agents on the cytokine expression levels —interleukin (IL)-1β, IL-6, IL-17, and IL-37 when patients have T2DM.

In this study, 168 eligible subject matter was split into two groups: 50 healthy individuals and 118 cases with T2DM, who were classified into two subgroups: 30 untreated patients and 88 patients treated with metformin-based therapy.

The outcome exhibited a significant increase within HbA1c% and proinflammatory cytokines (i.e., IL-1β, IL- 6, and IL-17), whereas IL-37 decreased considerably in untreated cases with T2DM compared to those in subjects who are healthy. Furthermore, the results showed increased levels Regarding waist size, body mass index and assessment using that homeostasis model, cholesterol, triglycerides, low-density lipoprotein levels, and heart danger elements in untreated cases with T2DM in comparison with hygienic subjects. Notably, treated patients with T2DM revealed an ameliorative impact on HbA1c, IL-6, IL-17, IL-37, IL-1β levels and lipid profile compared with untreated patients with T2DM.

Antidiabetic agents may have a beneficial activity on the inflammatory status by reducing blood glucose levels, hyperlipidemia, and proinflammatory cytokines. The anti-inflammatory activity of IL-37 can apply a potentially effective therapeutic goal in treating T2DM and its complications.

1. Introduction

The cause of the metabolic condition known as type 2 diabetes mellitus (T2DM) is a variety of reasons (Galicia-Garcia et al., 2020). Insulin resistance or T2DM has been clearly described as a state of systemic inflammation, including both innate and adaptive immunity (Zhong et al., 2015). Metformin's anti-inflammatory activity is supported by both basic and clinical studies (Abd El-Hameed, 2020); moreover, it prevents hepatocytes and macrophages from producing proinflammatory cytokines (Abd El-Hameed et al., 2021).

Diabetes and atherosclerosis appear to be linked through many pathophysiological routes; dyslipidemia with higher inflammation and levels of atherogenic low-density lipoprotein (LDL-c) have been proposed (Poznyak et al., 2020). Cytokines affect the liver, brain, adipose tissue, and pancreatic β-cells, altering lipid metabolism considered the main risk factor for atherosclerosis, obesity, and insulin resistance linked to T2DM (Zatterale et al., 2020). The inflammatory reaction of the human cell, or IL-1β is implicated in a number of illnesses, including autoimmune disorders, chronic heart failure, atherosclerosis, and type 2 diabetes; moreover, it suppresses the activity of β-cells and induces apoptosis of pancreatic β-cells (Tomita, 2018). In addition to proinflammatory elements, elevated glucose levels enhance IL-6 production (Abd El-Hameed, 2020).

Moreover, IL-17, a proinflammatory cytokine, was a part of the evolution of T2DM and function a critical part in inflammation, T2DM and insulin resistance (Abdel-Moneim et al., 2018). IL-17 is a strong

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inflammatory cytokine that inflames tissue and infiltrates extra inflammatory cells into target organs (Kuwabara et al., 2017). However, IL-37 has been described to have anti-inflammatory activities by suppressing innate responses. IL-37 changes the cytokine balance during acute and chronic inflammation to reduce inflammation, demonstrating its importance as a pivotal factor in restoring inflammatory homeostasis (Wang et al., 2018). Moreover, this inflammatory cytokine occupies an influential role in the genesis and advancement of diabetes (Cao et al., 2024).

Understanding the roles of cytokines in diabetes may help identify clinically relevant mechanisms that contribute to inflammation, insulin resistance, and T2DM. Notably, proinflammatory cytokine to anti-inflammatory cytokine ratios could indicate the imbalance of proinflammatory and anti-inflammatory forces and might predict diabetes progression and complications. Accordingly, no published studies have addressed the contribution of proinflammatory cytokine to anti- inflammatory cytokine ratios to T2DM and glycemic control. Moreover, one of the most aspects that have been extensively research of the non-glycemic impacts of antidiabetic agents is their impacts on inflammatory processes, which are poorly understood. Therefore, this investigation explores the impact of anti-diabetic medications on cytokine expression IL-1β, IL-17, IL-6 and IL-37 in cases with T2DM.

2. Material and subjects

2.1. Study population

All cases were chosen from the outpatient clinic of General Institution of Health Insurance, Beni-Suif, Egypt. The study proposal was conducted in compliance with the Helsinki announcement and well clinical follow up recommendations. All individuals were notified what the goal is and nature the research, and everyone's prior aware of consent was sought before their involvement. The General Institutions of Healthy Insurance Committee provided its approval (BSU/2016/12).

T2DM was identified in patients using the World Health Organization's 1999 standards. Participants in the study who were healthy controls had no kin in the first degree who had diabetes and no diabetes mellitus type 1 (T2DM). Individuals with any history of neoplastic or autoimmune disorders, asthma, allergies, respiratory disorder, thyroid disease, chronic inflammation, kidney failure, liver diseases, cardiovascular disease, infectious diseases, and alcoholism were left out of the study. Additionally, patients who had treatment alterations two months before participation were excluded from this study.

