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The Effect of a Vegetarian vs Conventional Hypocaloric Diabetic Diet on Thigh Adipose Tissue Distribution in Subjects with Type 2 Diabetes: A Randomized Study

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ABSTRACT

Objective: The aim of our study was to compare the effects of a vegetarian and a conventional diet on thigh adipose tissue distribution in subjects with type 2 diabetes (T2D).

Methods: Seventy-four subjects with T2D were randomly assigned to either follow a vegetarian diet (V, $n = 37$) or a control group who followed an isocaloric conventional anti-diabetic diet (C, $n = 37$). Both diets were calorie restricted (−500 kcal/day). To measure insulin sensitivity, the hyperinsulinemic (1 mU. $kg^{-1}.min^{-1}$) isoglycemic clamp was conducted. β-Cell function was assessed using a mathematical model after a test meal. Magnetic resonance imaging of the thigh was performed. All subjects were examined at 0, 3, and 6 months. Statistical analyses were performed using repeated measures analysis of variance and a multivariate regression model.

Results: Greater reduction was observed in total leg area in V (−13.6 cm^2 [95% confidence interval [CI], −14.2 to −12.9] in V vs −9.9 cm^2 [95% CI, −10.6 to −9.2] in C; Gxt $p < 0.001$). The reduction in subcutaneous fat was comparable in response to both diets (Gxt, $p = 0.64$). Subfascial fat was reduced only in response to a vegetarian diet (−0.82 [95% CI, −1.13 to −0.55] cm^2 in V vs −0.44 [95% CI, −0.78 to +0.02] cm^2 in C; Gxt, $p = 0.04$). The reduction in intramuscular fat tended to be greater in response to a vegetarian diet (−1.78 [95% CI, −2.26 to −1.27] cm^2 in V vs −0.57 [95% CI, −1.06 to −0.09] cm^2 in C; Gxt, $p = 0.12$). Changes in subcutaneous and subfascial fat correlated with changes in glycated hemoglobin (HbA1c), fasting plasma glucose, and β-cell insulin sensitivity. After adjustment for changes in body mass index (BMI), correlations remained significant for changes in fasting plasma glucose and β-cell insulin sensitivity and with changes in triglycerides.

Conclusions: Our data indicate the importance of both subcutaneous and subfascial fat in relationship to glucose and lipid metabolism.

Abbreviations: BMI , body mass index; C , control group; FPG , fasting plasma glucose; Gxt , interaction between group and time; HbA1c , glycated hemoglobin; MCR , metabolic clearance rate of glucose; OPLS , orthogonal projections to latent structure; T2D , type 2 diabetes; V , vegetarian group

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Introduction

Dietary intervention is one of the key components in type 2 diabetes (T2D) management [1]. A vegetarian diet is a promising way to reduce the energy intake by consuming foods with a low energy density, with a fair degree of patient adherence [2,3].

The beneficial effects of a vegetarian diet on body weight, glycemic control, blood lipids, insulin sensitivity, and oxidative stress markers compared to a conventional diet have been demonstrated by us and others previously [2–4]. A vegetarian diet was also reported to reduce the content of intramuscular lipids [5].

It has been demonstrated that thigh adipose tissue distribution (especially subfascial and intramuscular fat) is associated with insulin sensitivity [6]. In this secondary analysis of our 6-month randomized trial we studied thigh adipose tissue distribution in response to a vegetarian diet and a conventional diet, and we tested the association with glucose and lipid metabolism in patients with type 2 diabetes.

Materials and methods

The characteristics of the sample and the methods are described in detail elsewhere [3]. Briefly, 74 subjects with T2D treated by oral hypoglycaemic agents, both men (47%) and women (53%) were recruited. A 6-month randomized, open parallel design was used. The subjects were randomly assigned either into the vegetarian group (V, $n = 37$) or the control group (C, $n = 37$), who received a conventional diet. Both diets were designed to be calorie-restricted (−500 kcal/d) based on

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the indirect calorimetry measurement [7]. The second 12 weeks of the diet were combined with aerobic exercise. All meals during the study were provided. Participants were examined at baseline and at 3 and 6 months. The study protocol was approved by the Institutional Ethics Committee.

