Waist-height ratio and the risk of severe diabetic eye disease in type 1 diabetes: a 15-year cohort study

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Disclosure summary: EBP reports receiving lecture honorariums from Eli Lilly, Abbott, AstraZeneca, Sanofi, Boehringer Ingelheim and is an advisory board member of Sanofi. P-H.G. reports receiving lecture honorariums from Astellas, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Medscape, MSD, Mundipharma, Novo Nordisk, PeerVoice, Sanofi, Sciarc and being an advisory board member of Astellas, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Medscape, MSD, Mundipharma, Novo Nordisk, and Sanofi. No other potential conflicts of interest relevant to this article were reported. VH and CF report no conflict of interest.
Abstract

Context: Obesity prevalence has increased in type 1 diabetes (T1D). However, the relationship between body composition and severe diabetic eye disease (SDED) is unknown.

Objective: To investigate the associations between body composition and SDED in adults with T1D.

Methods: From 5401 adults with T1D in the Finnish Diabetic Nephropathy Study, we assessed 3468, and 437 underwent dual-energy X-ray-absorptiometry for body composition analysis. The composite outcome was SDED, defined as proliferative retinopathy, laser treatment, anti-VEGF treatment, diabetic maculopathy, vitreous hemorrhage, and vitrectomy. Logistic regression analysis evaluated the associations between body composition and SDED. Multivariable Cox regression analysis assessed the associations between the anthropometric measures and SDED. Subgroup analysis was performed by stages of albuminuria. The relevance ranking of each variable was based on the z statistic.

Results: During a median follow-up of 14.5 (IQR 7.8-17.5) years, 886 SDED events occurred. Visceral/android fat ratio was associated with SDED (OR 1.40, z=3.13), as well as the percentages of visceral (OR 1.80, z=2.45) and android fat (OR 1.28, z=2.08), but not the total body fat percentage. Waist-height ratio showed the strongest association with the SDED risk (HR=1.28, z= 3.73), followed by the waist (HR 1.01, z=3.03), body mass index (HR 1.03,
z=2.33), and waist-hip ratio (HR 1.15, z=2.22). The results were similar in normo- and microalbuminuria, but not significant in macroalbuminuria. A WHtR ≥ 0.5 increased the SDED risk by 28% at the normo- and microalbuminuria stages.

**Conclusions:** WHtR, a hallmark of central obesity, is associated with SDED in individuals with type 1 diabetes.

**Keywords:** retinopathy, type 1 diabetes, body composition, waist-height ratio, nephropathy
Introduction

Diabetic retinopathy (DR) is a common microvascular complication of diabetes, which may progress to severe stages and even to blindness. It is the fifth most common cause of blindness and visual impairment worldwide (1). From 1990 to 2015, the crude global prevalence of each cause of blindness and visual impairment decreased, except for DR, which increased (1). Given that the incidence of type 1 diabetes increases by 4.2% annually also among young adults (2), it is possible in the future, there will be an even higher number of individuals who have to cope with type 1 diabetes.

The knowledge of modifiable risk factors, early diagnosis, and treatment are crucial to avoid the progression and the burden of DR. Although there are well-known risk factors for severe diabetic eye disease (SDED) in individuals with type 1 diabetes (3–5), it is still unknown whether central obesity is related to SDED in those individuals. A few cross-sectional studies have been conducted in individuals with type 1 diabetes to assess the relationship between body mass index (BMI) and DR, but the results are controversial (6,7). Furthermore, BMI may not reflect central obesity (8,9), which has been considered a risk factor for DR in individuals with type 2 diabetes (10,11).

Considering that the prevalence of obesity has increased in type 1 diabetes along with the last decades (12), it is important to understand whether the fat distribution, especially the visceral fat, is a risk factor for SDED in this population. Thus, this study aimed to explore the associations between body composition and SDED in adults with type 1 diabetes.
Materials and methods

Study design

This study included two different analyses. First, an observational prospective study was conducted to investigate the impact of anthropometric measures related to central obesity (waist-height ratio (WHtR), waist-hip ratio (WHR), and waist circumference (WC)) and BMI as a measure of general obesity on the risk of SDED in a large cohort of adults with type 1 diabetes.

Second, a cross-sectional analysis was performed to investigate the association between body composition and the prevalence of any retinopathy except SDED or SDED. Furthermore, a similar cross-sectional analysis was performed to evaluate the association between WHtR (representing central obesity) and the Early Treatment of Diabetic Retinopathy Study (ETDRS) grading(13).

Study population

The Finnish Diabetic Nephropathy (FinnDiane) Study is a nationwide, prospective, multicenter (93 centers across Finland) study since 1997, that aims to identify risk factors for type 1 diabetes complications and recruitment of new participants is still ongoing.