2.2. Study design

The study consisted of 168 participants of both sexes categorized as healthy controls ($n = 50$) and patients with T2DM ($n = 118$), who were subdivided into two series: untreated patients with diabetes ($n = 30$) and treated cases with diabetes ($n = 88$). The 88 patients were treated day using metformin monotherapy or metformin plus sulfonylureas, insulin, or both. A structured questionnaire was used to collect demographic information from the subjects. Venous blood samples (5 mL) were assembled from overnight fasted cases via venous puncture and divided into three plain vacationer tubes (Becton–Dickinson, Franklin Lakes, NJ, USA). The first one was subsequently centrifuged for ten min. at 4000 rpm. Serum samples were aliquot immediately and separated, and kept at − 40 °C. Regarding to the second sample for glucose estimation, potassium fluoride tubes were used and the measurements occurred immediately. On the third tube, the blood sample was obtained on ethylenediaminetetraacetic acid for estimating glycosylated hemoglobin (HbA1c%), and then, by using centrifugation the separated sediment blood cells were washed with normal saline and centrifuged several times to isolate buffy code leukocytes, which, until real-time polymerase chain reaction, were kept at 80 °C (RT-PCR).

2.3. Laboratory assays

Blood glucose levels were determined according to the reagent kit purchased from Biochon (Germany). HbA1c% was estimated according to the reagent kit obtained from Cobas Integra 800 (Roche, Basel, Switzerland). Diagnostic Products Corporation's radioimmunoassay kit (Los Angeles, USA) was used to assess serum insulin levels. Using the Bonora et al. equation was used to construct the Insulin Resistance Homeostatic Model Assessment (HOMA-IR) (Bonora et al., 2002). Total cholesterol (TC), triglyceride (TG), and high-density lipoprotein cholesterol (HDL-c) levels where levels were assessed utilizing reagent kits acquired from the Reactivos Spinreact Company (Spain). Friendewald's equation was used to determine the low -density lipoprotein (LDL) and very- low -density lipoprotein (VLDL) concentrations (LDL-c) (Friedewald et al., 1972). The cardiovascular risk (CVR) indices were calculated in accordance with Ross (Ross, 1993).

2.4. Detection of gene expression using RT-PCR

Total IL-6, IL-1β, IL-17, and IL-37 utilization a tissue extraction kit bought from Qiagen (Germany), RNA was isolated from blood samples. The sequences of the DNA were amplified on StepOnePlus RT-PCR using the multiplex PCR process. RT-PCR was performed on a 20-μL system employing 10-μL 1 × SsoFast EvaGreen Supermix (Bio-Rad, Hercules, CA, USA), 2-μL cDNA, 6-μL RNase/DNase-free water, and 500 nM of the after-primer pair series: IL-1β: 5′- CAGAGAGTCCTGTGCTGAAT-3′ (fore) and 5′- GTAGGAGAGGTCAGAGAGGC-3′ (backward); IL-6: 5′-CCAATCTGGATTCAATGAGGAG-3′ (fore) and 5′-GGTCAGGGGTGGTTATTGCATC-3′ (backward); IL-17: 5′-CTTCCCCCGGACTGTGATGGTCAA-3′.

(fore) and 5′- TCATGTGGTAGTCCACGTTCCCAT-3′ (backward); IL-37: 5′- GCTCAGGTGGGCTCCTGGAA-3′ (fore) and 5′-GCTGACCTCACTGGGGCTCA-3′ (backward); and β- actin: 5′-CTGTCTGGCGGCACCACCAT-3′ (fore) and 5′-GCAACTAAGTCATAGTCCGC-3′ (backward). The following criteria applied to the thermal cycler: 4 min at 95.5 °C, proceeded by 40 round of 16 s all in 95.5 °C, 55 °C, and 72 °C. Each reaction was ramped from 60 °C to 95 °C using a melting curve. For each procedure, calculation was made to decide the proportional quantity of mRNA as well as the precise moment the fluorescent signal crossed an arbitrary threshold in the centered around the log-linear amplification phase. The amplification data were examined with the producing company algorithm using the Livak and Schnittger (Shakeel et al., 2018) method, and the outcomes were then normalized to beta -actin. Statistic evaluation.

2.5. Statistical analysis

The data is displayed as mean ± standard deviation. Windows version of Statistical Package for the Social Science (SPSS) (version 22.0; IBM Corp., Armonk, NY, USA) used for all statistical evaluations. To compare groups and identify any significant differences, least significant difference and a one-way analysis of variance T- test was utilized. A straightforward linear correlation research was conducted using the Med Calc statistical program to ascertain the degree of interdependence between variables (Ostend, Belgium). Statistical result was signal by P values lower than 0.05.

3. Results

The results detect a substantial superfast in the standard of diabetic duration, family history, waist volume, body mass index (BMI), and blood pressure, blood glucose, HbA1c, HOMA-IR, TC, TG, VLDL, LDL-c, and CVR factors (i.e., RF-1, RF-2 and atherogenic index) in comparison to healthy controls in both groups with diabetes. Additionally, both groups of diabetic patients had significantly lower HDL-c and anti-atherogenic risk factor values than did healthy people. Treatment with

antidiabetic agents revealed a significant improvement in BMI, HbA1c, blood glucose, HOMA-IR, lipid profile, IL17/IL37 ratio and anti-atherogenic risk factor compared with those in untreated patients with diabetes (Table 1).

