Relationship between the FTO Genotype and Early Chronic Kidney Disease in Type 2 Diabetes: The Mediating Role of Central Obesity, Hypertension, and High Albuminuria

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Abstract

Introduction: Single nucleotide polymorphisms (SNP) in the fat mass and obesity-associated (FTO) gene have been associated with type 2 diabetes (T2D) and its complications. The aim of the present research was to investigate which and how (directly or indirectly) clinical and metabolic variables mediate the association between fat mass and the FTO gene and early chronic kidney disease (CKD) in individuals with T2D. Methods: This cross-sectional study was conducted in a sample of 236 participants with T2D (53.4\% women, mean age 60 ± 10 years). DNA samples were genotyped for the rs7204609 polymorphism (C/T) in the FTO gene. Clinical, anthropometric, and metabolic data were collected. Path analysis was used to evaluate the associations. Results: Of the sample, 78 individuals with T2D had CKD (33\%). Presence of the risk allele (C) was higher among participants with CKD (21.8 vs. 10.8\%; \(p = 0.023\)). This polymorphism was positively associated with higher waist circumference, which in turn was associated with higher glycated hemoglobin and higher blood pressure. A higher blood-pressure level was associated with higher urinary albumin excretion (UAE) and as expected, higher UAE was associated with CKD. Path analysis showed an indirect relationship between the FTO gene and early CKD, mediated by waist circumference, blood-pressure levels, and UAE. Conclusions: These findings suggest that the C allele may contribute to genetic susceptibility to CKD in individuals with T2D through the presence of central obesity, hypertension, and high albuminuria.

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Keywords
Type 2 diabetes · Obesity-associated gene · Path analysis · Albuminuria · Chronic kidney disease
Type 2 diabetes (T2D) accounts for 90–95% of all diabetes [1]. However, its pathogenesis and complications are difficult to characterize, and both environmental and genetic risk factors play fundamental roles in these processes [1, 5, 6]. The relevance of genetic factors to the development and progression of T2D has been widely investigated [7, 8].

In this sense, genome-wide association studies have identified an association between polymorphisms of the fat mass and obesity-associated (FTO) gene and T2D in several populations [9], as well as associations with CKD [10–12]. The FTO gene is located on the long arm of the Chromosome 16 on the position 12.2 and consists of 9 exons, occupying an area of >400 kb [13]. The expression of the FTO gene is associated with regulation of food intake and energy balance [14, 15]. Moreover, the FTO gene has been linked with central obesity [16], hypertension [17], and poor glycemic control [18]. All of these conditions are related to T2D [1] and to increased CKD rates [19, 20]. In Brazilians with T2D, the rs7204609 polymorphism of the FTO gene has been associated with high levels of urinary albumin excretion (UAE), [21] an important early clinical marker of CKD [22]. The rs7204609 polymorphism (C/T), however, has been little investigated, and its influence on the renal function is still unknown.

The primary objective of this study is to evaluate whether the polymorphism rs7204609 is associated with presence of CKD in individuals with T2D, and whether it is mediated by other conditions. We hypothesized that this polymorphism would influence early CKD either directly or indirectly, that is, through other clinical and metabolic conditions.

**Materials and Methods**

**Patients and Study Design**

This cross-sectional study was conducted in a sample of 236 individuals with T2D (defined as age 30 years or older at the onset of diabetes, no history of ketoacidosis or documented ketonuria, and, in insulin users, initiation of insulin therapy at least 5 years after diagnosis).

We selected individuals according to the following criteria: 24-h UAE < 200 μg/min, absence of urinary tract infection or other renal diseases, and absence of heart failure (New York Heart Association class IV). Participants with macroalbuminuria (UAE >200 μg/min) were not included because they are usually the subject of specific recommendations. All medications in use were maintained during the study. The Ethics Committee approved the protocol (#2015-0625), and participants gave their written informed consent for participation.

This study was designed and conducted in accordance with the STrengthening the REporting of Genetic Association studies reporting recommendations, an extension of the STROBE Statement (online suppl. material; for all online suppl. material, see www.karger.com/doi/10.1159/000516118).

**Anthropometrical, Clinical, and Metabolic Assessment**

Body weight and height of the participants (not wearing coats or shoes) were obtained using an anthropometric scale, with measurements recorded to the nearest 100 g for weight and to the nearest 0.1 cm for height. Body mass index (kg/m²) was calculated as weight (kilograms) divided by height (meters) squared. Waist circumference was measured midway between the margin of the lowest rib and the iliac crest, near the umbilicus, using a flexible, non-stretch fiberglass tape. Central obesity was defined by a waist circumference ≥94 cm for men and ≥80 cm for women [23].

