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# The relationship between FGF23 and body composition according to albuminuria stage in type 1 diabetes

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ABSTRACT

*Aims:* Fibroblast growth factor 23 (FGF23) and obesity are linked to kidney disease. However, the relationship between FGF23 and body composition is unclear. Associations between FGF23 and body composition were investigated in type 1 diabetes from the Finnish Diabetic Nephropathy Study according to albuminuria stages.
*Methods:* Data were available from 306 adults with type 1 diabetes (229 normal albumin excretion rate, $T1D^{normo}$; 38 microalbuminuria, $T1D^{micro}$; 39 macroalbuminuria, $T1D^{macro}$), and 36 controls. Serum FGF23 was measured by ELISA. Body composition was assessed with dual-energy X-ray absorptiometry. Associations between body composition and serum FGF23 were investigated using linear regression models.
*Results:* Compared with $T1D^{normo}$, individuals with more advanced kidney disease were older, had longer diabetes duration, higher serum hsCRP, and higher FGF23 concentration. However, FGF23 concentration was comparable between $T1D^{normo}$ and controls. Adjusted for potential confounders, in $T1D^{micro}$, FGF23 was positively associated with the percentages of total fat, visceral fat, and android fat tissues, while negative associations between FGF23 and lean tissue were observed. FGF23 was not associated with body composition in $T1D^{normo}$, $T1D^{macro}$, and controls.
*Conclusions:* In type 1 diabetes, the relationship between FGF23 and body composition is dependent on albuminuria stages.

## 1. Introduction

Fibroblast growth factor 23 (FGF23), a hormone mainly produced by the osteocytes, plays a crucial role in bone metabolism [1]. While bones and kidneys are well-known target organs for FGF23, receptors for FGF23 are also found in other tissues [2]. However, not much is known about its role in tissues such as fat and muscle. In elderly individuals, high serum concentration of FGF23 is associated with left ventricular hypertrophy [3], while in mice, the use of anti-FGF23 antibodies improves muscle strength [4]. Regarding the fat tissue, FGF23 has been positively associated with central obesity in individuals with human immunodeficiency virus infection [5], in elderly [6], and in individuals without diabetes and with normal kidney function [7]. However, the relationship between FGF23 and muscle or fat tissue is unknown in individuals with type 1 diabetes at different stages of diabetic kidney disease, a prevalent complication of diabetes.

Considering that obesity is causally related to diabetic kidney disease in type 1 diabetes [8], and that visceral fat [9–11] and low lean mass [12–14] are linked to cardiovascular and chronic kidney disease in the general population, it emphasizes the importance to understand the relationship between body composition and FGF23, a potential predictor of chronic kidney disease and overall mortality [15–17]. This study was, therefore, undertaken to explore the associations between FGF23 and body composition in adults with type 1 diabetes stratified by stages of diabetic kidney disease.

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## 2. Material and Methods

### 2.1. Subjects

Study subjects were participants in the Finnish Diabetic Nephropathy (FinnDiane) Study. Included, in the current analyses, were 306 individuals with type 1 diabetes with known concentration of serum intact FGF23, and anthropometric and body composition measurements, as explained in more detail below. Individuals with estimated glomerular filtration rate (eGFR) $< 15$ ml/min/1.73 $m^2$, and those on dialysis or those having received a kidney transplant were excluded. Data were also available from 36 healthy controls. The study protocol was approved by the Ethics Committee of Helsinki and Uusimaa Hospital District. The study was carried out in accordance with the Declaration of Helsinki and its later amendments. Study subjects provided written informed consent prior to participation.

During the FinnDiane Study visit, several measurements were conducted, as previously described [18]. Among others, height and body weight were measured in light clothing. While seated, blood pressure was measured twice after a minimum of a ten-minute rest. The mean of the two measurements was calculated and used in the analyses. Smoking was self-reported. In the current analyses, distinction between current smokers and non-smokers was made. Data on leisure-time physical activity were collected using a validated questionnaire, as previously described [19]. In the analyses, physical activity was entered as a continuous variable, metabolic equivalent of task hours.

### 2.2. Determination of diabetic kidney disease

The stages of diabetic kidney disease, in those with type 1 diabetes, were assessed based on the urinary albumin excretion rate (UAER) in at least two out of three timed 24-h or overnight urine collections. Classification into those with normal UAER ($T1D^{normo}$, UAER $< 20$ μg/min or $< 30$ mg/24 h), microalbuminuria ($T1D^{micro}$, UAER $\geq 20$ and $< 200$ μg/min or $\geq 30$ and $< 300$ mg/24 h), and macroalbuminuria ($T1D^{macro}$, UAER $\geq 200$ μg/min or $\geq 300$ mg/24 h) were made. The eGFR was calculated using the CKD-*EPI* formula [20].