Additionally, the findings showed that diabetes patients had significantly rise standard of IL-6, IL-1β, and IL-17 mRNA expression than did healthy people. Moreover, the data found a significant decrease in IL-37 mRNA levels of expression when patients have diabetes in comparison to those in sanitary Pearson. Treated cases with diabetes showed an ameliorative effect on expression levels of IL-6, IL-1β, and IL-17 in comparison, untreated cases with diabetes (Fig. 1). Furthermore, There were positive associations among IL-1β and HbA1c% ($r = 0.386$; $P < 0.001$), BMI ($r = 0.358$; $P < 0.001$), TC ($r = 0.190$; $p < 0.01$), TG ($r = 0.449$; $P < 0.001$) (Fig. 2), HOMA-IR ($r = 0.221$; $P < 0.01$), fasting blood sugar (FBS) ($r = 0.210$; $p < 0.05$) and postprandial blood glucose (PPBS) ($r = 0.310$; $p < 0.001$) (Table 2).

Furthermore, IL-6 was positive relation for HbA1c% ($r = 0.415$; $P < 0.001$), BMI ($r = 0.321$; $P < 0.001$), TC ($r = 0.098$; $p = 0.10$), TG ($r = 0.412$; $P < 0.001$) (Fig. 3), HOMA-IR ($r = 0.053$; $P > 0.05$), FBS ($r = 0.288$; $p < 0.001$) and PPBS ($r = 0.450$; $p < 0.001$) (Table 2).

Moreover, IL-17 showed positive correlation with HbA1c% ($r = 0.507$; $P < 0.001$), BMI ($r = 0.335$; $P < 0.001$), TC ($r = 0.241$; $p < 0.001$), TG ($r = 0.443$; $P < 0.01$) (Fig. 4), HOMA-IR ($r = 0.201$; $P > 0.01$), FBS ($r = 0.288$; $p < 0.001$) and PPBS ($r = 0.449$; $p < 0.001$) (Table 2).

Otherwise, IL-37 indicate negative correlation for HbA1c%, ($r = -0.403$; $P < 0.001$), BMI ($r = -0.334$; $P < 0.001$), TC ($r = -0.152$; $P < 0.05$), TG ($r = -0.368$; $P < 0.001$) (Fig. 5), HOMA-IR ($r = -0.108$; $P = 0.171$), FBS ($r = -0.220$; $P < 0.001$), and PPBS ($r = -0.344$; $p < 0.001$) (Table 2).

Table 1
The participants' characteristics and lipid profiles of healthy controls, untreated patients with diabetes, and treated patients with diabetes.

Parameter	Healthy control	untreated diabetic	Treated patients
N=	**50**	**30**	**88**
Gender;			
M. ♂ N (%)	25(50)	15(50)	48(55)
F. ♀ N (%)	25(50)	15(50)	40(45)
F. history N (%)	1(2)	8(27)	34(39) ***###
Age (yrs.)	42 ± 16	49 ± 15	59 ± 9.0***###
Diab. Duration (yrs.)	0.0 ± 0.0	0.02 ± 0.01	9.32 ± 7.9***###
BMI (kg/cm.)	24.99 ± 3.0	36.47 ± 5.0***	9.32 ± 7.9***###
Waist circumference (cm.)	83 ± 14	114 ± 5.0**	111 ± 13**
Bp1 (Hz)	121 ± 15	143 ± 26*	152 ± 22*
Bp2 (Hz)	77 ± 6	92 ± 19*	88 ± 11*
HbA1c %	5.11 ± 0.51	9.78 ± 1.46***	7.96 ± 2.06***###
FBS (mg/dL)	86 ± 7	180 ± 35***	160 ± 74***
PPBS (mg/dL)	107 ± 13	310 ± 72***	226 ± 79***#
HOMA-IR	2.20 ± 0.3	3.87 ± 0.9***	3.27 ± 0.3***###
Total cholesterol (mg/dL)	165 ± 23	289 ± 18***	212 ± 58***#
Triglycerides (mg/dL)	82 ± 16	205 ± 40***	109 ± 60###
HDL (mg/dL)	49 ± 9	42 ± 5	53 ± 10**#
LDL (mg/dL)	100 ± 27	206 ± 19***	147 ± 53***##
vLDL (mg/dL)	16 ± 3	41 ± 8***	22 ± 12###
Risk factor 1	3.50 ± 0.8	7.04 ± 1.12**	5.13 ± 1.55*
Risk factor 2	2.16 ± 0.8	5.03 ± 0.96***	3.57 ± 1.45*
Anti-Atherogenic factor	46 ± 22	17 ± 3***	28 ± 12***#
IL17/IL37 ratio	0.993 ± 0.03	43.23 ± 21.13***	6.27 ± 2.86***###

P*: significant relative to healthy control; P#: significant relative to untreated patients with diabetes. N, number; BMI, body mass index; HbA1c%, glycosylated hemoglobin; FBS, fasting blood glucose; Bp1, systolic blood pressure; Bp2, diastolic blood pressure; PPBS, postprandial blood glucose; HOMA-IR, Homeostatic Model Assessment of Insulin Resistance; HDL, high-density lipoprotein; LDL, low-density lipoprotein; vLDL, very-low-density lipoprotein; IL, interleukin.