For the longitudinal analysis, from a total of 5401 individuals with type 1 diabetes in the FinnDiane cohort, 1933 individuals were excluded due to SDED at baseline. Thus, we assessed 3468 individuals for the occurrence of SDED. Then, since no anthropometric was associated with SDED in the macroalbuminuria stage, we limited the analyses to 3146 individuals with normo- and microalbuminuria from which 437 had their body composition evaluated by dual-energy-X-ray-absorptiometry (DXA), that was included in the regular
FinnDiane study visit since 2011. Among all FinnDiane participants, we have 1319 individuals with ETDRS grading at baseline visit. Then, after excluding 551 individuals with SDED at baseline, we included 768 individuals in a sensitivity longitudinal analysis for the association between WHtR and SDED. The baseline visit occurred between the years 1997 and 2017 during which the participants underwent a thorough clinical examination, blood and urine samples were collected and several questionnaires were completed by the participants. The same procedures were repeated at each follow-up visit. Type 1 diabetes was defined as age at onset of diabetes under 40 years and permanent insulin treatment initiated within a year from the diabetes diagnosis. The study protocol followed the principles of the Declaration of Helsinki as revised in 2000 and was approved by the Ethical Committee of Helsinki and Uusimaa Hospital District. Written informed consents were obtained from each FinnDiane participant, but it was not appropriate or possible to involve patients or the public in the design, or conduct, or reporting, or dissemination plans of our research.

Diabetic nephropathy (DN) stages

DN stage was based on the individuals’ urinary albumin excretion rate (UAER) in timed overnight or 24h urine (mg/24h) collections. Normoalbuminuria was defined as a UAER < 20µg/min or < 30 mg/24h in at least two out of three consecutive urine samples. Microalbuminuria was defined as UAER ≥ 20 and < 200µg/min or ≥ 30 and < 300 mg/24h and macroalbuminuria as UAER ≥ 200µg/min or ≥ 300 mg/24h.
Diabetic Retinopathy

The composite outcome was SDED, defined as proliferative diabetic retinopathy (PDR), the initiation of laser treatment or anti-vascular endothelial growth factor (anti-VEGF), diabetic maculopathy, vitreous hemorrhage and vitrectomy identified from the Care Register for Health Care until the end of 2017, whatever comes first. The diabetic retinopathy classification at baseline was based on the FinnDiane questionnaire in which the participant as well as the attending physician answered the question of whether the participant had or did not have previous diabetic retinopathy and/or had undergone laser treatment for diabetic eye disease. Furthermore, this information was later double-checked by a physician from the FinnDiane Study Group by reviewing the patient files for all potential information on retinal screening and ophthalmology consultations. Thus, participants were categorized into no retinopathy, any retinopathy except SDED and SDED. In a subset of participants, ETDRS grading data were available for further sensitivity analysis and they were classified at baseline according to the ETDRS grading as no retinopathy (ETDRS 10), mild non-proliferative diabetic retinopathy (NPDR)(ETDRS 20 and 35), moderate NPDR (ETDRS 43 and 47), severe NPDR (ETDRS 53) and PDR (ETDRS 61-85)(13).

Body composition and anthropometric measurements

Body composition was assessed by DXA (GE Healthcare Lunar version 16, Wisconsin, USA) according to the manufacturer’s instructions and visceral fat was measured by the CoreScan software (14) during the years 2015 to 2019 as part of the routine FinnDiane visits. The fat and lean mass were adjusted for the total body weight and are presented as percentages such as body fat mass percentage, android fat mass percentage, visceral fat mass percentage, body lean mass percentage, and appendicular lean mass percentage. The term
appendicular lean mass refers to the lean mass of both legs and arms. BMI was calculated as total body weight (kilograms) divided by the square of the height (meters). WC was measured in centimeters by a stretch-resistant tape at the horizontal plane midway between the superior iliac crest and the lower margin of the lowest rib. The hip circumference was measured with the same tape around the widest part over the great trochanters and WHR and was calculated by dividing the WC by the hip circumference. The WHtR was calculated by dividing the WC by the height and values < 0.5 were considered normal for both sexes (15).

**Statistical analyses**

Data on categorical variables are presented as frequencies, continuous variables as means (± standard deviation, SD) for normally distributed values and otherwise as medians (interquartile range, IQR). Between-group comparisons were performed with the χ² test for categorical variables, with ANOVA for normally distributed continuous variables and with Mann-Whitney or Kruskal-Wallis test for non-normally distributed continuous variables.

