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RESEARCH ARTICLE

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The fat mass, estimated glomerular filtration rate, and chronic inflammation in type 2 diabetic patients

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Abstract

Background: The aim of the study was to analyze the degree of obesity and its associations with age, gender, inflammation, an estimated glomerular filtration rate (eGFR), and liver function in type 2 diabetes mellitus (T2DM) patients.

Methods: A total of 874 consecutive adult Caucasian T2DM patients from outpatient diabetic clinic were included in the study. The relative fat mass (RFM) and body mass index (BMI) were used as obesity markers. Serum creatinine and cystatin C were used for the GFR estimation. Serum high-sensitive C-reactive protein (hsCRP) was used as the indicator of inflammation.

Results: The median, interquartile range (IQR) of RFM in females was higher than that in males (44.8 (42.3-47.2) % vs 31.3 (28.8-34.1) %, respectively; $P < .0001$). The median (IQR) of BMI in females was no higher than that in males (30 (27-34) kg/m^2 vs 30 (27-34), respectively; $P = .5152$). The obesity prevalence was 99% in males and 98% in females according to RFM. BMI recognized obesity in 51% males and 53% females. RFM was positively associated with hsCRP in both males ($r_s = .296$, $P < .0001$) and females ($r_s = .445$, $P < .0001$). ALT was positively correlated with eGFRcys in both males ($r_s = .379$, $P < .0001$) and females ($r_s = .308$, $P < .0001$).

Conclusion: The RFM equation leads to higher obesity prevalence compared to BMI. Women have higher RFM compared to men. The kidney function was positively correlated with ALT serum concentrations.

KEYWORDS

abdominal fat, adipose tissue, alanine transaminase, body mass index, cystatin C, diabetes mellitus, glomerular filtration rate, inflammation, kidney diseases, obesity

1 | INTRODUCTION

Type 2 diabetes mellitus (T2DM) is associated with compromised health-related quality of life[1] and premature death from vascular disease and several types of cancers.[2]

Insulin resistance is the earliest feature in the development of T2DM. Insulin resistance is induced by obesity, inflammation,[3] and low physical activity.[4]

Conversely, physical activity accompanied by weight loss leads to improvement in insulin sensitivity.[5]

The positive energy balance leads to body weight gain.[6] Obese adipose tissue is characterized by the presence of leukocytes with subsequent increased production of pro-inflammatory cytokines leading to chronic subclinical inflammation.[7] The insulin receptor signal transduction is inhibited by inflammatory cytokines, which leads to the development of insulin resistance.[8]

The body mass index (BMI) is the most common index of the amount of whole-body adipose tissue. Mainly, the visceral adipose tissue induces the chronic inflammation and development of T2DM.[9] Recently, a relative fat mass (RFM) was suggested as a better estimator of whole-body fat percentage.[10] Lack of physical activity is associated with abdominal adiposity and low-grade inflammation independent of BMI.[11]

Simple obesity increases the risk of chronic kidney disease (CKD) independently of other risk factors.[12] CKD is a frequent long-term complication in elderly T2DM patients. Current clinical practice uses mainly the estimated glomerular filtration rate from serum creatinine (eGFRcrea) for the estimation of GFR.[13] However, older people may lose their muscle mass due to chronic conditions, which leads to overestimation of true GFR.

Cystatin C is an alternative marker of GFR, which does not depend on muscle mass[14] but some non-GFR factors also affect its serum concentration.[15] Cystatin C has the ability to select people at higher cardiometabolic risk compared to creatinine.[16] T2DM is also associated with nonalcoholic fatty liver disease (NAFLD).[17]

However, RFM is a new estimator of fat mass and the associations between RFM, eGFR, and chronic inflammation are unclear in T2DM patients. Therefore, we performed the study to analyze the degree of obesity and its associations with age, gender, inflammation, the estimated glomerular filtration rate (eGFR), and liver function in T2DM patients.

