

C-REACTIVE PROTEIN AND BODY MASS INDEX IN PATIENTS WITH TYPE -2 DIABETES MELLITUS AND DIABETIC RETINOPATHY

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Abstract

Background and aims: C-reactive protein (CRP) is an inflammatory biomarker that may be associated with diabetic retinopathy (DR). The body mass index (BMI) is an important element, frequently evaluated in patients with diabetes mellitus. The purpose of this study was to determine the relationship between CRP, BMI and existing DR in type 2 diabetes (T2DM) subjects. **Material and method:** Thirty T2DM patients aged 35-50 were subjected to a general, ophthalmologic and fundus examination. **Results:** 9 of the 30 patients (30%) didn't presented changes in the fundus examination. 15 (50%) presented minor retinal changes while 6 (20%) were diagnosed with DR: one case of nonproliferative diabetic retinopathy, 2 cases of pre-proliferative DR and 3 cases of proliferative DR. In patients with normal fundus examination and minor retinal changes, CRP was positive in the majority of the cases (95.8%). CRP was positive in only one patient in the group with diagnosed DR. BMI was increased in 85.71% of the patients with retinal changes: angi sclerosis or DR and in only 22.22% of the patients without retinal changes. **Conclusions:** Lower CRP and higher BMI were associated with higher prevalence of DR.

key words: diabetes, C-Reactive Protein, Body Mass Index, diabetic retinopathy.

Background and aims

Diabetes, a metabolic condition characterized by high blood glucose, is considered as the epidemic of the 21st century. The ocular complications of diabetes mellitus are numerous and include an abnormal

lacrimal secretion with a high incidence of the dry-eye syndrome [1], uveitis, cataract, neurophthalmic disorders, neovascular glaucoma and retinopathy.

Diabetic retinopathy is the leading cause of blindness in patients with poor metabolic

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control and a history of the disease of more than 15-20 years.

C-reactive protein (CRP) is an inflammatory biomarker involved in endothelial dysfunction and atherogenesis [2-4]. This biomarker plays a critical role in the pathogenesis and progression of cardiometabolic disease [5]. C-reactive protein is reported to be increased in diabetes mellitus [6] and had been associated with macrovascular disease and microvascular complications, but not diabetic retinopathy (DR) [7-8]. This acute phase protein seems to be useful for identifying patients who are at risk of developing diabetes, hypertension, dyslipidemia (elevated triglycerides, decreased HDL cholesterol) and obesity and provides information regarding the prognostic of these diseases [5,9,10]. CRP was also found positive in patients with macular degeneration which is frequently associated with the metabolic syndrome.

High body mass index (BMI) – an indicator of obesity - was associated with type 2 diabetes mellitus (T2DM) [11,12] and is an important element that needs to be frequently evaluated in diabetic patients.

The purpose of this study was to determine whether there is an association between CRP, BMI and the presence of DR in T2DM subjects.

Material and method

Thirty T2DM patients aged 35-50 years, with or without diabetic retinopathy of various degrees were included in our study.

Diabetic patients were admitted in the study based on diagnosis according the ADA criteria or confirmed history of diagnosed type 2 diabetes, with or without diabetes

medication. The ADA criteria consist in one of the four abnormalities: hemoglobin A1C (A1C), fasting plasma glucose (FPG), random elevated glucose with symptoms, or abnormal oral glucose tolerance test (OGTT).

The exclusion criteria was represented by: type 1 diabetes, autoimmune diseases (such as rheumatoid arthritis, lupus), use of steroids, oral contraceptives or immunosuppressive drugs, inflammatory intestinal disease, tuberculosis, malignancies, history of recent heart failure, surgery or microbial infection, macular degeneration and pregnancy.

Clinical data were collected from all patients using direct patient interview. Recorded parameters included sex, age, symptoms, history of diabetes. Every patient was subjected to a detailed general and ophthalmic examination.

Serum CPR was measured using an immuno-turbidimetric assay. We considered as normal (CRP negative) the values between 0-1.0 mg/dL.

The BMI (also known as the Quetelet index) was calculated as weight (kilograms) divided by the squared height (m²). Height was measured using a wall-mounted measuring tape, and the weight with a digital scale. Patients with BMI between 25 and 29.9 were considered to be overweight and those with a BMI higher than 30 obese.

Structures of the eye were assessed with slit lamp biomicroscopy examination. All the subjects underwent direct ophthalmoscopy after dilation by Tropicamid drops. Diabetic retinopathy was graded according to Early Treatment Diabetic Retinopathy Study (ETDRS) criteria [13].

The statistical analysis was performed using Microsoft Excel and EpiInfo version

3.5.1. The significance level was considered 0.05. The relative risk with its confidence interval was calculated in order to assess the association between two variables.

Results

After direct ophthalmoscopy, we divided the patients in 3 groups: group I-9 patients (30%) with no modification at fundus examination, group II-15 patients (50%) with minor retinal changes (non diabetic angiopathy or angiosclerosis) and group III-6 patients (20%) with diabetic retinopathy.

