Association of Mean Ocular Perfusion Pressure and Diabetic Retinopathy in Type 2 Diabetes Mellitus: Sankara Nethralaya Diabetic Retinopathy Epidemiology and Molecular Genetic Study (SN-DREAMS, Report 28)

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PURPOSE. To elucidate the distribution of mean ocular perfusion pressure (MOPP) and to study the relationship between MOPP and diabetic retinopathy (DR) in a south Indian subpopulation with diabetes.

METHODS. This study was a population-based, cross-sectional evaluation of 1368 subjects, aged ≥40 years, with type 2 diabetes. DR was diagnosed on the basis of the modified Klein classification. Systolic and diastolic blood pressure (SBP and DBP) were recorded with a mercury sphygmomanometer. Intraocular pressure (IOP) was assessed by applanation tonometry. MOPP was derived by the formula: MOPP = 1⁄3(DBP − 1⁄3(SBP − DBP) − IOP.

RESULTS. The mean ± SD for MOPP was 52.6 ± 9.0 mm Hg, higher in the women than in the men (P = 0.046). In comparison to subjects without DR, MOPP was higher in the men with sight-threatening DR (STDR) (P = 0.030) and higher in women with any DR (P = 0.008) and non-STDR (P = 0.006). However, on multivariate analysis after adjustment for all factors, MOPP was found not to be associated with DR (OR = 1.02, 95% CI = 0.99–1.03; P = 0.149), non-STDR (OR = 1.02, 95% CI = 0.99–1.03; P = 0.312), or STDR (OR = 1.02, 95% CI = 0.98–1.05; P = 0.358).

CONCLUSIONS. Univariate analysis revealed very small differences in the association of MOPP and DR in both sexes which are probably of no clinical significance. Multivariate analysis showed no association between MOPP and DR. There seems to be very little evidence of a link between MOPP and DR. It may be more informative to evaluate the association in longitudinal studies.

Diffuse retinopathy (DR) is one of the leading causes of blindness today. However, the causes of vascular pathology in this disease are not fully understood.1–3 Although, chronic hyperglycemia initiates the processes,4 the factors that link elevated glucose levels to vascular cell dysfunction, capillary dropout, tissue hypoxia, and abnormal angiogenesis, remain poorly described.2,5,6 Dysfunctional retinal perfusion can explain few aspects of the pathophysiology of DR.1 Subjects with diabetes have dysfunctional retinal perfusion.1,2 Although these deficiencies may in part reflect responses to a primary event occurring in the retinal microvasculature, they may independently contribute to the development and progression of this disease.1 The blood flow in any tissue is generated by perfusion pressure. The circumferential stress in a vessel is directly proportional to the perfusion pressure.7 A higher perfusion pressure can increase the circumferential stress damage to the vessel wall, leading to a continuing propensity to dilate with subsequent hyperperfusion.8 At the same time, high perfusion pressure can reduce retinal perfusion by causing auto-regulation of the retinal vasculature,9 though the diabetic vascular system is known for its abnormal autoregulatory capacity.9 In any case, both increased and decreased retinal blood flow are detrimental in the development of DR.2 Moreover, higher perfusion pressure and the resultant stress changes can also increase the net pressure gradient from vessels to tissue, leading to more fluid leaving the retinal capillaries (Starling’s forces)10 and an increased risk of rupture (Laplace’s law).10 Since there is no lymphatic circulation to drain away this excess interstitial fluid, increased leakage will result in retinal edema and diabetic maculopathy and vessel rupture will cause hemorrhages and capillary dropout, manifesting as clinical DR.11

The MOPP is expressed as two thirds of the difference between the mean arterial pressure (MAP) and the IOP. Since MOPP is a potentially modifiable factor, knowing its relationship to diabetic retinopathy and maculopathy can be useful in preventing such diabetes complications.

MOPP has been implicated in the development of DR.8,12–15 However, the relationship between MOPP and DR, as studied in previous reports remains unclear. Some studies have shown that high ocular perfusion pressure is associated with the progression of DR.8,12,13 and others have suggested that MOPP decreases as DR worsens.14 Another study also reported higher MOPP with macular edema.15

The present study was conducted to elucidate the distribution of MOPP, the systemic factors associated with MOPP, and its relationship with DR, in a population-based sample of subjects with type 2 diabetes in south India.

