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A high lean body mass is not protecting from type 2 diabetes in the presence of a high body fat mass

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Abstract

Aim

Most studies examining the associations between body composition and type 2 diabetes have been cross-sectional with prevalent diabetes diagnosis or they have analyzed only fat or lean body mass. Hence, the combined effect of fat and lean body mass on the risk of developing type 2 diabetes remains unclear. We investigated whether baseline lean and fat body mass taken simultaneously into account are associated with incidence of type 2 diabetes over a 15-year follow-up in older adults.

Methods

We studied 704 men (n=297) and women (n=407) from the Helsinki Birth Cohort Study (mean age 61 years at baseline) without diabetes at baseline. Bioelectrical impedance analysis was used to derive baseline fat mass index (FMI, fat mass/height^2) and lean mass index (LMI, lean mass/height^2), dichotomized at sex-specific medians. Incident diabetes was defined as the composite of fasting plasma glucose (FPG) $\geq$ 7.0 mmol/l, haemoglobin A_{1c} (HbA_{1C}) $\geq$ 6.5% (48 mmol/mol) or physician-based diagnosis.

Results

After a median 14.8 (range 12.5–16.8) years of follow-up, 110 incident diabetes cases occurred (15.6%). Participants with high FMI and LMI at baseline had higher composite incidence of type 2 diabetes ($p < 0.001$), and significantly increased risk of type 2 diabetes after adjustment for potential confounding factors (sex, physical activity, education and body mass index) compared to the other participants.

Conclusion

Contrary to a general belief greater muscle mass is not protective against type 2 diabetes. High LMI accompanied with high FMI seem to predict subsequent development of type 2 diabetes.

Key words:

Fat mass index, lean mass index, type 2 diabetes

Abbreviations:

BCAA, branched-chain amino acid

BIA, bioelectrical impedance analysis

DXA, dual-energy X-ray absorptiometry

FPG, fasting plasma glucose

FMI, fat mass index

MET, metabolic equivalent

LMI, lean mass index

LTPA, leisure-time physical activity

Introduction

The global epidemics of obesity and type 2 diabetes in combination with an aging population represent a serious challenge to healthcare and global economy. A concomitant increase in type 2 diabetes parallels the increased incidence of obesity. Nearly one third of the world´s adult population is overweight or obese [1], and 1 in 11 adults has type 2 diabetes [2]. The highest prevalence of type 2 diabetes is among the older adults [3].

Although the relationship of excess adiposity to insulin resistance and type 2 diabetes is a long-recognized phenomenon [4-6], it is obscure how body composition, i.e. lean mass and fat mass, relate to the development of type 2 diabetes.

In clinical practice obesity is typically estimated by body mass index (BMI). Although BMI is a useful measure of overweight and obesity predicting many health outcomes [7,8], a downside of BMI is that it does not account for body composition and it is less applicable to older adults [9]. Instead, measurement of body composition and splitting BMI into lean mass index (LMI) and fat mass index (FMI), defined as lean/fat mass divided by the square of height analogously to BMI, may be a more suitable approach.

Our recent study demonstrated that among 60 year old men high LMI accompanied with high FMI was associated with insulin resistance, whereas in women LMI had little influence on glucose metabolism [10]. Previous cross-sectional studies have also demonstrated that increased appendicular skeletal muscle mass in elderly Koreans and in postmenopausal women muscle mass was related to insulin resistance [11,12]. Hence, it may be assumed that the more lean mass, the higher the risk of developing type 2 diabetes in an elderly population.

Several cross-sectional studies have investigated body composition in persons with type 2 diabetes compared with healthy controls. The results have been inconsistent. Persons with type 2 diabetes have been shown to have more lean mass and truncal fat mass as well as greater muscle and abdominal adipose tissue areas than persons with normal glucose tolerance [13,14]. Some smaller studies reported no difference in total lean mass in premenopausal women with type 2 diabetes compared to controls [15-17].