From the 6 patients with DR, one (16.66%) had nonproliferative diabetic retinopathy (NPDR), 2 (33.33%) had

preproliferative DR (PPDR) and 3 (50%) proliferative diabetic retinopathy (PDR).

From the 30 patients included in the study, 11 patients (36.67%) had a normal BMI, 12 patients (40%) were overweight and only 7 (23.33%) were obese.

In group I, the majority of the patients (7 patients – 77.78%) had a BMI<25 and only 2 (22.22%) were overweight.

In group II, only 4 patients (26.67%) had normal weight, the majority were overweight – 10 patients (66.67%) or obese – 1 patient (6.66%).

In group III, from the 6 patients, none was normal weight, 2 were overweight (33.33%) and 4 were obese (66.67%) (Figure 1).

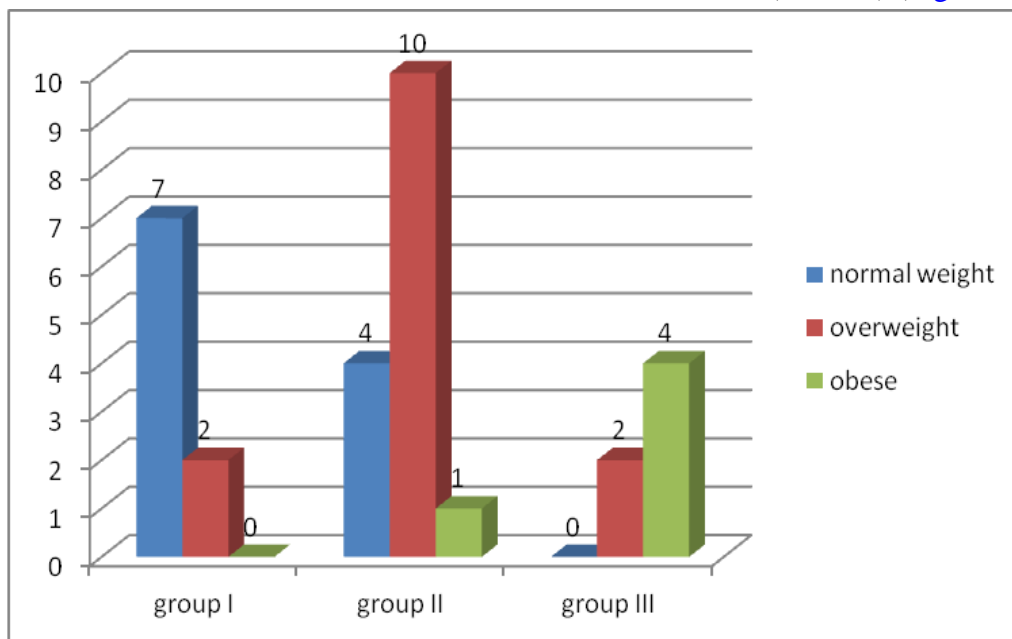


Figure 1. BMI in the three studied groups of patients.

From the 30 patients included in the study, 36.67% had a normal BMI, 40% were overweight and only 23.33% obese. Our study shows that retinal changes in the fundus examination are associated with abnormal BMI. Thus, only 4 out of the 21 patients (19.05%) with retinal changes had a normal BMI, the other 17 (80.05%) having BMI over 25.

Analyzing the relationship between BMI>25 and the retinal modifications we found that there is a strong association between them for the entire studied population. This was indicated by a relative risk of 2.46 (CI=1.11-5.46) with a strong statistical significance (p=0.002). Therefore, our study shows that a BMI over 25 is a risk

factor for the appearance of minor or severe retinal modifications.

After collecting the results for the CRP lab analysis, we found that in group I-with no retinal modifications and group II-with minor retinal changes (angiopathy, angiosclerosis), CRP was positive (>1.0 mg/dL) in the

majority of the patients: 9 patients (100%), respectively 14 patients (93.33%). In contrast, in group III 5 patients (83.33%) had a negative CRP (<1.0 mg/dL) compared to only one patient (16.67%) with positive CRP ([Figure 2](#)).