4. Discussion

T2DM is a chronic inflammatory condition, and both obesity and T2DM are featured by systemic low-grade inflammation (Donath et al., 2019). The relation among pro/anti-inflammatory cytokines also the pathogenicity of T2DM and treatments is one of the hot research topics. Here, we investigated the potential association between expression standard of IL-6, IL-1β, IL-17, and IL-37 and IL-17/IL-37 ratio with antidiabetic therapy for T2DM. Overall, this study showed that metformin monotherapy and dual therapy substantially reduced HbA1c%, blood glucose levels, HOMA-IR, BMI, lipid profile, the expression levels of anti- and proinflammatory cytokines, and the IL-17/IL-37 ratio compared with those in healthy controls, indicating their hypoglycemic, hypolipidemic, and anti- inflammatory effects.

Obesity has been more prevalent globally in the past decades, leading to an increase in the rat of obesity-related illnesses, like T2DM (Bowers and Singer, 2021). Increased BMI is accompanied by a reversible elevation in the levels of FBS, insulin, and TGs and impaired glucose tolerance (Abd El-Hameed, 2022). Among the patients with T2DM in this study, dyslipidemia and atherogenesis were the most dominant symptoms. T2DM was characterized by raised levels of LDL-c, TC, *v*LDL, TGs, and depressed level of HDL-c. Thus, the most essential factor that helps normalize lipids in diabetes is diabetic treatment (Abd El-hameed et al., 2021). Systemic inflammation is induced by hyperglycemia, loss of insulin resistance, insulin signaling, and abnormalities in lipid metabolism (Abd El-Hameed et al., 2021). In patients with diabetes, dyslipidemia-induced inflammation shares to pathogenic procedure that ultimately results in diabetic complications. However, glycemic control has an anti-atherogenic benefit in terms of lowering cholesterol and inflammatory biomarker levels which are essential for atherosclerosis in diabetic cases (Yilmaz et al., 2016).

Chronic inflammation, as a result of proinflammatory cytokine production, for example, tumor necrosis factor-alpha (TNF-α), IL-6, and C-reactive protein, acts a pivotal part in the etiology of vascular complications and atherosclerosis (Abd El-hameed et al., 2021). Importantly, the obtained results revealed a marked increase in expressions of IL-6, IL-1β, and IL-17 (inflammatory cytokines) in untreated cases diabetes, which have been improved markedly after the administration of metformin-based therapies. Furthermore, direct relationship was noticed among IL-6, IL-1β, and IL-17 and HbA1c% and FBS.

HOMA-IR also has a marked positive correlation with IL-6, IL-1β, and IL-17. In this regard, several inflammatory cytokines, for example, IL-1β, played a significant function in insulin resistance and inflammation induced by obesity (Um et al., 2011). T2DM is commitment to high expressions of IL-1β and IL-6 (Spranger et al., 2003). IL-1β affects insulin production and apoptosis of β-cells (Böni-Schnetzler et al., 2018). Chronic low-grade inflammation is an established cause of obesity-related disorders (including T2DM) since it raises levels of IL-6 and IL-1β (proinflammatory cytokine), in growing tissues and circulation (Bowers and Singer, 2021). Furthermore, Insulin resistance is enhanced by IL-1 and IL-6 by stimulating kinases (Conti et al., 2018). IL-6 might be linked to the serine phosphorylation of IRS-1 by c-Jun N-terminal kinase 1 and the activation of nuclear factor-κB by IκB kinase, (NF-κB), and production of SOCS-3; thereby, it may alter insulin resistance (Yamauchi and Kadowaki, 2008). Moreover, IL-6 gene polymorphism is a critical factor for diabetic nephropathy in Greek and Turkish patients with T2DM (Papaoikonomou et al., 2013).

Patients with T2DM might produce more IL-17 than healthy controls (Telikani et al., 2019). Franco et al. (Franco et al., 2017) have shown significantly elevated IL-17 levels when cases T2DM is not well controlled. Additionally, T cells induce chronic inflammation in cases with diabetes by producing IL-17 (Jagannathan-Bogdan et al., 2011). Combination therapy might enhance T2DM treatment by inhibiting