2 | MATERIALS AND METHODS

2.1 | Patients

This is a retrospective cross-sectional observational study. A total of 874 Caucasian consecutive patients with T2DM from outpatient diabetic clinic in Zlín (Czech Republic) were included in the study. The median (range) of their age was 68 (19-97) years. There were 474 males and 400 females. Data were collected from September 2018 to March 2019.

Waist circumference was measured by nurse as the widest waist circumference. All anthropometric parameters were measured by nurse on the same day as blood sampling.

The anthropometric parameters were calculated according to the following equations:

RFM (for males) = 64 − (20 × (height/waist))

RFM (for females) = 76 − (20 × (height/waist))

Height and waist circumference were measured in centimeters.

BMI = weight/height^2

Obesity was defined as BMI of at least 30 kg/m^2 for both genders or RFM ≥ 33.9% for women and ≥ 22.8% for men.[10]

2.2 | Laboratory methods

Fasting blood samples were collected by nurse using 6 mL VACUETTE® red top tubes with clot activator (Greiner Bio-One GmbH, Kremsmünster, Austria).

Serum creatinine was measured by the enzymatic method traceable to international standard reference material of NIST SRM 967.[18]

Cystatin C was measured by standardized immunoturbidimetric assay traceable to European Reference Material ERM-DA471/IFCC.[19]

The CKD-EPI equations were used for the estimation of GFR.[20,21] The CKD was defined as the eGFR value below 60 mL/min/1.73 m^2.[22]

The hsCRP method used six-point calibration traceable to European Reference Material ERM-DA472/IFCC. The systemic chronic inflammation was defined as serum hsCRP levels of ≥2.0 mg/L.[23]

The alanine aminotransferase activity (ALT) was measured in the presence of pyridoxal-5-phosphate. The kinetic method uses coupled enzyme reaction, and the rate of nicotinamide adenine dinucleotide phosphate (NADPH) consumption is measured at 340 nm.

2.3 | Statistical tests

The D'Agostino-Pearson test was used for normal distribution assessment. The normal distribution was rejected. We used nonparametric tests for statistical testing. The level of significance was defined as a *P* value below.05. The Spearman rank correlation coefficient was used for association evaluation. Mann-Whitney test for independent samples was employed for comparison of medians.

The analysis of data was performed by R statistical programming language version 3.6.0 (R Core Team).

3 | RESULTS

The median, interquartile range (IQR) of RFM in females was higher than that in males (44.8 (42.3-47.2) % vs 31.3 (28.8-34.1) %, respectively; $P < .0001$). The median (IQR) of BMI in females was no higher than that in males (30 (27-34) kg/m^2 vs 30 (27-34), respectively; $P = .5152$). The obesity prevalence was 99% in males and 98% in females according to RFM. BMI recognized obesity in 51% males and 53% females. RFM was positively associated with hsCRP in both males ($r_s = .296$, $P < .0001$) and females ($r_s = .445$, $P < .0001$). ALT was positively correlated with eGFRcys in both males ($r_s = .379$, $P < .0001$) and females ($r_s = .308$, $P < .0001$).

The clinical characteristics and sex differences are shown in Table 1.