Blood pressure was measured using the auscultatory method using a standard mercury sphygmomanometer (Korotkoff phases I and V). Two measurements were obtained, to the nearest 2 mm Hg, after a 10-min rest. Hypertension was defined as the blood pressure >130/80 mm Hg on 2 occasions or use of antihypertensive drugs [1, 24].

Blood samples were obtained after a 12-h fast. Glycated hemoglobin (HbA1c) was determined by ion-exchange high-performance liquid chromatography (Merck-Hitachi L-9100 glycated hemoglobin analyzer, reference range, 4.7–6.0%; Merck, Darmstadt, Germany). UAE was measured by an immunoturbidimetric method (Microalb; Ames-Bayer, Tarrytown, NY) using urine samples with albumin concentrations of 30 and 100 mg/L. The intra-assay and inter-assay coefficients of variation at our laboratory were both 6% [25].

The presence of CKD was evaluated as described elsewhere [1]. According to 24-h UAE results, the study participants were classified as having normoalbuminuria (UAE <20 μg/min) or microalbuminuria (UAE >20–199 μg/min). Microalbuminuria was always confirmed in a second urine sample [26]. We calculated the estimated glomerular filtration rate (eGFR) using the CKD-Epidemiology Collaboration formula, considering creatinine levels, sex, race, and age [27].

**Genotyping for FTO Polymorphism**

Peripheral blood samples were collected from all the participants for DNA extraction. Detection of the rs7204609 FTO Single nucleotide polymorphism (SNP) was performed by allelic discrimination assay (TaqMan SNP Genotyping Assays, Applied Biosystems, CA) using the ABI PRISM 7000 Real-Time PCR System, and genotypes were read using automated software (SDS1.1, Applied Biosystems, CA). Reactions were run in 10-μL volumes using an amplification protocol of 95°C for 10 min, followed by 40 cycles of 95°C for 15 s, and then 60°C for 1.5 min.

**Statistical Analyses**

Statistical analysis was performed in IBM SPSS® Statistics 26 software. The unpaired Student’s t test, the Mann-Whitney U test, and the χ² test were used as appropriate. Genotypes were analyzed using risk alleles. In the rs7204609 (C/T) polymorphism, the risk allele is the C allele. For analysis, all the participants with the putative C allele were pooled together (CT and CC genotypes) and compared with those without the C allele (TT genotypes). A χ² test was also used to evaluate Hardy-Weinberg equilibrium and assess
the frequency distribution of genotypes. The results were expressed as mean (SD), median (interquartile range), or absolute and relative frequency. p values <0.05 were considered statistically significant.

MPlus® software, version 5.0, was used both to analyze the relationship between the presence of the C allele and CKD and to investigate, via the path analysis, the mediating role of selected variables in relationships involving the waist circumference, blood pressure, HbA1c, and UAE. The path analysis is a subset of structural equation modeling [28] an extension of regression analysis that allows simultaneous exploration of the complex relationships between multiple variables [29].

In the path analysis, explanatory variables may affect the outcome variable directly or indirectly. Direct effects represent a direct relationship between the variables, that is, relationships which are not mediated by other variables in the model. They can be interpreted as a regression coefficient. In turn, indirect effects express a sequence of paths with at least 1 intermediate or mediating variable. They are calculated by multiplying the direct effects between the variables involved in that path. Finally, the total effect is calculated from the sum of direct and indirect effects between the 2 variables [30, 31]. Thus, in this study, the term “effect” is used in the sense of association not causality.

Standardized and nonstandard coefficients were estimated with their respective p values. Odds ratios were obtained from exponentiation of nonstandard effects. The robust maximum likelihood method, which does not require the assumption of normality in multivariate data, was used to estimate the parameters [30].

Analyses of the variables associated with CKD included additional adjustments for age and sex. A selection of different measures was used to verify the fit of the model. The root mean square error of approximation and the standardized root mean square residual are both based on the model residuals; values <0.06 indicate that the theoretical model fits the data [32–34]. The Tucker-Lewis index and comparative fit index were also estimated, with values >0.90 indicating the good model fit [30, 32].