In a longitudinal setting, higher total lean mass [18-20] and higher body fat percentage [21] are known to be associated with a higher incidence of diabetes. However, in one study the association disappeared after adjusting for measures of fat mass [18,20] and in another study lean mass indexed to body weight was positively related to type 2 diabetes among young adults and old men [19,21].

Taken together, the association of body composition and incidence of type 2 diabetes - especially the combined influence of lean mass and fat mass on the development of type 2 diabetes - is far from complete understanding.

Thus, the aim of this study was to examine the combined effect of baseline LMI and FMI on subsequent development of type 2 diabetes during a nearly 15-year period of follow-up among older adults without diabetes at baseline.

Methods

Participants

The Helsinki Birth Cohort Study (HBCS) includes 8760 men and women who were born at Helsinki University Central Hospital between 1934 and 1944. Of these people, 2691 individuals were randomly selected to participate in a clinical examination in 2001–2004 to reach a target of 2000 participants. In total, 2003 individuals participated in the baseline clinical examination. The age range of the participants was 56–69 years (mean 61 years) at baseline. Follow-up examinations were performed in 2017–2018 when the participants were 72–84 years old (mean 75 years). Participants with diabetes at baseline were excluded from the present analysis. Thus, 704 participants with sufficient data were identified.

Measurements at baseline

Trained study nurses performed all clinical measurements. Body composition was assessed by bioelectrical impedance analysis (BIA) using the InBody 3.0 eight-polar tactile electrode system (Biospace Co, Ltd, Seoul, Korea) [22]. The instrument estimates lean body mass and body fat mass by segmental multi-frequency (5, 50, 250, and 500 kHz) analysis. The measurements were made with the subject standing in light indoor clothing on the four foot electrodes on the platform of the analyzer and gripping the two palm and thumb electrodes. This method was chosen because of its practicality in large epidemiologic studies [22,23]. Lean and fat mass indices were calculated as follows: lean mass index (LMI, kg/m^2) = lean mass/height^2 and fat mass index (FMI, kg/m^2) = fat mass/height^2.

Lean and fat mass indices were divided according to median values, separately for men and women, and four body composition categories were created: (A) low FMI and low LMI (LFLL), (B) low FMI and high LMI (LFHL), (C) high FMI and low LMI (HFLL), (D) high FMI and high LMI (HFHL).

Height and weight were measured in light indoor clothing without shoes. Height was measured with a Kawi stadiometer to the nearest 0.1 cm. Weight was measured on Seca Alpha 770 scales to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Waist circumference was measured at the level midway between the lowest rib and the iliac crest, and rounded to the nearest 0.1 cm. The participants were asked to breathe out gently at the time of measurement, and the tape was held firmly in a horizontal position. The average of the two measurements was calculated.

The clinical examination included a 2-hour 75-g oral glucose tolerance test and blood tests after an overnight fast, and measurement of blood pressure.

Plasma insulin concentrations were determined by two-site immunometric assay. The HOMA-β and HOMA-IR for an index of the β-cell function and insulin resistance were calculated using the following formulas: HOMA-β (%) = (20 × FPI)/(FPG − 3.5) and HOMA-IR = FPG × FPI/22.5, respectively, where FPI is fasting plasma insulin concentration (mU/l) and FPG is fasting plasma glucose (mmol/l) [24].

Serum cholesterol and triglyceride concentrations were measured with the use of standard enzymatic methods.

Blood pressure was measured by the study nurse with a calibrated mercury sphygmomanometer (Omron Matsutaka Europe, Hoofdorp, the Netherlands) with participants in a sitting posture, after resting ten minutes with the cuff placed on the right arm. The mean of two readings taken at intervals of at least two minutes was used determine blood pressure level.

