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Effects of semaglutide and empagliflozin on oxygenation, vascular autoregulation, and central thickness of the retina in people with type 2 diabetes: A prespecified secondary analysis of a randomised clinical trial☆,☆☆

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ABSTRACT

Aims: Semaglutide and empagliflozin have shown cardiovascular protection. In SUSTAIN-6, semaglutide was associated with an increased risk of diabetic retinopathy. We investigated whether changes in retinal oxygenation, retinal vascular autoregulation, and central retinal thickness are altered by semaglutide, empagliflozin or the combination.

Methods: This study was a prespecified, secondary outcome from a randomised, 32 weeks partly placebo-controlled, partly open-label, clinical trial on the effects of semaglutide and empagliflozin on arterial stiffness and kidney oxygenation. A total of 120 participants with type 2 diabetes, established or high risk of cardiovascular disease and age ≥50 years were randomised into four parallel groups (semaglutide, empagliflozin, the combination or tablet placebo, n = 30 for each group). We primarily hypothesized that semaglutide would increase venular oxygenation.

Results: We found no changes in retinal arteriolar, venular or venular-arteriolar oxygenation nor in retinal vessel diameter regardless of treatment group.

Semaglutide increased central retinal thickness compared to placebo with ~1 % (3.8 μm 95 % CI [0.9;6.7], p = 0.009) with no changes in the empagliflozin or combination group.

Conclusion: Neither semaglutide, empagliflozin nor the combination alters markers of retinal function. The effect of semaglutide on central retinal thickness was small, but the clinical significance is uncertain.

1. Introduction

Hyperglycaemia is a well-established risk factor for the development and progression of diabetic retinopathy, and tight glycaemic control is accordingly an important goal in the prevention of diabetic retinopathy.[1–3]

Recently, semaglutide, a glucagon-like peptide 1 receptor agonist (GLP-1ra) and empagliflozin, a sodium glucose-cotransporter 2 inhibitor (SGLT-2i), both glucose-lowering drugs, have shown cardiovascular protection in large outcome trials.[4,5] Surprisingly, in the Trial to Evaluate Cardiovascular and Other Long-term Outcomes with Semaglutide in Subjects with Type 2 Diabetes (SUSTAIN-6) semaglutide was

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associated with an 1.2 %-point (hazard ratio 1.76, [95 % CI 1.11, 2.78], p = 0.02) increase in the risk of retinopathy complications (including vitreous haemorrhage, blindness or the need for treatment with an intravitreal agent or photocoagulation).[4] Empagliflozin and other SGLT-2i's have not been associated with increasing risk of retinopathy.[6] The effect of the combination therapy with both SGLT-2i and GLP-1ra on the retina remains to be elucidated.

Manifest diabetic retinopathy is characterized by morphological changes including microaneurysms, haemorrhages and neovascularization.[3] The physiological changes preceding and leading to these changes have not yet been fully determined. Several factors may be involved including metabolic and vascular changes.[7–9] It has not been investigated whether semaglutide or empagliflozin alter retinal oxygenation, retinal vascular function, or central retinal thickness.

We therefore assessed the effects of semaglutide, empagliflozin, and the combination versus placebo on these physiological parameters in patients with type 2 diabetes and high cardiovascular risk.

Our primary aim was to evaluate changes in retinal oxygenation assessed by retinal oximetry. Second, we wanted to investigate the effect on retinal vascular autoregulation induced by flickering light measured with the Dynamic Vessel Analyzer and central retinal thickness measured by Optical Coherence Tomography scanning.

2. Subjects, materials and methods

This was a prespecified, secondary outcome of the SEMPA (Effect of Empagliflozin and Semaglutide on Cardio-Renal Target Organ Damage in Patients with Type 2 Diabetes – A Randomised Trial, EudraCT 2019-000781-38) trial: a 32-week randomised, partly placebo-controlled partly open-label trial, designed primarily to assess the combined and separate effects of semaglutide and empagliflozin on arterial stiffness and kidney oxygenation. Data on kidney oxygenation has been reported previously.[10] Prespecified, secondary endpoints included change in retinal oxygenation, retinal vascular autoregulation, and central retinal thickness.

2.1. Study design

We performed an investigator-initiated 32-week randomised, partly placebo-controlled, partly open-label trial comprising 120 participants.