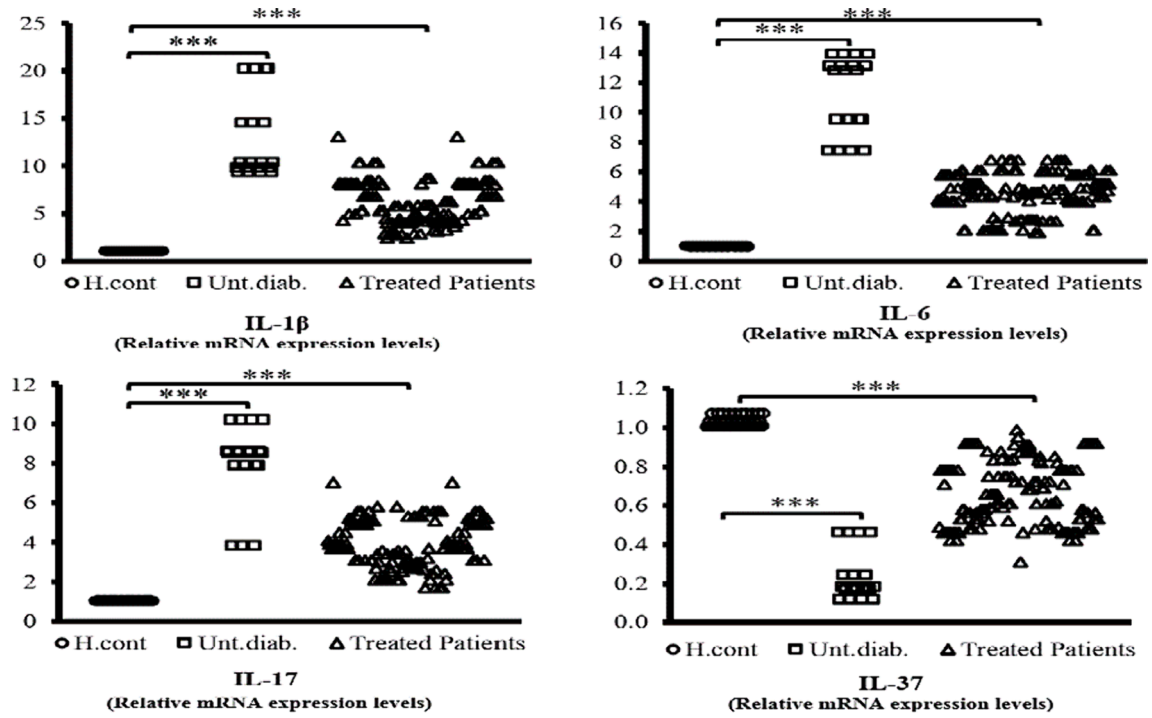

Fig. 1. IL-1β, IL-6, IL-17, and IL-37 in healthy controls, untreated diabetics, and treated diabetic patients. Interleukin, IL.

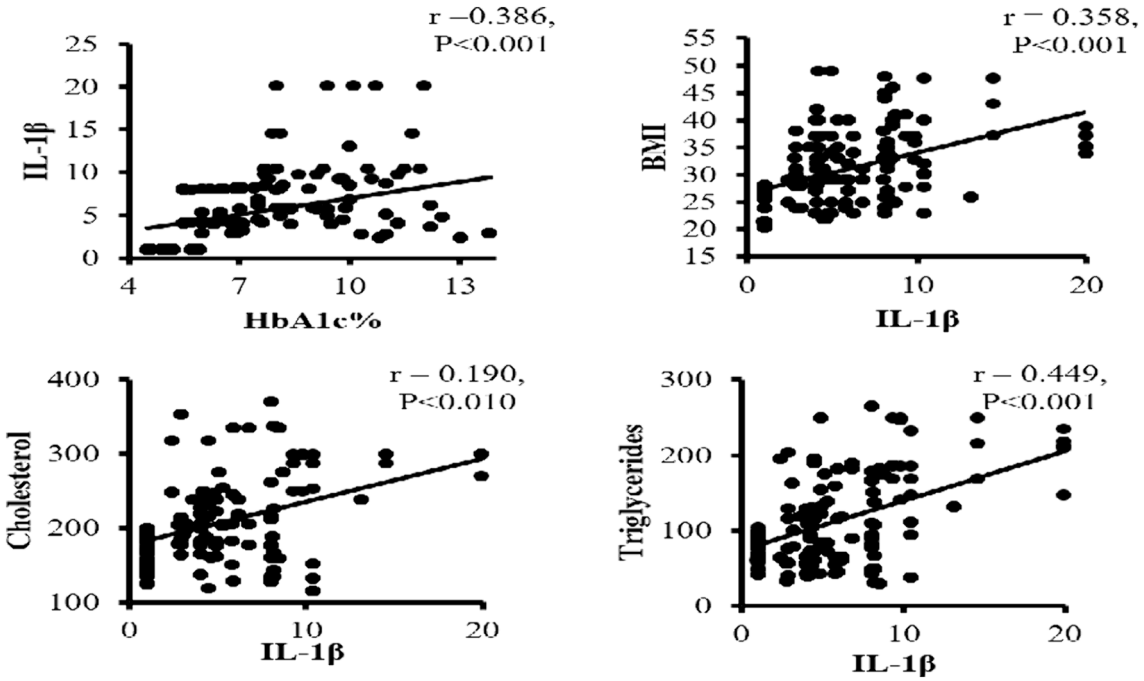

Fig. 2. Correlation of IL-1β with HbA1c%, BMI, total cholesterol, and triglycerides. Interleukin, IL; Glycosylated hemoglobin, HbA1c; BMI, Body mass index.

interferon-gamma and IL-17 production (Telikani et al., 2019). Our results demonstrated a direct relationship among IL-1 and IL-17. Furthermore, IL-17 stimulates IL-1ß and chemokine production and hence causes inflammation and tissue injury (Festa et al., 2000). Given the well-known influence of IL-1ß in the development of chronic inflammatory illness, it is reasonable to assume that IL-17 mediates its activity by elevating the release of these proinflammatory cytokines (Ferretti et al., 2003). Recent data have proposed that IL-17 is contributory in the progress of T2DM by playing a role in the resistance to insulin and inflammation. Importantly, IL-17 promotes NF-κB pathway by stimulating the production of IL-1β, IL-6, and TNF-α which cause insulin resistance and the development of T2DM (Abdel-Moneim et al., 2018).

