SERUM VISFATIN IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND DIABETIC RETINOPATHY

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BACKGROUND: The primary cause of blindness in diabetics is diabetic retinopathy (DR), the most common microvascular complication of diabetes, and visual impairment. Visfatin is an adipocytokine that aids in insulin activity during gestational diabetes and pregnancy.
AIM: This study aimed to estimate serum visfatin levels in DR, proliferative (PDR), non-proliferative (NPDR), and healthy subjects (HS).
MATERIALS AND METHODS: A 120-patient case-control study with a history of T2DM for more than 5 years as well as 30 healthy subjects enrolled in the study. Patients group divided into three sub-groups, DM, PDR, and NPDR. Visfatin levels were measured using a commercially available enzyme-linked immunosorbent assay kit. Triglyceride (TG), serum cholesterol (TC), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C) levels and glycated haemoglobin (HbA1c) were assessed.
RESULTS: The PDR patients and patients with poor glycemic control showed significantly increased visfatin levels compared with the HS group and T2DM patients without DR. The TC, TG, and DR group's LDL-C levels were noticeably higher and significantly greater in PDR than in the group of HS.
CONCLUSION: Visfatin levels have been linked to both the severity and existence of DR. and more in patients with poor glycemic control. Elevated lipids were associated with DR risk.

KEYWORDS: diabetic retinopathy; lipid profile; type 2 diabetes mellitus; glycemic control; visfatin.

СЫВОРОТОЧНЫЙ ВИСФАТИН У ПАЦИЕНТОВ С САХАРНЫМ ДИАБЕТОМ 2 ТИПА И ДИАБЕТИЧЕСКОЙ РЕТИНОПАТИЕЙ

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ОБОСНОВАНИЕ. Основной причиной слепоты у пациентов с сахарным диабетом (СД) является диабетическая ретинопатия (ДР) — наиболее распространенное микрососудистое осложнение СД — и нарушение зрения. Висфатин — это адипоцитокин, который способствует активности инсулина при гестационном диабете и беременности.
ЦЕЛЬ. Целью данного исследования было оценить уровни висфатина в сыворотке крови у пациентов с СД 2 типа (СД2), пролиферативной ДР, непролиферативной ДР и у здоровых лиц.
МАТЕРИАЛЫ И МЕТОДЫ. В исследовании приняли участие 120 пациентов с историей СД2 более 5 лет и 30 здоровых участников. Группа пациентов была разделена на три подгруппы: СД2, с пролиферативной и с непролиферативной ДР. Уровни висфатина измерялись с использованием коммерчески доступного набора для иммуноферментного анализа. Были оценены уровни триглицеридов (ТГ), общего холестерина (ОХ), холестерина липопротеинов низкой плотности (ЛПНП), холестерина липопротеинов высокой плотности (ЛПВП) и гликированного гемоглобина (HbA_{1c}).
РЕЗУЛЬТАТЫ. У пациентов с пролиферативной ДР и пациентов с плохим гликемическим контролем наблюдалось значительное повышение уровней висфатина по сравнению с группой здоровых контролей и пациентами с СД2 без ДР. Уровни ОХ, ТГ и ЛПНП в группе ДР были заметно выше и значительно превышали показатели в группе здоровых контролей.
ЗАКЛЮЧЕНИЕ. Уровни висфатина связаны как с тяжестью, так и с наличием ДР, и более высоки у пациентов с плохим гликемическим контролем. Повышенный уровень липидов ассоциирован с риском ДР.

КЛЮЧЕВЫЕ СЛОВА: диабетическая ретинопатия; липидный профиль; сахарный диабет 2 типа; гликемический контроль; висфатин.

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BACKGROUND

Diabetic retinopathy (DR) is one of the most prevalent micro-vascular side effects of diabetes and is the main cause of blindness and visual impairment. The main risk factors for DR are increased diabetes mellitus DM duration and poor glycemic control [1]. The DR normally has two phases, the first is Diabetic retinopathy with non-proliferative aspects (NPDR) and proliferative aspects (PDR). The PDR includes neovascularization elements, vitreous fluid bleeding, and new blood vessels that sprout on the surface of the retina and may bleed. There are no symptoms in DR, however, they are detected only through a retinal photograph, the three NPDR stages are mild, moderate, and severe [2, 3].