Information on education years and lifestyle was obtained using a questionnaire administered at baseline. Smoking was dichotomized (current smoker yes/no). Leisure-time physical activity (LTPA) was assessed with the validated 12-month Kuopio Ischemic Heart Disease questionnaire [25]. With the questionnaire information on type, mean duration/month and mean frequency/month of LTPA was collected. For each intensity grade, activity-specific metabolic equivalent (MET) values were used. Total LTPA, including both non-conditioning (e.g., housework) and conditioning (e.g., resistance training) physical activity, was computed and is expressed in METhours per week.

Measurements at the follow up

Fasting plasma glucose (FPG) and haemoglobin A1c (HbA1c) concentrations were measured. The study participants were determined to have type 2 diabetes if they reported to have type 2 diabetes diagnosed by a physician in a questionnaire, or if their FPG value was ≥ 7.0 mmol/l or HbA1c value was ≥ 6.5% (48 mmol/mol) [26]. Composite incidence of type 2 diabetes was calculated based on these criteria. Plasma glucose concentrations were measured according to the hexokinase method.

Informed consent

Written informed consent was obtained from each participant before any procedures were carried out. The Ethics Committee for Epidemiology of Helsinki and Uusimaa Hospital District approved the study.

Statistical analysis

Data are expressed as the mean and standard deviation (SD), the median and interquartile range (IQR), or counts and percentages, as appropriate. Statistical comparisons between the four body composition categories were made by using chi-square test or generalised linear models (ANOVA, logit models) with appropriate distribution and link functions. Adjusted models included sex, LTPA, education years and BMI

at baseline as covariates. Relationships between fat mass index and lean mass index were derived from linear regression models. The significance for pairwise comparisons were correct for multiplicity using Hommel's multiple comparison procedure (at significance level 0.05). Normal distributions were evaluated graphically and with the Shapiro–Wilk W test. All analyses were performed with Stata 16.1 (StataCorp LP; College Station, TX, USA).

Results

The study included 704 participants (mean age 61 ± 3 years at baseline, 58% women) without diabetes at baseline. The relationships between fat mass index and lean mass index and the median-split categories of body composition in women and men are shown in Figure 1.

The characteristics of the participants at baseline are presented in Table 1 according to gender-specific categorization as having low or high FMI or LMI. The four body composition categories (LFLL, LFHL, HFLL, HFHL) did not differ with respect to sex, LTPA, smoking and total cholesterol. BMI and waist circumference increased with increasing FMI and LMI. Persons with high FMI had higher body fat percentage, higher concentrations of 2-h plasma glucose, fasting and 2-h plasma insulin, and triglycerides than persons with low FMI. Participants in the HFHL category had the highest FPG and LDL concentrations, systolic and diastolic blood pressure and the lowest HDL concentrations.

Median follow-up time was 14.8 years, during which incident type 2 diabetes occurred in 8.9% in the LFLL category (n = 22), 10.5% in the LFHL category (n = 11), 10.5% in the HFLL category (n = 11), and 26.6% in the HFHL category (n = 66), respectively.

In the HFHL category, concentrations of HbA_{1c} and FPG at follow-up, number of subjects diagnosed with type 2 diabetes by a physician and the composite incidence of type 2 diabetes were significantly higher than in all other categories (for all, $p < 0.001$) (Fig. 2).

After adjustment of sex, LTPA, education years and BMI at baseline HFHL was associated with an increased risk of type 2 diabetes compared to the other categories (LFLL: odds ratio (OR) 0.41, 95% CI 0.19–0.91; LFHL: OR 0.44, 95% CI 0.20–0.98; HFLL: OR 0.39, 95% CI 0.19–0.83). There was no difference between LFLL, LFHL and HFLL categories in relation to the risk of developing type 2 diabetes ($p = 0.97$).

Discussion

Our study suggests that persons with high FMI and high LMI have the most unfavorable cardiometabolic risk profile. The combination of high FMI and high LMI among community-living 60 year old adults is

associated with an elevated risk of developing type 2 diabetes during a 15-year follow-up period. Contrary to a general belief that greater muscle mass – the predominant part of lean body mass – is protective against type 2 diabetes is not supported by our findings. Our results indicate, that a high lean mass accompanied with fatness may be detrimental for glucose regulation and may predict subsequent development of type 2 diabetes.