After excluding the individuals with SDED at baseline, a multivariable Cox regression analysis was used to assess the association between the anthropometric measures and the risk of SDED adjusted for baseline covariates such as age at onset of diabetes, duration of diabetes, sex, glycated hemoglobin A1c (HbA1c), systolic blood pressure (SBP), triglycerides, smoking, lipid-lowering medication, any retinopathy except SDED, estimated glomerular filtration rate (eGFR) and DN stages. Then, in a subset of 768 participants, a sensitivity analysis for the association between WHtR and the risk of SDED was performed using a similar model but replacing the covariate any retinopathy except SDED at baseline with ETDRS grading at baseline. Follow-up time was counted from the baseline visit until one of the components of
SDED occurred, death or until the end of 2017. First analyses were done in the pooled population. However, the interaction terms between the DN stage, all anthropometric measures and SDED were significant, indicating that the effect on the risk of SDED was depending on the DN stage. Therefore, further analyses were performed separately according to DN stages. Since in the subgroup analyses by DN stages, no anthropometric measure was associated with the risk of SDED at the macroalbuminuria stage, we used a final model which comprised of the pooled group of individuals with normo- and microalbuminuria. The relevance ranking of each variable was based on z statistics (3). Given that WHtR was the anthropometric measure most strongly associated with the risk of SDED, we performed a score ranking of WHtR and the other risk factors (HbA1c, age at onset of diabetes, duration of diabetes, triglycerides, systolic blood pressure, smoking, sex, lipid-lowering medication, any retinopathy except SDED, eGFR and DN stages) using z statistics.

Since the interactions between sex and the anthropometric measurements or body composition variables were not significant, the analyses were conducted by pooling men and women together.

Finally, we used the %FINDCUT SAS macro tool to identify an optimal cutoff point for the WHtR to classify individuals at high risk versus low risk of SDED (16). After the establishment of the cutoff value, two groups were created and the risk of SDED was compared between the groups.

In the cross-sectional analysis, a multinominal logistic regression model was used to evaluate the associations between body composition, any retinopathy except SDED or SDED, taking the no retinopathy as the reference group. The model was adjusted for HbA1c, SBP, triglycerides, smoking, lipid-lowering medication, eGFR and DN stages. The same model
was used in the cross-sectional analysis to evaluate the association between WHtR and baseline ETDRS grading.

All analyses were performed with the Statistical Analysis System version 9.4 (SAS Institute, Cary, NC, USA).

Results

Association between anthropometric measures and SDED

In the longitudinal dataset including all 3468 individuals with type 1 diabetes, the median age was 34.8 (IQR 25.7-45.1) years 51.2% were female and the median duration of diabetes was 15.3 (8.2-23.4) years. During a median follow-up of 14.5 (7.8-17.5) years, 886 incident cases of SDED occurred, giving an incidence rate of 25.6%. The baseline characteristics of all individuals according to the incidence of SDED are depicted in Table 1.

In the analysis including all individuals, the WHtR was the anthropometric measure strongest associated with the risk of SDED (HR=1.28 for 0.1 increase, z= 3.73), followed by WC (HR 1.01 for 1 cm increase, z=3.03), BMI (HR per 1kg/m2 increase 1.03, z=2.33) and WHR (HR 1.15 for 0.1 increase, z=2.22) (Table 2). In the subgroup analysis by each eye disease outcome, the WHtR was associated with maculopathy (HR 1.48, 95% CI 1.25-1.75, p<0.0001) and PDR (HR 1.22, 95% CI 1.02-1.45, p=0.03) with or without laser or anti-VEGF treatment, but not with vitreous hemorrhage (HR 1.14, 95% CI 0.83-1.55, p=0.42) with or without vitrectomy.

In a sensitivity analysis including individuals with EDTRS grading at baseline, using the no retinopathy (ETDRS 10) as the reference group in a multinominal logistic regression model, the WHtR was associated with increased odds of having NPDR (OR 1.91, 95% CI 1.06-3.47,
p=0.03) or PDR (OR 3.24, 95% CI 1.66-6.31, p=0.0006) at baseline. Furthermore, the WHtR was also associated with the risk of SDED after adjusting for all covariates plus baseline ETDRS grading (HR 1.36, 95% CI 1.02-1.83, p=0.039) in a subset of 768 individuals.

In the score ranking of the relevance of SDED risk factors, WHtR appeared in the sixth position (HR 1.25, 95% CI 1.09-1.42, z= 3.25). The top-ranking variable was HbA1c (HR 1.50, 95% CI 1.44-1.56, z=18.09), followed by any retinopathy except SDED at baseline (HR 1.90, 95% CI 1.60-2.25, z=7.41), the presence of albuminuria (HR 1.61, 95% CI 1.35-1.92, z=5.34), age at onset of diabetes (HR 0.99, 95% CI 0.98-0.99, z=-3.60), and triglycerides (HR 1.19, 95% CI 1.11-1.28, z=4.77).

Subgroups by DN stages

In the subgroup analysis by DN stages, WHR was no more associated with SDED in the individuals with normo- and microalbuminuria (Table 2). At the macroalbuminuria stage, no anthropometric measure was associated with SDED.

