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Are Features of the Metabolic Syndrome Associated with Macular Thickness in Individuals without Diabetes Mellitus?

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Abstract

Background: Maculopathy is a common feature at diagnosis of type 2 diabetes. However, it is not known whether macular thickening, a potential preclinical sign of macular oedema, occurs in individuals with risk factors for diabetes.

Purposes: To examine whether macular thickness is increased in individuals with features of the metabolic syndrome, namely waist circumference, blood pressure, and fasting levels of triglycerides, HDL-cholesterol and glucose in non-diabetic individuals.

Methods: 50 non-diabetic Caucasian individuals were recruited (25 males, age range: 26-78 years, BMI range: 20-46 kg/m^2). Macular thickness, divided into fovea and the inner and outer temporal, nasal, superior and inferior quadrants, was assessed by Optical Coherence Tomography. Additional assessments included: arterial blood pressure, fasting glucose and lipid profile (including triglycerides and HDL-cholesterol), BMI and waist circumference. Features of the metabolic syndrome were collectively entered into a forced regression model to examine their relationship with thickness in the macular subdivisions.

Results: Fovea thickness was within the normal range for all participants. Features of the metabolic syndrome were not collectively associated with macular thickness. However, mean arterial blood pressure (MAP) was independently associated with macular thickness in all regions (standardized beta>0.381, p<0.05) except for the outer nasal quadrant (standardized beta=0.346, p=0.071) and a vascular fovea region (standardized beta=0.105, p=0.591).

Conclusions: MAP, independent of other features of the metabolic syndrome, is associated with thickness in the inner and outer quadrants of the macular. Further research is needed to fully elucidate this relationship. However, potential explanations include altered pressure autoregulation (pressure or metabolic induced) and microvascular rarefaction.

Keywords: Metabolic syndrome; Diabetes mellitus; Microvascular; Macular oedema; Macular thickness

Introduction

Diabetes mellitus is associated with vascular dysfunction, which can present as diabetic retinopathy, nephropathy, neuropathy, heart disease as well as generalized vascular dysfunction, for example impaired skin microvascular function. In fact, vascular dysfunction may precede the development of type 2 diabetes as there is extensive evidence that alterations in avascular function and structure occur in individuals at an increased risk of diabetes. For example, generalized vascular dysfunction has been observed in the skin microcirculation in individuals with fasting hyperglycemia [1], in women with previous gestational diabetes [2], and in 3 month old infants of low birth weight [3].

As stated above the retina is prone to diabetes related damage, which may present as diabetic retinopathy, maculopathy and macular oedema. In common with generalized vascular dysfunction, retinal vascular abnormalities (as indicated by arteriovenous nicking, focal arteriolar narrowing and wider venular diameters) and retinopathy have also been described in individuals at an increased risk of diabetes, for example in obese individuals [4], and in individuals with the metabolic syndrome [5,6]. Wong et al. observed these retinal abnormalities in individuals with the metabolic syndrome were particularly associated with hypertension and diabetes [6]. Kawasaki et al. observed individuals with the metabolic syndrome (as defined by the IDF) were more likely to have retinopathy and a wider venular diameter [5]. Upon further examination they observed that in these individuals a large waist circumference was associated with wider venular diameter and retinopathy lesions; a higher blood pressure was associated with focal arteriolar narrowing, arteriovenous nicking, enhanced arteriolar wall reflex and narrower arteriolar diameter; and a higher triglyceride level was associated with enhanced arteriolar wall reflex. However, despite this wealth of information about the vessel structure, little is known about macular thickness in these individuals with risk factors for type 2 diabetes.

The aims of this study were therefore to examine whether macular thickness is increased with features of the metabolic syndrome, namely increased waist circumference, raised blood pressure, raised fasting levels of triglycerides and glucose, and low fasting levels of HDL cholesterol in individuals without diabetes mellitus.