Results

A total of 236 individuals with T2D were enrolled in this study (60.1 ± 10.3 years of age; 11 [6–18] years of diabetes duration, 52.7% was female and 86.4% were white). Among them, 33% of participants had CKD. The mean body mass index was 28.6 ± 4.2 kg/m² and 83.9% had central obesity. The medians of the HbA1c levels were 7.0 (6.3–8.1) percent, UAE was 6.4 (3.5–33.0) µg/min, and the eGFR was 85 (71.2–101.0) mL/min/1.73 m². Also, the hypertension was present in 88.1% in all the participants. With regard to drug treatment, 94.9% used oral antihyperglycemic agents, 5.1% only diet and 55.5% used ACE inhibitors. Finally, the genotype frequencies of each

Table 1. Characteristics of study participants, by the categorized presence of CKD

| Variables                        | Presence of CKD | p value |
|----------------------------------|-----------------|---------|
|                                 | no (n = 158)    | yes (n = 78) |
| Sex, n (%)                       | 95 (75.4)       | 31 (24.6) | 0.003** |
| Female, n (%)                    | 63 (57.3)       | 47 (42.7) |         |
| Age, years                       | 57.5±10.8       | 61.3±9.9 | 0.008** |
| Duration of diabetes, years      | 11.0 (7.0–18.0) | 10.0 (5.0–16.0) | 0.147 |
| Risk allele on rs7204609 FTO SNP, n (%) | 17 (10.8)    | 17 (21.8) | 0.023** |
| Central obesity, n (%)*          | 131 (82.7)      | 67 (85.9) | 0.477   |
| HbA1c, %                         | 7.4±1.6         | 7.4±1.5  | 0.940   |
| Diabetes treatment, n (%)         |                 |         |         |
| Only diet                         | 5 (41.7)        | 7 (58.3) |         |
| Oral antidiabetic agents          | 105 (75)        | 35 (25)  |         |
| Insulin                           | 15 (53.6)       | 13 (46.4) |         |
| Insulin + oral antidiabetic agents| 33 (58.9)       | 23 (41.1) |         |
| Hypertension, n (%)               | 134 (64.4)      | 52 (66.4) | 0.072   |
| ACE inhibitors, n (%)             | 79 (50)         | 52 (66.4) | 0.056   |
| UAE (µg/min)                      | 3.5 (3.4–8.6)   | 57.4 (33.6–96.3) | <0.001** |
| eGFR (mL/min per 1.73 m²)         | 84.5 (71.2–98.0) | 86.0 (71.5–104.2) | 0.454  |

Data are expressed as number of patients with the characteristic (%), mean ± SD or median (25th percentile, 75th percentile) and compared using chi-square, Student t, and Mann-Whitney U test, respectively. CKD, chronic kidney disease; SNP, single nucleotide polymorphism; FTO, fat mass and obesity-associated; HbA1c, glycated hemoglobin; ACE, angiotensin-converting enzyme inhibitors; UAE, urinary albumin excretion; eGFR, estimated glomerular filtration rate.* Elevated waist circumference ≥94 cm for men and ≥80 cm for women. ** p value has statistical significance (p < 0.05).
rs7204609 allele were 85.2% for TT, 13.1% for CT, and 1.7% for CC (online suppl. Table 1). No deviation from Hardy-Weinberg equilibrium was observed ($\chi^2 = 2.739; p = 5.642$).

Table 1 lists the study participants’ characteristics, according to the presence of CKD. The proportion of CKD was higher in men and in older participants. There was a higher proportion of the C allele presence among individuals with CKD than among those without CKD (21.8 vs. 10.8%; $p$ value =0.023). More aggressive treatment of diabetes was more common in individuals without CKD than in individuals with CKD. As expected, those participants with CKD had higher UAE levels than those without CKD (57.4 [33.6–96.3] vs. 3.5 [3.4–8.6]; $p < 0.001$). The relation to central obesity, glycemic control, or the presence of hypertension was not significant.

The path analysis achieved a satisfactory fit according to the root mean square error of approximation (0.000), standardized root mean square residual (0.015), comparative fit index (1.000), and Tucker-Lewis index (1.192) indices. Table 2 shows the direct, indirect, and total coefficients for the mediation relations. The only significant indirect effect was observed in the relationship between the FTO rs7204609 polymorphism and CKD mediated by waist circumference, blood pressure, and UAE ($p = 0.045$). Each 1 mg/min increase in UAE was associated with a 0.8% (CI 95% 0.7–0.9%) increase in CKD odds (online suppl. Table 2).