Moreover, diabetes treatments have indirect anti-inflammatory effects by regulating weight gain, hyperglycemia, and lipid profile, which have a beneficial impact on inflammatory status and atherosclerosis (Saisho, 2015). In this regard, metformin has the potential to decrease inflammatory responses by inhibiting oxidative stress, NK-κB, increasing nitric oxide (NO) bioavailability (Saisho, 2015) and downregulating mRNA expression and serum inflammation levels biomarkers, like IL-1β, TNF-α, IL-6 and IL-17 (Choi et al., 2021). Furthermore, metformin, in a

Table 2
Correlations of IL-37, IL-1β, IL-6, and IL-17A with carbohydrate profile.

Correlations	IL-37	IL-1β	IL-6	IL-17A
FBS	−0.220***	0.210***	0.288***	0.288***
PPBS	−0.344***	0.310***	0.450***	0.449***
HOMA-IR	−0.108	0.221***	0.053	0.201**

* Correlation is significant at the 0.050 level (2-tailed).
** Correlation is significant at the 0.010 level (2-tailed).
*** Correlation is significant at the 0.001 level (2-tailed).
IL: Interleukin, FBS: fasting blood glucose, PPBS: postprandial blood glucose, HOMA-IR: homeostatic model assessment of insulin resistance.

dose-based on way, reduced the IL-1β- prompted release of IL-8 and IL-6 in endothelial cells (Isoda et al., 2006) also diminution the IL-17 inflammatory profile by rising autophagy and refinement mitochondrial bioenergetics (Bharath et al., 2020). Metformin's anti-inflammatory action may be due to changes in macrophage polarization to the M2 phenotype; decrease in the development of NO, prostaglandin E2, and proinflammatory cytokines; stimulation of adenosine monophosphate-activated protein kinase to decrease NF-κB activation via the phosphoinositide-3-kinase–Akt vascular smooth muscle cell (Jing et al., 2018). Otherwise, Abd El-Hameed (Abd El-Hameed, 2020) have reported that polydatin decrease inflammatory responses by reducing NF-κB, TNF-α, and caspase-3 activation. In a search for IL-1 inhibitors, a family of sulfonylurea-containing molecules was developed and named ''cytokine-release inhibitory drugs'' (Febbraio, 2014).

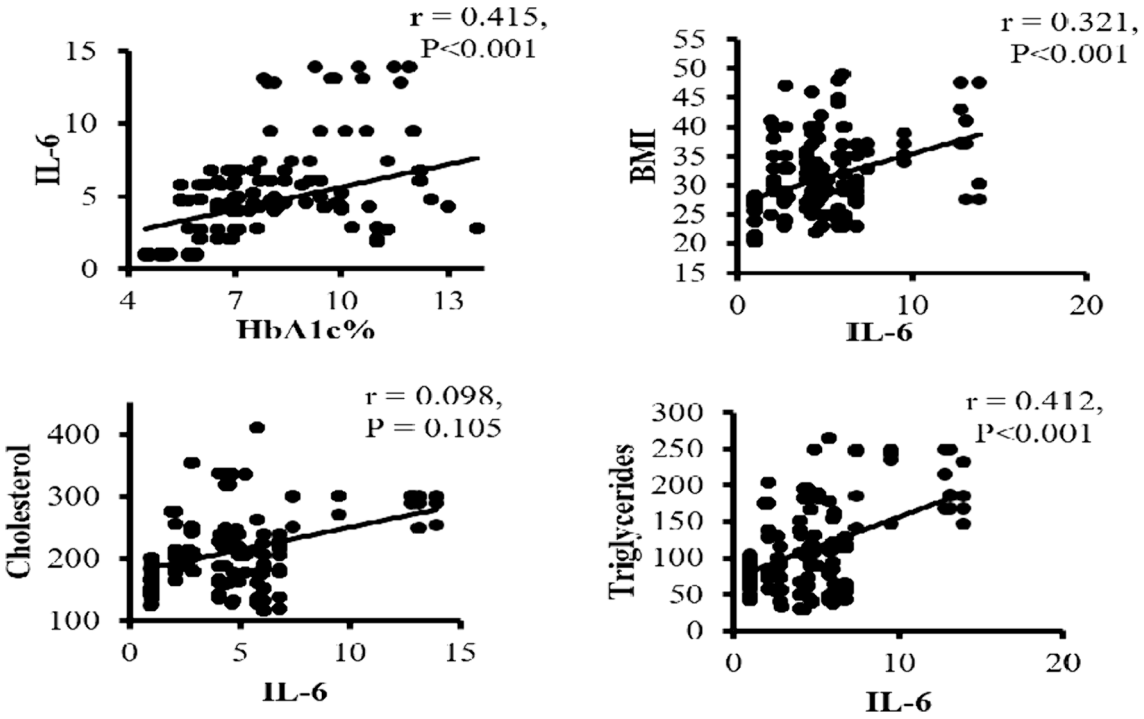

Fig. 3. Correlation of IL-6 with HbA1c%, BMI, total cholesterol, and triglycerides. Interleukin, IL; Glycosylated hemoglobin, HbA1c; BMI, Body mass index.