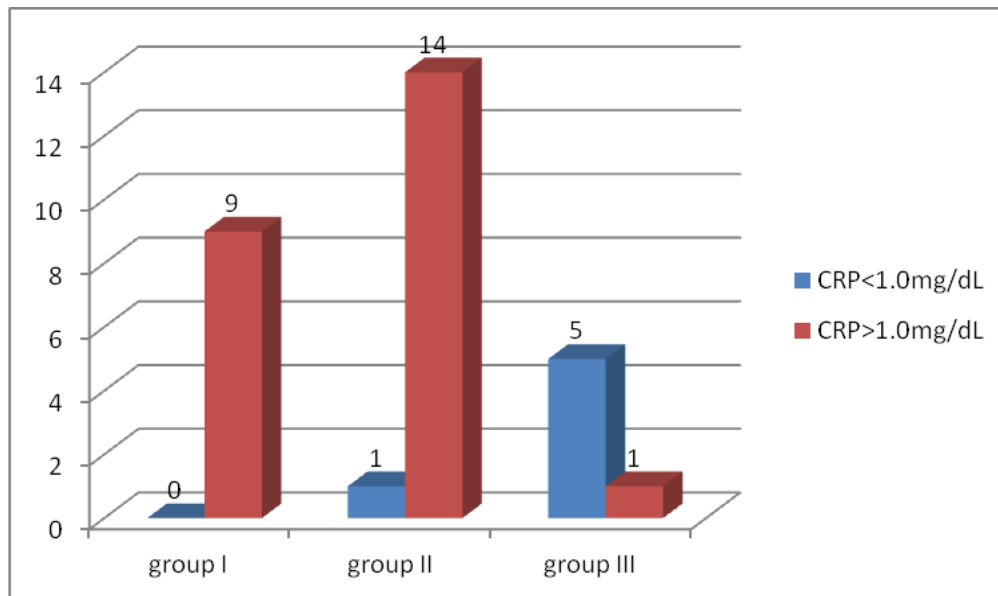


Figure 2. CRP in the three studied groups of patients.

We observed that the majority of patients (24 i.e. 80.00%) had a positive CRP. Positive CRP seems to be associated with diabetes, but has no specificity for the retinal modifications. Thus, CRP was negative in the majority of the cases with diabetic retinopathy. The presence of CRP was associated with normal or minor retinal modifications.

Statistical analysis indicated a relative risk of 20 (CI= 2.84-140.83) with a strong statistical significance ($p < 0.001$) for the association between absence of CRP and DR. In contrast, no statistical significant association between the absence of CRP and normal or minor retinal modifications (RR=1.64, CI= 1.18-2.28, $p = 0.42$) was found. Therefore the absence of CRP is associated only with DR and not with angiosclerosis.

Discussions

We identified that patients with lower CRP and higher BMI have a higher prevalence of diabetic retinopathy. There are many studies supporting the idea that CRP is a risk biomarker of macrovascular and microvascular diseases [14-16].

The Singapore Malay Eye Study showed that patients with diabetes and higher levels of BMI and CRP are less likely to have diabetic retinopathy [17]. In the EURODIAB study, positive CRP was initially associated with DR severity after adjusting with sex, age, history of the diabetes, HbA(1c), systolic blood pressure, but after the correlation with the BMI it had no significance [18].

In a longitudinal study of patients with type 2 diabetes, Spijkerman et al. found that C-reactive protein was not significantly associated with the presence or progression of retinopathy. They showed that the most important act to prevent the development and progression of retinopathy is glycaemic control [19].

In the Hoorn Study it was reported that the inflammatory activity and endothelial dysfunction were associated with retinopathy, suggesting their involvement in the pathogenesis of retinopathy. The additional adjustment for BMI did not modify the results [20].

A study on Pima Indian diabetic patients measured the C-reactive protein and showed no significant modification with the severity of diabetic retinopathy [21].

In the multi-ethnic study of atherosclerosis, Nguyen et al. evaluated the relation between C-reactive protein and the prevalence, severity or progression of DR. CRP levels were not associated with any DR or vision threatening DR. The study concluded that there is limited clinical use of these biomarkers for the prediction of diabetic retinopathy [22].

In the Wisconsin Epidemiologic Study of Diabetic Retinopathy, CRP levels were not associated with the prevalence, severity or progression of DR [23].

Regarding the effect of BMI on DR risk, a population-based study performed in southern Wisconsin suggested that obesity in persons with older-onset diabetes is not related to the long-term incidence of microvascular and macrovascular complications and that body mass is not associated with the progression of retinopathy [24]. In a population-based cross

sectional study by Van Leiden *et al.* (2005), the prevalence of DR was positively associated with BMI [25]. A study from Al-Naeem area (Kuwait) showed that body mass index >30 and duration of diabetes are significant risk factors for DR [26].

On the other hand, in a Jordanian study, BMI showed no significant association with DR or macular edema [27]. However, other studies reported that the severity of DR was inversely correlated with BMI, patients with DR having associated lower BMI levels. Thus, Rani *et al.* reported that duration of diabetes and lower BMI are risk factors associated with any DR [28]. In the Cree population of James Bay, DR was related to lower BMI [29]. The same results were found in other studies such as the multiethnic population of Mauritius [11] as well as a study in south India [30]. On the opposite side, in developed countries, such as UK, higher BMI is associated with DR in subjects with type 2 diabetes [31]. However, the association of BMI and DR has not been consistently demonstrated in all studies.

Studies shows that the different results may be caused by the multiple factors found in a diabetic population such as: environmental variation, racial differences, stress and economic or social status.

However, due to the small size of our study group, the statistical conclusions cannot be extended to the diabetic population in general. Another limitation of the study is the classification we have used to stage diabetic retinopathy; the ETDRS tends to be replaced by the International Clinical Diabetic Retinopathy Disease Severity Scale. We have preferred the ETDRS classification because it was more frequently met in the references we have used.

Conclusions

We report that diabetic patients with lower CRP and higher BMI have a higher prevalence of diabetic retinopathy. Further research is needed to understand the role of inflammation and body mass index on diabetic retinopathy risk in T2DM subjects.

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