Diet

The vegetarian diet (~60% of energy from carbohydrates, 15% protein, and 25% fat) consisted of vegetables, grains, legumes, fruits, and nuts. Animal products were limited to a maximum of one portion of low-fat yogurt a day. The conventional diabetic diet was administered according to the dietary guidelines of the Diabetes and Nutrition Study Group of the European Association for the Study of Diabetes [8]. It contained 50% of energy from carbohydrates, 20% protein, less than 30% fat (≤7% saturated fat, less than 200 mg/d of cholesterol/day).

High adherence to the prescribed diet was defined as the average daily energy intake being no more than 100 kcal in excess of the prescribed; medium adherence was less than 200 kcal in excess. Additional criteria for high adherence to the vegetarian diet were average daily cholesterol intake ≤ 50 mg and for medium adherence less than 100 mg. In the control group, the average daily cholesterol limit was ≤200 mg for high adherence and less than 300 mg for medium adherence.

Exercise

Participants were asked not to alter their exercise habits during the first 12 weeks. Then (weeks 13–24) they were prescribed an individualized exercise program based on the history of physical activity and initial spiroergometric examination, which measured maximal oxygen consumption and maximal performance. Participants exercised at 60% of maximal heart rate twice a week for 1 hour under professional supervision plus once a week at home or at the sports center with the same intensity; they were given a heart rate monitor and a pedometer for individual physical activities and were repeatedly instructed on how to use them. Adherence to the exercise program was defined as more than 75% of prescribed visits at the sports center (18/24).

Medication

Participants were asked to continue their preexisting medication regimens, except when hypoglycemia occurred repeatedly (plasma glucose determined at the laboratory < 4.4 $mmol.l^{-1}$ or capillary glucose reading < 3.4 $mmol.l^{-1}$ accompanied by hypoglycemic symptoms). In such cases, medications were reduced by a study physician following a standard protocol. All participants were given an Accu-Chek Go glucometer (Roche, Basel, Switzerland) and were instructed on how to use it.

Procedures

All measurements were performed at 0, 3, and 6 months on an outpatient basis, after 10- to 12-hour overnight fasting with only tap water allowed *ad libitum*.

Hyperinsulinemic isoglycemic clamp

To measure insulin sensitivity, the hyperinsulinemic (1 $mU.kg^{-1}.min^{-1}$) isoglycemic clamp, lasting 3 hours, was conducted as previously described [9,10]. Insulin sensitivity was estimated as the metabolic clearance rate of glucose (MCR) calculated during the last 20 minutes of the clamp after correction for changes in glucose pool size [9,10]. The steady state was reached when the coefficient of variability was less than 5%.

β-Cell function

Modeling analysis of beta cell function was performed during standard meal tests. Insulin secretory rates were calculated from plasma C-peptide levels by deconvolution [11] and expressed per square meter of estimated body surface area. The dependence of insulin secretory rates on glucose levels was modeled separately for each patient and each study day. The beta cell model used in the present study, describing the relationship between insulin secretion and glucose concentration, has been described in detail previously [12–14].

Briefly, insulin secretion consists of 2 components. The first component represents the dependence of insulin secretion on absolute glucose concentration at any time point and is characterized by a dose–response function. Characteristic parameters of the dose response are insulin secretion at a fixed glucose concentration and the mean slope in the observed glucose range. The dose response was modulated by a potentiation factor, which accounts for several agents (prolonged exposure to hyperglycemia, nonglucose substrates, gastrointestinal hormones, and neurotransmitters). The potentiation factor was set to be a positive function of time and to an average of one during the experiment. It thus expresses a relative potentiation of the secretory response to glucose.

The second insulin secretion component represents a dynamic dependence of insulin secretion on the rate of change of glucose concentration. Termed the *derivative component*, it is described by a single parameter, rate sensitivity. This secretion component is related to early insulin release [12,13].

The model parameters (the parameters of the dose response, the rate sensitivity, and the potentiation factor) were estimated from glucose and C-peptide concentration by regularized least squares, as described previously [12,13]. Estimation of the individual model parameters was performed blinded for the randomization of patients for treatment.

Magnetic resonance imaging

Magnetic resonance images were obtained using an Avanto 1.5T MRI scanner (Siemens, Etlingen, Germany) at start (0) and after 3 and 6 months. Subjects were measured in the supine position. Fat compartments in the thigh muscles were determined from transversal images obtained using a T1-weighted turbospin echo sequence from the right leg. Sequence parameters included turbofactor 2, repetition time TR = 450 ms, echotime TE = 11 ms, numbers of slices 23, slice thickness 6 mm, matrix 256 × 232, and the field of view varied between 200 × 181 mm^2 to 300 × 272 mm^2 depending on the thigh size.