The trial consisted of two parallel designs: 1) A double blind, placebo-controlled, randomised clinical trial to evaluate the effects of empagliflozin 10 mg once-daily (Jardiance®, Boehringer Ingelheim International GMBH, Germany) versus matching tablet placebo, and 2) a parallel-group intervention open-label trial of once-weekly subcutaneous semaglutide (Ozempic®, Novo Nordisk A/S, Denmark) in combination with double-blinded tablet empagliflozin or tablet placebo treatment. Outcomes were assessed at baseline, and after 16 and 32 weeks. The study design is shown in Supporting information Fig. S1. Details on randomisation, study drugs and authority approvals are given in Supporting information. All participants gave written informed consent.

2.2. Study population

We included participants with a diagnosis of type 2 diabetes and glycated haemoglobin level (HbA1c) $\geq$ 48 mmol/mol (6.5 %). Key inclusion criteria were either i) age $\geq$ 50 years and established cardiovascular disease (CVD) (e.g., previous cardiovascular, cerebrovascular, or peripheral vascular disease) OR ii) age $\geq$ 60 years and high risk of cardiovascular disease (e.g., smoker, micro- or macroalbuminuria, persistent hypertension despite antihypertensive treatment).

Key exclusion criteria included estimated glomerular filtration rate $\leq$ 45 mL/min/1.73m^2 or treatment with an SGLT-2i, GLP-1ra or dipeptidyl-peptidase 4 inhibitor 30 days before randomisation. A complete list of in- and exclusion criteria is found in Supporting information.

Potential participants were primarily identified through The Danish Health Data Authority, which provided data extractions, with information on persons with a diagnosis of type 2 diabetes living in the Central Region of Denmark. These individuals were contacted by letter. If they responded, we sent written information about the project. Potentially eligible persons were invited for a screening visit, where S.G. and L.V. evaluated their potential for inclusion through interview, physical examination, and medical records before final enrolment and randomisation. Participant flow is depicted in Supporting information Fig. S2.

2.3. Data collection and analysis

Data were collected between August 2019 and February 2022. Examinations included ophthalmological examinations, blood and urine samples and measurement of office blood pressure. All examinations were performed on the same day. Blood pressure was measured on the right arm using Riester Champion N (Riester GmbH; Jungingen, Germany) with the participant in a supine position, resting for at least 5 min in a quiet room. Mean systolic blood pressure and mean diastolic blood pressure were calculated as an average from three consecutive measurements. On each study day, participants refrained from eating for at least 2 h and abstained from caffeine for at least 3 h before examinations. No smoking was allowed on the study days. Participants were instructed to take their prescribed medication as usual (except hypoglycaemic drugs). All examinations were performed by trained personnel. Ophthalmological examinations were undertaken at the Department of Ophthalmology, Aarhus University Hospital, Denmark. Other investigations took place at the Medical Research Laboratory, Aarhus University Hospital, Denmark. All data analyses were carried out blinded to treatment allocation.

2.4. Ophthalmological examinations

Ophthalmological examinations included assessment of intraocular pressure (Tonoref, Nidek, Gamagori Aichi, Japan), measurement of best-corrected visual acuity and slit-lamp examination. The pupils were then dilated with tropicamide 1 % and phenylephrine 10 % eye drops, followed by fundus photography (Topcon, model TRC50 DX, Tokyo, Japan), and measurement of central retinal thickness using Ocular Coherence Tomography scanning (Heidelberg OCT, V.1.7.0.0, Heidelberg Instruments, Heidelberg, Germany). Retinal oxygenation was assessed using the Oxymap T1 (Oxymap, Reykjavik, Iceland), and finally, retinal arterial and venular diameters and their response to flickering light were assessed using the Dynamic Vessel Analyzer (Imedos, Jena, Germany). Retinopathy was graded according to international guidelines.[11,12]

2.5. Retinal oximetry

The procedure and principles have been described in detail elsewhere.[13] In short, the participant was positioned in front of the fundus camera of the oximeter, and five fundus photographs were obtained, one centred on the fovea, two centred on the optic disc and the other two images displaced one disc diameter upwards and downwards temporally, so that the larger temporal vascular arcades were in the centre of the image. The automated software Oxymap Analyzer 2.5 (V10927) estimated the oxygen saturation in the vessels. The best optic disc-centred image of the left eye (321 eyes) was selected for further analysis. In case of poor image quality, the right eye would be used instead (3 eyes). For further details, see Supporting information.