### 2.3. Body composition and anthropometric measures

Body composition was evaluated using dual-energy X-ray absorptiometry (DXA, GE Healthcare Lunar version 16, Wisconsin, USA) according to the manufacturer's instructions. Visceral fat was measured by CoreScan [21]. The percentages of body fat, android fat, visceral fat, total lean tissue, and appendicular lean tissue were calculated dividing respective values by total body weight, multiplied by 100. Appendicular lean tissue refers to the lean tissue of both legs and arms.

Body mass index (BMI) was calculated as total body weight in kilograms divided by the square of the height in meters. Using a stretch-resistant tape measure, waist circumference was measured at the horizontal plane midway of the superior iliac crest and the lower margin of the last rib. Hip circumference was measured around the widest part of the great trochanters. The waist-hip ratio was calculated by dividing the waist circumference by the hip circumference. The waist-height ratio was calculated by dividing the waist circumference by the height.

### 2.4. Biochemical assays

Blood was drawn and $HbA_{1c}$ was determined locally using standardized assays. Serum lipid and lipoprotein concentrations were measured centrally at the research laboratory of Helsinki University Hospital. Serum triglyceride concentration was measured using a Konelab 60i analyser (Thermo Fisher Scientific Inc., Waltham, MA, USA), and serum HDL-cholesterol concentration was measured with an HTS 7000 plus Bio Assay Reader (Perkin Elmer Inc., Waltham, MA, USA). Serum intact FGF23 concentration was measured by ELISA kits (Kainos Laboratories Inc., Japan). Serum high-sensitivity C-reactive protein (hsCRP) concentration was measured by immunoassay (Modular analyzer, Roche Diagnostics, Mannheim Germany).

### 2.5. Statistical analyses

Descriptive data are presented as mean ± standard deviation for continuous parametric variables, median (interquartile range) for continuous non-parametric variables, and percentage for categorical variables. For comparisons involving several groups, we used ANOVA, Kruskal-Wallis test, and Chi-square test, respectively. For comparisons between $T1D^{micro}$ and $T1D^{normo}$, $T1D^{macro}$ and $T1D^{normo}$, and $T1D^{normo}$ and healthy controls we used the independent samples' *t*-test for continuous parametric variables, the Mann-Whitney *U* test for continuous non-parametric variables, and Chi-square test or Fisher exact test when the cells had an expected number below 5 for categorical variables. For the analyses with the healthy controls, we created an age- and sex-matched sample from the population of $T1D^{normo}$ using the case-control matching tool in SPSS. For the associations between FGF23, body composition and anthropometric measures we used linear regression models adjusted for multiple variables such as sex, age, smoking, physical activity, estimated glomerular filtration rate and $HbA_{1c}$. The regression analyses were done separately for each group of albuminuria stage using the same model. A two-tailed *P* value $< 0.05$ was considered statistically significant. All data were analysed using IBM SPSS Statistics for Windows, Version 28.0 (IBM Corp, Armonk, NY, USA).

## 3. Results

### 3.1. $T1D^{normo}$, $T1D^{micro}$, and $T1D^{macro}$

Data were available from 229 $T1D^{normo}$, 38 $T1D^{micro}$, and 39 $T1D^{macro}$. Compared to $T1D^{normo}$, individuals with more advanced diabetic nephropathy were older, had longer diabetes duration, higher serum hsCRP concentration, higher FGF23 concentration, and higher proportion of users of renin-angiotensin-aldosterone system inhibitor (RAASi) (Table 1). Except for the albuminuria stage and eGFR, there were no differences between $T1D^{micro}$ and $T1D^{macro}$ groups (Table S1).

The three groups with different stages of albuminuria had comparable body weights but differed in some anthropometric and body composition variables (Table 1). Indeed, compared to the other groups, individuals with $T1D^{normo}$ had lower abdominal fatness, represented by waist circumference, waist-hip ratio, waist-height ratio, visceral fat mass, visceral fat percentage, visceral fat volume, android fat percentage (Table 1).