Visfatin first called a pre-B cell colony-enhancing factor (PBEF), appeared to induce the production of the pro-inflammatory cytokines in human monocytes and may function as a growth factor to stimulate cellular growth, proliferation, and cellular differentiation. Crucially, visfatin (PBEF) was discovered in the peri-vascular fat of blood vessels, such as the coronary artery or aorta, in both human and animal models. Given that it was dysregulated in neutrophils and inhibited or delayed their apoptosis in experimental inflammation and sepsis, PBEF was an inflammatory cytokine [4, 5]. Visfatin, with its insulin-mimetic actions, was identified to be predominantly expressed. Visfatin is an adipokine that has been suggested to have a role in glucose homeostasis due to its informed glucose-lowering effect and plays a key role in the aetiology of cardiovascular disease and insulin resistance [6, 7]. Visfatin produces hypoglycemia by inhibiting the release of glucose from liver cells and promoting the usage of glucose in adipocytes and myocytes. Visfatin attaches to the insulin receptor at a location different from that of the insulin. Visfatin is up-regulated by inflammation, hyperglycemia, hypoxia, and so forth, and is down-regulated by insulin [5, 8, 9].

There is still a great deal of disagreement over how lipids contribute to the pathophysiology of DR. Serum lipid levels have been linked to DR, according to certain research. While TC, TG, and LDL-c levels were positively correlated with DR, HDL-C was found to be inversely correlated with DR [10]. However, a recent large epidemiology study found that lipid levels, including those of low-density LDL-C and TC, were associated with a lower risk of DR in people of Malay, Indian, and Chinese ethnicities. Furthermore, no recognized differences between DR risk and lipid levels have been discovered by other studies [11]. As a result, data regarding the relationship between DR and serum lipid levels have been erratic and ambiguous. The aim of this study estimate serum of visfatin levels in Diabetic Retinopathy patients DR (proliferative PDR and non-proliferative NPDR), and to investigate the relationship between glycemic control and serum lipid levels in type two diabetes mellitus T2DM at different stages of DR.

RESEARCH AIM

This study aimed to estimate serum visfatin levels in DR, proliferative (PDR), non-proliferative (NPDR), and healthy subjects (HS).

MATERIALS AND METHODS

Study design and patients

A Randomized case-control study, one hundred twenty patients who were previously diagnosed to have T2DM more than 5 years duration with age ranging from 18 to 64 years. Patients group divided into three sub-groups, DM without Retinopathy (DM), PDR, and NPDR. Thirty apparently healthy, age-matched were enrolled in the study as healthy subjects (HS) group which was conducted from January 2022 until April 2022. Before this investigation, the patients had no prior history of ophthalmological disorders. Individuals who have a history or medical evidence of hypertension, ischemic heart disease, and nephropathy, individuals who have recently taken lipid-lowering drugs within the last three months, chronic inflammatory disease, and any disease predisposing to vasculitis were excluded. Protein urea was excluded by simple dipsticks pot urine albumin-creatinine ratio.

Place and period of the research

Place of the research

National diabetes center/Mustansiriyah University.

Period of the research

From January 2022 until April 2022

Methods

Diagnosis of Diabetic Retinopathy

Diagnosis of the DR was done by an ophthalmologist when the presence of scars from retinal photocoagulation laser, cotton wool spots, microaneurysms, and/or retinal haemorrhages was seen by slit lamp examination.

Sample collection and clinical laboratory analysis

Each patient and member of the HS group had 10 ml of blood extracted during the morning after at least an eight-hour overnight fast, all measurements were taken, HbA1c was performed using the HPLC method, and an automated chemical analyzer determined the lipid profile. An enzyme-linked immunosorbent assay (ELISA) kit was used to measure the serum visfatin levels.

The research was conducted in line with the Helsinki Declaration. Obtained informed consent from all participants before their involvement. Furthermore, the study received ethical approval from the ethics committee of the National diabetes center/ Mustansiriyah University.

Statistical analysis

The SPSS software (version 20, SPSS) was employed in the data analysis. The results were presented as mean ±SE. A one-way ANOVA test was used to detect the significance of differences among groups. Person correlation tests have been used to distinguish the difference between variables. Statistical significance was defined as a P value of <0.05.

Ethics review

The Ethics Committee conducted a comprehensive review of the research report submitted by us on 22-11-2021. The review process included an evaluation of the study's

objectives, methodology, participant recruitment procedures, informed consent process, confidentiality measures, and plans for data management.

Based on the information provided in the research report and any supplementary materials submitted by the researchers, the Ethics Committee determined that the study protocol adequately addresses ethical considerations and safeguards the rights and well-being of research participants. Additionally, the Committee assessed the potential risks and benefits associated with participation in the study and found them to be reasonable and justified.

