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Role of omentin 1 and IL-6 in type 2 diabetes mellitus patients with diabetic retinopathy

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***Abstract*---**The study included 60 diabetic patients (30 patients type 2 diabetes mellitus complicated with diabetic retinopathy (DR) and 30 patients T2DM not complicated with DR). The study also included 30 healthy control individuals defended as subjects who apparently haven't any chronic diseases. investigations were done including IL-6 and serum omentin-1. Fundus examination was carried out by an expert ophthalmologist. The study showed that the lowest mean of serum omentin-1 was recorded (P<0.05) in DR patients (687 pg/ml), and the highest (P<0.05)was in the control group (3540.625 pg/ml), The study also demonstrated that there was a significant decrease (P<0.05) in DM patients (991.2 pg/ml). The study also showed that serum IL-6 was increased significantly(P<0.05) in DR patients (253.7 pg/ml) as compared with the control group (35.33 pg/ml), The study also showed that serum IL-6 was increased significantly (P<0.05) in DM patients (102.5 pg/ml). The study showed negative correlation of serum omentin-1 concentrations with IL-6 in DR patients.

***Keywords*---**Omentin-1, IL-6; type 2 diabetes mellitus, diabetic retinopathy.

Introduction

Diabetes mellitus is a chronic illness characterized by an increase in blood sugar levels caused by insufficient insulin production, either absolute or relative(Scanlon et al., 2017). In terms of public health, this is a major concern. Diabetes mellitus is becoming more common, and by 2025, the number of people with the disease will have doubled. It is estimated that it affects around 170

million people worldwide. It is sometimes referred to as the "silent disease," because it causes no symptoms until it has progressed to the point of causing serious organ damage(Haneen et al., 2021). Diabetic retinopathy is the leading cause of lengthy visual loss in those over the age of 20. Retinopathy is a vasculopathy caused by the breakdown of the blood-retinal barrier and the closure of retinal capillaries. Recent research suggests that DR begins as a neuro-retinopathy, with vascular changes occurring early in the illness(Stewart, 2017). Nonetheless, Diabetic retinopathy continues to be a major cause of acquired vision loss in working-age adults around the world.

Omentin-1 is a novel 34-kilodalton protein. Human plasma has a large amount of him, which is primarily produced from visceral omental adipose tissue (Aleksandrova et al., 2016). omentin was characterized after it was discovered in a human omental adipose tissue cDNA library (AY549722). The UniProt code for this protein is Q8WWAO. Omentin-2 is a homolog with 83 percent amino acid identity to omentin (Mustafa et al., 2020a). It is produced in mesothelial cells, vascular smooth muscle cells (VSMCs), and endothelial cells (ECs), especially in Visceral Adipose Tissue (VAT), epicardial fat, small intestine, colon, thymus, ovary, and testis, as well as intestinal Paneth cells and airway and intestinal goblet cells(Mustafa et al., 2020a). The functions of omentin-1 in physiological, pathophysiological, and clinical characteristics have piqued researchers' curiosity(Mustafa et al., 2020a). In type 2 diabetes patients, serum omentin-1 levels are reduced in correlation with the existence of the three major complications: retinopathy, nephropathy, and neuropathy (Aktas et al., 2014). In vascular smooth cells, omentin-1 has recently been shown to have anti-inflammatory properties. Inflammation is linked to the onset of DR. As a result, omentin-1 may have a role in the development of DR(Mustafa et al., 2020b).

