Lifestyle Genomics

Research Article

Lifestyle Genomics 2021;14:73–80
DOI: 10.1159/000516118

Received: January 19, 2021
Accepted: March 23, 2021
Published online: June 16, 2021

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

Júlia Marchetti[a] Karla P. Balbino[b] Helen Hermana M. Hermsdorff[b] Leidjaira L. Juvanhol[b] José Alfredo Martinez[c] Thais Steemburgo[a]

[a]Postgraduate Program in Food, Nutrition, and Health, Universidade Federal do Rio Grande do Sul – UFRGS, Porto Alegre, Brazil; [b]Department of Nutrition and Health, Universidade Federal de Viçosa – UFV, Viçosa, Brazil; [c]Centro de Nutrición, Universidad de Navarra, Pamplona, IMDEA (CSIC-UAM) Precision Nutrition Program CIBERobn, Instituto Carlos III, Madrid, Spain

Keywords
Type 2 diabetes · Obesity-associated gene · Path analysis · Albuminuria · Chronic kidney disease

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.

Introduction

Diabetes is a metabolic disorder characterized by sustained hyperglycemia. This is one of the main factors responsible for the development and progression of diabetes-associated chronic microvascular damage, which includes chronic kidney disease (CKD) [1]. According to the literature, CKD occurs in 20–40% of individuals with diabetes and is one of its most prevalent complications [1–4].

karger@karger.com
www.karger.com/lfg

Correspondence to:
Thais Steemburgo, tsteemburgo@gmail.com

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/m^2) 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, nonstretch fiberglass tape. Central obesity was defined by a waist circumference ≥94 cm for men and ≥80 cm for women [23].

Blood pressure was measured by 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-mL 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 χ^2 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 χ^2 test was also used to evaluate Hardy-Weinberg equilibrium and assess

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* (%) Female, *n* (%)	95 (75.4) 63 (57.3)	31 (24.6) 47 (42.7)	0.003**
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)	0.009**
Insulin	15 (53.6)	13 (46.4)	
Insulin + oral antidiabetic agents	33 (58.9)	23 (41.1)	
Hypertension, *n* (%)	134 (64.4)	52 (66.6)	0.072
ACE inhibitors, *n* (%)	79 (50)	52 (66.6)	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 m^2)	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 ($p < 0.05$).

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 2 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/m^2 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 m^2. 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 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
	UAE (μg/min)	Indirect	0.022	0.036	0.543
	HbA1c (%)	Indirect	0.003	0.007	0.639
	HbA1c (%) → UAE (μg/min)	Indirect	−0.001	0.002	0.636
	Waist circumference → HbA1c (%) → UAE (μg/min)	Indirect	0.002	0.003	0.499
	Blood pressure	Indirect	−0.003	0.009	0.687
	Blood pressure → UAE (μg/min)	Indirect	−0.001	0.002	0.636
	Waist circumference → blood pressure → UAE (μg/min)	Indirect	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	Indirect	−0.044	0.025	0.084
	HbA1c (%) → UAE (μg/min)	Indirect	0.009	0.013	0.489
	Blood pressure → UAE (μg/min)	Indirect	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.

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).