RESULTS

Serum visfatin level for the three groups of diabetes, DM without Retinopathy, Proliferative Retinopathy, and Non-Proliferative Retinopathy was increased in comparison to control with (P=0.0001) as shown in Table 1, but visfatin level was more increased in patients with diabetic proliferative retinopathy in comparison to DM without Retinopathy, and with Non-Proliferative Retinopathy.Describe any adverse events that occurred during the medical intervention. Any medical events (diseases, injuries, unscheduled surgical interventions, etc.), laboratory and instrumental observations, which connects with the ongoing medical intervention (preventive, diagnostic, therapeutic, screening) can not be excluded, should be considered adverse. Note if no adverse events occurred.

The HbA1c level for the three patient groups DM without Retinopathy, PDR and NPDRwas significantly higher in comparison to control with (P=0.0001), as shown in table 1, but HbA1c value was increased in patients having PDR in comparison to DM without Retinopathy and NPDR group.

Table 2 shows the correlation coefficient of visfatin with HbA1C in all groups. The result of the correlation coefficient showed the presence of a positive correlation between visfatin with HbA1C in DM without retinopathy and PDR groups (r=0.213, p<0.005), (r=0.153, p=0.004) respectively and negative correlation in the control group. The result of the correlation coefficient showed the presence of no correlation between visfatin with HbA1C in the PDR group as shown in Table 2.

Patients in the DR groups had lower HDL-C levels than patients with DM without retinopathy and controls (P<0.0001), indicating that their lipid profiles were generally greater than the healthy population's. Additionally, the mean serum concentrations of TC, LDL-C, and TG were significantly higher (P<0.0001) in the DR groups compared with the control group. (Tables 3, 4, 5, and 6).

DISCUSSION

A recent study showed that visfatin stimulates migration, invasion, and neovascularization in the chick embryo membrane and the formation of new endothelial cells in humans. Moreover, visfatin activates kinase signaling in endothelial cells which in turn stimulates angiogenesis [12]. Also, visfatin is claimed to promote cell migration that regulates vascular endothelial growth factor, which is an important regulator for the angiogenesis of DR [13, 14]. This may explain the role of visfatin in the pathogenesis of DR through the angiogenesis process, Visfatin is a marker of inflammation produced from the endothelial cells and promotes the release of cytokines and chemokines like interleukin-6 in response to pro-inflammatory stimulus and increased with progressive -cell deterioration [15, 16].

Many studies have shown that Serum levels of adipokines such as visfatin were found to be higher in the PDR patients compared to control [17]. Indicating that visfatin plays a main role in the pathogenesis of DR. The results of this paper showed that the visfatin levels were elevated significantly in the PDR and NPDR patients compared to control [18, 19].

Much evidence claims that visfatin can directly promote endothelial dysfunction or act on the vascular cells through oxidative stress and inflammation rather than a direct effect on the endothelial function to evoke the process of the DR [20].

The DR was found to be increased significantly with poor glycemic control as demonstrated by the CURES Eye Study [21], this finding was also reached in this study where DR in both types, proliferative and non-proliferative was much higher in patients with poorly controlled diabetes

Table 1. Visfatin level and HbA1c in diabetes mellitus without retinopathy, proliferative retinopathy, non-proliferative retinopathy and healthy controls groups.

Parameter	DM (40)	NPDR (40)	PDR (40)	HS (30)	P-value
Visfatin (ng/mL)	(19.35±1.53)[a, b],	(15.73±1.210)[d]	(22.65±1.646)[g]	(5.97±0.914)	0.0001*
HbA1c (%)	(5.08±0.120)[a,c]	(9.03±0.409)[d,f]	(8.04±0.100)[g]	(7.74±0.476)	0.0001*

a: state whether there is a significant difference between the DM without Retinopathy with Control; b: state whether there is a significant difference between DM without Retinopathy with PDR; c: state whether there is a significant difference between the DM without Retinopathy with NPDR; d: state whether there is a significant difference between the NPDR and with Control; f: state whether there is a significant difference between the NPDR with PDR; g: state whether there is a significant difference between the PDR with Control.

* — P≤0.05 is significant.

Table 2. Correlation of visfatin with HbA1c in all groups.

		DM without retinopathy	NPDR	PDR	HS
HbA1c	r	0.213*	0.008	0.153*	-0.165
	P	0.005	0.971	0.004	0.486

* — P≤0.05 is significant.