2.6. Dynamic vessel analyzer

The setup and use of the Dynamic Vessel Analyzer has already been described in detail[14] and is further outlined in the Supporting information. To summarize, the Dynamic Vessel Analyzer consists of a fundus

camera connected to a video recorder and computer system. The software measures the diameter of the vessels 25 times per second for each 10 μm throughout the examination. The Dynamic Vessel Analyzer recordings were performed on the left eye unless this was not possible. Each recording lasted for 6 min with three phases of each 2 min. The first phase served as baseline and was carried out during rest. In the second phase, retina was stimulated by flickering lights at 12.5 Hz. The third phase was obtained during restitution, see Supporting information Fig. S3. The measured diameters from the first 200 μm along the vessel segment obtained during the last 45 s of each phase were used for further analysis. Average vessel diameters were obtained from a subsequent analysis, in which the same vessel segment was marked, and the video replayed. The diameters sampled from the first resting phase in the two duplicate measurements were compared, and if they differed by >1 %, a third replay was carried out. Preferably the two analyses in which the vessel diameters differed ≤1 % were sampled and averaged. Otherwise, the two measurements with the smallest deviation were chosen. In 13 % (77 of 590 arteries or venules) diameters differed between 1.01 % and 4.63 % with an extreme outlier at 9.4 %.

2.7. Optical coherence tomography

Central retinal thickness was measured by Optical Coherence Tomography scanning using the infrared and Optical Coherence Tomography 30° ART protocol which scans an array of 19 horizontal Optical Coherence Tomography scans with an angular width of 20°, each with a vertical spacing of 0.0.8°. The average retinal thickness in each eye within a central circle with a diameter of 1 mm was calculated as the central retinal thickness.[15]

2.8. Outcomes

We hypothesized that, after 32 weeks of treatment, 1) semaglutide would increase venular saturation as compared to placebo and that 2) empagliflozin would have no effect compared to placebo. Secondary outcomes were changes in arteriolar and venular diameters as well as change in central retinal thickness.

2.9. Statistical analysis

Distribution of data was evaluated using histogram and quantile-quantile plots. Variables are presented as mean ± standard deviation and median (interquartile range (IQR)) as appropriate. Dichotomous data are presented as n (%).

Data were analysed in an intention-to-treat manner. We used a linear mixed model for repeated measurements with restricted maximum likelihood and the Kenward-Roger approximation for changes in 1) retinal oxygenation (arteriolar, venular or the difference arterio-venular (dAV)), 2) arteriolar and venular diameters and 3) central retinal thickness. The model used fixed effects of the outcome variable and the interaction of treatment and time. Random effects were considered to each participant, and to each eye in the model of central retinal thickness. We used one multivariate repeated measurement model to compare treatment groups. As suggested by Fitzmaurice et al[16] and due to the randomised design, the model calculates one, common baseline value, and a common value for the semaglutide and combination group at week 16, before the addition of empagliflozin to the combination group. In exploratory analyses, the change in the following parameters was in turn added to the three models: HbA1c, body mass index (BMI), and office systolic blood pressure.

Statistical analyses were performed using Stata/IC 15 (StataCorp., College Station, Texas, USA). As this was a prespecified, secondary outcome, no formal power calculation was implemented.

3. Results

From May 2019 to June 2021, 180 persons were screened of whom 120 persons were enrolled as prespecified. The trial ended as scheduled after last participants last visit February 2022.

Table 1 presents baseline characteristics of the study population. Age, sex, BMI, and HbA1c were comparable between groups. Ophthalmological measures were comparable as well as the use of antidiabetic medication (except insulin) and blood pressure medication. Office systolic blood pressure was slightly higher in the placebo and empagliflozin group and a history of CVD was higher in the combination group.

3.1. Retinal arteriolar and venular oxygenation

In total, 324 data points (90 % of 360 planned) were eligible for analysis, Supporting information Fig. S2. After 32 weeks there were no significant differences in arteriolar saturation between groups, Fig. 1a, nor in venular saturation or dAV, Fig. 1b–c.

Adjustment for changes in HbA1c, BMI or office systolic blood pressure did not alter the results significantly in either arteriolar, venular or dAV measures.

3.2. Dynamic vessel analyses

A total of 295 videos from 119 unique participants (82 % of 360 planned) were eligible for analysis, Supporting information Fig. S2. During flicker, we found no significant diameter change in arterioles or venules in any of the within- or between group comparisons, Fig. 2a–b. Adjustment for HbA1c, BMI, or office systolic blood pressure did not alter the results (data not shown).

3.3. Central retinal thickness

Datapoints from a total of 662 eyes (92 % of 720 planned; 328 right eyes and 334 left eyes) were eligible for analysis. At baseline, central retinal thickness values ranged between 235 and 382 μm with a mean ± SD of 285 μm ± 24. We found a statistically significant 1 % increase in central retinal thickness in the semaglutide group compared to placebo (3.8 μm [95 % CI 0.9, 6.7], p = 0.009), Table 2 and Fig. 3. We found no changes in the empagliflozin or combination groups.