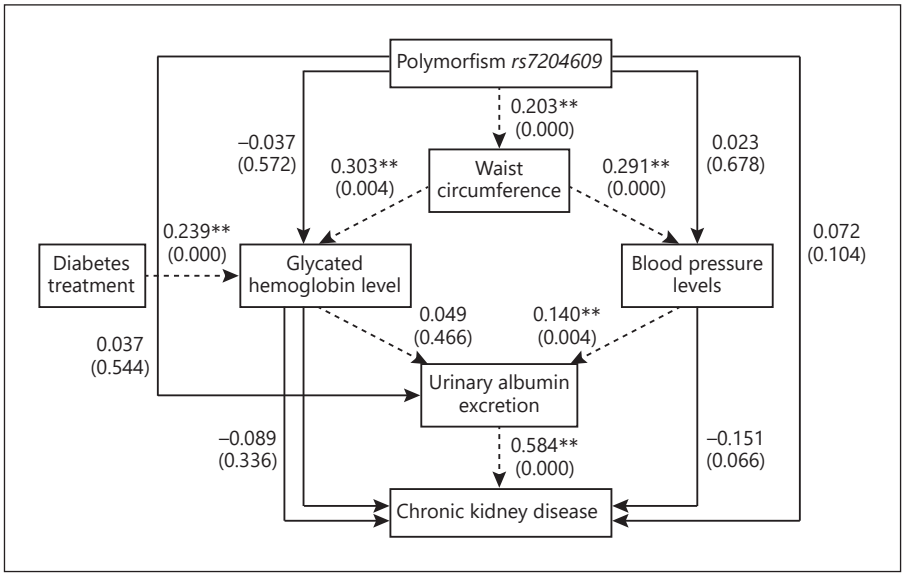

Fig. 1. Path analysis for the relationship between the FTO gene and CKD in individuals, with T2D. In path analysis, all variables were considered continuous, except for the presence of the risk allele of the rs7204609 polymorphism of the FTO gene (C allele), diabetes treatment (4 categories: only diet, oral antidiabetic agents, insulin, and insulin + oral antidiabetic agents) and the presence of CKD. Associations, with CKD, were further adjusted for age and sex. Standardized coefficients and *p* values were used as the parameter estimates in path analysis. Dashed lines indicate paths, with statistical significance. ** *p* value <0.01. FTO, obesity-associated gene; CKD, chronic kidney disease.

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 the mechanisms to the diabetes-related CKD, especially the genetic factors.

Acknowledgement

The authors are grateful to the special research project "Obesidad, Nutricion y Salud" (LE/97), run by the University of Navarra (Spain), and to Brazil's research funding agency, the "Conselho Nacional de Desenvolvimento Cientıfico e Tecnológico" (CNPq), for the financial support. HHM Hermsdorff is a CNPq Research Productivity Fellow.

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.

Funding Sources

This work was supported by the FIPE – Fundo de Incentivo à Pesquisa do Hospital de Clínicas de Porto Alegre. The work was also financially supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico' (CNPq; Brazil). T.S. was a recipient of a CNPq scholarship.

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.