In the unadjusted linear regression model, FGF23 was associated with the visceral fat tissue at the microalbuminuria stage, but not at the normo- and macroalbuminuria stages (Fig. 1). Also at the microalbuminuria stage, FGF23 was in the unadjusted model associated with all anthropometric measures related to abdominal fatness such as waist circumference [standardized beta 0.45, 95 % confidence interval (0.04, 0.36), $p = 0.017$], waist-hip ratio [0.52, ($1.2 \times 10^{-4}$, $1.8 \times 10^{-3}$), $p = 0.005$], waist-height ratio [0.45, ($6.7 \times 10^{-5}$, $2.0 \times 10^{-3}$), $p = 0.018$], but not with BMI that represents total body fatness [$p = 0.25$]. After adjusting for multible covariates (sex, age, smoking, physical activity, eGFR, and $HbA_{1c}$), FGF23 was again not associated with any of the anthropometric or body composition variables in $T1D^{normo}$ and in $T1D^{micro}$ (Table S2). In $T1D^{micro}$, instead, it showed a positive association with the mass and percentages of abdominal fat tissues (visceral and android fat tissues), a positive association with total fat tissue percentage and a negative association with the percentages of lean tissues (total and appendicular lean tissues) (Table S2).

### 3.2. $T1D^{normo}$ vs Healthy controls

A total of 72 age- and sex-matched $T1D^{normo}$ were identified for the

**Table 1**
Participant characteristics according to albuminuria stages.

| | $T1D^{normo}$ n = 229 | $T1D^{micro}$ n = 38 | $T1D^{macro}$ n = 39 | †p-value |
|---|---|---|---|---|
| Men, % | 46.7 | 44.7 | 59.0 | 0.33 |
| Age, years | 43.8 (36.5, 53.5) | 50.1 (42.9, 58.2)** | 53.7 (47.5, 56.7)** | <0.001 |
| Diabetes duration, years | 22.9 (19.7, 37.4) | 37.6 (29.3, 42.2)*** | 37.0 (32.7, 43.7)*** | <0.001 |
| Current smoker, % | 7.9 | 11.1 | 17.9 | 0.14 |
| LTPA, METh | 18 (9, 32) | 21 (8, 31) | 8 (5, 27)* | 0.09 |
| eGFR, ml/min/1.73 $m^2$ | 105 (92, 113) | 91 (73, 106)*** | 60 (40, 87)*** | <0.001 |
| CKD stage 1, % | 79.0 | 52.6 | 23.1 | |
| CKD stage 2, % | 20.1 | 34.2 | 30.8 | |
| CKD stage 3, % | 0.9 | 13.2 | 35.9 | |
| CKD stage 4, % | 0 | 0 | 10.3 | |
| FGF23, pg/ml | 58 (42, 75) | 75 (51, 104)** | 93 (58, 147)*** | <0.001 |
| Systolic blood pressure, mmHg | 132 (122, 144) | 135 (127, 150) | 145 (125, 168)** | 0.003 |
| Diastolic blood pressure, mmHg | 75 (70, 82) | 73 (68, 80) | 76 (69, 84) | 0.48 |
| RAASi users, % | 27.2 | 84.2*** | 86.1*** | <0.001 |
| Total cholesterol, mmol/l | 4.4 (4.0, 5.0) | 4.6 (3.9, 5.3) | 4.3 (3.9, 5.1) | 0.77 |
| HDL-cholesterol, mmol/l | 1.61 (1.33, 1.93) | 1.54 (1.19, 1.86) | 1.52 (1.18, 1.86) | 0.39 |
| Triglyceride, mmol/l | 0.9 (0.7, 1.2) | 1.0 (0.7, 1.7) | 1.1 (0.8, 1.7)** | 0.002 |
| $HbA_{1c}$, mmol/mol | 63 (56, 71) | 68 (61, 77)* | 66 (55, 76) | 0.046 |
| $HbA_{1c}$, % | 7.9 (7.3, 8.6) | 8.4 (7.7, 9.2)* | 8.2 (7.2, 9.1) | 0.046 |
| Insulin units/Kg/day | 0.54 (0.40, 0.70) | 0.65 (0.46, 0.76) | 0.53 (0.46, 0.71) | 0.30 |
| hsCRP, mg/l | 0.9 (0.5, 2.5) | 1.7 (0.8, 2.7)* | 1.5 (0.7, 4.8)* | 0.015 |
| Anthropometric measures | | | | |
| Body weight, kg | 77.5 (67.3, 88.2) | 77.9 (64.8, 96.4) | 82.7 (69.9, 90.9) | 0.44 |
| Waist circumference, cm | 88 (80, 97) | 93 (83, 108)* | 95 (84, 107)** | 0.001 |
| Waist-hip ratio | 0.88 (0.83, 0.93) | 0.91 (0.86, 1.00)** | 0.94 (0.89, 1.01)*** | <0.001 |
| Waist-height ratio | 0.50 (0.47, 0.55) | 0.54 (0.48, 0.63)** | 0.56 (0.49, 0.61)** | <0.001 |
| Body mass index, kg/$m^2$ | 25.8 (23.4, 28.3) | 27.1 (23.6, 31.1)* | 27.4 (24.2, 30.5) | 0.049 |
| Lean tissue | | | | |
| Total lean tissue, kg | 50.4 (44.9, 61.0) | 50.9 (45.1, 64.3) | 54.8 (45.1, 60.8) | 0.78 |
| Total lean tissue, % | 69.1 (62.7, 74.3) | 66.7 (63.2, 71.4) | 67.6 (61.1, 73.7) | 0.35 |
| Appendicular lean tissue, kg | 22.6 (19.7, 28.3) | 23.1 (19.0, 29.4) | 24.4 (19.5, 27.7) | 0.98 |
| Appendicular lean tissue, % | 30.9 (27.6, 34.2) | 29.9 (26.8, 32.4) | 29.8 (27.4 32.8) | 0.13 |
| Fat tissue | | | | |
| Total fat tissue, kg | 23.2 (17.3, 30.0) | 26.2 (18.3, 34.0) | 26.3 (19.8, 31.2) | 0.24 |
| Total fat tissue, % | 30.7 (25.6, 36.8) | 33.3 (28.6, 36.8) | 32.4 (26.3, 38.9) | 0.30 |
| Visceral fat tissue, g | 496 (256, 1109) | 600 (371, 2165)* | 1097 (589, 1868)*** | <0.001 |
| Visceral fat tissue, % | 0.7 (0.4, 1.3) | 0.8 (0.5, 2.6)* | 1.4 (0.7, 2.2)*** | <0.001 |
| Visceral fat tissue, $cm^3$ | 535 (273, 1210) | 636 (393, 2295)* | 1163 (624, 1980)*** | 0.001 |
| Android fat tissue, g | 1942 (1155, 2972) | 1962 (1346, 4018) | 2634 (1664, 3651)* | 0.05 |
| Android fat tissue, % | 2.6 (1.7, 3.4) | 2.9 (1.8, 4.3) | 3.1 (2.1, 4.0)* | 0.029 |