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Methods

Participants

50 non-diabetic Caucasian individuals (age range of 26 to 78 years) were recruited for this study (Table 1 for participant characteristics). Exclusion criteria were diabetes, overt cardiovascular disease, Raynaud's phenomenon, age less than 18 or over 80 years and any anti-hypertensive, oral hypoglycaemic or lipid lowering therapies. Seven of the participants had the metabolic syndrome, as defined by the International Diabetes Federation (April 2005). None of the participants had clinically defined microalbuminuria. There was only one participant who smoked (cigars), who refrained from smoking on the mornings of the study. Ethics approval was granted by the Local Exeter and North Devon Medical Research Ethics Committee, and written informed consent was obtained from all participants. The studies conformed to the principles outlined in the declaration of Helsinki.

Assessments

Participants attended study visits in the morning following an overnight fast for an ophthalmology examination; assessment of macular thickness; brachial artery blood pressure; fasting blood samples. 24 hour albumin excretion rate and albumin/creatinine ratio were also assessed.

Ophthalmology examination: The ophthalmologic examination included best-corrected visual acuity, intraocular pressure and dilated fundus examination with a 90 Diopter Volk Lense and two field (30° and 50°) non-stereoscopic retinal photographs of each eye (Zeiss FF450 digital fundus camera).

Macular thickness: Following bilateral pupil dilation Optical Coherence Tomography (OCT) was used to quantify retinal thickness (Stratus OCT 3000, Carl Zeiss) using the fast macular thickness scanning protocol. This scanning protocol assesses both the macular thickness and volume on the basis of six 6 mm long radial scans (each scan rotated by 30°), with intersection in the foveolar region. 128 equally spaced samples are taken along each radial scan. At each of these 128 sample points it makes 1024 equally spaced measurements over a depth of 2 mm. OCT measures the macular thickness between the vitreoretinal interface and the interface between the inner and outer photoreceptors segments. These interfaces are determined by changes in reflectivity from the reflected light (original light source: broad bandwidth near infrared light beam with a central wavelength of 820 nm). The Stratus OCT software (ver 4.0.7) automatically determined the thickness and volume of the total macular area as well as in 9 subdivision of the macular. The fovea is defined as the central disc of the scan, with a radius of 500 μm, surrounded by two concentric rings (radiuses of 1.5 and 3 mm). Both concentric rings are further divided into four quadrants: temporal; superior; nasal; inferior. This technique is reproducible in healthy participants [7]. In our hands the intra-individual coefficient of variation for the assessment of fovea thickness was 2.6% (mean (standard deviation): 182.0 (4.8) μm) and ranged from 0.3 to 2.1% in the other macular subdivisions, determined from 1 participant on 4 separate occasions.

Arterial blood pressure: Blood pressure was taken 5 times at 1 minute intervals at the brachial artery using a semi automatic blood pressure recorder (Critikon Dinamap™, Florida, USA). The mean of the final three inflations were taken as the representative blood pressure.

Waist circumference: Waist circumference was measured three times, at the end of a normal expiration, at the level of the iliac crest. The third reading was recorded as the measurement of waist circumference.

Haemostatic and urine assessments: Standard haemostatic and urine measurements included: Glycated haemoglobin (HbA1c) (normal range: 4.0-6.0%, equivalent to IFCC HbA1c: 20-42 mmol/mol); Fasting glucose; lipid profile (total cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides); urinary creatinine and urinary albumin. A urine albumin excretion rate of more than 20 μg/min with an albumin/creatinine ratio greater than 3.5 mg/mmol in women and 2.5 mg/mmol in men being indicative of microalbuminuria.

Statistical analysis

Data are presented as mean (standard deviation). As there was no difference in fovea thickness or intraocular pressure between the right and left eye. Data from both eyes were averaged and used in subsequent data analysis. Linear regression was used to examine whether features of the metabolic syndrome (based on the IDF definition April 2005) were associated with macular thickness. Each of the nine subdivisions of the macular OCT scan was entered into a separate forced regression model as the dependent with features of the metabolic syndrome (waist circumference, mean arterial blood pressure and fasting levels of triglycerides, HDL cholesterol and glucose) entered as independent parameters. With a sample size of 50, the study was powered to detect, with up to 5 and 2 predictors in the model, an effect size (f^2) of 0.38 and 0.27, respectively, at the 5% level with 90% power.