References

1 American Diabetes Association. 7. Diabetes technology: standards of medical care in diabetes-2020. Diabetes Care. 2020;43(Suppl 1): S77–52.
2 Tuttle KR, Bakris GL, Bilous RW, Chiang JL, Boer IH, Goldstein-Fuchs J, et al. Diabetic kidney disease: a report from an ADA Consensus Conference. Diabetes Care. 2014;37: 2864–83.
3 Afkarian M, Zelnick LR, Hall YN, Heagerty PJ, Tuttle K, Weiss NS, et al. Clinical manifestations of kidney disease among US adults with diabetes, 1988–2014. JAMA. 1988-20142016;316:602–10.
4 De Boer IH; DCCT/EDIC Research Group. Kidney disease and related findings in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study. Diabetes Care. 2014; 37(1):24–30.
5 Wu Y, Ding Y, Tanaka Y, Zhang W. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. Int J Med Sci. 2014;11:1185–200.
6 Sladek R, Rocheleau G, Rung J, Dina C, Shen L, Serre D, et al. A genome-wide association study identifies novel risk loci for type 2 diabetes. Nature. 2007;445:881–5.
7 Li H, Kilpeläinen TO, Liu C, Zhu J, Liu Y, Hu C, et al. Association of genetic variation in FTO with risk of obesity and type 2 diabetes with data from 96,551 East and South Asians. Diabetologia. 2012;55:981–95.
8 Fawwad A, Siddiqui IA, Basit A, Zeeshan NF, Shahid SM, Nawab SN, et al. Common variant within the FTO gene, rs9939609, obesity and type 2 diabetes in population of Karachi, Pakistan. Diabetes Metab Syndr. 2015;10:43–7.
9 Yang Y, Liu B, Xia W, Yan J, Liy H, Hu L, et al. FTO genotype and type 2 diabetes mellitus: spatial analysis and meta-analysis of 62 case-control studies from different regions. Genes. 2017;8(2):70.
10 Hubacek JA, Viklicky O, Dlouha D, Bloudickovam S, Kubinova R, Peasey A, et al. The FTO gene polymorphism is associated with end-stage renal disease: two large independent case–control studies in a general population. Nephrol Dial Transplant. 2012;27:1030–5.
11 Taira M, Imamura M, Takahashi A, Kamatani Y, Yamauchi T, Araki S, et al. A variant within the FTO confers susceptibility to diabetic nephropathy in Japanese patients with type 2 diabetes. PLoS One. 2018;13(12):e0208654.
12 Osman WM, Jelinek HF, Tay GK, Hassan MH, Almahmeed W, Khandoker AH, et al. Genetics of diabetic kidney disease: a follow-up study in the Arab population of the United Arab Emirates. Mol Genet Genomic Med. 2019;7(12):e985.
13 Gerken T, Girard CA, Tung Y-CL, Webby CJ, Saudek V, Hewitson KS, et al. The obesity-associated FTO gene encodes a 2-oxoglutarate-dependent nucleic acid demethylase. Science. 2007;318(5855):1469–72.
14 Hardy R, Wills AK, Wong A, Elks CE, Wareham NJ, Loos RJF, et al. Life course variations in the associations between FTO and MC4R gene variants and body size. Hum Mol Genet. 2010;19(3):545–52.
15 Olszewski PK, Fredriksson R, Olszewska AM, Stephansson O, Alsio J, Radomska KJ, et al. Hypothalamic FTO is associated with the regulation of energy intake not feeding reward. BMC Neurosci. 2009;10:129.
16 Loos RJ, Yeo GS. The bigger picture of FTO: the first GWAS-identified obesity gene. Nat Rev Endocrinol. 2014;10(1):51–61.
17 Pausova Z, Syme C, Abrahamowicz M, Xiao Y, Leonard GT, Perron M, et al. A common variant of the FTO gene is associated with not only increased adiposity but also elevated blood pressure in French Canadians. Circ Cardiovasc Genet. 2009;2:260–9.
18 Freathy RM, Timpson NJ, Lawlor DA, Xiao Y, Leonard GT, Perron M, et al. Common variation in the FTO gene alters diabetes-related metabolic traits to the extent expected given its effect on BMI. Diabetes. 2008;57:1419–26.
19 Kazancioğlu R. Risk factors for chronic kidney disease: an update. Kidney Int Suppl (2011). 2013;3:368–71.
20 National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. Am J Kidney Dis. 2002;39(Suppl 1):S1–266.
21 Steemburgo T, Azevedo MJ, Gross JL, Milagro F, Campion J, Martinez JA. The rs7204609 polymorphism in the Fat Mass and Obesity-Associated gene is positively associated with central obesity and microalbuminuria in patients with type 2 diabetes from Southern Brazil. J Ren Nutr. 2012;22(2):228–36.
22 Molitch ME, DeFronzo RA, Franz MJ, Keane WF, Mogensen CE, Parving H, et al. Nephropathy in diabetes. Diabetes Care. 2004; 27(Suppl 1):S79–83.
23 Alberti KG, Eckel RH, Grundy SM, Zimmet PZ, Cleeman JI, Donato KA, et al. Harmonizing the metabolic syndrome. Circulation. 2009;120(16):1640–5.
24 Whelton PK, Carey RM, Aronow WS, Casey DE, Collina KJ, Himmelfarb CD, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol. 2018;71:e127–248.
25 Camargo JL, Lara GM, Wendland AE, Gross JL, De Azevedo MJ. Agreement of different immunoassays for urinary albumin measurement. Clin Chem. 2008;54:925–7.
26 Gross JL, Azevedo MJ, Silveiro SP, Canani LH, Caramori ML, Zelamnovitz T. Diabetic nephropathy: diagnosis, prevention, and treatment. Diabetes Care. 2005;28:164–76.
27 Levey AS, Stevens LA, Schmid CH, Zhang Y, Castr AF, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150:604–12.
28 Bentler PM, Stein JA. Structural equation models in medical research. Stat Methods Med Res. 1992;1(2):159–81.
29 Gamborg M, Andersen PK, Baker JL, Budtz-Jorgensen E, Jensen G, Sorensen TI. Life course path analysis of birth weight, childhood growth, and adult systolic blood pressure. Am J Epidemiol. 2009;169:1167–78.
30 Kline RB. Principles and practice of structural equation modeling. New York: Guilford Press; 2004. Vol. 2.
31 Hair JF, Black WC, Babin BJ, Anderson RE, Tatham RL. Análise multivariada de dados. 6th ed. Porto Alegre: Bookman; 2009.
32 Hu LT, Bentler PM. Cutoff criteria for fit indexes in covariance structure analysis: conventional criteria versus new alternatives. Struct Equ Model. 1999;6(1):1–55.
33 Hooper D, Coughlan J, Mullen M. Structural equation modeling: guidelines for determining model fit. J Business Res Methods. 2008;6: 53–60.
34 Baltar VT, Xun WW, Johansson M, Ferrari P, Chuang S, Relton C, et al. A structural equation modelling approach to explore the role of B vitamins and immune markers in lung cancer risk. Eur J Epidemiol. 2013;28:677–88.
35 Thomas MC, Brownlee M, Suszlak K, Sharma K, Jandeleit-Dahm KA, Zoungas S, et al. Diabetic kidney disease. Nat Rev Dis Primers. 2015;1:15018.
36 Wickman C, Kramer H. Obesity and kidney disease: potential mechanisms. Semin Nephrol. 2013;33:14–22.
37 Da Silva PM, Carvalho D, Nazare J, Martins L, Aguiar C, Manso MC, et al. Prevalence of microalbuminuria in hypertensive patients with or without type 2 diabetes in a Portuguese primary care setting: the RACE (Microalbumin Screening Survey) study. Rev Port Cardiol. 2015;34(4):237–46.
38 Lee YY, Yang CK, Weng YM, Chuang CH, Yu W, Chen JC, et al. All components of metabolic syndrome are associated with microalbuminuria in a Chinese population. PLoS One. 2016;11(6):e0157303.
39 Bonnet F, Marre M, Halimi JM, Stengel B, Lange C, Laville M, et al. Waist circumference and the metabolic syndrome predict the development of elevated albuminuria in non-diabetic subjects: the DESIR Study. J Hypertens. 2006;24:1157–63.
40 Phani NM, Vohra M, Rajesh S, Adhikari P, Nagri SK, D'Souza SC, et al. Implications of critical PPARγ2, ADIPOQ and FTO gene polymorphisms in type 2 diabetes and obesity-mediated susceptibility to type 2 diabetes in an Indian population. Mol Genet Genomics. 2016;291:193–204.