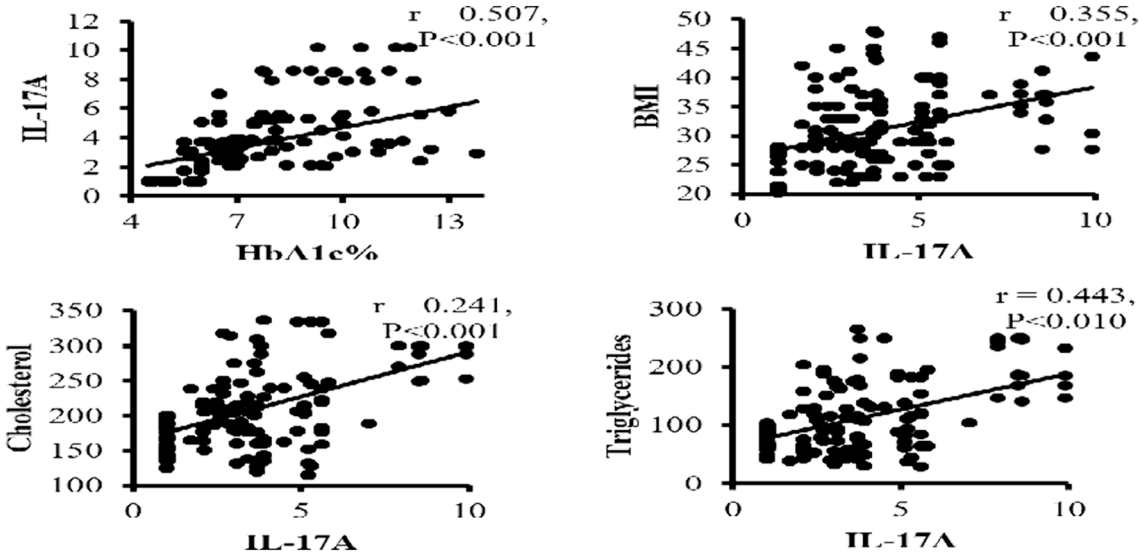

Fig. 4. Correlation of IL-17A with HbA1c%, BMI, total cholesterol, and triglycerides. Interleukin, IL; Glycosylated hemoglobin, HbA1c; BMI, Body mass index.

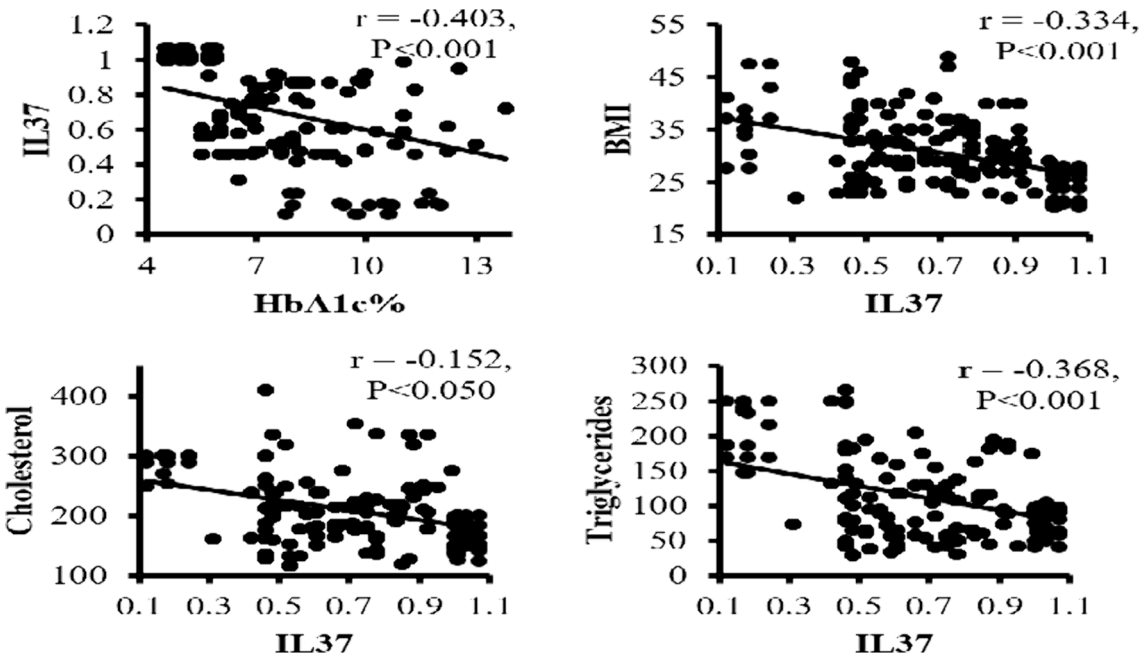

Fig. 5. Correlation of IL-37 with HbA1c%, BMI, total cholesterol, and triglycerides. Interleukin, IL; Glycosylated hemoglobin, HbA1c; BMI, Body mass index.