Table 3. Cholesterol in diabetes mellitus without retinopathy, proliferative retinopathy, non-proliferative retinopathy and healthy controls groups.

Cholesterol (mmol/L)	DM (40)	NPDR (40)	PDR (40)	HS (30)
Mean±SE	4.63±0.386	5.42±0.228	6.00±0.483	4.10±0.195
Range	2.90-9.80	2.50-6.38	2.00-10.20	2.58-6.00
P value compared to Control	0.309	0.001*	0.075	
P value compared to PDR	0.462	0.782	24	
P value compared to NPDR	0.021*			
P value comparing All groups	0.002*			

* — P≤0.05 is significant

Table 4. Triglycerides in diabetes mellitus without retinopathy, proliferative retinopathy, non-proliferative retinopathy and healthy controls groups.

TG (mmol/L)	DM (40)	NPDR (40)	PDR (40)	HS (30)
Mean±SE	1.57±0.140	2.20±0.203	2.62±0.273	1.09±0.08
Range	1.10-3.90	0.36-4.17	0.80-5.10	0.60-1.90
P value compared to Control	0.145	0.0001*	0.0001*	
P value compared to PDR	0.019*	0.526		
P value compared to NPDR	0.071			
P value comparing All groups	0.0001*			

* — P≤0.05 is significant

Table 5. LDL-cholesterol in diabetes mellitus without retinopathy, proliferative retinopathy, non-proliferative retinopathy and healthy controls groups

LDLc (mmol/L)	DM (40)	NPDR (40)	PDR (40)	HS (30)
Mean±SE	3.33±0.163	3.64±0.25	4.08±0.25	1.77±0.13
Range	1.90-5.52	1.55-5.56	2.00-5.83	1.22-3.33
P value compared to Control	0.0001*	0.0001*	0.0001*	
P value compared to PDR	0.615	0.724		
P value compared to NPDR	0.080			
P value comparing All groups	0.0001*			

* — P≤0.05 is significant

Table 6. HDL-cholesterol in diabetes mellitus without retinopathy, proliferative retinopathy, non-proliferative retinopathy and healthy controls groups.

HDL-c (mmol/L)	DM (40)	NPDR (40)	PDR (40)	HS (30)
Mean±SE	2.97±0.38	2.82±0.04	1.26±0.40	3.67±0.20
Range	0.10-7.40	0.96-1.55	0.10-7.10	1.40-4.28
P value compared to Control	0.0001*	0.250	0.989	
P value compared to PDR	0.002*	0.606		
P value compared to NPDR	0.0001*			
P value comparing All groups	0.0001*			

* — P≤0.05 is significant

patients and the results go with other study outcomes like the Kumamoto study [18] . United Kingdom According to prospective studies, good glycemic control (HbA1c ≤7%) will reduce the incidence of development and progression of the DR because tight control of blood glucose affects micro and macro-vascular complications in diabetic patients [22].

As the HbA1c levels depend on the blood glucose concentration and as DM causes reduces in insulin levels, these may lead to an increase in the atherogenic index of plasma and insulin resistance values that progress to pancreatic beta-cell dysfunction and this triggers visfatin release as an inflammatory marker and initiation of retinopathy process. So good glycemic control as early as possible when diabetes is diagnosed is very important for diabetic patients to prevent visual impairment due to the development of retinopathy. The data of this paper show that except for moderate NPDR, the majority of T2DM patients with DR did not achieve targeted glycemic control. Therefore, maintaining adequate glycemic control may have some advantages in lowering the risk of the development and progression of DR [23].

The presence and development of the DR are still significantly influenced by glycemic control [24]. In addition to the conventional approaches for determining the risk of DR, serum visfatin levels may serve as novel biomarkers since they were associated with the existence and severity of DR [25]. Finally, it is difficult to evaluate the impact of the serum level of visfatin alone on different stages of DR and the vitreous level of visfatin is needed to compare its effect, and also a larger sample is more confirmative to verify such results [26].

The relationship between cholesterol levels and DR has been investigated in many studies, although the findings have been conflicting. In contrast to T C, TG, and LDL-c levels, which were favourably correlated with DR, a cross-sectional study including 224 DM patients revealed an inverse relationship between HDL-C levels and DR [19]. In a population-based cross-sectional investigation with 626 participants, Gurlevik U. found a correlation between DR and higher plasma levels of TG, LDL-C, and TC, and both studies following the current study results [27].