To the best of our knowledge, the combined effect of lean mass and fat mass indexed to body height on development of type 2 diabetes has not been previously investigated. Similar to our findings, in a substudy of the Look AHEAD trial, participants with type 2 diabetes had more lean mass and more truncal fat mass, yet, less total fat mass, than healthy controls [13]. Further, in the Health ABC study, muscle and abdominal adipose tissue areas were larger in persons with type 2 diabetes than in persons with normal glucose tolerance [14]. Maiolo et al. reported non-significantly more lean mass and less fat mass in women with type 2 diabetes compared to women with normal glucose tolerance [15]. Svendsen and Hassager detected more total fat mass in premenopausal but not in postmenopausal women with type 2 diabetes compared to healthy controls. Additionally, they found no difference in total lean mass irrespective of age, menopausal or diabetes status [16]. Furthermore, Poynten et al. observed no difference in lean mass nor fat mass between weight and BMI-matched controls and persons with type 2 diabetes [17].

Both in the longitudinal Health ABC Study and in the Danish Diet, Cancer and Health cohort study total lean mass was positively associated with a higher incidence of type 2 diabetes. This association appeared to be largely explained by the fact that those with more lean mass had also more fat mass because no association remained significant after adjusting for body size and body composition or fat mass [18,20]. Kalyani et al. observed in the Baltimore Longitudinal Study of Aging, that higher total lean mass was associated with a higher risk of type 2 diabetes even after accounting for total body fat [19]. Hong et al. reported a positive relationship between body fat percentage and incident type 2 diabetes in Korean men and women with a median age of 39 years at baseline [21]. However, both in the study by Kalyani et al. and in the study by Hong et al. opposite findings were observed. In other words relative lean mass, i.e. lean mass indexed to body weight, was inversely associated with the incidence of type 2 diabetes in men in the study of Kalyani et al. and in both genders in the study of Hong et al. [19,21]. Nevertheless, participants with low relative lean mass may have high relative fat mass, and the latter may be the cause of their higher incidence of type 2 diabetes. This potential confounder is of concern when lean mass is indexed to body weight, because increases in fat mass translate to reductions in the lean mass fraction of body weight. To obviate such difficulty, this confounder is less relevant, as lean/fat mass is divided by the square of height analogously to BMI, the approach we adopted. Additionally, by dividing participants into body composition categories, we aimed at reducing confounding between fat and lean mass indices.

We showed that the markers of glucose regulation were the highest in the HFHL category also at baseline indicating a disturbance in glucose metabolism among persons in the HFHL category even before overt hyperglycemia develops. Considering underlying pathophysiological mechanisms increased skeletal muscle lipid infiltration has been shown to impair the normal physiological function of skeletal muscle and to be an independent risk factor for insulin resistance and type 2 diabetes [27-30]. A greater muscle lipid content was also observed to be a characteristic feature of older adults with type 2 diabetes [14].
In respect of metabolomics, that is, determination of small particles in serum related to metabolism, circulating amino acids, especially branched-chain amino acids (BCAAs), have been linked to obesity, insulin resistance, and type 2 diabetes [31-33]. BCAAs have been introduced to be indicators of metabolic disturbances rather than that of obesity [31,34]. BCAA overload may even have a causal role in developing insulin resistance and type 2 diabetes [31,35]. In our study population, both FMI and LMI have been shown to associate positively with BCAAs in both genders regardless glucose concentrations [36].