In explorative analyses with adjustment for HbA1c, the treatment effect of semaglutide became non-significant. All other adjustments did not alter the estimates, Table 2.

3.4. Adverse events

A total of 16 adverse events were reported. 4 was related to the study drugs (3 with obstipation and 1 with urinary tract infection).

4. Discussion

This article presents a secondary prespecified analysis on retinal oxygenation, retinal vascular autoregulation, and central retinal thickness from a 32 week randomised, partly placebo-controlled, partly open-label trial on semaglutide, empagliflozin or their combination in people with type 2 diabetes. We found no effect of semaglutide, empagliflozin or the combination on retinal oxygenation or vascular diameters. We observed a small, but probably not clinically relevant, increase in central retinal thickness in the semaglutide group.

4.1. Effects of semaglutide

In the SUSTAIN-6 trial, semaglutide was associated an increased risk of retinopathy complications.[4] This worsening of diabetic retinopathy has been suggested to be associated with the rapidity and magnitude of improvement in glycaemic control.[17] However, whether semaglutide

Table 1
Baseline characteristics.

	Placebo	Semaglutide	Empagliflozin	Combination
Clinical				
No. of participants	30	30	30	30
Age, years	66.7 ± 6.8	69.7 ± 6.6	70.4 ± 6.6	69.5 ± 6.8
Male sex	24 (80)	26 (87)	22 (73)	25 (83)
Body-mass index, kg/m^2	27.7 ± 4.3	27.9 ± 5.3	27.6 ± 5.1	26.4 ± 4.0
Duration of diabetes, years	9.5 (5.0–12.0)	10.5 (4.0–17.0)	11.0 (5.0–19.0)	9.5 (4.5–12.5)
Office systolic blood pressure, mm Hg	144 ± 25	139 ± 17	142 ± 14	138 ± 16
Office diastolic blood pressure, mm Hg	82 ± 11	78 ± 8	78 ± 9	76 ± 9
History of cardiovascular disease	15 (50)	19 (63)	22 (73)	24 (80)
HbA1c, mmol/mol	59 (51–68)	59 (51–63)	57 (52–63)	57 (51–68)
HbA1c, %	7.5 (6.8–8.4)	7.5 (6.8–7.9)	7.4 (6.9–7.9)	7.4 (6.8–8.4)
Ophthalmology				
Saturation				
Artery	96.8 ± 5.2	95.2 ± 3.9	94.0 ± 6.0	95.8 ± 4.5
Venule	56.6 ± 10.6	58.3 ± 9.2	58.1 ± 9.5	58.3 ± 8.0
Difference, artery − venole, %point	40.1 ± 9.6	36.8 ± 6.9c	35.9 ± 8.6c	37.4 ± 6.7c
Central retinal thickness, dxt. (μm)	292.6 ± 25.5	283.0 ± 23.4	276.9 ± 29.8	288.1 ± 25.4
Central retinal thickness, sin. (μm)	285.4 ± 23.9	283.2 ± 19.0	281.8 ± 27.5	293.9 ± 31.5
Retinal vessel analyzer				
Artery, change diameter	0.4 (−0.9–5.0)	1.4 (−0.5–3.9)	1.9 (0.7–5.5)	1.9 (0.5–4.3)
Venule, change diameter	5.5 ± 2.5	5.0 ± 3.2	5.1 ± 4.3	6.5 ± 3.4
Retinopathy, any	4 (13)	5 (17)	6 (20)	6 (20)
Retinopathy, grading, right				
Grade 0	26 (90)	26 (90)	26 (90)	25 (86)
Grade 1	3 (10)	3 (10)	4 (13)	1 (3)
Grade 2	0 (0)	0 (0)	0 (0)	1 (3)
Grade 3	0 (0)	0 (0)	0 (0)	0 (0)
Grade 4	0 (0)	1 (4)	0 (0)	0 (0)
Retinopathy, grading, left				
Grade 0	28 (93)	25 (83)	24 (80)	26 (87)
Grade 1	2 (7)	4 (13)	6 (20)	1 (3)
Grade 2	0 (0)	0 (0)	0 (0)	1 (3)
Grade 3	0 (0)	0 (0)	0 (0)	0 (0)
Grade 4	0 (0)	1 (4)	0 (0)	0 (0)
Visual acuity, dxt. (ETDRS)	90 (84–93)	86 (83–90)	89 (85–91)	89 (85–90)
Visual acuity, sin. (ETDRS)	88 (85–90)	86 (84–90)	86 (84–90)	86 (85–90)
Intraocular pressure, dxt. (mm Hg)	15.5 ± 3.2	14.2 ± 3.2	16.2 ± 3.3	13.8 ± 2.1
Intraocular pressure, sin. (mm Hg)	15.6 ± 3.0	14.6 ± 3.5	16.5 ± 2.9	13.8 ± 2.5
Medication				
Metformin	26 (87)	27 (90)	26 (87)	29 (97)
Insulin therapy	7 (23)	7 (23)	9 (30)	3 (10)
Renin-angiotensin-aldosterone system blocker	25 (83)	24 (80)	23 (77)	27 (90)
Calcium antagonist	16 (53)	14 (47)	12 (40)	13 (43)
β blocker	8 (27)	16 (53)	10 (33)	13 (43)
Thiazide/loop diuretics	9 (30)	13 (43)	13 (43)	7 (23)