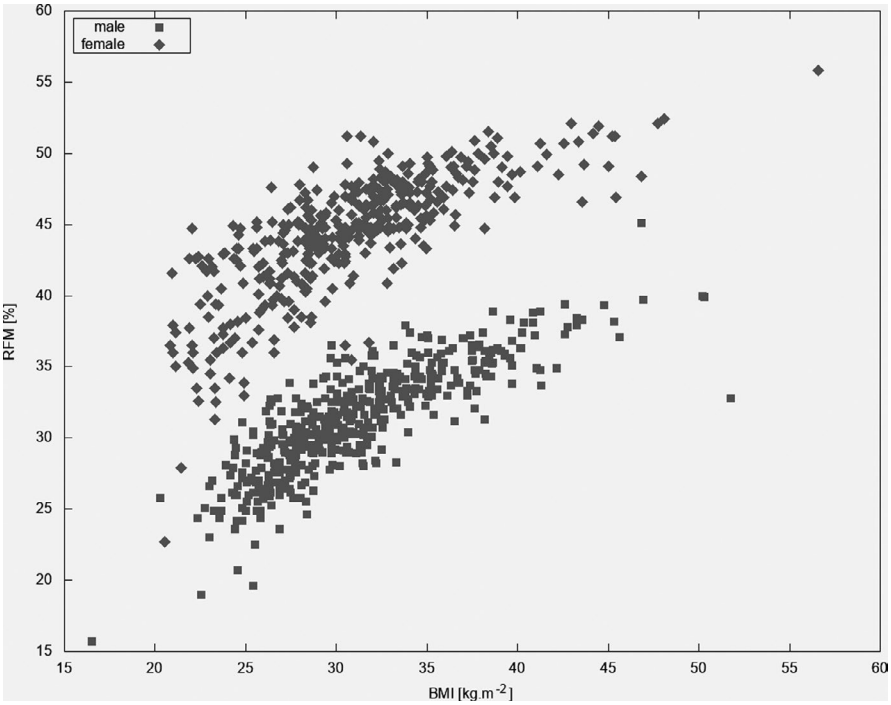
RFM and BMI in males and females are displayed in Figure 1.

TABLE 1 The clinical characteristics and sex differences

Variable	Males (n = 474) Median (IQR)	Females (n = 400) Median (IQR)	*P*
Age (y)	66 (58-72)	71 (63-79)	<.0001
RFM (%)	31.3 (28.8-34.1)	44.8 (42.3-47.2)	<.0001
BMI (kg/m^2)	30 (27-34)	30 (27-34)	.5152
eGFRcrea (mL/min/1.73 m^2)	79 (62-92)	71 (54-87)	.0017
eGFRcys (mL/min/1.73 m^2)	77 (61-95)	65 (51-84)	<.0001
hsCRP (mg/L)	1.9 (1.0-4.2)	2.4 (1.0-5.4)	.0265
ALT (ukat/L)	0.48 (0.34-0.67)	0.35 (0.26-0.49)	<.0001

Abbreviations: ALT, alanine aminotransferase; BMI, body mass index; eGFRcrea, estimated glomerular filtration rate from serum creatinine; eGFRcys, estimated glomerular filtration rate from serum cystatin C; hsCRP, high-sensitive C-reactive protein; RFM: relative fat mass.

FIGURE 1 The relative fat mass (RFM) and body mass index (BMI) in males and females



The associations between markers of obesity, age, eGFR, chronic inflammation, and ALT for all patients are displayed in Table 2.

The prevalence of obesity, CKD, and chronic inflammation in T2DM patients are shown in Table 3.

4 | DISCUSSION

We found much higher prevalence of obesity by RFM compared to BMI in T2DM patients. The RFM was higher in females compared to males. The positive association with hsCRP was observed for both RFM and BMI.

Batsis et al analyzed results from National Health and Nutrition Examination Survey (NHANES) performed between 1999 and 2004, and showed lower obesity rate according to BMI compared to body fat mass measurement by dual-energy X-ray absorptiometry. Participants of the NHANES study were recruited from general population, and obesity limits of body fat mass amount were defined at 25% for males and 35% for females. In the NHANES study, mean male percentage body fat was 30.6% at ages 60-79 years. Females in the same age range had mean percentage body fat of 42.6%.[24] Our study confirmed lower BMI-marked obesity rate in both sexes. These results support current knowledge on pathophysiological development of T2DM. Fat mass promotes both insulin resistance and chronic inflammation development. The diagnosis of T2DM is at the end of these interrelated pathophysiological processes. It may be reason that nearly, all T2DM patients were obese by RFM.

Schorr et al demonstrated differences in body composition between men and women. Women had higher percentage of fat mass, and men had larger visceral adipose tissue, which means higher cardiometabolic risk for men.[25] It is consistent with our RFM results, which are significantly different between males and females.