Results

Fovea thickness was within the normal range defined by Chan et al. [8] using the OCT 3000 systems in all participants, results are

	Mean (SD)	Range
Sample number (number of men)	50 (25)	
Age (years)	53.5 (11.8)	26-78
BMI (kg/m^2)	28.6 (6.1)	20-46
Waist circumference (cm)	94.4 (15.8)	69-139
Mean arterial blood pressure (mmHg)	91.4 (11.1)	69-116
Fasting glucose (mmol/l)	4.9 (0.5)	4.0-6.9
Glycated HbA1c (%)	5.5 (0.4)	3.9,6.3
Total cholesterol (mmol/l)	5.37 (0.84)	3.7, 7.4
HDL-cholesterol (mmol/l)	1.54 (0.42)	0.72, 2.32
LDL-cholesterol (mmol/l)	3.21 (0.62)	2.17, 5.22
Triglycerides (mmol/l)	1.19 (0.46)	0.46, 2.40
ACR (mg/mmol)	0.62 (0.27)	0.22, 1.44
AER (μg/min)	5.35 (2.82)	2.11, 15.36
Intraocular pressure (mmHg)	15.1 (3.2)	10, 22

Table 1: Participant characteristics.

Parameter	Mean (standard deviation)
Fovea thickness (μm)	214.6 (19.9)
Inner Quadrants:	
Temporal	268.4 (14.4)
Superior	278.1 (16.9)
Nasal	282.3 (16.4)
Inferior	281.0 (15.6)
Outer Quadrants:	
Temporal	226.9 (12.5)
Superior	243.9 (11.8)
Nasal	264.3 (16.4)
Inferior	237.2 (14.3)

Table 2: Macular thickness of the nine subdivisions of the macular.

presented in Table 2. There was no evidence of diabetes related retinal abnormalities in any of the participants.

Collectively features of the metabolic syndrome were not associated with thickness of any of the nine subdivisions of the macular (fovea model: r^2=0.083, p=0.622, inner quadrants: $r^2 \leq 0.167$, $p \geq 0.153$, outer quadrants: $r^2 \leq 0.199$, $p \geq 0.111$). However, mean arterial pressure was independently associated with macular thickness in the inner quadrants, and with all the outer quadrants except for the nasal quadrant that did not quite reach significance. No association was observed between mean arterial blood pressure and fovea thickness (Table 3 for standardized beta results). None of the other parameters entered into the model (waist circumference, triglycerides, HDL-cholesterol and fasting glucose) were independently associated with thickness in any region of the macular (waist: standardized betas ranged from 0.011 to -0.219, p values ranged from 0.299 to 0.956; Triglycerides: standardized betas ranged from 0.195 to -0.279, p values ranged from 0.142 to 0.318; HDL-cholesterol: standardized betas ranged from 0.010 to -0.161, p values ranged from 0.448 to 0.955; fasting glucose: standardized betas ranged from -0.033 to -0.317, p values ranged from 0.062 to 0.852 in all regions).

Discussion

This study has shown that features of the metabolic syndrome (namely increased waist circumference, raised blood pressure, raised fasting levels of triglycerides and glucose, and low fasting levels of HDL cholesterol) are not collectively associated with macular thickness in non-diabetic individuals. However, within these models mean arterial blood pressure was independently and positively associated with thickness in all the macular subdivisions (inner and outer quadrants) except for the fovea.

The observation that means arterial blood pressure is not associated with fovea thickness in these non-diabetic individuals may be due to the fact that the fovea is an avascular zone that receives it nutrients from the underlying choroid circulation, whereas the inner and outer quadrants of the macular are predominately supplied nutrients from the retinal microcirculation. Thus the observed differences in the relationship between systemic blood pressure with the fovea and the vascular regions of the macular may reflect the different vascular networks that supply them and their differing regulatory mechanisms. However, this situation may alter as diabetes and clinical significant macular oedema develop as posturally induced changes in fovea thickness have been shown to be both independent and dependent of systemic arterial blood pressure in this patient group [8,9].