When we analyzed the standardized coefficients for direct effects in the path analysis, high UAE was, as expected, positively associated with CKD ($p < 0.001$). A positive association was also observed between the high blood pressure and high UAE ($p = 0.004$). The waist circumference was positively associated with the blood pressure ($p < 0.001$) and with glycated hemoglobin ($p = 0.004$). The presence of the C allele in the FTO gene was associated with higher waist circumference values ($p < 0.001$) but did not have a significant direct effect on CKD (shown in Fig. 1).

**Table 2. Direct, indirect, and total coefficients for the mediation relations**

| Relation | Mediators | Effect | Standardized coefficient | SE | $p$ value |
|----------|-----------|--------|--------------------------|----|-----------|
| Risk allele on rs7204609 FTO SNP → CKD | | Direct | 0.072 | 0.044 | 0.104 |
| | | Indirect | 0.022 | 0.036 | 0.543 |
| | | HbA1c (%) | 0.003 | 0.007 | 0.639 |
| | | HbA1c (%) → UAE (µg/min) | −0.001 | 0.002 | 0.636 |
| | | Waist circumference → HbA1c (%) → UAE (µg/min) | 0.002 | 0.003 | 0.499 |
| | | Blood pressure | −0.003 | 0.009 | 0.687 |
| | | Blood pressure → UAE (µg/min) | −0.001 | 0.002 | 0.636 |
| | | Waist circumference → blood pressure → UAE (µg/min) | 0.005 | 0.002 | 0.045 |
| | Total | 0.087 | 0.061 | 0.153 |

| Waist circumference → CKD | HbA1c (%) | Indirect | −0.027 | 0.035 | 0.441 |
| Blood pressure | −0.044 | 0.025 | 0.084 |
| HbA1c (%) → UAE (µg/min) | 0.009 | 0.013 | 0.489 |
| Blood pressure → UAE (µg/min) | 0.024 | 0.010 | 0.019 |
| Total | −0.038 | 0.047 | 0.412 |

| HbA1c (%) → CKD | UAE (µg/min) | Direct | −0.089 | 0.093 | 0.336 |
| | | Indirect | 0.029 | 0.039 | 0.469 |
| Total | −0.060 | 0.100 | 0.544 |

| Blood pressure → CKD | UAE (µg/min) | Direct | −0.151 | 0.082 | 0.066 |
| | | Indirect | 0.082 | 0.029 | 0.005 |
| Total | −0.069 | 0.092 | 0.450 |

| UAE (µg/min) → CKD | Direct | 0.584 | 0.059 | 0.000 |

Bold $p$ values are statistically significant ($p < 0.05$). FTO, fat mass and obesity-associated; SNP, single nucleotide polymorphism; CKD, chronic kidney disease; HbA1c, glycated hemoglobin; UAE, urinary albumin excretion; SE, standard error. All variables were considered continuous, except for the presence of the risk allele of the rs7204609 polymorphism of the FTO gene (C allele) and for the presence of CKD.
Discussion

CKD is one of the most prevalent microvascular complications and occurs in 20–40% of the individuals with diabetes [1–4]. In fact, in our sample, 33% of participants had CKD. Presence of the risk allele (C) in the FTO gene was more frequent in these participants than those without the disease (21.8 vs. 10.8%; \( p = 0.023 \)). These findings indicate a relevant relationship between the rs7204609 polymorphism and CKD, which, to the best of our knowledge, has not been reported previously. Studies in Czech, Japanese, and Emirati populations have demonstrated a relationship between CKD and FTO variants—rs17817449, rs56094641, and both rs1421086 and rs17817449 polymorphisms, respectively [10–12].

Studying the factors that trigger CKD caused by diabetes is difficult because of several issues related to the underlying condition [19, 20]. Our path analysis found no significant direct effect of the FTO gene on CKD. However, we detected an indirect effect mediated by the central obesity, blood pressure, and UAE, all of which are conditions or biomarkers related to the renal function [19, 20, 35–37]. In a Chinese population, components of the metabolic syndrome (including central obesity and hypertension) were associated with higher UAE, a well-known predictor of CKD [38]. Although the mechanisms are not fully understood, central obesity in conjunction with hypertension and diabetes could be responsible for increased endothelial permeability and intraglomerular capillary pressure, with consequent development of CKD [39].