The findings in our study have several clinical implications. Our results challenge the general assumption that more skeletal muscle mass is beneficial for glucose homeostasis. Instead, we showed that obese people are not protected against the risk of developing type 2 diabetes by having a high lean mass - quite the opposite. Our findings indicate that among people without excess body fat the size of lean mass, which is mostly composed of skeletal muscle tissue, is not crucial for glucose regulation, whereas having more adipose tissue together with higher lean mass contribute to development of type 2 diabetes. In obese people higher amount of lean mass might be a natural consequence: more muscle mass is needed to carry the excess body fat. Our findings could help direct public health resources toward programs that target weight management to people, who might benefit most. Preventive strategies should focus on obesity prevention and weight loss through aerobic exercise and dietary changes in order to reduce the risk of type 2 diabetes [37,38]. Such approaches may indeed be the most appropriate for overweight/obese individuals, who would likely benefit more from losing excess fat than gaining more muscle.

A strength of this study is that we simultaneously took into account both fat and lean mass and their interaction, which may have a mutual confounding effect on development of type 2 diabetes. The study includes a representative sample of 60 year old individuals at baseline. Follow-up time was notable 15 years. Limitations of our study include that use of dual-energy X-ray absorptiometry (DXA) in assessing body composition would have ensured better validity. However, the BIA method has been validated against DXA and is acceptably reliable for body composition measurements [39]. Additionally, body composition was assessed only at the baseline and measuring body composition does not take into account metabolism of fat nor muscle tissue. A characteristic feature of studies consisting of older adults, including the present study,

is that there is a considerable loss of participants in the follow-up. These factors may have influenced our results.

In conclusion, greater amount of both fat and lean mass is associated with development of type 2 diabetes among adults in their sixties. Future studies are needed to investigate whether changes in body composition in later life alter the risk of developing type 2 diabetes.

Conflicts of interest

The authors declare that there is no conflicts of interest associated with this manuscript.

Authors´ contributions

SR drafted the manuscript with major input from all authors. HK performed statistical analyses. All authors contributed to the interpretation of data and critically reviewed and approved the final manuscript before submission. SR is the guarantor of this work.

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	FMI low		FMI high		P-value [multiple comparison]*
	LMI low (A)	LMI high (B)	LMI low (C)	LMI high (D)	
Women, n (%)	147 (60)	56 (53)	56 (53)	148 (60)	0.48
Demographic					
Age, years	61 (3)	61 (2)	62 (3)	61 (3)	0.045 [B/C]
Education years	12.7 (3.5)	12.1 (3.2)	12.2 (3.6)	11.6 (3.0)	<0.001 [A/D]
BMI, kg/m^2	23.3 (1.7)	25.7 (1.3)	26.9 (1.5)	30.7 (3.1)	<0.001 [All]
% Fat	24.1 (6.2)	22.5 (5.4)	31.8 (6.2)	33.2 (7.2)	<0.001 [A/C, A/D, B/C, B/D]
Waist, cm					
women	79 (6)	85 (6)	89 (6)	98 (9)	<0.001 [All]
men	89 (6)	95 (5)	100 (5)	107 (9)	<0.001 [All]
METhours per week	40.9 (24.3)	39.2 (25.6)	35.8 (23.1)	37.0 (27.3)	0.20
Current smoker, % (n)	15 (38)	23 (24)	18 (19)	13 (33)	0.15
Laboratory					
FPG, mmol/l	5.31 (0.53)	5.33 (0.47)	5.48 (0.51)	5.59 (0.54)	<0.001 [A/C, A/D, B/D]
2-h PG, mmol/l	6.33 (1.62)	6.34 (1.68)	7.19 (1.64)	7.02 (1.57)	<0.001 [A/C, A/D, B/C, B/D]
Fasting plasma insulin, mU/l	6.32 (3.51)	7.26 (4.22)	10.75 (16.00)	12.13 (12.71)	<0.001 [A/C, A/D, B/C, B/D]
2-h plasma insulin, mU/l	48.6 (33.6)	51.9 (49.2)	79.1 (48.2)	87.8 (69.2)	<0.001 [A/C, A/D, B/C, B/D]
Homa-β, %	72 (38)	85 (58)	117 (179)	125 (150)	<0.001 [A/D, B/D]
Homa-IR	1.52 (0.93)	1.72 (0.99)	2.62 (3.79)	3.02 (3.04)	<0.001 [A/C, A/D,B/D]
Cholesterol, mmol/l					
Total	5.83 (0.97)	5.97 (0.87)	5.98 (1.10)	6.05 (1.10)	0.13
HDL	1.79 (0.43)	1.72 (0.46)	1.63 (0.40)	1.54 (0.39)	<0.001 [A/C,A/D, B/D]
LDL	3.52 (0.81)	3.71 (0.78)	3.70 (0.94)	3.78 (0.89)	0.011 [A/D]
Triglycerides, mmol/l	1.17 (0.60)	1.21 (0.55)	1.46 (0.77)	1.64 (0.82)	<0.001 [A/C, A/D, B/C, B/D]
Clinical					
Blood pressure, mmHg					
Systolic	137 (19)	139 (20)	143 (21)	148 (17)	<0.001 [A/C, A/D, B/D]
Diastolic	85 (10)	85 (9)	89 (10)	91 (10)	<0.001 [A/C, A/D, B/D]