TABLE 2 Spearman's rank correlation coefficients between markers of obesity, age, eGFR, chronic inflammation, and ALT

	Sex	RFM	BMI	Age	eGFR crea	eGFR cys	hsCRP	ALT
RFM	M		**0.851****	−0.068	0.044	**−0.114**	**0.296****	0.060
	F		**0.804****	−0.001	−0.049	**−0.193***	**0.445****	0.008
BMI	M	**0.851****		**−0.282****	**0.142**	0.031	**0.284****	**0.178****
	F	**0.804****		**−0.203****	0.072	−0.048	**0.470****	0.092
Age	M	−0.068	**−0.282****		**−0.598****	**−0.577****	−0.082	**−0.474****
	F	−0.001	**−0.203****		**−0.668****	**−0.681****	**−0.140**	**−0.340**
eGFR crea	M	0.044	**0.142**	**−0.598****		**0.762****	−0.020	**0.336****
	F	−0.049	0.072	**−0.668****		**0.845****	0.060	**0.233****
eGFR cys	M	**−0.114**	0.031	**−0.577****	**0.762****		**−0.208****	**0.379****
	F	**−0.193****	−0.048	**−0.681****	**0.845****		−0.083	**0.308****
hsCRP	M	**0.296****	**0.284****	−0.082	−0.020	**−0.208****		−0.033
	F	**0.445****	**0.470****	**−0.140**	0.060	−0.083		0.000
ALT	M	0.060	**0.178****	**−0.474****	**0.336****	**0.379****	−0.033	
	F	0.008	0.092	**−0.340****	**0.233****	**0.308****	0.000	

Abbreviations: ALT, Alanine aminotransferase; BMI, Body mass index; eGFR crea, estimated glomerular filtration rate from serum creatinine; eGFR cys, estimated glomerular filtration rate from serum cystatin C; hsCRP, high-sensitive C-reactive protein; RFM: relative fat mass.

$P < .01$ (bold).

*$P < .001$ (bold).

**$P < .0001$ (bold); 474 males, 400 females.

TABLE 3 The prevalence of obesity, CKD, and chronic inflammation in T2DM patients

	Males (n = 474)	Females (n = 400)	*P*
Obesity by RFM	469 cases (98.9%)	392 cases (98.0%)	.921
Obesity by BMI	242 cases (51.1%)	212 cases (53.0%)	.747
CKD according to eGFRcrea	100 cases (21.1%)	132 cases (33.0%)	.090
CKD according to eGFRcys	105 cases (22.2%)	155 cases (38.8%)	.0001
Chronic inflammation by hsCRP	233 cases (49.2%)	221 cases (55.3%)	.313

Abbreviations: BMI, body mass index; CKD, chronic kidney disease; eGFRcrea, estimated glomerular filtration rate from serum creatinine; eGFRcys, estimated glomerular filtration rate from serum cystatin C; hsCRP, high-sensitive C-reactive protein; RFM, relative fat mass.

Park et al reported positive association between obesity and hsCRP.[26] It is consistent with our results.

Leung et al found higher hsCRP in people with central obesity compared to subjects without central obesity. Waist circumference was measured at the widest point of the waist.[27] It supports our results of increased hsCRP in patients with higher results of both RFM and BMI.

Wang et al showed in the meta-analysis involving 22 cohorts, with a total of 40 735 participants and 5,753 cases, that elevated CRP levels were significantly associated with increased risk of T2DM.[28] This interrelationship between T2DM and inflammation may be in accordance with our finding of high proportion of elevated levels of hsCRP in our cohort of patients with overt T2DM.

Dias et al reported that the GFR was decreasing with increasing mean values of nutritional indicators of abdominal obesity regardless of sex.[29] Our study found inverse trends in association between RFM and eGFRcys in females ($r_s = -.193$, $P < .0001$) and in males ($r_s = -.114$, $P = .01$).