Thus, after excluding the individuals with macroalbuminuria and unknown stage of albuminuria at baseline, 3146 individuals remained for further analysis, of which 24.3% developed SDED during a median follow-up of 15.0 (IQR 8.4-17.6) years (Table 1). At baseline, the median age was 34.3 (25.3-44.4) years, 51.9% were women and the median duration of diabetes was 14.7 (7.9-22.6) years. Among the individuals with normo- and microalbuminuria, at baseline, 99.6% of those with obesity (BMI > 30kg/m²), 69.1% of those with overweight (BMI ≥ 25kg/m² and < 30kg/m²) and 10.7% of those with normal weight (BMI < 25kg/m²) presented a WHtR ≥ 0.5. Baseline clinical characteristics according to the incidence of SDED in individuals with normo- and microalbuminuria are shown in Table 1.
Among those with normo- and microalbuminuria, the WHtR was the anthropometric measure strongest associated with the risk of SDED (HR 1.32 for 0.1 increase, z= 3.86), followed by WC (HR 1.01 for 1 cm increase, z=3.04) and BMI (HR 1.03 per 1kg/m² increase, z=2.73)(Table 2). The results were similar when individuals with normo- or microalbuminuria were analysed separately. The risk of SDED in the group with normo- and microalbuminuria was 28% higher (HR 1.28, 95% CI 1.08-1.50) in individuals with a WHtR ≥ 0.5 compared to the individuals with a WHtR < 0.5 (Figure 1).

In the score ranking of the relevance of SDED risk factors, at the normo- and microalbuminuria stages, WHtR appeared at the fifth position (HR 1.32, 95% CI 1.15-1.52, z=3.86). HbA1c was again the most important risk factor (HR 1.53, 95% CI 1.46-1.61, z=18.04), followed by any retinopathy except SDED at baseline (HR 2.02, 95% CI 1.68-2.42, z=7.60), triglycerides (HR 1.20, 95% CI 1.11-1.29, z=4.77) and the age at onset of diabetes (HR 0.98, 95% CI 0.97-0.99, z=−4.35).

Association between body composition and SDED

The individuals with SDED presented similar body weight and lean mass (total and appendicular lean mass), notwithstanding that they had a higher percentage of body fat mass, visceral fat mass, android fat mass and a lower percentage of body lean mass and appendicular lean mass compared to those without SDED. Consequently, they had higher ratios of visceral and android fat to appendicular lean mass (Table 3).

The variables of body composition most strongly associated with the presence of SDED were the visceral fat/android fat mass ratio (OR 1.40 per 0.1 increase, z=3.13), followed by the android fat/appendicular lean mass ratio (OR 1.91 per 0.1 increase, z=2.13) and the visceral
fat/appendicular lean mass ratio (OR 1.16 per 0.01 increase, z=2.45) (Table 4). The percentages of visceral and android fat were positively associated with SDED, whereas the percentage of appendicular lean mass was negatively associated with SDED (Table 4). Interestingly, the percentages of the total body fat and the total body lean masses were not associated with SDED (Table 4). Using the “no previous retinopathy” in the FinnDiane questionnaire as the reference group in a multinomial logistic regression model, the visceral fat mass percentage was also associated with any retinopathy except SDED at baseline (OR 1.63, 95% CI 1.03-2.59, p=0.04), however, the total body fat mass percentage was not (OR 1.01, 95% CI 0.97-1.05, p=0.62). The associations between body composition and SDED are shown in Table 4.

**Discussion**

In this study, we showed that a simple measure such as the WHtR is associated with an increased risk of SDED in adults with type 1 diabetes, placing it among the six most important risk factors for SDED in this population. Furthermore, we found that the central body fat distribution is associated with the presence of SDED. We are not aware of any other studies in a large cohort of individuals with type 1 diabetes that have assessed such relationships, especially stratified by different stages of albuminuria.