METHODS

The details of the study design and methodology are described elsewhere.16 The study was approved by the Institutional Review Board, and written informed consent was obtained from the subjects according to the Declaration of Helsinki.17 The study population was selected by multistage systematic random sampling. The sampling was stratified based on socioeconomic criteria. In the first stage of the study, divisions were selected by using computer-generated random numbers.
has been identified as an independent risk factor for open-angle glaucoma, and glaucoma is documented to have a protective influence against DR (Williams PD. IOVS 2004;45:ARVO E Abstract 4101). Hence, we further excluded 46 subjects with glaucoma (IOP > 21 mm Hg) from the analysis, so that the direct association between MOPP and DR could be assessed independent of the relationship of either to glaucoma. Thus, 1368 subjects were analyzed in this study.

MAP is calculated as: MAP = DBP + 1/3(SBP − DBP), where the difference between the systolic and diastolic blood pressures is identified as the pulse pressure. MOPP is calculated from two thirds of the difference between MAP and IOP and two thirds is added to the formula to estimate ophthalmic artery pressure. Hence, MOPP is derived using the following relation: MOPP = 1/3(DBP + 1/3(SBP − DBP) − IOP).

**Diabetic Retinopathy.** All patients had their fundus photographed with the 45° four-field stereoscopic digital photography (Visucamilite Fundus Camera; Carl Zeiss Meditec) after pupillary dilation. DR was diagnosed based on the modified Klein classification (Modified Early Treatment Diabetic Retinopathy Study scales). For those who showed symptoms of any DR, additional 30° seven-field digital stereo pairs were taken. The prevalence of DR in the general population older than 40 years in our study was found to be 3.5%. DR was divided into mild, moderate, and severe nonproliferative diabetic retinopathy (NPDR) and proliferative diabetic retinopathy (PDR); clinically significant macular edema (CSME), and non-CSME was graded as absent or present. Mild and moderate NPDR was defined as non−sight-threatening diabetic retinopathy (non-STDR) and severe NPDR, PDR, and CSME were defined as sight-threatening DR (STDR). The grading was performed by two independent observers in a masked fashion; the grading agreement was high (κ = 0.83).

**Statistical Analysis**

A computerized database was created for all the records. Statistical software (SPSS for Windows, ver.13.0 SPSS Science, Chicago, IL) was used for the analyses. All the data are expressed as the mean ± SD or as percentage, if categorical. Statistical significance was assumed at P ≤ 0.05. Univariate and multivariate logistic regression analyses were performed to elucidate the risk factors for microangiopathies. The odds ratio (OR), with 95% confidence interval (CI), was calculated for the studied variables. The factors that were used for multivariate analyses included the factors associated with MAP (age, sex, duration of diabetes, age at onset of diabetes, glycosylated hemoglobin, BMI, WC, micro- and macroalbuminuria, serum total cholesterol, serum triglycerides, serum HDL, and anemia) as well as the factors associated with IOP (height and weight of the subject and central corneal thickness).

**RESULTS**

Table 1 describes the baseline characteristics of the study population. Of the 1368 subjects, 875 (64%) had systemic hypertension. The mean ± SD for SBP, DBP, MOPP, and IOP, in the overall study population, were 139.0 ± 20.8 mm Hg (median, 140), 82.0 ± 11.4 mm Hg (median, 80), 52.6 ± 9.0 mm Hg (median, 51.4), and 14.80 ± 2.9 mm Hg (median, 14), respectively. The women had higher SBP (P < 0.0001), DBP (P = 0.082), OPP (P = 0.046), and IOP (P = 0.004) than the men. The women had lesser age (P = 0.017), lesser duration of diabetes (P < 0.0001), higher BMI (P < 0.0001), lower WC (P < 0.0001), and higher serum cholesterol (P < 0.0001) than the men. In our study population, 972 (71.1%) subjects were being treated with oral hypoglycemic agents, 66 (4.8%) were being treated with insulin, and 1025 (74.9%) were on exercise and diet control.