Wang et al performed meta-analysis of 21 studies, which concluded that obesity increases the risk for CKD in the general population, and the association appears to be stronger in women than in men. Overweight people have a 40% higher risk for CKD.[30] Our cohort of T2DM patients had high proportion of CKD patients according to both eGFRcrea and eGFRcys. The negative correlation between RFM and eGFRcys was also higher in women compared to men.

Adiga et al reported positive correlation between eGFR and ALT in T2DM patients.[31] The positive association between ALT and both eGFRcrea and eGFRcys in our patients is in accordance with this study.

The development of T2DM is much more complex. Qiu et al reported that blood microbiome may play a role in the development of T2DM.[32] Ghasemi et al showed that genetic polymorphism has a role

in T2DM development.[33] Peng et al demonstrated that serum carbohydrate antigen 153 negatively correlates with renal function in T2DM patients.[34] We did not include these laboratory tests in our study. The limitations of this study are the absence of the reference methods for the determination of body fat percentage and GFR.

In summary, the RFM equation leads to much higher obesity prevalence compared to BMI. This knowledge of body composition should impact the clinical practice. Women have higher RFM compared to men. The positive association with hsCRP was observed for both RFM and BMI. The kidney function was positively correlated with serum ALT concentration.

ETHICAL APPROVAL

The study was approved by the Institutional Hospital Ethics Committee in Zlín, Czech Republic, and performed according to the Declaration of Helsinki. The informed consent was obtained from all patients.