Data are shown as median interquartile range for continuous variables and percentages for categorical variables. †Comparisons among the three groups were done using Kruskal-Wallis test for continuous variables, and Chi-square test for categorical variables. *Comparisons between $T1D^{micro}$ and $T1D^{normo}$, $T1D^{macro}$ and $T1D^{normo}$ were done using the Mann-Whitney *U* test for continuous variables, and Chi-square test or Fisher exact test when the cells had an expected number below 5 for categorical variables. T1D, type 1 diabetes; normo, normal albumin excretion rate; micro, microalbuminuria; macro, macroalbuminuria; LTPA, leisure-time physical activity; METh, metabolic equivalent of task hour; eGFR, estimated glomerular filtration rate; CKD, chronic kidney disease; CKD stage 1, estimated glomerular filtration rate > 90 ml/min/1.73 $m^2$; CKD stage 2, estimated glomerular filtration rate 60–89 ml/min/1.73 $m^2$; CKD stage 3, estimated glomerular filtration rate 30–59 ml/min/1.73 $m^2$; CKD stage 4, estimated glomerular filtration rate 15–29 ml/min/1.73 $m^2$; FGF23, intact fibroblast growth factor 23; RAASi, renin-angiotensin-aldosterone system inhibitor; hsCRP, high-sensitivity C-reactive protein. *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

36 healthy controls. Relative to the $T1D^{normo}$, controls reported higher level of physical activity and had lower eGFR, $HbA_{1c}$, and hsCRP (Table 2). Serum FGF23 concentration was comparable between $T1D^{normo}$ and controls. Apart from the higher appendicular lean tissue percentage in the healthy controls, the two groups were comparable with respect to the anthropometric and body composition measurements (Table 2). Finally, similarly to the $T1D^{normo}$, no associations between FGF23 and the anthropometric and body composition measurements were observed in the healthy controls (Table S3).