Interleukin-6 formerly known as B-cell stimulatory factor-2 is a multifunctional cytokine. IL-6 is involved in a number of processes, including hematopoietic cell development and differentiation, as well as immunological and inflammatory responses(Senthilkumar et al., 2018). T cells and macrophages produce most of the IL-6. Other cells involved in the inflammatory response, such as monocytes, fibroblasts, endothelial cells, and keratinocytes, express IL-6 since it is a multipurpose cytokine(Ning, 2020). IL-6 is upregulated in most inflammatory situations, despite its reputation as a pro-inflammatory cytokine. Interleukin-6 (IL-6) is a pleiotropic cytokine that is one of the main causes of retinal vascular inflammation in DR patients(Sharma, 2021). "Classical signaling" refers to IL-6 signaling through its membrane-bound IL-6 receptor. Importantly, IL-6 signaling can be exhibited in cells that lack the membrane-bound IL-6 receptor via a soluble IL-6 receptor (sIL-6R), a process known as "trans-signaling.". There is growing evidence in the literature that IL-6 classical signaling is anti-inflammatory, whereas IL-6 trans-signaling causes IL-6 to be pro-inflammatory(Sharma, 2021). The present study was conducted to elucidate the role of omentin-1 and IL-6 in the pathogenesis of DR. We aimed to assess and compare the serum levels of omentin-1 and IL-6 in T2DM patients with and without DR

Materials and Methods

Study design

This case-control (comparative) study was conducted in Ramadi General Hospital from November 1, 2021 to February 28, 2022.

Study protocol and laboratory analysis

The study comprised 60 diabetic patients (30 with T2DM complicated by DR and 30 without T2DM complicated by DR), aged 50 to 70, who attended Al Nahrain Clinics. An expert ophthalmologist performed a fundus examination on all participants to determine whether they had diabetic retinopathy. The study also included 30 healthy control volunteers who did not appear to have any chronic conditions. Clinical data and anthropometric parameters were collected after obtaining informed written consent from each study patients. About 5 ml of venous blood was drawn from all patients. The sample was centrifuged at 4000 rpm for 5 mintues and serum was separated. Serum levels of Omentin-1 (FINE TEST ®, China) and IL-6 (FINE TEST ®, China) estimated using commercially available ELISA kits and readings taken using Biotech ELISA reader.

Statistical analysis

A statistical analysis of data was carried out using SPSS version 22. The statistical importance level was set as P value less than 0.05. Descriptive statistics consist of mean, standard deviation (SD), and standard error (SE) was calculated for each parameter. The comparisons among cases and controls were computed by Independent-Samples T-Test.The Correlations between the diffrente of parameters were studied via Pearson's correlation (r=−1 to 1).

Results

The study showed that the lowest mean ($P<0.05$) of serum was recorded in DR patients (687 pg/ml), and the highest was in the control group (3540.625 pg/ml), The study also demonstrated that there was a significant decrease ($P<0.05$) in DM patients (991.2 pg/ml) as shown in figure1. The study also showed that serum IL-6 was increased significantly ($P<0.05$) in DR patients (253.7 pg/ml) as compared with the control group (35.33 pg/ml), The study also showed that serum IL-6 was increased significantly ($P<0.05$) in DM patients (102.5 pg/ml) as shown in figure.Additionally the study showed negative correlation between omentin-1 and IL-6 ($P<0.05$) in DR patients (r: -.907**) and non-DR patients (r: -.874**). which is mean that serum omentin-1 is decreased when IL-6 is raised and vice versa.