Figure 1 shows the distribution of blood pressure according to sex, MOPP and IOP with increasing age. MOPP and IOP did not show any significant change with increasing age, (P =
We report the MOPP among subjects with type 2 diabetes and elucidate the systemic factors associated with MOPP and its association with DR. In the present study, the women had higher MOPP than the men. Also, SBP was found to be higher among the women than the men. Recently, Zheng et al.25 reported higher MOPP, higher DBP, but lower SBP in men than in women. The higher SBP in the women in the present study may be explained by the higher BMI22 and the poor health-seeking behavior of women on the Indian subcontinent.30

There was no significant trend of MOPP with age, as seen in Figure 1. We found a very small association of MOPP with the age at onset of diabetes and weight of the subject, which may not be clinically significant. We also found that MOPP is associated with the presence of nephropathy and serum lipids (triglycerides). There was no association with glycemic control and duration of diabetes. This lack of association is interesting, as poor glycemic control and longer duration of diabetes are the most important risk factors for DR. Kohner31 observed that retinal hyperperfusion was worse in those with poor diabetic control. Konno et al.32 observed a transition from decreasing retinal blood flow to increasing retinal blood flow in patients with longer duration of type 1 diabetes and suggested that there is a net decrease in the resistance to blood flow with longer duration of diabetes. Thus, longer duration of diabetes and poor glycemic control may be associated with increased retinal perfusion and a decrease in the resistance to flow. However, MOPP is calculated from IOP and measured brachial blood pressure, and it is unlikely that retinal
changes can explain any change or lack of change in MOPP. Moreover, blood flow changes are related to the complex pathologic alterations that occur in the diabetic retina and are not yet fully understood.32

On evaluating the relationship between MOPP and DR in both sexes, we found that in the men, higher MOPP was associated with STDR and CSME; whereas in the women, it was associated with any DR and non-STDR. However, the size of the differences found (in mm Hg) was very small, and most had only borderline statistical significance, which disappeared on adjusting for age, sex, duration of diabetes, age of onset of diabetes, and a higher MOPP in the PDR group than in the no DR group. Earlier, we reported an increased dysregulation among women in white populations. In the present study, as depicted in Table 1, female subjects had a higher prevalence of obesity, defined by BMI, in women than in men.25 This was attributed to the more frequent occurrence of vascular kines like adiponectin,33 leptin,34,35 hepatocyte growth factor,36 and zinc-alpha-2-glycoprotein37 in pathogenesis of DR and blood flow with severity of retinopathy in diabetes. Roy and Klein15 observed that after adjustment for the duration of diabetes, patients with a higher MOPP were, on an average, twice as likely to have macular edema and severe hard exudates than were those with lower MOPP.

Thus, there is contradictory evidence in literature regarding the relationship of MOPP with DR. However, none of these reports studied the sex-based association, which might explain these differences. A recent study evaluated the distribution of MOPP and its association with open-angle glaucoma and found that the association was stronger in women than in men.25 This was attributed to the more frequent occurrence of vascular dysregulation among women in white populations. In the present study, as depicted in Table 1, female subjects had a higher BMI than did male subjects. Earlier, we reported an increased prevalence of obesity, defined by BMI, in women than in men.25