## 4. Discussion

In the current study, FGF23 was positively associated with the total and abdominal (android and visceral) fat tissues in individuals with type 1 diabetes and microalbuminuria, whereas a negative association between FGF23 and lean tissue was observed. Conversely, there were no associations between FGF23 and body composition in individuals with type 1 diabetes and normal albumin excretion rate or macroalbuminuria. Serum FGF23 concentration of those with type 1 diabetes and normal albumin excretion rate was comparable to the healthy controls, suggesting that type 1 diabetes *per se* does not increase the FGF23 concentration. We are not aware of any previous studies investigating these associations in type 1 diabetes, especially at different stages of diabetic kidney disease.

In individuals with type 2 diabetes and reduced eGFR, elevated serum FGF23 concentrations, relative to individuals without diabetes, have been reported [22]. In the present study we compared the healthy controls with individuals with type 1 diabetes, who had normal albumin excretion rate and normal eGFR. It is therefore likely that in individuals with type 2 diabetes and reduced eGFR, as seen in the study by Wahl et al. [22], the increased serum FGF23 concentration was a consequence of the compromised renal function rather than diabetes, as reduced eGFR has been linked to higher serum FGF23 concentrations [15]. Notably, in another study, no difference in serum FGF23 concentration between individuals with type 2 diabetes and controls was observed [23] despite, like our study, higher concentrations were reported in those with diabetic kidney disease. It is of note that the two diabetes types are distinct entities and differ in their aetiologies, risk factors, disease presentations, and treatment modes. Therefore, the observations made in one population may not directly apply to the other. Nevertheless, the observations made in the two previous publications of individuals with type 2 diabetes [22,23] are in line with the current observations in individuals with type 1 diabetes, showing that the serum FGF23 concentration in diabetes is dependent on the stage of diabetic kidney disease and not on diabetes *per se*.

In the present study, FGF23 concentration was positively associated with all measures of abdominal fat (masses and percentages of android and visceral fat) in those individuals with type 1 diabetes, who had microalbuminuria. We hypothesize that insulin resistance and inflammation may be the mediator of the relationship between FGF23 and visceral fat, while diabetic kidney disease may further modulate the relationship. It is of note that serum FGF23 has been associated with low eGFR and high albumin excretion rate [15] as well as with insulin