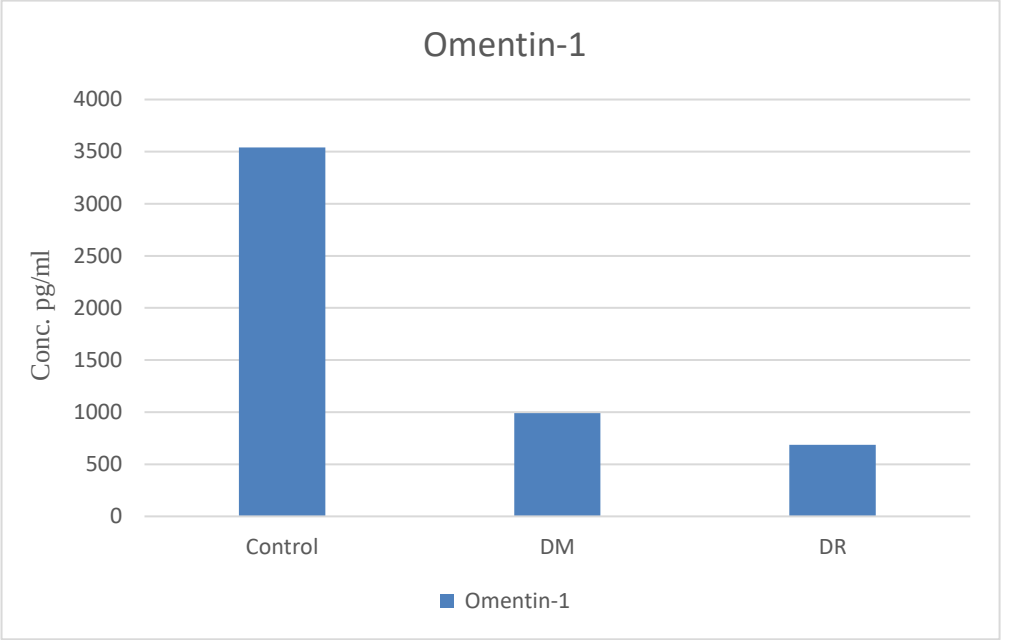

Figure 1. shows the significant effect of diabetic retinopathy and diabetes mellitus type 2 on the level of Omentin-1 in the serum

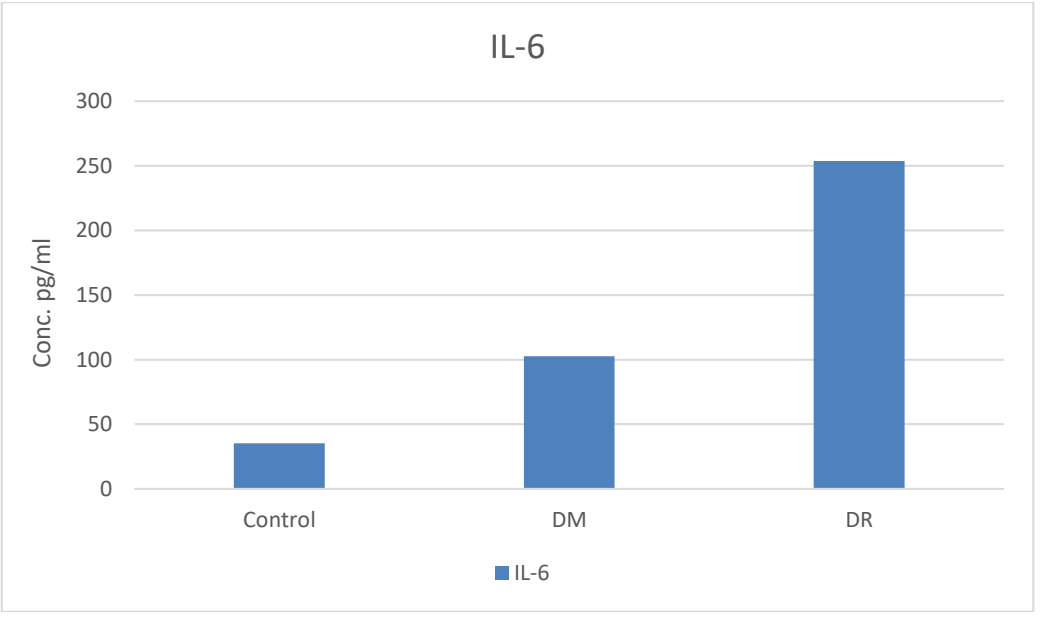

Figure 2. shows the significant effect of diabetic retinopathy and diabetes mellitus type 2 on the level of IL-6 in the serum