Table 3. Association of MOPP with DR and Diabetic Maculopathy

<table>
<thead>
<tr>
<th>Retinopathy</th>
<th>MOPP (mm Hg)</th>
<th>Overall</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Mean ± SD</td>
<td>P*</td>
<td>n</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>No DR</td>
<td>1124</td>
<td>52.3 ± 8.9</td>
<td>Ref</td>
<td>571</td>
</tr>
<tr>
<td>Any DR</td>
<td>244</td>
<td>55.6 ± 9.6</td>
<td>0.042</td>
<td>152</td>
</tr>
<tr>
<td>Non-STDR</td>
<td>200</td>
<td>53.4 ± 9.6</td>
<td>0.112</td>
<td>123</td>
</tr>
<tr>
<td>STDR</td>
<td>44</td>
<td>54.4 ± 9.7</td>
<td>0.126</td>
<td>29</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Maculopathy</th>
<th>MOPP (mm Hg)</th>
<th>Overall</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>Mean ± SD</td>
<td>P*</td>
<td>n</td>
<td>Mean ± SD</td>
</tr>
<tr>
<td>No maculopathy</td>
<td>164</td>
<td>53.7 ± 9.4</td>
<td>Ref</td>
<td>103</td>
</tr>
<tr>
<td>Non-CSME</td>
<td>64</td>
<td>53.5 ± 10.5</td>
<td>0.889</td>
<td>40</td>
</tr>
<tr>
<td>CSME</td>
<td>16</td>
<td>53.4 ± 8.8</td>
<td>0.903</td>
<td>9</td>
</tr>
</tbody>
</table>

Bold P values indicate significant results. MOPP, mean ocular perfusion pressure; DR, diabetic retinopathy; STDR, sight threatening diabetic retinopathy; CMSE, clinically significant macular edema.
prompted us to evaluate the sex-based differences between MOPP and DR. However, we did not find any significant association of MOPP with DR, non-STDR, and STDR in multivariate analyses.

Although the direct relationship of MOPP and DR has not been studied in many reports, there are many studies that have evaluated the association of retinal blood flow with DR. An overview of retinal perfusion abnormalities in the different stages of DR shows contradictory findings. One of the first hints of altered retinal blood flow in patients with diabetes mellitus came from Kohner et al., who reported increased hints of altered retinal blood flow in patients with diabetes.

Table 4. Multivariate Logistic Regression Analysis of MOPP with DR with Sequential Adjustment of Risk Factors