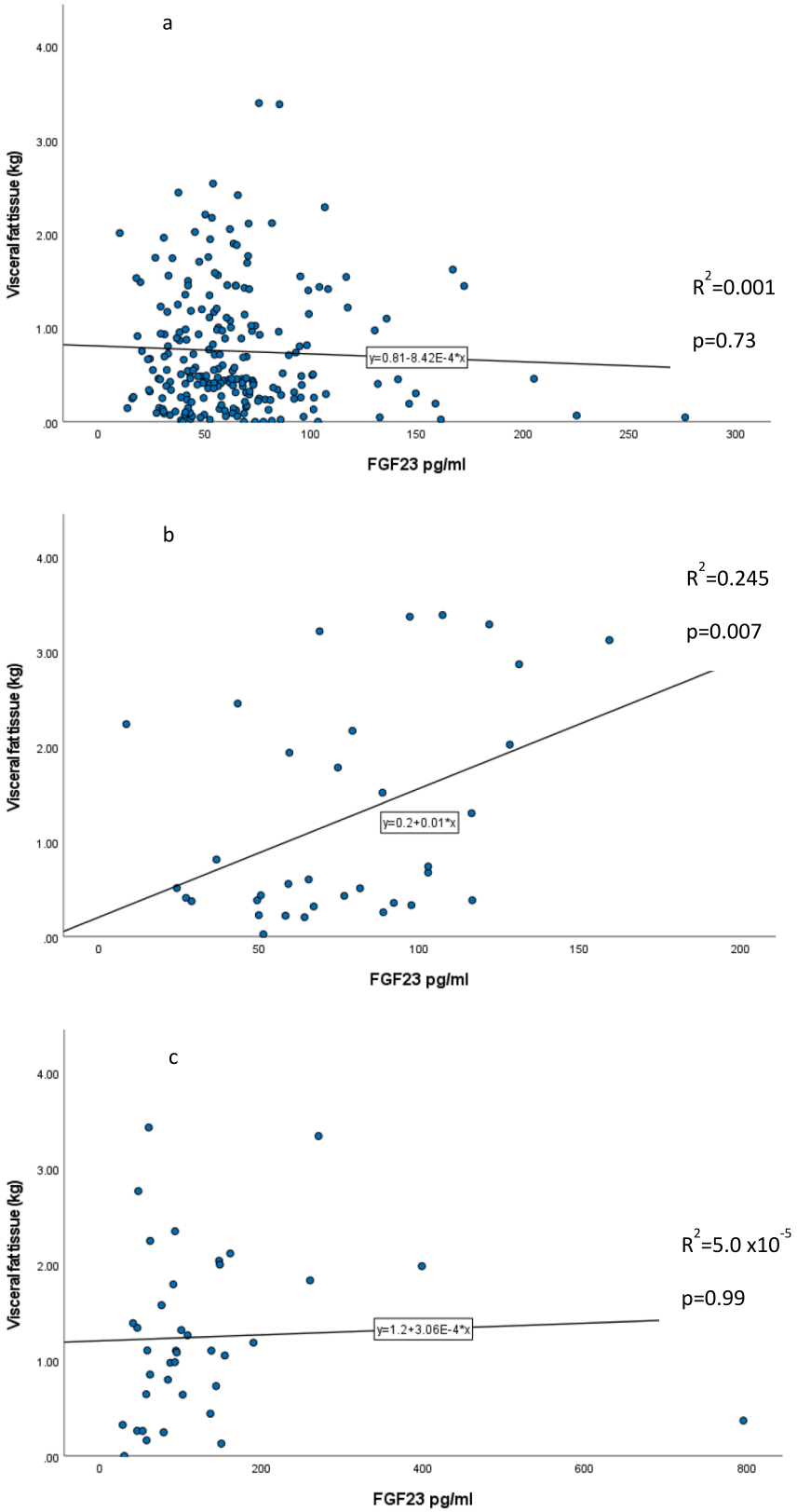


**Fig. 1. Relationship between FGF23 and visceral fat tissue according to albuminuria stages.** Unadjusted linear regression models were used to study the associations between FGF23 and visceral fat tissue in individuals with type 1 diabetes and normoalbuminuria (Fig. 1a), microalbuminuria (Fig. 1b), and macroalbuminuria (Fig. 1c).

**Table 2**
Characteristics of participants with diabetes and normoalbuminuria compared to controls without diabetes.

| | $T1D^{normo}$ n = 72 | Controls n = 36 | P |
|---|---|---|---|
| Men, % | 69.4 | 69.4 | 1 |
| Age, years | 37.3 ± 6.9 | 34.5 ± 7.5 | 0.06 |
| Current smoker, % | 9.7 | 12.5 | 0.73 |
| LTPA, METh | 17 (8, 29) | 26 (17, 41) | 0.02 |
| eGFR, ml/min/1.73 $m^2$ | 112 ± 13 | 104 ± 15 | 0.002 |
| FGF23, pg/ml | 62 (49, 83) | 60 (50, 75) | 0.56 |
| Systolic blood pressure, mmHg | 130 (122, 142) | 129 (119, 136) | 0.12 |
| Diastolic blood pressure, mmHg | 79 (72, 84) | 73 (70, 82) | 0.08 |
| Total cholesterol, mmol/l | 4.4 (3.9, 4.9) | 4.9 (4.1, 5.3) | 0.08 |
| HDL-cholesterol, mmol/l | 1.49 (1.23, 1.89) | 1.41 (1.26, 1.64) | 0.47 |
| Triglyceride, mmol/l | 1.0 (0.7, 1.6) | 0.8 (0.7, 1.2) | 0.23 |
| $HbA_{1c}$, mmol/mol | 65 ± 12 | 34 ± 4 | <0.001 |
| $HbA_{1c}$, % | 8.1 ± 1.1 | 5.3 ± 0.4 | <0.001 |
| hsCRP, mg/l | 1.1 (0.5, 2.8) | 0.2 (0.1, 0.8) | <0.001 |
| Anthropometric measures | | | |
| Body weight, kg | 80.9 ± 15.9 | 79.8 ± 15.2 | 0.73 |
| Waist circumference, cm | 89 (81, 98) | 83 (77, 99) | 0.20 |
| Waist-hip ratio | 0.90 ± 0.08 | 0.89 ± 0.08 | 0.75 |
| Waist-height ratio | 0.49 (0.47, 0.54) | 0.47 (0.44, 0.53) | 0.07 |
| Body mass index, kg/$m^2$ | 24.9 (23.6, 28.2) | 24.4 (22.5, 27.9) | 0.25 |
| Lean tissue | | | |
| Total lean tissue, kg | 57.8 (45.8, 65.6) | 58.5 (50.6, 64.6) | 0.52 |
| Total lean tissue, % | 70.7 ± 8.8 | 73.2 ± 7.3 | 0.13 |
| Appendicular lean tissue, kg | 26.5 (20.6, 30.7) | 26.9 (22.7, 30.0) | 0.38 |
| Appendicular lean tissue, % | 32.2 ± 4.5 | 34.1 ± 3.2 | 0.02 |
| Fat tissue | | | |
| Total fat tissue, kg | 22.2 (16.2, 30.3) | 19.4 (14.4, 27.9) | 0.16 |
| Total fat tissue, % | 29.3 ± 8.8 | 26.8 ± 7.3 | 0.13 |
| Visceral fat tissue, g | 477 (255, 1109) | 442 (151, 1379) | 0.61 |
| Visceral fat tissue, % | 0.6 (0.4, 1.3) | 0.6 (0.2, 1.3) | 0.63 |
| Visceral fat tissue, $cm^3$ | 525 (299, 1297) | 469 (160, 1462) | 0.44 |
| Android fat tissue, g | 1995 (1116, 2867) | 1407 (968, 2895) | 0.20 |
| Android fat tissue, % | 2.6 ± 1.1 | 2.3 ± 1.1 | 0.24 |
| Ratios of fat and lean tissue | | | |
| Visceral fat mass/android fat mass | 0.32 ± 0.18 | 0.33 ± 0.19 | 0.86 |
| Visceral fat mass/appendicular lean mass | 0.02 (0.01, 0.04) | 0.02 (0.01, 0.05) | 0.42 |
| Android fat mass/appendicular lean mass | 0.08 ± 0.05 | 0.07 ± 0.04 | 0.11 |