Table 1. The characteristics of study participants at baseline according to gender-specific categorization as having low or high fat mass index (FMI) or lean mass index (LMI).

Data are mean (SD), except where indicated.

FPG, fasting plasma glucose; 2-h PG, 2-hour plasma glucose

*Hommel's multiple comparison procedure was used to correct significance levels for post hoc testing ($p < 0.05$).

Figure legends:

Figure 1. The relationship between fat mass index (FMI) and lean mass index (LMI) in women and men at baseline. The line shows estimated linear regression with 95% confidence intervals.
The dashed lines indicate medians of FMI and LMI.

Figure 2. Mean haemoglobin A_{1c} (HbA_{1c}) and fasting plasma glucose, percentage of subjects with type 2 diabetes diagnosed by a physician and the composite incidence of type 2 diabetes (DM) at follow-up according to body composition category at baseline: A low fat mass index (FMI) and low lean mass index (LMI), B low FMI and high LMI, C high FMI and low LMI, D high FMI and high LMI (HFHL).

There were no gender difference nor interactions between FMI and LMI on these variables.

Error bars are for 95% Cis.

Comparison of the HFHL category to the other categories $p < 0.001$, for all.

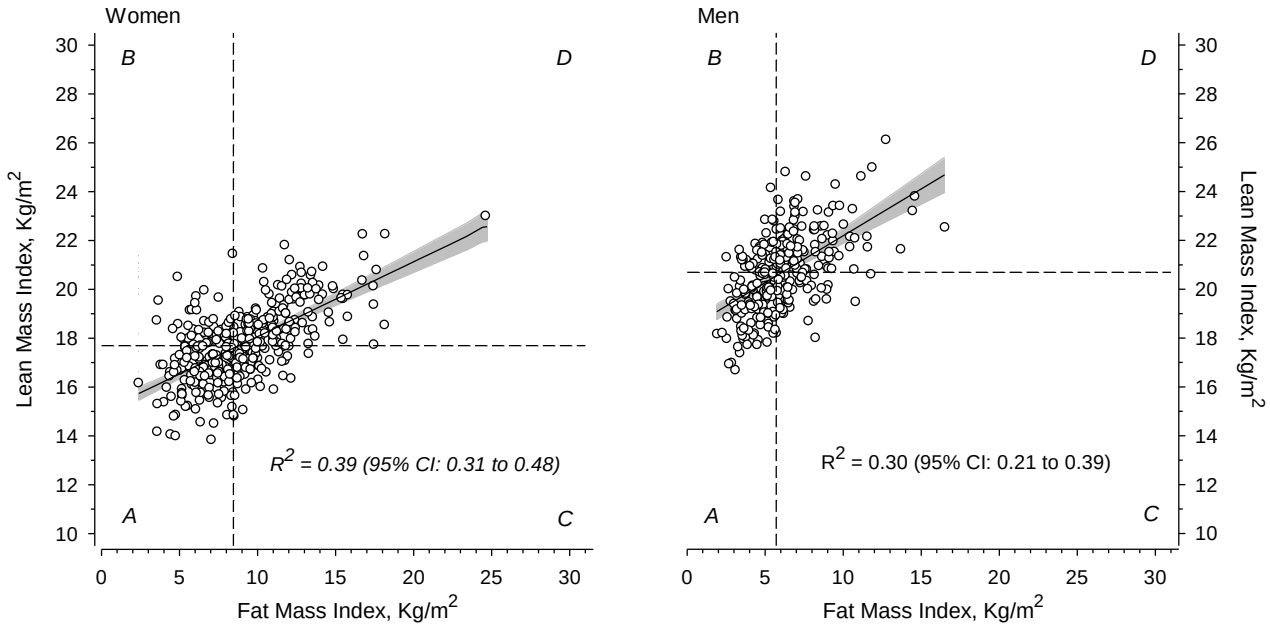

Figure 1.

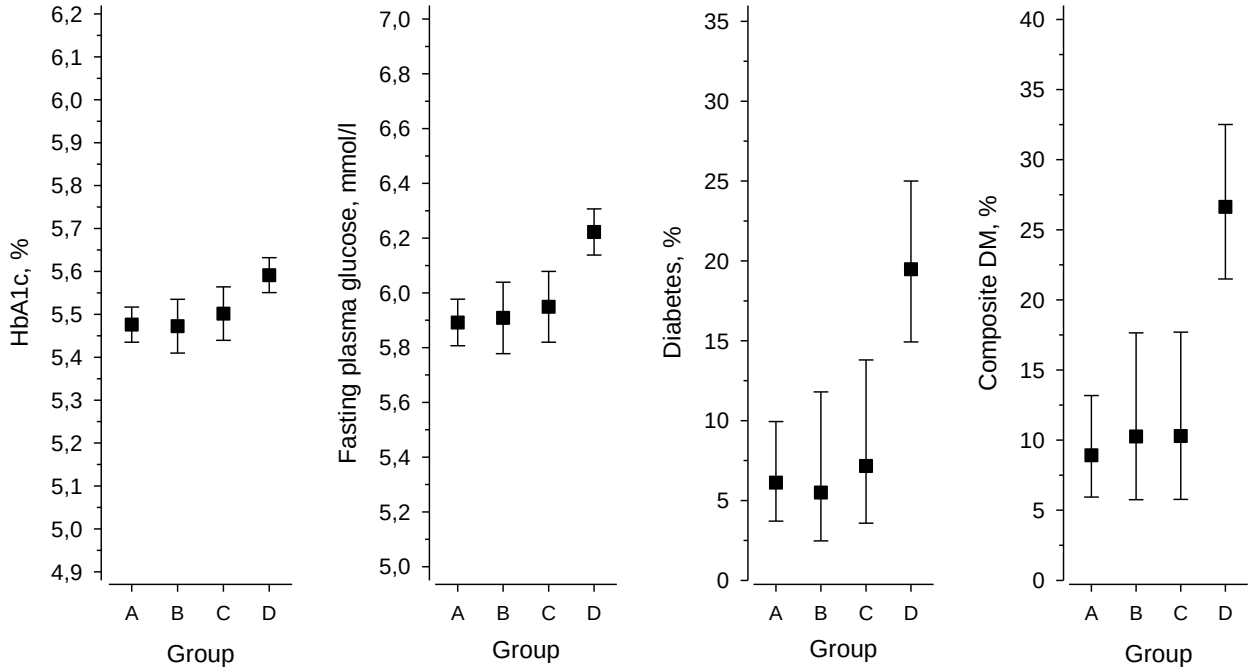

Figure 2.