Online-Only Supplemental Material

Retinal capillary damage is already evident in hypertensive patients with prediabetes and associated with HbA1c levels in the non-diabetic range

Supplement Appendix

Definitions for prediabetes, normal glucose metabolism and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR)

The patient groups in our study were defined using HbA1c based on American Diabetes Association guideline recommendation (1). Patients with HbA1c below 5.7% (39 mmol/mol) were categorized to have normal glucose metabolism and patients with HbA1c from 5.7 to 6.4% (39 to 46 mmol/mol) were considered to have prediabetes. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) was calculated according to the formula: (fasting insulin x fasting glucose)/22.5. Insulin resistance was defined as having a HOMA-IR $\geq$ 2.5 (2; 3).

Clinical Work up

After obtaining anthropometrics, systolic and diastolic office blood pressure (BP) levels, medical history was recorded and a physical examination was performed. All participants had unattended office BP measurements using automatic BP monitors (Omron HEM 907) and ambulatory BP monitor (Spacelabs 90207, Spacelabs Healthcare, Snoqualmie, Washington, United States) in a standardized fashion according to guideline recommendations (4). Blood samples and mid-stream urine were obtained within 4 weeks prior to OCT-A for routine biochemistry testing. The eGFR values were estimated using the CKD-EPI equation.

Details on OCT-A scans and analysis

Patients attended the Dobney Hypertension Centre (before 12:00 h), having fasted for 12 hours and abstained from strenuous exercise, caffeine and alcohol for 24 hours. All participants were seated quietly in semi dark room for 5 minutes. Patients were asked to take their usual BP medications after OCT-A was performed. The right eye was imaged and used for analysis. The capillary density was measured in 2 regions of interest; the foveal region (CDF; a circular region 1.5 mm in diameter centered on the fovea), and in the parafoveal region (CDPF; an annulus extending from the outside of the fovea region out to a diameter of 2.5 mm). The analysis of the OCT images was performed in a blinded fashion by an operator with no access to other relevant clinical data of the study population.

Study population

Patients with retinal disease (retinopathy, glaucoma, age-related macular degeneration) or previous retinal surgery were excluded. The most common drug types prescribed in both groups were calcium channel blockers (prediabetes/normal glucose metabolism: 40% / 48.4%), angiotensin receptor blockers (prediabetes/normal glucose metabolism: 35% / 35.5%), β-Blockers (prediabetes/normal glucose metabolism: 35% / 14.5%) and angiotensin-converting enzyme inhibitors (prediabetes/normal glucose metabolism: 25% / 19.4%).

Additional Statistical Approaches

Data are presented as means with standard deviation (SD) and percentages, respectively. Demographic comparisons were performed using a Chi-square test for categorical variables (sex). Distribution of data was checked by Kolmogorov–Smirnov test before further analysis. Two-tailed values of $p<0.05$ were considered statistically significant. Statistical analysis was performed using IBM SPSS Statistics 25.0.0.1, USA.

Reference

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Supplementary Table 1. Clinical characteristics of the study population

Parameter	Patients with normal glucose metabolism, (n=62), mean ± SD	Patients with prediabetes, (n=40), mean ± SD	p-value
Age, years	49.1 ± 16.6	59.4 ± 13.1	0.001
Gender, % male	53	60	0.588
Body weight, kg	91.1 ± 20.7	94.0 ± 26.0	0.540
BMI, kg/m²	30.5 ± 7.6	32.9 ± 7.3	0.141
Office SBP, mmHg	136.0 ± 27.5	135.9 ± 30.4	0.990
Office DBP, mmHg	84.7 ± 17.3	79.4 ± 19.1	0.177
Office HR, bpm	72.3 ± 15.7	69.8 ± 20.5	0.526
24-hour SBP, mmHg	134.2 ± 17.7	132.6 ± 18.4	0.674
24-hour DBP, mmHg	81.4 ± 10.9	76.6 ± 10.7	0.035
24-hour HR, bpm	74.8 ± 10.6	70.6 ± 11.5	0.075
eGFR, ml/min/1.73m²	91.1 ± 22.8	81.3 ± 23.3	0.044
UACR, mg/mmol creatinine	18.1 ± 69.1	8.6 ± 24.0	0.425
Fasting Glucose, mmol/l	5.1 ± 0.58	5.9 ± 0.95	<0.001
HbA1c, %	5.3 ± 0.22	5.9 ± 0.22	<0.001

Data are given as mean ± SD, SD- standard deviation, CKD- chronic kidney disease, BMI- body mass index, SBP- systolic blood pressure, DBP- diastolic blood pressure, HR- heart rate, bpm- beat per minute, eGFR- estimated glomerular filtration rate, UACR- urinary albumin creatinine ratio. HbA1c of 5.3% converts to 34 mmol/mol, 5.9% to 41 mmol/mol.

Supplementary Table 2. Illustration of the relationship of capillary density at foveal and parafoveal with clinical characteristics

	CDF	CDPF
Age	r=-0.425, p=<0.001	r=-0.287, p=0.004
BMI	r=-0.099, p=0.333	r=0.123, p=0.230
Office SBP	r=0.010, p=0.927	r=-0.086, p=0.409
Office DBP	r=0.043, p=0.810	r=0.037, p=0.837
24-hour SBP	r=0.174, p=0.091	r=-0.051, p=0.621
24-hour DBP	r=0.211, p=0.039	r=0.130, p=0.207
eGFR	r=0.220, p=0.031	r=0.294, p=0.003
UACR	r=-0.038, p=0.711	r=0.023, p=0.821
HbA1c	r=-0.388, p=<0.001	r=0.006, p=0.951
Glucose	r=-0.245, p=0.015	r=0.137, p=0.179

CDF- capillary density at the foveal region, CDPF- capillary density at the parafoveal region, BMI- body mass index, SBP- systolic blood pressure, DBP- diastolic blood pressure, eGFR- estimated glomerular filtration rate, UACR- urinary albumin creatinine ratio.