Sjournals
Scientific Journals
Scientific Journal of Medical Science (2013)2(5) 83-88
ISSN 2322-5025

Contents lists available at Sjournals
Scientific Journal of Medical Science
Journal homepage: www.Sjournals.com

Short communication

Carotid intima-media thickness seems not to correlate with the severity of diabetic retinopathy

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ARTICLE INFO

Article history:
Received 08 May 2013
Accepted 18 May 2013
Available online 28 May 2013

Keywords:
Diabetic retinopathy
Carotid intima-media thickness
B-mode sonography
Atherosclerosis

ABSTRACT

Diabetic retinopathy and vascular complications of diabetes have been studied for decades, with the aim of defining better their pathogenesis and time profile. The severity of diabetic retinopathy has clear consequences on the quality of life of patients, and trying to find correlates in other vascular territories will help a better understanding of the issue and early as well as more efficacious interventions. We tried to define the association between carotid intima-media thickness with the severity of diabetic retinopathy, since the first parameter has been widely considered as a reliable marker of the progression of atherosclerosis. However, our findings suggest that the value of carotid intima-media thickness although statistically higher in patients suffering from diabetic retinopathy compared to controls, was not correlated with the severity of the retinopathy itself.

1. Introduction

Vascular complications of diabetes are grossly classified as related to the processes of microangiopathy and of macroangiopathy, and these nosologic processes are considered to separately evolve within the disorder of

base, diabetes mellitus. Microangiopathies are represented from diabetic retinopathy (DR), diabetic nephropathy and diabetic neuropathy (Kollias and Ulbig, 2010; Forbes and Cooper, 2013). Macroangiopathies or macrovascular disorders on the other hand are represented from coronary arteries disease, peripheral arterial disease and ischemic stroke (Fowler, 2008; Papa, 2013).

There has been an increasing amount of data confirming correlations between diabetic nephropathy, especially when microalbuminuria is imputed (as a microangiopathic disorder), with cardiovascular disease (Romundstad et al., 2003). Always within the framework of microangiopathic hypothesis, other studies confirmed the correlation between diabetic retinopathy and end-stage atherosclerotic injuries (Fuller et al., 2001; Kim et al., 2002). The fact is however, that the latter studies are focused mainly at the end-stage changes of the atherosclerosis, albeit vascular complications may precede the onset of clinically overt diabetes (Haffner et al., 1990).

Of course, forecasting vascular complications of diabetes and implementing adequate therapies to prevent such complications has been a constant challenge to clinicians. Several parameters have been proposed to help an early diagnosis of atherosclerotic subclinical changes, aiming to better understand potentiality for complications in general. Carotid intima-media thickness (CIMT) has been considered as a surrogate for atherosclerosis progression and a marker of the latter; therefore CIMT has been proposed as a reliable parameter to quantitatively evaluate the risk of cardiovascular disease, and of stroke (Cobble and Bale, 2010).

Through trying to find correlations between CIMT and diabetic retinopathy of different subgroups, we aimed at defining the role of CIMT measurement as a predictor of the severity of micro and macroangiopathy. Both these pathological processes present several end-organ changes and morbid outcomes; thus a better understanding and monitoring, even through CIMT measuring, seems necessary.

2. Materials and methods

During the period September 1st, 2012 to December 30th, same year, we recruited 88 individuals in the present study. The first study subgroup (diabetic patients presenting retinopathy of diverse severity, thereafter the subgroup denoted as DR) was composed from 38 patients, all suffering from diabetes type 2; according to present and revised disease criteria (Alberti and Zimmet, 1999; Al-Hassan, 2003). The second study subgroup (thereafter denoted as controls) was composed from 50 individuals, all of them non-diabetics. The collected data (Table 1) were statistically corrected as related to the age and the gender of all recruited individuals.

The study was open-label, prospective and longitudinal, with patients and controls recruited consequentially during the over-mentioned period.

Demographic and biochemical values are summarized at the table below.

Table 1
Collected demographic and biochemical values of both study subgroups.

Parameter	DR subgroup	Controls
Age (years)	59.84 ± 10.06	56.1 ± 7.3
Sex (m/l)	38 (14/24)	50 (23/27)
Hypertension* (present at recruitment)	10 (26%)	9 (18%)
Diabetes (present at recruitment)	38 (100%)	---
Body-mass index kg/m^2	28.12 ± 2.3	24.6 ± 3.1
Fasting blood glucose mmol/L	6.94 ± 1.81	4.73 ± 1.79
Total blood cholesterol mmol/L	6.13 ± 2.10	5.13 ± 1.48
LDL cholesterol mmol/L	4.1 ± 1.01	2.97 ± 1.11
HDL cholesterol mmol/L	1.05 ± 0.29	1.41 ± 0.34
Triglycerides mmol/L	3.19 ± 1.01	2.01 ± 0.85
Smokers**	6 (16%)	23 (46%)

*Hypertension defined as systolic blood pressure ≥ 140 mm/Hg or diastolic blood pressure ≥ 90 mm/Hg and/or individual under treatment with antihypertensive drugs.