Discussion

Relation of serum Omentin-1 with diabetic retinopathy

The research reveals that when DM patients were compared to a control group, serum omentin-1 levels were significantly lower (P<0.05). Additionally, the study found that serum omentin-1 levels were substantially lower (P<0.05) in DR patients compared to DM patients without retinopathy figure 5. Furthermore, it was revealed that the serum omentin-1 level was significantly lower in diabetic patients compared to controls and in diabetics with DR compared to diabetics without DR (Abdelraouf Korany et al., 2018). Additionally, it was found that serum omentin-1 levels were considerably lower in DR patients compared to DM patients without retinopathy (Omae et al., 2017). Additionally, recent meta-analysis research found that T2DM patients had significantly lower serum omentin-1 levels than healthy controls (As, 2019). This effect may be explained by the fact that, while omentin-1 enhances insulin sensitivity, its deficiency may contribute to impaired glucose homeostasis in prediabetic patients (Du et al., 2016). Omentin-1 is required for effective glucose metabolism. In vitro, omentin-1 promotes insulin signaling by activating protein kinase B and insulin-mediated glucose transport in adipocytes, A clinical research of patients with diabetes mellitus discovered a correlation between serum and vitreous omentin levels and the severity of diabetic retinopathy, Experimental studies have shown that omentin has a significant vasodilatory impact in isolated vessels through endothelium-derived nitric oxide, a powerful vasodilator of the retinal arterioles (Wan et al., 2015).

Relation of serum IL-6 with diabetic retinopathy.

The research reveals that when DM patients were compared to a control group, serum IL-6 levels were significantly higher (P<0.05). Additionally, the study found that serum IL-6 levels were substantially higher (P<0.05) in DR patients compared to DM patients without retinopathy figure 6. Furthermore, it was revealed that the serum IL-6 level was significantly higher in diabetic patients compared to controls and in diabetics with DR compared to diabetics without DR. There is experimental and clinical evidence that DR is related to subclinical inflammatory disease of low severity (Barliya et al., 2017). Numerous studies have shown that a large number of inflammatory cytokines are involved in the early stages of DR and that diabetics' retinas express much more inflammatory cytokines (Chen et al., 2018; Miller & Fortun, 2018). IL-6 is a critical mediator of intraocular inflammation because it not only regulates the immune function but also mediates the inflammatory response process (Yao et al., 2019). Also IL-6 is a primary driver of the overall shift in the cytokine profile in the aqueous humor of DR patients and is involved in the inflammatory response (Rübsam et al., 2018). Additionally IL-6 has been shown to hinder the formation and development of retinal vascular endothelial cells, increase endothelial cell apoptotic, impair the vascular wall's normal function, and impact the retina's vascular permeability(Yao et al., 2019).

Correlation between omentin-1 and IL-6 in diabetic retinopathy

The study showed negative correlation between omentin-1 and IL-6 ($P<0.05$) in DR patients (r: -.907**) and non-DR patients (r: -.874**), which is mean that serum omentin-1 is decreased when IL-6 is raised and vice versa. Type 2 diabetes are considered chronic low-grade inflammatory conditions; inflammatory cytokines may have a role in the control of protein production in adipose tissue. In type 2 diabetes patients, circulation levels of the inflammatory cytokines TNF-a and IL-6 are elevated(Liu et al., 2016). Study showed serum omentin-1 concentrations were found to be inversely linked with TNF-a and IL-6 serum levels (YE et al., 2020). Another research implies that inflammation affected omentin levels (Rao et al., 2018) . Furthermore other study have shown that TNF-a and IL-6 influence the synthesis of additional adipokines such as leptin, adiponectin, and visfatin (Stojsavljević et al., 2014). Also our findings were in agreement with the study done by (Senthilkumar et al., 2018) shown that a decrease in serum omentin-1 levels leads to improved insulin resistance and, hence, poor management of diabetes in individuals with type 2 diabetes mellitus, resulting in consequences such as nephropathy.

Ethical Clearance

All experimental protocols were approved under the Anbar Health Directorate and all experiments were carried out in accordance with approved guidelines

Conclusion

In conclusion, decreased serum level of omentin-1 and increased serum levels of IL-6 in cases suggest that inflammation are important mechanisms in the pathogenesis of diabetic retinopathy in type 2 diabetes mellitus patients.

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