Regarding the effect of genetics, in our sample, the FTO gene was positively associated with the waist circumference values. This is consistent with the previous reports [7, 8, 40] suggesting genetic susceptibility to an obesity phenotype in individuals with T2D. Studies have shown that FTO polymorphisms are associated with higher food intake and increased hunger/reduced satiety [41]. The FTO gene is highly expressed in the hypothalamus region, which is involved in appetite regulation [15]. However, there is no information about the association of energy intake with the rs7204609 SNP. A possibility would be related to linkage disequilibrium with another polymorphism in the FTO gene. In this sense, the rs7204609 polymorphism is in the strong linkage disequilibrium with a common polymorphism in the FTO gene, the rs9939069 (\( D' = 5 \) and \( r^2 = 0.014 \); https://www.ncbi.nlm.nih.gov/probe/docs/projhapmap/), which has been associated with obesity, diabetes, and metabolic syndrome [42, 43].

In addition, the role of ethnicity should be considered when interpreting the influence of the rs7204609 polymorphism on obesity, as the association between rs7204609 and obesity has been shown to differ across different ethnic groups. In West Africans, for example, this polymorphism was positively associated with obesity, whereas in a Japanese population, the association was negative [44, 45].

Central obesity is a direct risk factor for deterioration of the renal function [35] and influences poor glycemic and blood-pressure control [46–48]. In our sample, higher waist circumference was associated with higher glycated hemoglobin and higher blood pressure, both of which are
among the leading risk factors for the development and progression of CKD [19, 20, 37]. Furthermore, the blood-pressure control and glycemic control are part of therapeutic strategies to prevent high UAE in individuals with T2D [49, 50]. In our sample, participants with higher blood-pressure levels had higher UAE levels. Hypertension can impair vascular endothelial function, leading to an elevated eGFR and high UAE [37, 51].

As expected, individuals with CKD had higher UAE values in our analysis. In 2015, a meta-analysis found that, for every 30% reduction in UAE, the risk of kidney disease decreased by 23.7% [52]. In our study, a 1-unit increase in UAE was associated with a 0.8% (CI 95% 0.7–0.9%) increase in the odds of CKD. We should stress that the presence of CKD was significantly more frequent among older and male members of our sample, which is consistent with the literature [53, 54].

Based on our results, we believe that changes in lifestyle, especially the control of obesity and blood pressure, are important factors in the treatment of diabetes and could promote vascular protection in this group of individuals. However, further intervention studies are needed to test the genetic variants of the FTO gene to confirm our findings. We did not find any studies on this topic that have applied the path analysis as a statistical method. Our analysis of the mediating effects of waist circumference, HbA1c, blood pressure, and UAE on the relationship between the FTO gene and CKD differentiates this study from the previous research.

However, the study also has limitations. First, the small sample size prevents generalization of our data, but it is sufficient for the analyses conducted. Moreover, the mediating association needs to be confirmed by further replication studies, particularly in other ethnic populations, since this study only enrolled individuals from the Southern Brazil. Second, medical conditions (such as macroalbuminuria and established renal disease) as exclusion criteria also would be a limiting factor. However, the inclusion of these participants would have biased the results. In addition, a positive association between diabetes treatment and glycemic control was demonstrated in the analysis. This may at least partly explain why we did not find an association between glycemic control and CKD.

Conclusion

In this study, the FTO gene polymorphism rs7204609 appears to contribute to genetic susceptibility to early CKD in individuals with T2D, possibly mediated by waist circumference, blood pressure, and UAE. These research findings may improve our understanding of the mechanisms to the diabetes-related CKD, especially the genetic factors.

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Statement of Ethics

This study was approved by the Hospital de Clínicas de Porto Alegre Ethics Board (2015.0625), and all of the participants provided written informed consent.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

Júlia Marchetti: conceptualization, methodology, formal analysis, data curation, and writing – the original draft; Karla P. Albino: formal analysis, writing – review and editing; Helen Hermana and M. Hermsdorff: conceptualization, methodology, formal analysis, supervision, and writing – review and editing; Leidjaira L. Juvanhol: formal analysis; José Alfredo Martinez: data curation and writing – review and editing; Thais Steemburgo: conceptualization, formal analysis, data curation, supervision, and writing – the original draft.
FTO Gene, Chronic Kidney Disease and Diabetes

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