Values are shown as mean (SD), median (IQR) or n (%).
Classification of diabetic retinopathy according to international guidelines: Grade 0: None, Grade 1: mild non-proliferative diabetic retinopathy (microaneurysms and/or dot haemorrhages only), Grade 2: moderate non-proliferative diabetic retinopathy (more than microaneurysms and/or dot haemorrhages but less than grade 3), Grade 3: severe non-proliferative diabetic retinopathy (>20 intraretinal haemorrhages in each of 4 quadrants or definite venous beading in at least 2 quadrants or prominent intraretinal vascular abnormalities in at least 1 quadrant and no proliferative diabetic retinopathy), Grade 4: proliferative diabetic retinopathy (neovascularization (active or treated by pan-retinal photocoagulation) or vitreous/preretinal haemorrhage).
History of cardiovascular disease includes at least one of the following: Single or multivessel or symptomatic coronary artery disease, acute myocardial infarction, coronary artery bypass grafting, stroke, transient ischemic attack, peripheral artery disease, prior coronary carotid, or peripheral revascularization, >50 % stenosis on coronary, carotid or lower arteries, chronic heart failure (New York Heart Association class II or III).

treatment per se potentially could have glucose-independent adverse effects on the retina remained unclarified after the SUSTAIN-6 trial. Diabetic retinopathy has been associated with increased retinal venular oxygenation.[8,18] We used the Oxymap T1 to test the hypothesis that semaglutide might increase retinal oxygenation in the venules. This method has shown good reproducibility.[19–22] However, semaglutide did not alter retinal oxygenation in neither arterioles nor venules.

Diabetic macular oedema is a consequence of vascular damage. It can develop in all stages of diabetic retinopathy and is defined by hard exudates in the presence of microaneurysm and blot haemorrhages.[23] Retinal thickening is observed in more severe diabetic macular oedema and can be quantified using ocular coherence tomography.[24] Central retinal thickness quantifies the thickness of retina in a central circle of 1 mm according to the early treatment in diabetes (ETDRS) grid.[25] At baseline, central retinal thickness values in our trial ranged between 235 and 382 μm with a mean of 285 μm ± 24 and no clinical signs of diabetic macular oedema. The variation in central retinal thickness between the groups were small, Table 1. A study in 122 people with diabetes and no or mild retinopathy, reported normative data on central retinal thickness to range between 213 and 346 μm with a mean of 270 μm ± 24,[26] and thus our data are in line with this.

A prospective study in a similar population regarded a 50 μm change to be indices for clinically relevant macular thickening,[27] which is twelve times the increase we found.

Klefter et al observed an increased central retinal thickness (1.5 %) during 1 year of treatment with an insulin pump in 31 people with type 1 diabetes who had no clinical signs of macular oedema at baseline.[28] A larger HbA1c reduction was seen in the insulin pump treated group as compared to regular insulin users. The authors speculate, that the increase in central retinal thickness in the insulin pump group could be due to improvements in glycaemia. We observed a very small increase in central retinal thickness in the semaglutide group. When we adjusted for HbA1c, the increase in central retinal thickness was attenuated. We therefore speculate, that alterations in central retinal thickness in our trial are associated with HbA1c changes. This suggests that the effect of semaglutide on central retinal thickness is at least in part carried by its glucose lowering effects. The participants in SUSTAIN-6, who experienced retinopathy complications had higher grades of diabetic