According to the Finn Diane Study, individuals with proliferative DR exhibited elevated levels of TC, LDL-C, and TG, in contrast to their non-proliferative DR counterparts and this goes parallel with our study finding [28].

We also observed that levels of TG, TC, and HDL-C were risk factors for DR. TRIG, TC, LDL-C, and HDL-C values, on the other hand, were not associated with DR. based on what Chatziralli et al. Regression analysis was used in their investigation, but it did not rule out the impact of additional confounding variables. like underlying diseases, lipid-lowering drugs in contrast to our study, and this could be one explanation for the discrepancy between their and our results [29].

Studies on the function of LDL-C in eye disease, particularly DR, are deficient. Only one clinical trial has demonstrated a significant positive connection between LDL-C and DR, suggesting that LDL-C is a sensitive measure for determining whether patients with DR will require laser treatment or not [30].

The reason why dyslipidemia is considered a risk factor for DR is still unknown. The following are some possible explanations for this. Inflammation, energy metabolism, and oxidative stress may all play a role in the genesis and progression of DR disease [31, 32]. Based on specific studies, diabetes mellitus (DR) is classified as a chronic inflammatory disease, indicating a potential involvement of lipid metabolism in the inflammatory state of DR [33, 34].

A relationship between lower cholesterol and diabetes Mellitus pro-inflammatory state. This correlation was linked to overexpression of inflammatory markers, including interleukin-6, vascular endothelial growth factor, and tumour necrosis factor-α. Inflammation-mediated angiogenic vitreous activity in DR was demonstrated by Rezzola et al. [35].

The main supply of reactive oxygen within cells and the site of oxidative damage are the mitochondria and the development of DR is thought to be significantly influenced by reduced adenosine triphosphate concentration, which is necessary for energy metabolism, and mitochondrial oxidative stress [36, 37].

Lipids have an impact on mitochondrial function and phospholipids directly, which alters the lipid composition of cell membranes involved in the DR pathogenesis [38].

The dyslipidemia's impact on DR at different stages has been reported in many studies. The relationship between lipid levels and DR has been the subject of numerous clinical and laboratory investigations, but the findings have been conflicting. A study involving 224 DM patients revealed that while CHOL, TG, and LDL-C levels were positively associated with DR, the HDL-C level was inversely correlated with the condition. In comparison to patients with non-proliferative DR, patients with PDR exhibited higher levels of TC, LDL-C, and TG, which is also in line with the findings of the current study [29].

There are certain restrictions on this study. Because it was a case-control single-center study, our findings might have been impacted by the lack of in-depth examination of the eating and lifestyle patterns of the patients. A multicenter, large-sample study is required to confirm the results.

CONCLUSION

Visfatin levels are more prevalent in patients with inadequate glycemic control and to be correlated with the severity and existence of the DR. Elevated levels of lipids, particularly TC, TG, and LDL-C, were found to be significant risk factors for developing DR, indicating that a major contributing factor to the beginning of and progression of DR.

OTHER INFORMATION

The source of financing. Mustansiriyah University - the National diabetes center for Research and and Ibn Al Haytham Ophthalmology Hospital often allocates internal funds and has programs to support faculty research projects. Professors and researchers can apply for institutional grants or use departmental resources to finance their studies.

Conflicts of interests. We identify the importance of publishing research findings that contribute to scientific knowledge in the field of diabetes and retinopathy. However, they affirm their commitment to conducting this study with integrity and transparency, regardless of the potential impact on their academic careers.

The authors confirm that these potential conflicts of interest have been disclosed to the journal editorial team. They are committed to

conducting this research with the highest standards of scientific rigour and integrity.

Participation of authors. Isam Noori Salman – significant contribution to the study design and to the obtaining, data analysis or interpreting results; writing an article; Noor Ulhuda G. Mohammed - significant contribution to the study design and to the obtaining, data analysis or interpreting results; writing an article; Safaa Ehssan Atta - significant contribution to the study design and to the obtaining, data analysis or interpreting results; writing an article; Baydaa Ahmed Abed significant contribution to the study design and to the obtaining, data analysis or interpreting results; writing an article; Rafal Salim – significant contribution to the study design and to the obtaining, data analysis or interpreting results; writing an article. All the authors approved the final version of the article before the publication and expressed their consent to be responsible for all aspects of the work, which implies proper investigation and resolving of issues related to the accuracy or integrity of any part of the work.

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