A possible explanation or contributor for the observed relationship between arterial blood pressure and macular thickness is the loss of, or compromise of, pressure autoregulation in the retinal circulation. The loss of, or compromise of, pressure autoregulation would result in an increase in capillary pressure, which may result in an increase of fluid filtration and thus the thickening of the macular. Retinal blood flow is primarily regulated by pressure and metabolic induced autoregulation, both of which are altered in individuals with type 2 diabetes and clinically significant macular oedema/maculopathy or retinopathy [10-12]. Alterations in metabolic vasodilatation (flicker induced) have also been observed in hypertensive, non-diabetic individuals. In addition, pressure induced autoregulation has been shown to decrease with age in an otherwise healthy population, as blood pressure also increased with age in this population; it may be a blood pressure effect rather than age per se [13]. In support of this suggestion, no association between age and macular thickness was observed in the present study (data not shown). An argument against pressure induced autoregulation contributing to the relationship between systemic blood pressure and macular thickness is the observation that pressure induced autoregulation was only compromised at mean arterial pressure exceeding 115 mmHg in healthy individuals [14], and the maximum MAP was 116 mmHg in this study. However, the study by Robinson et al. [15] was examining the effect of acute increases in blood pressure on pressure-induced autoregulation on 3 healthy participants, and thus it may not be feasible to extrapolate these observations to the current study.

An alternative explanation for the observed relationship between systemic blood pressure and macular thickness is microvascular rarefaction, which is a feature of hypertension. If microvascular rarefaction in the retinal circulation is occurring with increasing chronic systemic blood pressure there may be a corresponding rise in capillary pressure, thereby promoting fluid filtration and resulting in thickening of the vascular regions of the macular fed by the retinal circulation.

A limitation of the current study is the potential for a type 2 error. However, the fact that mean arterial pressure was consistently associated with thickness in all the inner and outer quadrants of the macular endorses the proposal that blood pressure is positively associated with thickness in these regions. An additional limitation of this study is that though it consistently shows that a higher blood pressure is associated with a thickening of the inner and outer quadrants of the macular it does not inform us of which retinal layer(s) is altering in response to pressure. With the continuing development of OCT it will be possible to explore this further in the future.

In summary, this study has shown that features of the metabolic

	Unstandardized beta (standard error)	Standardized beta	P values
Fovea thickness	0.189 (0.349)	0.105	0.591
Inner Quadrants:			
Temporal	0.641 (0.235)	0.504	0.010
Superior	0.766 (0.275)	0.512	0.008
Nasal	0.630 (0.276)	0.433	0.028
Inferior	0.659 (0.254)	0.479	0.013
Outer Quadrants:			
Temporal	0.449 (0.208)	0.404	0.037
Superior	0.458 (0.190)	0.438	0.021
Nasal	0.502 (0.271)	0.346	0.071
Inferior	0.482 (0.237)	0.382	0.049

Table 3: Association between macular thickness and mean arterial blood pressure. Unstandardized and standardized beta values for mean arterial pressure for the nine subdivisions of the macular, generated from the forced entered models based on features of the metabolic syndrome.

syndrome are not collectively associated with macular thickness in non-diabetic individuals. However, within these models mean arterial blood pressure was independently and positively associated with thickness in all the macular subdivisions (inner and outer quadrants) except for the fovea, an avascular zone, that is supplied nutrients by the choroid circulation. Possible explanations for the observed relationship between systemic blood pressure and macular thickness in these non-diabetic individuals include alterations in autoregulation, either pressure or metabolic induced, and also microvascular rarefaction in the retinal circulation. However, further research is required to fully elucidate the observed relationship between systemic blood pressure and macular thickness. By understanding this relationship it may provide valuable insight into development of sight threatening macular oedema and thus may ultimately result in improved prevention and therapeutic strategies.

Duality of Interest

The authors declare that there is no duality of interest associated with this manuscript.

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