Obesity is causally related to DN in individuals with type 1 diabetes (17), whilst its relationship with SDED is still unclear. Although studies including individuals with type 2 diabetes have shown that a higher BMI was associated with DR (18,19), a meta-analysis and systematic review revealed that being overweight or obese did not confer an increased risk of DR (20). Possibly, these discrepancies concerning the relationship between BMI and DR in individuals with type 2 diabetes are because BMI does not necessarily reflect the body fat
distribution, especially the central fat, which has been associated with DR in people with type 2 diabetes (10,11). Concerning studies in individuals with type 1 diabetes, the data are even more scarce, and the results are also controversial. Similar to our findings, a Belgian cross-sectional study (6), including 592 participants with type 1 diabetes, and the DCCT/EDIC study (3) have shown that individuals with DR presented with a higher BMI. A cross-sectional Australian study, including 501 adults with type 1 diabetes, found an association between the BMI >30kg/m² and DR (7). However, in the DCCT/EDIC study (3) the authors did not find an association between BMI and the progression of DR. Nevertheless, we have to take into consideration that we are looking at different endpoints. The DCCT/EDIC study evaluated the progression of DR, while the FinnDiane study did not look at each progressive stage of DR, but at the risk of developing a severe stage of diabetic eye disease. The discrepancies also may be explained by the fact that the DCCT/EDIC cohort is better clinically characterized including a greater number of individuals with ETDRS grading than the FinnDiane cohort. Another possible reason may be related to the relationship between body composition and SDED that was not explored in the DCCT/EDIC study. Since we showed that the visceral fat mass percentage but not the total body fat mass percentage is associated with SDED, differences in the body composition between the FinnDiane cohort and DCCT/EDIC cohort may explain different results, despite a similar BMI. In our study, BMI was positively associated with SDED, although it was the third of four anthropometric measures in the ranking of relevance. The weaker association, by z-value, between BMI and SDED compared to the association between WHtR and SDED may be due to the lower power of BMI compared to WHtR to estimate the visceral fat in individuals with T1D, according to previous research of our group (21). Recently, we also showed that although BMI and WHtR are associated with non-alcoholic fatty liver in adults with type 1 diabetes, WHtR shows a
stronger association than BMI (22). The observed differences between BMI and WHtR are even more relevant in clinical practice since, given that in the present dataset, 10.7% of the individuals with normal BMI and 69.1% of the overweight people presented a WHtR ≥ 0.5, which means that several individuals at high risk of SDED would not be recognized if only a BMI ≥ 30kg/m² would be considered as a risk factor.

The central fat, estimated by WHR, has been associated with DR in a few studies including individuals with type 2 diabetes (10,11). However, in the present study, it was the last of four anthropometric measures in the ranking of relevance and, beyond that, WHR was not associated with SDED in the subgroup analysis according to DN stages. To understand the disagreement with the literature, it is important to recognize that the present study included individuals with type 1 diabetes, which differs from those with type 2 diabetes in many aspects, furthermore, the WHR was not an estimator of visceral fat as good as the WHtR according to our previous research (21). In other words, it seems that visceral fat is the main factor for SDED, therefore, the stronger association between the anthropometric measure and the visceral fat, the better predictor.

In the present study, we showed for the first time that the percentage of visceral fat mass is closely associated with SDED in individuals with type 1 diabetes and that the ratio of visceral to android fat shows an even stronger association. This result emphasizes the greater relevance of the visceral fat for the risk of SDED compared to the android fat, which includes the visceral and subcutaneous fat located at the android region. Furthermore, the associations between SDED and the ratios of visceral and android fat to appendicular lean mass demonstrate the importance of having a balance in the body composition concerning lean mass to central fat mass, since the functional muscle tissue improves insulin sensitivity
whereas visceral fat increases insulin resistance. The mechanism involved in the relationship between visceral fat and SDED is still unknown, albeit some hypotheses can be suggested. Adipocytes from visceral fat produce plasminogen activator inhibitor type 1 (PAI-1) (23), which has been associated with end-stage proliferative DR in individuals with type 2 diabetes (24). Visceral fat also produces TNF-α (25), which has been associated with DR in individuals with type 1 diabetes (26), beyond leading to an inflammatory and insulin-resistant state (27), thus contributing to the increase in blood glucose and triglycerides, two relevant risk factors for SDED. Since insulin resistance has also been associated with low skeletal muscle mass (28), which has been associated with DR in type 2 diabetes (29), it may explain the negative association between SDED and the appendicular lean mass percentage, as well as the positive association between SDED and the ratios of central fat to appendicular lean mass in our study. Another possible link between SDED and visceral fat is the positive association between visceral fat and VEGF (30), which is involved in the pathogenesis of DR (31).

Another novelty of the present study was to show the contribution of WHtR alongside the well-known risk factors for SDED. Similarly to the results from the DCCT/EDIC study (3), we showed that the HbA1c is the most important risk factor for SDED in our cohort. However, we also found that central obesity, represented by WHtR, is another important risk factor. It is of note that the association between WHtR and the risk of SDED remained after adjusting for ETDRS grading in a subset of individuals.