**Smokers were hereby considered both light and heavy smokers, with light smokers consuming up to five cigarettes daily (Nikolla et al., 2013).

CIMT was evaluated in both subgroups through high resolution ultrasonography. The method has been recommended from several sources, and the methodology of measuring it in the B- mode ultrasonography has been detailed elsewhere (Stein et al., 2008; Mansouri et al., 2012). CIMT has been measured bilaterally and an average value was given; in both carotids the measuring was made at the distant wall of the distal segment of the vessel (Fig.1).

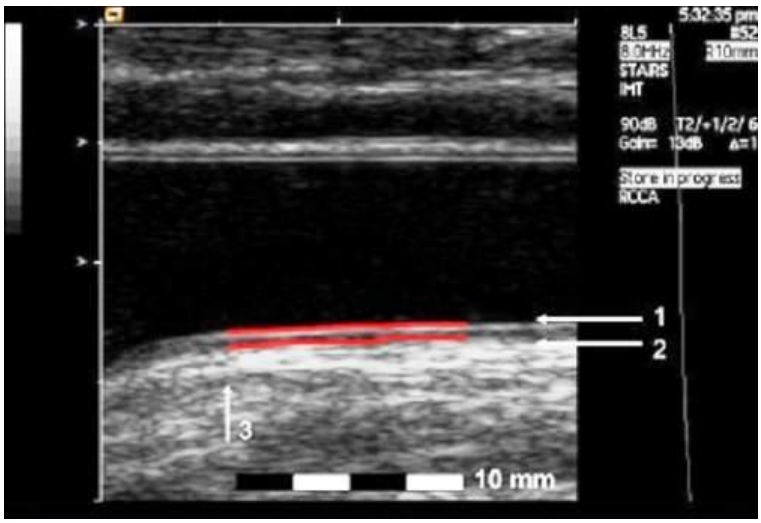

Fig. 1. Method of measuring CIMT in the common carotid artery; B- mode ultrasonography. (1) Lumen – intima border, (2) Adventitia – media border, (3) Transition point from common carotid artery into the carotid bulb.

Retinopathy staging was made according to the classification of the 'Early Treatment of Diabetic Retinopathy Study – ETDRS' (Yanoff and Duker, 2009). Such a classification is widely used, and represented a substantial modification of Airlie House staging of diabetic retinopathy (Klein et al., 1984). In fact, other classifications are available as well, with the pioneer Hirschberg classification as remote as dating in 1891 (Hirschberg, 1891; L'Esperance, 1998). For the sake of simplification, we have grouped our patients presenting diabetic retinopathy in three subgroups: DR [diabetic retinopathy] subgroup I (early non-proliferative diabetic retinopathy); DR subgroup II (advanced non-proliferative diabetic retinopathy) and DR subgroup III (proliferative diabetic retinopathy); such a grouping respects the majority of available classifications, and the evolving modality of the disorder, as implied in the staging itself.

Retinopathy staging was made through direct ophthalmoscopy, as well as through the indirect method, i.e. after the administration of a mydriatic drug (local tropicamide, solution 1%). All patients classified in the stages DR II and DR III through ophthalmoscopy underwent an additional intravenous fluorescein angiography, aiming at the precise determination of the severity of the retinopathy.

Statistical analysis was performed with SPSS 21.0 for Windows 7. The means of both study subgroups (diabetic patients vs. controls) were assessed through t-test; the differences of mean values were tested with the ANOVA one-way analysis of variances.

3. Results

We had a total of 38 patients suffering from diabetic retinopathy; 18 were classified as DR I (47.36%), 10 patients as DR II (26.32%) and the remaining 10 patients as DR III (26.32%).

CIMT average value in all DR patients was found 0.712 mm ± 0.128 mm; the same parameter in the controls was 0.641 mm ± 0.089 mm; the difference found was statistically important ($p < 0.01$; Figure 2).

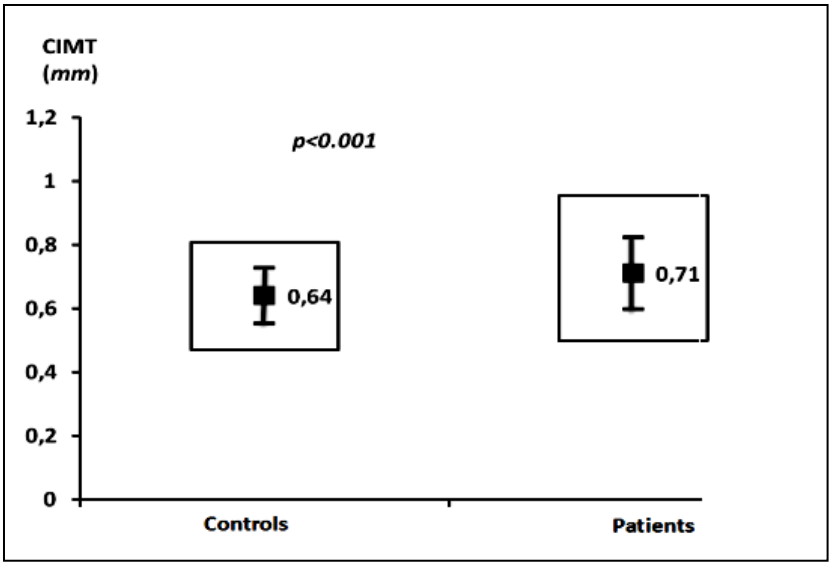

Fig. 2. Correlations between CIMT and the presence of diabetic retinopathy.