According to the available evidence, insulin therapy may be effective in reducing diabetes complications by lowering inflammatory processes (Yaribeygi et al., 2019), this improved knowledge of how anti-diabetic drugs protect against diabetes complications. Our data indicated a significant depletion in the expression level of IL-37 in cases diabetes contrast for hygienic topic, which was significantly, reduced the treated group. The results revealed that IL-37 negatively correlation with IL-1β and IL-17. Furthermore, IL-37 presented a noticeable passive relationship with HbA1c% and FBS. IL-37 depletion was markedly related to T2DM and insulin resistance (Li et al., 2019). A reduction in adipose tissue inflammation and improvements in insulin sensitivity are correlated with the enhanced expression of IL-37 in fat tissue. However, IL-37 can significantly decrease oxidative stress, apoptosis and inflammation enhanced by elevated glucose levels, which protects podocytes from hyperglycemia-induced injury (Zhang et al., 2020). The high expression of IL-37 and IL-1β is most likely intended to counterbalance inflammation during obesity (Li et al., 2019). IL-37 regulates the activation of cytokines, inclusive IL-1β, IL-10, and IL-6, via both intracellular and extracellular pathways (Zhaolin et al., 2019).

In diet-induced obesity, recombinant IL-37 improved insulin sensitivity (Nold-Petry et al., 2015). IL-37 may stimulate insulin production and, thus, the pathogenesis of diabetes (Conti et al., 2018). However, despite its potential role in liver obesity-induced insulin resistance, IL-37 shows that diabetes therapy improves glucose metabolism (Zhang et al., 2017). Ballak et al. (Ballak et al., 2014) have noticed that human-transgenic mice IL-37 (IL-37tg) have generalization standard and up than other anti-inflammatory cytokines, and adipocyte treatment in vitro with recombinant IL-37 inhibits adipogenesis. In mice as well as humans, Since IL-37 is a crucial anti-inflammatory regulator in inflammation caused by obesity, treating insulin resistance and T2DM with it may be a promising therapeutic approach. Furthermore, IL- 37 production was elevated in treated diabetic cases with antidiabetic treatments (Telikani et al., 2019). Combination therapy may facilitate the treatment of T2DM by exerting synergistic anti-inflammatory actions on the immune system via the overexpression of IL-37, and it may be used to control the inflammatory conditions of T2DM (Telikani et al., 2019). Furthermore, the inflammatory state is distinguished by an unbalanced among anti- and proinflammatory cytokines.

A relationship between proinflammatory cytokine to anti-proinflammatory cytokine ratios and the development of T2DM and its complications was reported, and the progression of T2DM was accelerated by an increased inflammatory state intensive. Furthermore, the data showed a significant association between these ratios and weakness homeostasis of glucose, insulin resistance, and abnormal lipid profiles, suggesting that the optimal modulation of cytokine ratios is an important aspect in managing T2DM and its associated complications (Abd El-Hameed, 2020). In this regard, proinflammatory cytokine to anti-inflammatory cytokine ratios (e.g., IL-17/IL-37) are increased to enhance the inflammatory state in cases with T2DM and are decreased after treatment with antidiabetic agents, as shown in this research (Table 1).

Thus, we speculated that elevated IL-37 levels antagonize inflammatory responses in patients with T2DM. Notably, more attempts will be needed to conduct clinical trials on specific therapies aimed at treating metabolic inflammation through the suppression of proinflammatory mediators or the activation of anti-inflammatory pathways.

There remain numerous limitations that must be considered. Firstly, the model measuring of this was modest research and needs differentiation based on the type of antidiabetic agent, duration of treatment, doses, and gender. Moreover, the tested cytokine's protein levels have not been reported in this investigation. More pieces of evidence are needed to show that metformin improves inflammation with other inflammatory biomarkers. Finally, the major limitation in drawing safe conclusions is the lack of randomized, large, double-blind, controlled trials on the topic or head-to-head research with other antidiabetic medications.

5. Conclusion

Our findings are consistent with the idea that antidiabetic medications used to maintain glycemic control in T2DM patients work in a variety of ways. They may reduce hyperglycemia and hyperlipidemia or function through anti-inflammatory mechanisms to influence the inflammatory state. We demonstrated that IL-6, IL-1β, IL-17, and IL-37 are influenced by diabetes-induced inflammation and decrease after the administration of metformin-based therapies. However, the data also suggested that the IL-17/IL-37 ratio is of crucial importance in T2DM pathophysiology and treatment and related complications and is

influenced by other metabolic diseases. Moreover, the immunosuppressive-anti-inflammatory action of IL-37 would be considered as a new effective treatment goal in treating T2DM and its complications. Additional prospective trials involving larger cohorts are necessary to create medical trials efficacy of metformin-based therapies in T2DM and explore their clinical benefits in diabetes and its complications.

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Ethics approval and consent to participate

General Institutions of Healthy Insurance Committee provided its approval (BSU/2016/12).

Availability of data and materials

This published article contains all of the data generated or analyzed during this research article.

CRediT authorship contribution statement

Abeer M. Abd El-Hameed: Writing – original draft, Writing – review & editing. **Areej A. Eskandrani:** Resources, Project administration, Software. **Eman Salah Abdel-Reheim:** Visualization, Investigation, Validation, Formal analysis, Methodology. **Adel Abdel Moneim:** Conceptualization, Data curation, Writing – original draft, Writing – review & editing, Visualization, Investigation, Validation, Formal analysis, Methodology, Supervision. **Wessam Addaleel:** Conceptualization, Funding acquisition, Data curation.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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