In this study, no anthropometric measure was associated with the risk of SDED in individuals with macroalbuminuria. Possibly, the advanced DN stage is such an important risk factor for SDED that overwhelms any other risk factor.
The present study has some limitations. We used the variable “any retinopathy at baseline” to adjust the analysis, but there was no detailed information on the grading of the retinopathy in the questionnaires. Another limitation is that we did not have information on ETDRS grading for all individuals at baseline and during FinnDiane follow-up visits, which hampers any assessment of the impact of body composition and WHtR on the progression of DR, like it was done with BMI in the landmark DCCT/EDIC study. However, we tried to mitigate this limitation by performing a sensitivity analysis that showed the WHtR was still associated with SDED after adjusting for baseline ETDRS grading. Another limitation of the present study is the fact it was conducted in a Caucasian-Finnish population with type 1 diabetes, therefore we cannot exclude whether ethnicity may have an impact on the results, since the waist threshold may differ according to ethnicity. On the other side, the WHtR threshold of 0.5 we found in our cohort for the risk of SDED was the same well-known WHtR threshold for cardiovascular risk and mortality (15,32) in the general population. Thus, our findings may motivate further studies to investigate the mechanisms involved in the relationship between visceral fat and SDED. This study has several strengths and the main one is the long-term follow up of a large cohort of individuals with type 1 diabetes. Second, the body composition was assessed by DXA, which is the gold standard method. Furthermore, we showed in a large sample of individuals with type 1 diabetes that, WHtR, a simple measure with a unique threshold for both sexes, is associated with the risk of a severe complication of diabetes in the absence and at the early stage of DN. From a clinical perspective, this study not only highlights a new modifiable risk factor for SDED but more importantly, it shows that a simple anthropometric measure related to central obesity is associated with SDED in individuals with type 1 diabetes. Given that WHtR is a modifiable
risk factor, our results reinforce the relevance of treating central obesity beyond blood glucose in individuals with type 1 diabetes.

In conclusion, the central distribution of body fat is associated with SDED and, the WHtR, a hallmark of central obesity, is associated with an increased risk of developing SDED in adults with type 1 diabetes. This study supports the inclusion of WHtR beyond BMI in the routine consultations of individuals with type 1 diabetes.
Acknowledgements

The skilled technical assistance of Anna Sandelin, Mira Korolainen, and Jaana Tuomikangas is gratefully acknowledged. The authors also acknowledge all people from the FinnDiane Study Group and all physicians and nurses at each FinnDiane center participating in patient recruitment and characterization.

Additional Information

Data availability

Restrictions apply to the availability of some or all data generated or analysed during this study to preserve patient confidentiality or because they were used under license. The corresponding author will on request detail the restrictions and any conditions under which access to some data may be provided.

Funding

This research was funded by grants from the Folkhälsan Research Foundation, Academy of Finland (299200 and 316664), Wilhelm and Else Stockmann Foundation, Liv och Hälsa Society, Helsinki University Central Hospital Research Funds (EVO), Novo Nordisk Foundation (NNF OC0013659) and the Finnish Diabetes Research Foundation.

Author’s contributions

EBP and VH were responsible for the study design and contributed equally to the manuscript preparation. VH was responsible for the statistical analysis. EBP, VH and PHG interpreted the results and contributed to writing the manuscript. CF contributed to the acquisition of the data and critical revision of the manuscript. PHG is the guarantor of this
work and takes full responsibility for the integrity of the data and the accuracy of the data analysis. All authors contributed to the final version.

Conflict of interest

EBP reports receiving lecture honorariums from Eli Lilly, Abbott, Astra Zeneca, Sanofi, Boehringer Ingelheim and is an advisory board member of Sanofi. P-H.G. reports receiving lecture honorariums from Astellas, Astra Zeneca, Boehringer Ingelheim, Eli Lilly, Medscape, MSD, Mundipharma, Novo Nordisk, PeerVoice, Sanofi, Sciarc and being an advisory board member of Astellas, Astra Zeneca, Bayer, Boehringer Ingelheim, Eli Lilly, Janssen, Medscape, MSD, Mundipharma, Novo Nordisk, and Sanofi. No other potential conflicts of interest relevant to this article were reported. VH and CF report no conflict of interest.
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Figure legend

Figure 1. Cumulative incidence of severe diabetic eye (SDED) disease in individuals with normo- and microalbuminuria according to the waist-height ratio threshold of 0.5. HR: hazard ratio, WHtR: waist-height ratio.
Table 1. Baseline clinical characteristics according to the incidence of severe diabetic eye disease