The center of the image stack was placed 169 mm above the knee joint cavity to ensure a reproducible position of the images.

The 3 middle slices from each measurement of each subject were evaluated. Although the selection could not ensure placement of the selected slices exactly in the middle of the thigh due to different body heights of the subjects, this uniform procedure ensured the same position of the selected slices during repetitive measurements in each subject.

Fat compartments were measured using a dedicated in-house software Seghak written in MATLAB (MathWorks, Natick, MA). The software automatically segmented the leg area against the background. Then the operator manually outlined the inner border of the subcutaneous fat tissue. The bone was also outlined manually and masked. Subfascial fat was segmented automatically after manual thresholding. After masking of the previous compartments, semiautomatic segmentation of the intramuscular fat was performed: the intramuscular fat compartment was automatically selected based on a threshold set manually according to a histogram. All steps were visually controlled by the rater; the software enabled interactive correction throughout the evaluation when necessary. The images were evaluated by 3 independent raters blind to the subject diagnosis and diet used. T1-weighted images together with color-coded masks are shown in Fig. 1.

Statistical analyses

The intention-to-treat analysis included all participants. Repeated measures analysis of variance models with between-subject and within-subject factors and interactions were used for evaluation of the relationships between continuous variables and factors. The factors treatment group, subject, and time were included in the model. Interactions between group and time (Gxt) were calculated for each variable. Within each group, paired comparison *t* tests were calculated to test whether the changes from baseline to 3 months, from baseline to 6 months, and from 3 to 6 months were statistically significant.

To eliminate skewed data distribution and heteroscedasticity, the original data were transformed to a Gaussian distribution before further processing by a power transformation using the statistical software Statgraphics Centurion, Version XV, from Statpoint Inc. (Herndon, VA). The transformed data underwent multivariate regression using the method of orthogonal projections to latent structure (OPLS) [15]. This method is effective in coping with the problem of severe multicollinearity within the matrix of independent variables. In our model, the metabolic variables (fasting plasma glucose, blood lipids, glycated hemoglobin [HbA1c], metabolic clearance rate of glucose, parameters of beta-cell function, resting energy expenditure) were chosen as the dependent variables and the thigh compartments represented the independent variables. The matrix was made up before and then after adjustment for changes in body mass index (BMI) and volume of visceral fat. The variability was separated into 2 independent components. The first component contained the variability in the thigh compartments, which was shared with metabolic variables