Data are shown as mean ± standard deviation for continuous parametric variables, median (interquartile range) for non-parametric continuous variables, and percentages for categorical variables. Between-group comparisons were done with independent samples' *t*-test for continuous parametric variables, Mann Whitney *U* test for non-parametric continuous variables, and Chi-square test, or Fisher exact test when the cells had an expected number below 5 for categorical variables. T1D, type 1 diabetes; normo, normal albumin excretion rate; LTPA, leisure-time physical activity; METh, metabolic equivalent of task hour; eGFR, estimated glomerular filtration rate; FGF23, intact fibroblast growth factor 23; hsCRP, high-sensitivity C-reactive protein.

resistance and inflammation in individuals with reduced eGFR (<60 ml/min/1.73 $m^2$) [24]. This may also explain the higher FGF23 concentration with advancing diabetic kidney disease in the current study, in which only 0.9 % of those with normal albumin excretion rate, 13 % of those with microalbuminuria and 51 % of those with macroalbuminuria had an eGFR < 60 ml/min/1.73 $m^2$. Moreover, relative to those with normal albumin excretion rate, individuals with micro- and macroalbuminuria exhibited greater amounts of visceral fat. Of note, visceral fat may contribute to the higher serum FGF23 concentrations, as it produces inflammatory cytokines such as the tumour necrosis factor alpha (TNF-α) [25,26]. Indeed, besides causing inflammation and insulin resistance [27] TNF-α may be a direct regulator of the production of FGF23 [28,29]. In support of this hypothesis, we observed higher hsCRP concentrations in those with micro- and macroalbuminuria, as compared with those with normal albumin excretion rate. Thus, the individuals with diabetic kidney disease (micro and macroalbuminuria) showed higher serum FGF23 concentration, higher amount of visceral fat and higher inflammation compared to those at normoalbuminuria stage. However, based on this cross-sectional study, it is not possible to ascertain whether the visceral fat contributed to the worsening of diabetic kidney disease or vice versa, or which factors contribute the most to the FGF23 concentration.