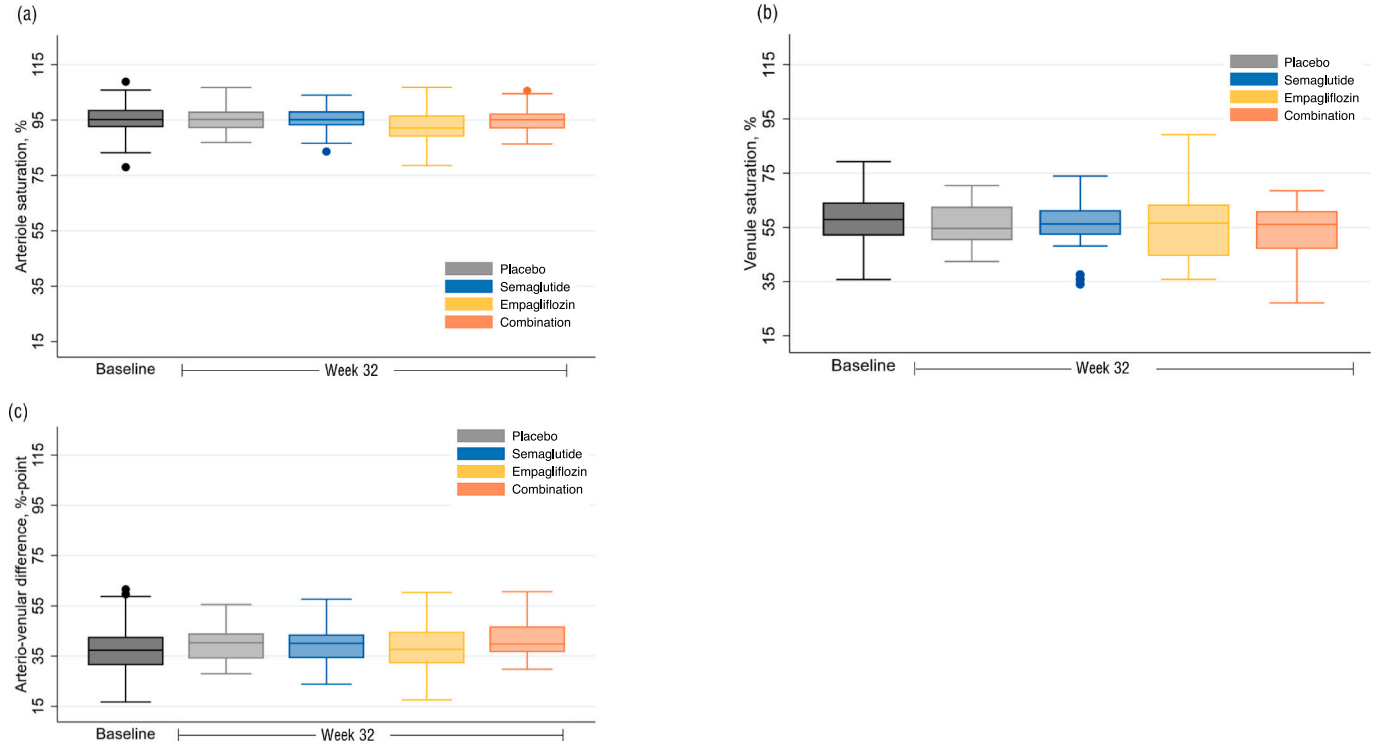

Fig. 1. Saturation (%) in arteriole (a), venule (b), arterio-venular difference (c).
Shown are boxplots with median and IQR. Whiskers present (Q1 − 1.5 * IQR) and (Q3 + 1.5 * IQR) respectively. Baseline data are presented for the total study population. Placebo, semaglutide, empagliflozin and combination are presented as week 32. There was no statistically significant difference in saturation in neither crude nor adjusted analysis between the active treatment groups and placebo in neither arteriole or venule or the arterio-venular difference.