|                         | ALL   | SDED (-) | SDED (+) | p-value | Normo- and Microalbuminuria | SDED (-) | SDED (+) | p-value |
|-------------------------|-------|----------|----------|---------|----------------------------|----------|----------|---------|
| n (%)                   | 2582  | 2380     | 886      | 766     | 25.4                        | 53.5     | 46.7     | 0.001   |
| Women (%)               | 52.8  | 53.5     | 46.5     | 46.7    | 53.5                        | 46.7     | 46.7     | 0.001   |
| Age (years)             | 35.4 (26.6-45.8) | 32.4 (23.9-43.5) | 35.1 (26.4-44.9) | 31.4 (23.4-43.2) | 0.0001 |
| Age at onset of diabetes (years) | 18.0 (11.5-27.4) | 14.2 (8.8-24.8) | 18.1 (11.6-27.2) | 14.1 (8.8-25.1) | 0.0001 |
| Duration of diabetes (years) | 14.8 (7.4-23.7) | 15.9 (10.4-22.3) | 14.4 (7.3-23.3) | 15.2 (10.0-21.3) | 0.06   |
| Height (cm)             | 171.5 ± 9.4 | 171.4 ± 9.3 | 0.68 | 171.5 ± 9.4 | 171.5 ± 9.2 | 0.68 |
| Weight (kg)             | 72.3 (63.9-81.3) | 74.5 (64.6-83.0) | 0.01 | 73.2 ± 13.0 | 0.02 |
| BMI (kg/m2)             | 24.5 (22.5-26.6) | 25.0 (22.7-27.6) | 0.0001 | 24.4 (22.5-26.5) | 25.0 (22.5-27.5) | 0.001 |
| WHR                     | 0.85 ± 0.08 | 0.86 ± 0.08 | 0.0001 | 0.85 ± 0.08 | 0.86 ± 0.08 | 0.0001 |
| WHtR                    | 0.48 (0.45-0.52) | 0.49 (0.46-0.54) | 0.0001 | 0.48 (0.45-0.52) | 0.49 (0.46-0.53) | 0.0001 |
| WC (cm)                 | 83.0 (76.0-90.0) | 85.0 (78.0-93.5) | 0.0001 | 83.0 (76.0-90.0) | 85.0 (78.0-93.0) | 0.0001 |
| HbA1c (%)               | 7.9 ± 1.29 | 9.2 ± 1.61 | <0.0001 | 7.93 ± 1.29 | 9.16 ± 1.60 | <0.0001 |
| Systolic blood pressure (mmHg) | 130 ± 16 | 132 ± 16 | <0.0001 | 128 (118-138) | 130 (120-140) | <0.01   |
| Diastolic blood pressure (mmHg) | 78±9 | 80 ± 9 | <0.0001 | 78 (71-84) | 80 (74-86) | <0.0001 |
| Total cholesterol (mmol/L) | 4.74 ± 0.91 | 5.00 ± 0.95 | <0.0001 | 4.65 (4.10-5.24) | 4.90 (4.31-5.55) | <0.0001 |
| HDL-cholesterol (mmol/L) | 1.41 ± 0.40 | 1.32 ± 0.38 | <0.0001 | 1.37 (1.14-1.64) | 1.27 (1.07-1.55) | <0.0001 |
| Triglycerides (mmol/L)   | 0.93 (0.70-1.28) | 1.12 (0.85-1.55) | <0.0001 | 0.91 (0.70-1.27) | 1.11 (0.83-1.51) | <0.0001 |
| eGFR (ml/min/1.73 m²)    | 101 (86-114) | 100 (84-115) | 0.28 | 100 ± 19 | 101 ± 20 | 0.21 |
| Diabetic nephropathy stages | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 | <0.0001 |
| Condition                        | Percentage | Mean | SD  | Median | IQR  |
|---------------------------------|------------|------|-----|--------|------|
| Normoalbuminuria                | 85.8       | 70.0 | 93.0| 80.9   |
| Microalbuminuria                | 6.4        | 16.5 | 7.0 | 19.1   |
| Macroalbuminuria                | 2.8        | 8.5  |    | -      |
| Nonclassified                   | 5.0        | 5.1  |    | -      |
| Any retinopathy except SDED (%) | 26.9       | 42.9 | <0.0001 |       |
| Lipid-lowering medication (%)   | 8.4        | 7.9  | 0.16| 7.7    | 6.3  |
| Smoking history (yes)           | 42.6       | 50.4 | <0.001| 41.8  | 48.9 | <0.001|

Data on categorical variables are presented as frequencies, continuous variables as means (± standard deviation, SD) for normally distributed values and otherwise as medians (interquartile range, IQR). Between-group comparisons were performed with χ² test, t-test and Mann-Whitney test, respectively. BMI: body mass index, WHR: waist-hip ratio, WHtR: waist-height ratio, WC: waist circumference, HbA1c: glycated hemoglobin, HDL: high-density lipoprotein, eGFR: estimated glomerular filtration rate, SDED: severe diabetic eye disease.
Table 2. Association between anthropometric measures and the risk of severe diabetic eye disease according to stages of diabetic nephropathy

|                        | HR (95% CI)       | z-value | p-value |
|------------------------|-------------------|---------|---------|
| All individuals n=3468 |                   |         |         |
| WHtR (per 0.1)         | 1.28 (1.13-1.47)  | 3.7337  | 0.0002  |
| WC (per 1 cm)          | 1.01 (1.00-1.02)  | 3.0310  | 0.002   |
| BMI (per 1 kg/m²)      | 1.03 (1.00-1.05)  | 2.3267  | 0.020   |
| WHR (per 0.1)          | 1.15 (1.02-1.29)  | 2.2210  | 0.026   |
| Normo- and microalbuminuria n=3146 |       |         |         |
| WHtR (per 0.1)         | 1.32 (1.15-1.52)  | 3.8562  | 0.0001  |
| WC (per 1 cm)          | 1.01 (1.00-1.02)  | 3.0360  | 0.002   |
| BMI (per 1 kg/m²)      | 1.03 (1.01-1.06)  | 2.7325  | 0.006   |
| WHR (per 0.1)          | 1.13 (1.00-1.29)  | 1.8892  | 0.059   |