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REFERENCES

1. Cannon A, Handelsman Y, Heile M, et al. Burden of Illness in Type 2 Diabetes Mellitus. *J Manag Care Spec Pharm*. 2018;24:S5-S13.
2. Rao Kondapally Seshasai S, Kaptoge S, Thompson A, et al. Fasting glucose, and risk of cause-specific death. *N Engl J Med*. 2011;364:829-841.
3. Stafeev IS, Vorotnikov AV, Ratner EI, et al. Latent inflammation and insulin resistance in adipose tissue. *Int J Endocrinol*. 2017;2017:1-12.
4. Eisenmann JC, DuBose KD, Donnelly JE. Fatness, fitness, and insulin sensitivity among 7- to 9-year-old children. *Obesity*. 2007;15:2135-2144.
5. Swift DL, Houmard JA, Slentz CA, et al. Effects of aerobic training with and without weight loss on insulin sensitivity and lipids. *PLoS ONE ONE*. 2018;13:e0196637.
6. Vandevijvere S, Chow CC, Hall KD, et al. Increased food energy supply as a major driver of the obesity epidemic: a global analysis. *Bull World Health Organ*. 2015;93(7):446-456.
7. Suganami T, Ogawa Y. Adipose tissue macrophages: their role in adipose tissue remodeling. *J Leukoc Biol*. 2010;88:33-39.
8. Wellen KE, Hotamisligil GS. Inflammation, stress, and diabetes. *J Clin Invest*. 2005;115:1111-1119.
9. Janochova K, Haluzik M, Buzga M. Visceral fat and insulin resistance - what we know? *Biomedical Papers*. 2019;163(1):19-27.
10. Woolcott OO, Bergman RN. Relative fat mass (RFM) as a new estimator of whole-body fat percentage — A cross-sectional study in American adult individuals. *Sci Rep*. 2018;8:10980.
11. Wedell-Neergaard A-S, Eriksen L, Grønbæk M, et al. Low fitness is associated with abdominal adiposity and low-grade inflammation independent of BMI. *PLoS ONE*. 2018;13(1):e0190645.
12. Sikorska D, Grzymislawska M, Roszak M, et al. Simple obesity and renal function. *J Physiol Pharmacol Off J Pol Physiol Soc*. 2017;68:175-180.
13. Kim KS, Park SW, Cho YW, et al. Higher prevalence and progression rate of chronic kidney disease in elderly patients with Type 2 diabetes mellitus. *Diabetes Metab J*. 2018;42:224-232.
14. Jeon YL, Kim MH, Lee W-I, et al. Cystatin C as an early marker of diabetic nephropathy in patients with type 2 diabetes. *Clin Lab*. 2013;59:1221-1229.
15. Stevens LA, Schmid CH, Greene T, et al. Factors other than glomerular filtration rate affect serum cystatin C levels. *Kidney Int*. 2008;75:652-660.
16. Shlipak MG, Matsushita K, Ärnlöv J, et al. Cystatin C versus creatinine in determining risk based on kidney function. *N Engl J Med*. 2013;369:932-943.
17. Manoria P, Inamdar S, Kumar R. Hepatobiliary dysfunction in Type-2 diabetes mellitus. *J Fam Med Prim Care*. 2017;6:563-567.
18. Dodder NG, Tai SS-C, Sniegoski LT, et al. Certification of creatinine in a human serum reference material by GC-MS and LC-MS. *Clin Chem*. 2007;53:1694-1699.
19. Grubb A, Blirup-Jensen S, Lindström V, et al. First certified reference material for cystatin C in human serum ERM-DA471/IFCC. *Clin Chem Lab Med*. 2010;48:1619-1621.
20. Levey AS, Stevens LA, Schmid CH, et al. A new equation to estimate glomerular filtration rate. *Ann Intern Med*. 2009;150:604-612.
21. Inker LA, Schmid CH, Tighiouart H, et al. Estimating glomerular filtration rate from serum creatinine and Cystatin C. *N Engl J Med*. 2012;367:20-29.
22. Kidney Disease | Improving Global Outcomes. Chapter 1: Definition and classification of CKD. *Kidney Int Suppl*. 2013;3:19-62.
23. Kostapanos MS, Elisaf MS. JUPITER and satellites: Clinical implications of the JUPITER study and its secondary analyses. *World J Cardiol*. 2011;3:207-214.
24. Batsis JA, Mackenzie TA, Bartels SJ, et al. Diagnostic accuracy of body mass index to identify obesity in older adults: NHANES 1999–2004. *Int J Obes*. 2016;40:761-767.
25. Schorr M, Dichtel LE, Gerweck AV, et al. Sex differences in body composition and association with cardiometabolic risk. *Biol Sex Differ*. 2018;9:28.
26. Park C-H, Do JG, Lee Y-T, et al. Sarcopenic obesity associated with high-sensitivity C-reactive protein in age and sex comparison: a two-center study in South Korea. *BMJ Open*. 2018;8(9):e021232.
27. Leung WKC, Yu AP, Lai CWK, et al. Association of markers of proinflammatory phenotype and beige adipogenesis with metabolic syndrome in chinese centrally obese adults. *J Diabetes Res*. 2018;2018:8956509.
28. Wang X, Bao W, Liu J, et al. Inflammatory markers and risk of Type 2 diabetes. *Diabetes Care*. 2013;36:166-175.
29. Dias RSC, Calado IL, de Alencar JD, et al. Abdominal obesity and reduction of glomerular filtration. *Rev Assoc Médica Bras*. 2018;64:346-353.
30. Wang Y, Chen X, Song Y, et al. Association between obesity and kidney disease: a systematic review and meta-analysis. *Kidney Int*. 2008;73:19-33.
31. Adiga US, Malawadi BN. Association of diabetic nephropathy and liver disorders. *J Clin Diagn Res*. 2016;10:BC05-BC07.
32. Qiu J, Zhou H, Jing Y, Dong C. Association between blood microbiome and type 2 diabetes mellitus: A nested case-control study. *J Clin Lab Anal*. 2019;33:e22842.
33. Ghasemi H, Karimi J, Khodadadi I, Saidijam M, Tavilani H. Association between rs2278426 (C/T) and rs892066 (C/G) variants of ANGPTL8 (betatrophin) and susceptibility to type2 diabetes mellitus. *J Clin Lab Anal*. 2019;33:e22649.
34. Peng Y-F, Lin H, Han M-M, Li L. Serum carbohydrate antigen 153 and renal function in patients with type 2 diabetes mellitus. *J Clin Lab Anal*. 2018;32:e22461.

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