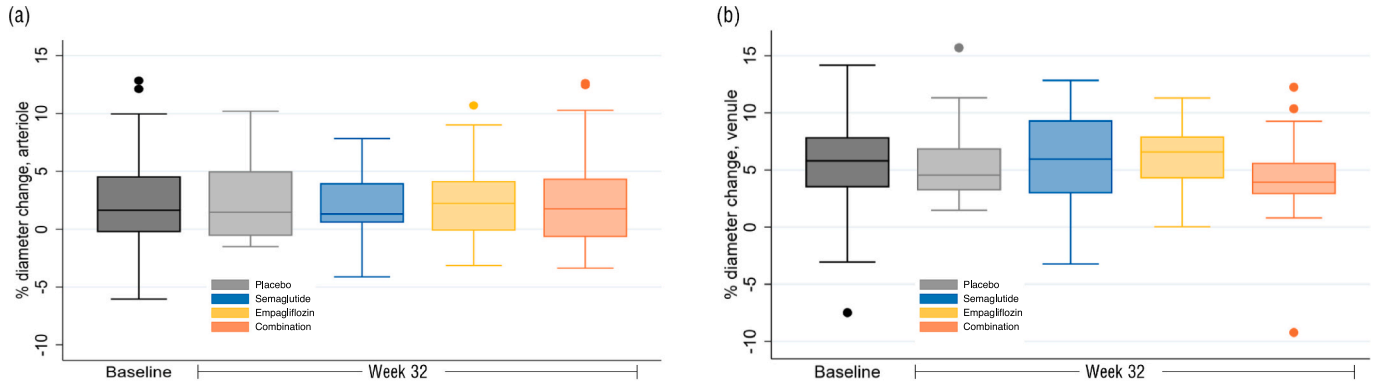

Fig. 2. Change (%) in diameter during flicker in the arteriole (a) and the venule (b).
Shown are boxplots with median and IQR. Whiskers present (Q1 − 1.5 * IQR) and (Q3 + 1 * IQR) respectively.
Baseline data are presented for the total study population. Placebo, semaglutide, empagliflozin and combination are presented as week 32. There was no statistically significant difference in diameter change in neither crude nor adjusted analysis between the active treatment groups and placebo in neither arteriole or venule.

retinopathy at baseline as compared to the entire study population who did not experience any complications. The increased risk of retinopathy observed in SUSTAIN-6 could be due to the magnitude of and rapid improvements in glucose as previously suggested[17] rather than glucose-independent effects of semaglutide on the retina per se. The ongoing FOCUS trial (NCT03811561) will shed more light on this.

4.2. *Effects of empagliflozin*

Retinal hypoxia contributes to the complex pathophysiology of diabetic retinopathy.[29] Ultimately, this drives the formation of vascular endothelial growth factor and, thus, angiogenesis. It has previously been shown that diabetes increases retinal arteriolar and venular oxygenation, probably because of morphological changes, increased arterio-venous shunting, and increased oxygen affinity of haemoglobin.[8,18,30,31] We found no significant change in oxygenation in the arterioles, venules or the dAV in the empagliflozin group. Furthermore, we did not see any changes in central retinal thickness in the empagliflozin group.

A meta-analysis on the effect of SGLT-2i's on ocular events in large, clinical outcome trials[6] found no difference in the risk ratio (0.98 [95 % CI 0.84, 1.16]) as compared to placebo, indicating little or no effect of SGLT-2i's in relation to ocular disease progression. Our data support, that empagliflozin does not influence retinal oxygenation, vascular autoregulation, or central retinal thickness.

Several studies have shown diminished response to flickering light in

Table 2
Central retinal thickness.

Treatment group versus baseline	Baseline	Crude model		Adjusted for HbA1c		Adjusted for office systolic blood pressure		Adjusted for BMI	
		Week 32	p	Week 32	p	Week 32	p	Week 32	p
Placebo	285.5 (281.3,289.7)	−0.77 (−2.9,1.3)	0.475	−0.73 (−2.9,1.4)	0.499	−0.9 (−3.0,1.2)	0.393	−0.7 (−2.8,1.4)	0.519
Semaglutide	285.5 (281.3,289.7)	3.07 (1.1,5.0)	0.002*	1.0 (−1.00,3.0)	0.333	2.9 (0.9,4.9)	0.003*	3.2 (1.2,5.1)	0.002*
Empagliflozin	285.5 (281.3,289.7)	−0.38 (−2.5,1.7)	0.726	−0.7 (−2.9,1.4)	0.542	−0.3 (−2.4,1.8)	0.756	−0.29 (−2.5,1.9)	0.793
Combination	285.5 (281.3,289.7)	0.22 (−1.9,2.4)	0.840	−2.3 (−4.7,0.09)	0.06	−0.3 (−2.5,1.8)	0.776	0.52 (−1.7,2.8)	0.654
Active treatment versus placebo									
Semaglutide	N/A	3.8 (0.9,6.7)	0.009*	1.7 (−1.2,4.7)	0.247	3.9 (0.99,6.7)	0.008*	3.9 (0.9,6.8)	0.008*
Empagliflozin	N/A	0.39 (−2.6,3.4)	0.799	0.06 (−2.9,3.1)	0.967	0.6 (−2.3,3.6)	0.695	0.4 (−2.6,3.4)	0.790
Combination	N/A	1.0 (−2.0,4.0)	0.516	−1.6 (−4.7,1.6)	0.337	0.6 (−2.4,3.6)	0.690	1.2 (−1.8,4.3)	0.434

Change (μm) in central retinal thickness. Values are shown as estimated marginal means (95 % CI) or estimated marginal mean difference (95 % CI) as appropriate. Baseline estimate is shown as a common estimate from the linear mixed model. Values marked with * are considered statistically significant.