Multivariable Cox regression model was adjusted for age at onset of diabetes, duration of diabetes, sex, glycated hemoglobin A1c, systolic blood pressure, triglycerides, smoking, lipid-lowering medication, any retinopathy except SDED, and estimated glomerular filtration rate. DN stage was also included as a covariate in the Cox regression model with ALL individuals. CI: confidence interval. WHtR: waist-height ratio, WC: waist circumference, BMI: body mass index, WHR: waist-hip ratio.
Table 3. Body composition according to the prevalence of severe diabetic eye disease

|                          | SDED (-)         | SDED (+)        | p-value |
|--------------------------|------------------|-----------------|---------|
|                          | 293 (67)         | 144 (33)        |         |
| Total body weight (kg)   | 74.4 (64.5-86.8) | 77.5 (67.1-85.8)| 0.34    |
| Total body fat mass (kg) | 23.3 (17.4-29.1) | 26.1 (19.2-33.4)| 0.02    |
| Total body fat mass (%)  | 31.1 (25.8-36.4) | 34.1 (27.6-40.8)| <0.01   |
| Android fat mass (kg)    | 1.79 (1.13-2.72) | 2.24 (1.48-3.29)| <0.01   |
| Android fat mass (%)     | 2.40 (1.70-3.30) | 3.00 (2.00-3.90)| <0.001  |
| Visceral fat mass (kg)   | 0.45 (0.18-1.02) | 0.69 (0.40-1.50)| <0.0001 |
| Visceral fat mass (%)    | 0.62 (0.26-1.23) | 0.93 (0.55-1.73)| <0.0001 |
| Total body lean mass (kg)| 47.0 (41.4-56.5) | 45.7 (42.0-54.3)| 0.52    |
| Total body lean mass (%) | 65.2 (60.3-70.3) | 62.8 (55.8-68.5)| 0.01    |
| Appendicular lean mass (kg)| 20.8 (17.9-25.8) | 20.0 (18.0-24.3)| 0.24    |
| Appendicular lean mass (%)| 28.9 (26.1-31.6) | 26.8 (24.4-30.4)| <0.001  |
| Visceral fat/android fat mass ratio | 0.29 (0.14-0.42) | 0.36 (0.24-0.49)| <0.0001 |
| Visceral fat/appendicular lean mass | 0.02 (0.01-0.05) | 0.04 (0.02-0.07)| <0.0001 |
| Android fat/appendicular lean mass | 0.08 (0.06-0.12) | 0.11 (0.07-0.15)| <0.0001 |

Data are presented as medians (interquartile range, IQR). Between-group comparisons were performed with Mann-Whitney test. SDED: severe diabetic eye disease.
Table 4. Associations between body composition and the prevalence of severe diabetic eye disease

| Body composition                                      | OR (95%CI)   | z-value | p-value |
|--------------------------------------------------------|--------------|---------|---------|
| Visceral fat/android fat mass ratio (per 0.1)           | 1.40 (1.13-1.73) | 3.1287  | 0.002   |
| Android fat/appendicular lean mass ratio (per 0.1)      | 1.91 (1.05-3.47) | 2.1328  | 0.03    |
| Visceral fat/appendicular lean mass ratio (per 0.01)    | 1.16 (1.03-1.31) | 2.4478  | 0.01    |
| Visceral fat mass percentage (per 1%)                   | 1.80 (1.12-2.88) | 2.4466  | 0.04    |
| Android fat mass percentage (per 1%)                    | 1.28 (1.03-1.59) | 2.0813  | 0.03    |
| Appendicular lean mass percentage (per 1%)              | 0.93 (0.84-1.02) | -1.5030 | 0.13    |
| Total body lean mass percentage (per 1%)                | 0.97 (0.93-1.01) | -1.3088 | 0.19    |
| Total body fat mass percentage (per 1%)                 | 1.03 (0.99-1.07) | 1.3010  | 0.19    |

The logistic regression model was adjusted for age at onset of diabetes, duration of diabetes, sex, glycated hemoglobin A1c, systolic blood pressure, triglycerides, smoking, lipid-lowering medication, estimated glomerular filtration rate and DN stage. OR: odds ratio. CI: confidence interval. Appendicular means both arms and legs. The percentage of body fat and lean mass are related to total body weight.
Figure 1

Cumulative incidence of SDED (%)