41 Speakman JR. The "Fat Mass and Obesity Related" (FTO) gene: mechanisms of impact on obesity and energy balance. Curr Obes Rep. 2015;4(1):73–91.
42 Frayling TM, Timpson NJ, Weedon MN, Zeggini E, Freathy RM, Lindgren CM, et al. A common variant in the FTO gene is associated with body mass index and predisposes to childhood and adult obesity. Science. 2007; 316:889–94.
43 Sjogren M, Lyseenko V, Jonsson A, Berglund G, Nilsson P, Groop L, et al. The search for putative unifying genetic factors for components of the metabolic syndrome. Diabetologia. 2008;51:2242–51.
44 Hotta K, Nakata Y, Matsuo T, Kamhara S, Kotani K, Komatsu R, et al. Variations in the FTO gene are associated with severe obesity in the Japanese. J Hum Genet. 2008;53:546–53.
45 Adeyemo A, Chen G, Zhou J, Shriner D, Doumatey A, Huang H, et al. FTO genetic variation and association with obesity in West Africans and African Americans. Diabetes. 2010;59:1549–54.
46 Silva RC, Silva DA, Bastos JL, Peres KG, Gonzales-Chica DA. Anthropometric measures change and incidence of high blood pressure levels among adults: a population-based prospective study in Southern Brazil. J Hypertens. 2017;35(1):39–46.
47 Feng RN, Zhao C, Wang C, Niu Y, Li K, Guo F, et al. BMI is strongly associated with hypertension, and waist circumference is strongly associated with type 2 diabetes and dyslipidemia, in northern Chinese adults. J Epidemiol. 2012;22:317–23.
48 Fujita M, Sato Y, Nagashima K, Takahashi S, Hata A. Predictive power of a body shape index for development of diabetes, hypertension, and dyslipidemia in Japanese adults: a retrospective cohort study. PLoS One. 2015; 10:e0128972.
49 Emdin CA, Rahimi K, Neal B, Callender T, Perkovic V, Patel A. Blood pressure lowering in type 2 diabetes: a systematic review and meta-analysis. JAMA. 2015;313(6):603–15.
50 Boussageon R, Bejan-Angoulvant T, Saadatian-Elahi M, Lafont S, Bergeonneau C, Kassai B, et al. Effect of intensive glucose lowering treatment on all-cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ. 2011;343:d4169.
51 Thompson JE, Smith W, Ware LJ, Mels CMC, Van Rooyen JM, Huisman HW, et al. Masked hypertension and its associated cardiovascular risk in young individuals: the Africa-PREDICT study. Hypertens Res. 2016; 39:158–65.
52 Heerspink HJ, Kröpelin TF, Hoekman J, de Zeeuw D, Rooyen JM, Huisman HW, et al. Drug-induced reduction in albuminuria is associated with subsequent renoprotection: a meta-analysis. J Am Soc Nephrol. 2015;26(8): 2055–64.
53 Gheith O, Farouk N, Nampoory N, Halim MA, Al-Otaibi T. Diabetic kidney disease: worldwide difference of prevalence and risk factors. J Nephropharmacol. 2016;5(1):49–56.
54 Alicic RZ, Rooney MT, Tuttle KR. Diabetic kidney disease: challenges, progress, and possibilities. Clin J Am Soc Nephrol. 2017;12(12): 2032–45.