The crosstalk between inflammation and FGF23 has been described before and, beyond TNF-α, other inflammatory pathways are also involved, including nuclear factor kappa-light-chain-enhancer of B-cells (NF-kB) and the hypoxia-inducible factor 1-alpha (HIF-1α) [2]. Since there are no reported data on FGF23 receptors in human adipocytes, it is plausible to assume that the positive association between FGF23 and fat tissue is secondary to the inflammatory status of diabetic kidney disease and abdominal obesity in individuals with type 1 diabetes. The inflammatory hypothesis could also explain the positive association between FGF23 and fat tissue in individuals with human immunodeficiency virus infection and fat accumulation in the trunk [5], in elderly people with metabolic syndrome [6], and in a sample of individuals with abdominal obesity [7]. On the contrary, the hypothesis of inflammation does not explain the absence of associations between FGF23 and fat tissue in those with macroalbuminuria, in the current study. After all, in this group there was a higher number of individuals with reduced eGFR, higher visceral fat content, and higher concentrations of hsCRP, relative to those with normal albumin excretion rate. Whether other factors in advanced kidney disease may have changed the relationship between FGF23 and fat tissue, is not known. Also in a previous study, however, the positive association between FGF23 and inflammatory cytokines, BMI, and waist circumference was lost in the individuals with reduced eGFR and macroalbuminuria [30].

It is possible that other confounding factors, such as vitamin D3, are involved in the relationship between FGF23 and fat tissue. In mice, for example, it has been reported that the effect of FGF23 on fat accumulation is dependent on the vitamin D3 receptor [31], and in humans FGF23 reduces the synthesis of $1,25(OH)_2D_3$ [32]. Another possible mediator between FGF23 and the fat tissue is adipocyte-derived adiponectin [25], which in rodents has been shown to regulate the FGF23 levels in serum and the expression of Klotho in the kidney [33]. Taken together, it seems that the interactions between circulating FGF23 and visceral fat, insulin resistance, and inflammation are significant only at the early stages of diabetic kidney disease. Instead, with emerging macroalbuminuria, other factors interfering with these relationships may be involved.

In line with the observations linking serum FGF23 and visceral fat, in those with microalbuminuria, we also observed a positive association between FGF23 and the anthropometric measures related to abdominal fatness. Although not all the anthropometric measures were still associated after fully adjustments, they can be used as a proxy of visceral fatness [34] and high FGF23 concentration.

The literature concerning the relationship between FGF23, and muscle tissue is scarce. Although a previous study showed that high FGF23 concentrations are associated with left ventricular hypertrophy in the elderly, especially in those with reduced eGFR [3], FGF23 was, in the current study, negatively associated with skeletal muscle. Since a significant association was observed only with the percentage of lean tissue, but not with the lean tissue mass, and only in individuals with microalbuminuria, it is possible that the negative association between FGF23 and the percentages of total lean and appendicular lean tissues only mirrors the positive association between FGF23 and fat tissue, in this group. Consequently, this suggests, that not the amount of lean tissue but other factors likely influence the association between FGF23

and the lean tissue.

Finally, we found no studies reporting expression of FGF23 receptors or FGF23 co-receptor Klotho, required for direct cellular effects, in human adipocytes or myocytes. Hence, it reinforces the idea of indirect mechanisms involved in the relationship between serum FGF23 and body composition.

Cross-sectional design is a major limitation of the current study, as it precludes us from making any inferences of causality. Another limitation is the absence of measurements of vitamin D3, TNF-α, HIF-1α, NF-kB, and adiponectin that could have helped us to understand the interactions between FGF23 and body composition, particularly in the groups with albuminuria. Regardless of these limitations, our observations motivate further studies to investigate the mechanisms involved in the relationships between FGF23, visceral fat, and muscle mass. Furthermore, this study provides important information, since serum FGF23 is a predictor of the progression of kidney disease, and we found that simple measures that estimate the visceral fat, such as waist circumference, waist-hip ratio, and waist-height ratio, are associated with the serum FGF23 concentration at an early stage of diabetic kidney disease in unadjusted models. Prospective studies are needed to ascertain the impact of the visceral fat and the related anthropometric measures on the risk of progression of diabetic kidney disease in this population.

In conclusion, the associations between FGF23 and body composition is related to the emergence of albuminuria in type 1 diabetes, not evident in individuals with normal albumin excretion rate.

**Ethical approval**

All procedures followed were in accordance with the ethical standards of the responsible committee (Ethics Committee of Helsinki and Uusimaa Hospital District, Helsinki, Finland) and with the 1964 Helsinki Declaration and its later amendments. Informed consent was obtained from all individual participants included in the study.

## Declaration of Competing Interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: PHG reports receiving lecture honorariums from Astellas, Astra Zeneca, Bayer, 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, Medscape, MSD, Mundipharma, Nestlè, Novo Nordisk, and Sanofi. EBP reports receiving lecture honorariums from Eli Lilly, Abbott, Astra Zeneca, Sanofi, Boehringer Ingelheim and is an advisory board member of Sanofi. All other authors declare no conflicts of interest.

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## Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2023.110620.

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