The average values of CIMT in all three DR subgroups are summarized at the Table 2.

Table 2
CIMT values in three subgroups of DR patients.

DR subgroup	Total number of patients	CIMT value (millimetres)
I	18	0.669 ± 0.09
II	10	0.741 ± 0.107
III	10	0.761 ± 0.137

The statistical analysis showed no significance in the associations between CIMT absolute values and severity of diabetic retinopathy (DR staging), with a p value of 0.076 (Figure 3).

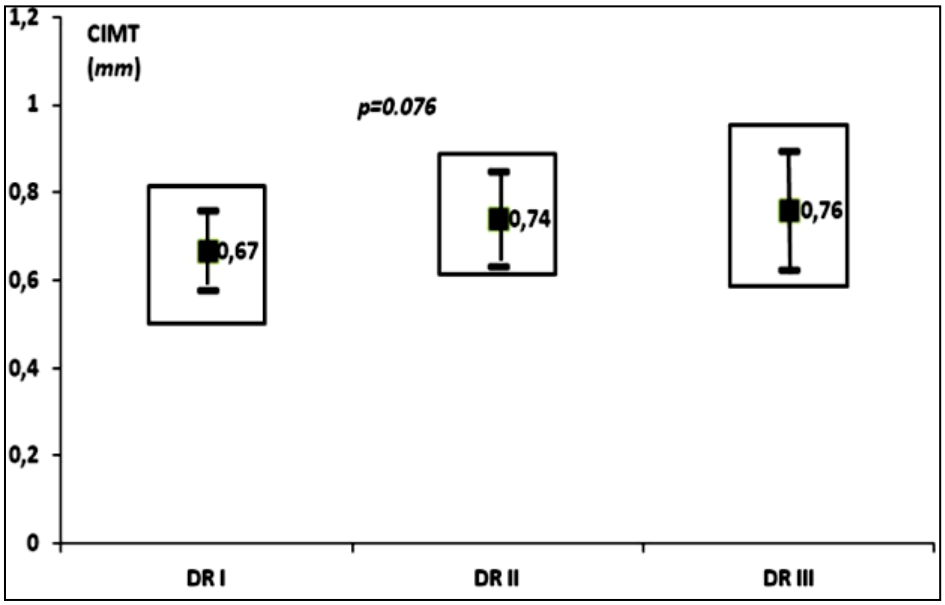

Fig. 3. Correlations between absolute values of CIMT and stage of DR.

4. Discussion

In the present study we have tried to evaluate correlations between CIMT, as an early indicator of macrovascular changes related to atherosclerosis, with diabetic retinopathy, as an independent indicator of microvascular pathological changes.

We found that the relative majority of patients presented DR of stage I, with early changes (47% of the totality). One of the major findings of the study was that patients with DR had significantly higher values of CIMT (Figure 2). Such a finding might suggest that micro- and macrovascular complications of diabetes will somehow have in common one or several similar pathophysiological mechanisms, and several sources seem to confirm the hypothesis (Cheung et al., 2007; Grauslund et al., 2009). Nevertheless, the present study showed no correlation between the CIMT value and the severity of retinopathy (Figure 3).

Identification of patients with asymptomatic carotid stenosis, who are at increased risk of stroke, would improve the yield of prophylactic invasive treatment (Struga and Vyshka, 2012). After studying retrospectively 512 carotid ultrasonographies, the same authors found a strong correlation between carotid stenosis and diabetes as a nosology per se (Struga and Vyshka, 2012). This study, however, was not focused on CIMT measuring, nor was it confronting data with complications of diabetes, like the retinopathy described herein.

Carotid ultrasonography and specific parameters such as CIMT will timely predict future and severe ischemic complications, not only in the cerebral region, but practically in all arterial territories; a recent study re-confirmed its value in confront with other traditional cardiovascular risk prediction models (Van den Oord et al., 2013)

5. Conclusion

Our findings suggest that retinal changes found in diabetic patients will of course have their counterparts in other vascular territories, because the process of micro- and macrovascular alterations seems to follow unrelentingly common pathways. Due to such a conclusion, we suggest a thorough carotid evaluation in patients suffering from diabetic retinopathy; such evaluations have to be completed with further examination of other atherosclerotic markers.

The severity of diabetic retinopathy has clear consequences on the quality of life of patients, and trying to find correlates in other vascular territories will help a better understanding of the issue and early as well as more efficacious interventions (Fenwick et al., 2012).

Prospective and large-scale studies are still requested, to better define associations between microvascular and macrovascular disorders in diabetic patients. Profiling patients' subgroups and taking into consideration other factors, including risk factors of another nature, but also evaluating the role of medications that patients are consuming, are all of them elements that will shape future research on the field.

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