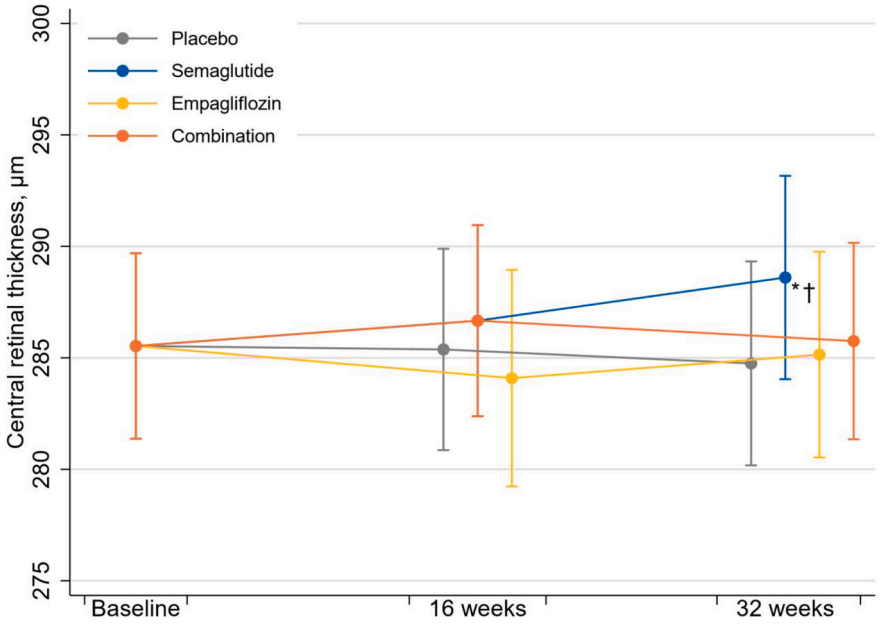

Fig. 3. Central retinal thickness (μm). Estimated marginal means (margins 95 %CI). *p = 0.009 vs placebo, †p = 0.002 vs baseline.

people with diabetes.[32–35] However, our data do not indicate that treatment with semaglutide or empagliflozin alters this.

4.3. Strengths and limitations

Our trial has both strengths and limitations. It is the first randomised, clinical trial to investigate the retinal vascular effects of semaglutide and empagliflozin in a population with type 2 diabetes and manifest or high risk of CVD. Moreover, we had few missing datapoints, which strengthens our estimates. Most of the participants did not have diabetic retinopathy and are therefore potentially different to those who are susceptible to worsening retinopathy, which complicates the generalisability.

The study was not powered to detect differences in the retinal outcomes and these findings must therefore be considered exploratory. Furthermore, our follow-up time was only 32 weeks, and our ophthalmological tests may not have captured all the possible events described in the SUSTAIN-6 trial. Our data indicates, that there are no alterations in retinal oxygenation or retinal vessel diameter due to treatment with semaglutide, empagliflozin or the combination. We do not consider the observed small increase in central retinal thickness in the semaglutide group (which was attenuated when adjusting for HbA1c) to be clinically relevant. However, this finding needs additional evaluation in studies including patients with more advanced retinopathy.

5. Conclusion in summary

In conclusion, neither empagliflozin, semaglutide nor the combination altered retinal oxygenation or vascular diameter. A small increase in central retinal thickness was seen in the semaglutide group; however, this was attenuated when adjusting for HbA1c.

Disclosures

S.G. and L.V. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

CRediT authorship contribution statement

Søren Gullaksen: Investigation, Formal analysis, Writing – original draft, Writing – review & editing, Supervision, Project administration.

Liv Vernstrøm: Investigation, Supervision, Project administration, Writing – review & editing. **Steffen Skovgaard Sørensen:** Investigation, Writing – review & editing. **Kristian Løkke Funck:** Conceptualization, Methodology, Writing – review & editing. **Line Petersen:** Investigation, Writing – review & editing. **Toke Bek:** Investigation, Writing – review & editing. **Per Løgstrup Poulsen:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition. **Esben Laugesen:** Conceptualization, Methodology, Writing – review & editing, Funding acquisition.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jdiacomp.2023.108472.

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