<table>
<thead>
<tr>
<th>Association of MOPP with DR, non-STDR, and STDR</th>
<th>No DR vs. Any DR</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>No DR vs. Non-STDR</th>
<th>OR (95% CI)</th>
<th>P</th>
<th>No DR vs. STDR</th>
<th>OR (95% CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOPP, unadjusted</td>
<td>1.01 (0.99–1.03)</td>
<td>0.134</td>
<td></td>
<td>1.01 (0.99–1.02)</td>
<td>0.403</td>
<td></td>
<td>1.02 (0.99–1.06)</td>
<td>0.111</td>
<td></td>
</tr>
<tr>
<td>Adjusted for sex</td>
<td>1.01 (0.99–1.03)</td>
<td>0.094</td>
<td></td>
<td>1.01 (0.99–1.02)</td>
<td>0.335</td>
<td></td>
<td>1.03 (0.99–1.06)</td>
<td>0.088</td>
<td></td>
</tr>
<tr>
<td>Adjusted for age, sex</td>
<td>1.01 (0.99–1.03)</td>
<td>0.102</td>
<td></td>
<td>1.01 (0.99–1.02)</td>
<td>0.343</td>
<td></td>
<td>1.03 (0.99–1.06)</td>
<td>0.093</td>
<td></td>
</tr>
<tr>
<td>Adjusted for age, sex, duration of DM</td>
<td>1.02 (1.01–1.03)</td>
<td>0.032</td>
<td></td>
<td>1.01 (0.99–1.03)</td>
<td>0.185</td>
<td></td>
<td>1.03 (1.00–1.07)</td>
<td>0.051</td>
<td></td>
</tr>
<tr>
<td>Adjusted for age, sex, duration, BMI</td>
<td>1.03 (1.01–1.04)</td>
<td>0.003</td>
<td></td>
<td>1.02 (1.00–1.03)</td>
<td>0.047</td>
<td></td>
<td>1.04 (1.01–1.07)</td>
<td>0.018</td>
<td></td>
</tr>
<tr>
<td>Adjusted for age, sex, duration, BMI, HbA1c</td>
<td>1.03 (1.01–1.04)</td>
<td>0.003</td>
<td></td>
<td>1.02 (1.01–1.05)</td>
<td>0.05</td>
<td></td>
<td>1.04 (1.01–1.07)</td>
<td>0.020</td>
<td></td>
</tr>
<tr>
<td>Adjusted for age, sex, duration, BMI, HbA1c, cholesterol</td>
<td>1.03 (1.01–1.04)</td>
<td>0.003</td>
<td></td>
<td>1.02 (1.00–1.04)</td>
<td>0.047</td>
<td></td>
<td>1.04 (1.01–1.07)</td>
<td>0.021</td>
<td></td>
</tr>
<tr>
<td>Adjusted for age, sex, duration, BMI, HbA1c, cholesterol, HDL</td>
<td>1.03 (1.01–1.04)</td>
<td>0.003</td>
<td></td>
<td>1.02 (1.00–1.05)</td>
<td>0.047</td>
<td></td>
<td>1.04 (1.01–1.07)</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>Adjusted for age, sex, duration, BMI, HbA1c, cholesterol, HDL, TG</td>
<td>1.03 (1.01–1.04)</td>
<td>0.003</td>
<td></td>
<td>1.02 (1.00–1.05)</td>
<td>0.045</td>
<td></td>
<td>1.04 (1.00–1.07)</td>
<td>0.028</td>
<td></td>
</tr>
<tr>
<td>Adjusted for age, sex, duration, BMI, HbA1c, cholesterol, HDL, TG, albuminuria</td>
<td>1.02 (1.00–1.03)</td>
<td>0.048</td>
<td></td>
<td>1.02 (0.99–1.03)</td>
<td>0.101</td>
<td></td>
<td>1.02 (0.98–1.05)</td>
<td>0.368</td>
<td></td>
</tr>
<tr>
<td>Adjusted for age, sex, duration, BMI, HbA1c, cholesterol, HDL, TG, albuminuria, WC</td>
<td>1.02 (1.00–1.03)</td>
<td>0.048</td>
<td></td>
<td>1.02 (0.99–1.03)</td>
<td>0.101</td>
<td></td>
<td>1.02 (0.98–1.05)</td>
<td>0.38</td>
<td></td>
</tr>
<tr>
<td>Adjusted for age, sex, duration, BMI, HbA1c, cholesterol, HDL, TG, albuminuria, WC, onset of DM</td>
<td>1.02 (0.99–1.03)</td>
<td>0.149</td>
<td></td>
<td>1.02 (0.99–1.05)</td>
<td>0.512</td>
<td></td>
<td>1.02 (0.98–1.05)</td>
<td>0.358</td>
<td></td>
</tr>
</tbody>
</table>

Data are the OR (95% CI). Bold P values indicate significant results. MOPP, mean ocular perfusion pressure; DR, diabetic retinopathy; STDR, sight threatening diabetic retinopathy; DM, diabetes mellitus; BMI, body mass index; HbA1c, glycosylated hemoglobin; HDL, high density lipoproteins; TG, triglycerides; WC, waist circumference.

The limitations of our study include its cross-sectional design and its focus on patients with type 2 diabetes only. Whether our results can be extrapolated to patients with type 1 diabetes is unclear. Another limitation is the unavailability of data on how many were treated for high IOP or high blood pressure. Since this information is not available, the treatment is a possible confounder in this study. Also, we did not study the retinal blood flow in our study population. It will be interesting to study the retinal blood flow and MOPP in both sexes.

In univariate analyses, we found very small sex-related differences in MOPP (of 1 mm of Hg, which is approximately 2% of the mean), which are probably of no clinical significance. On multivariate logistic regression analyses of MOPP with DR with sequential adjustment of risk factors, we did not find any significant association between MOPP and DR. However, the present study evaluated the MOPP association at a single time point, rather than prospectively. Hence, future prospective studies may provide more information about the association between the MOPP and DR, if any, although the clinical significance of such an association seems little only.

CONCLUSION

We report no association of MOPP with DR, non-STDR, and STDR. There seems to be very little evidence for a link between MOPP and DR, at least a link that is significant. Since DR is a multifactorial disease and perfusion pressure and vascular factors are likely to be involved in its pathophysiology, it may be more informative to evaluate these associations in prospective studies.

References