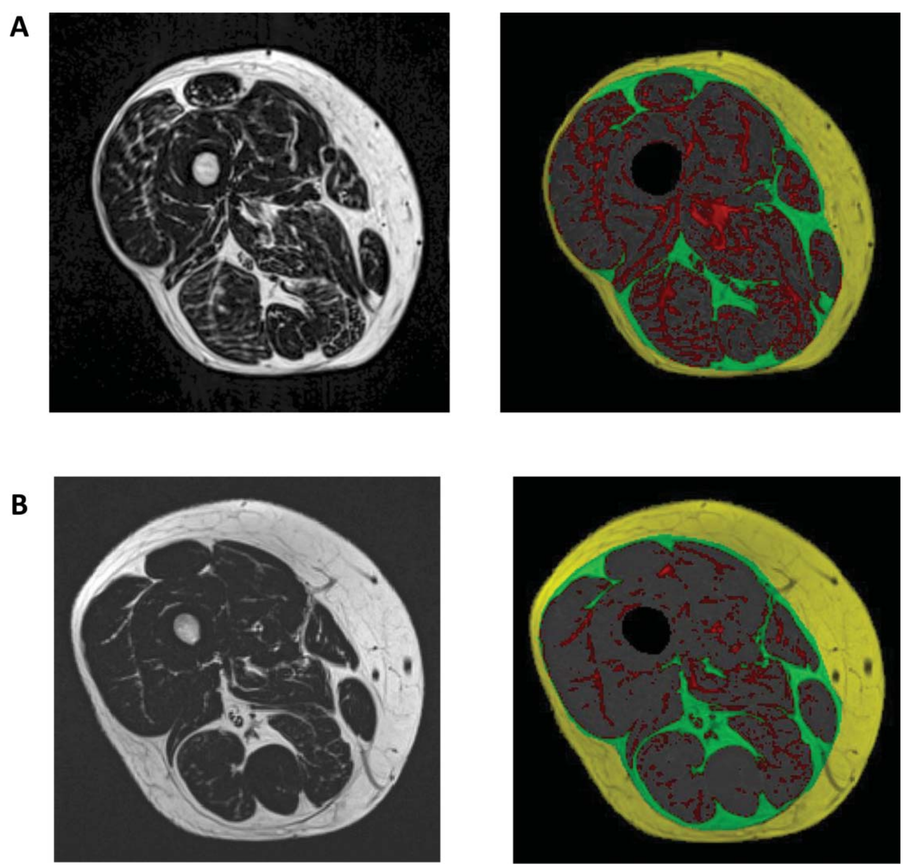

Figure 1. MR images of the thigh. An example of 2 subjects with similar total fat content but different distribution. T1-weighted magnetic resonance images together with color-coded masks (yellow = subcutaneous fat, green = subfascial fat/beneath the fascia, red = intramuscular fat) are presented. Subject A (total fat area 153 cm^2) had considerable intramuscular fat infiltration (39% of total fat content) and a moderate portion of subcutaneous fat (43%); subject B (total fat area 149 cm^2) had low intramuscular fat content (15%) and a dominant subcutaneous fat layer (64%). The content of subfascial fat was similar (18% in subject A and 21% in subject B).

(the predictive component), and the second component contained the variability shared within the thigh compartments (the orthogonal component). The OPLS enabled us to find the best predictors as well as the best combination of predictors for estimation of metabolic variables from thigh compartments. After standardization of the variables, the OPLS model can be expressed as follows:

$$\mathbf{X} = \mathbf{T}_p\mathbf{P}_p^t + \mathbf{T}_0\mathbf{P}_0^t + \mathbf{E}$$
$$\mathbf{Y} = \mathbf{T}_p\mathbf{P}_p^t + \mathbf{F},$$

where **X** is the matrix with l independent variables and i subjects and **Y** is the matrix of m dependent variables and i subjects. In our data, $\mathbf{T}_p$ represents the vector of component scores from the predictive components and i subjects extracted from **Y**, $\mathbf{T}_0$ is the vector of component scores from the orthogonal components and i subjects extracted from **X**, $\mathbf{P}_p$ represents the vector of component loadings for the predictive component extracted from **Y**, $\mathbf{P}_0$ represents the vector of component loadings for the orthogonal component extracted from **X** and l independent variables, and **E** and **F** are the error terms.

The statistical software SIMCA-P Version 11.5 (Umetrics AB, Umeå, Sweden) used for data analysis allowed finding the number of the relevant components using the prediction error sum of squares and also allowed the detection of multivariate nonhomogeneities and testing the multivariate normal distribution and homoscedasticity (constant variance).

Results

Data are presented as means with 95% confidence intervals. The vegetarian diet was almost twice as effective in reducing body weight compared to the conventional hypocaloric diet (−6.2 kg [95% confidence interval (CI), −6.6 to −5.3] in V vs −3.2 kg [95% CI, −3.7 to −2.5] in C; Gxt $p < 0.001$) [3]. Greater reduction was also observed in total leg area in V (−13.6 cm^2 [95% CI, −14.2 to −12.9] in V vs −9.9 cm^2 [95% CI, −10.6 to −9.2] in C; Gxt $p < 0.001$; Fig. 2A). The greater weight loss in V was accompanied by greater muscle loss in V (−5.0 cm^2 [95% CI, −5.7 to −4.3] in V vs −1.7 cm^2 [95% CI, −2.4 to −1.0] in C; Gxt $p <$ 0.0001; Fig. 2B), which was reversed partially in V after the addition of exercise (+1.3 cm^2 [95% CI, 0.7 to −2.0]; $p < 0.05$; Fig. 2B). The reduction in subcutaneous fat was comparable in response to both diets (−6.0 cm^2 [95% CI, −6.4 to −5.6] in V vs −5.9 cm^2 [95% CI, −6.3 to −5.6] in C; Gxt, $p = 0.64$; Fig. 2C). Subfascial fat was reduced only in response to a vegetarian diet (−0.82 cm^2 [95% CI, −1.13 to −0.55] in V vs −0.44 cm^2 [95% CI, −0.78 to +0.02] in C; Gxt, $p = 0.04$; Fig. 2D). The reduction

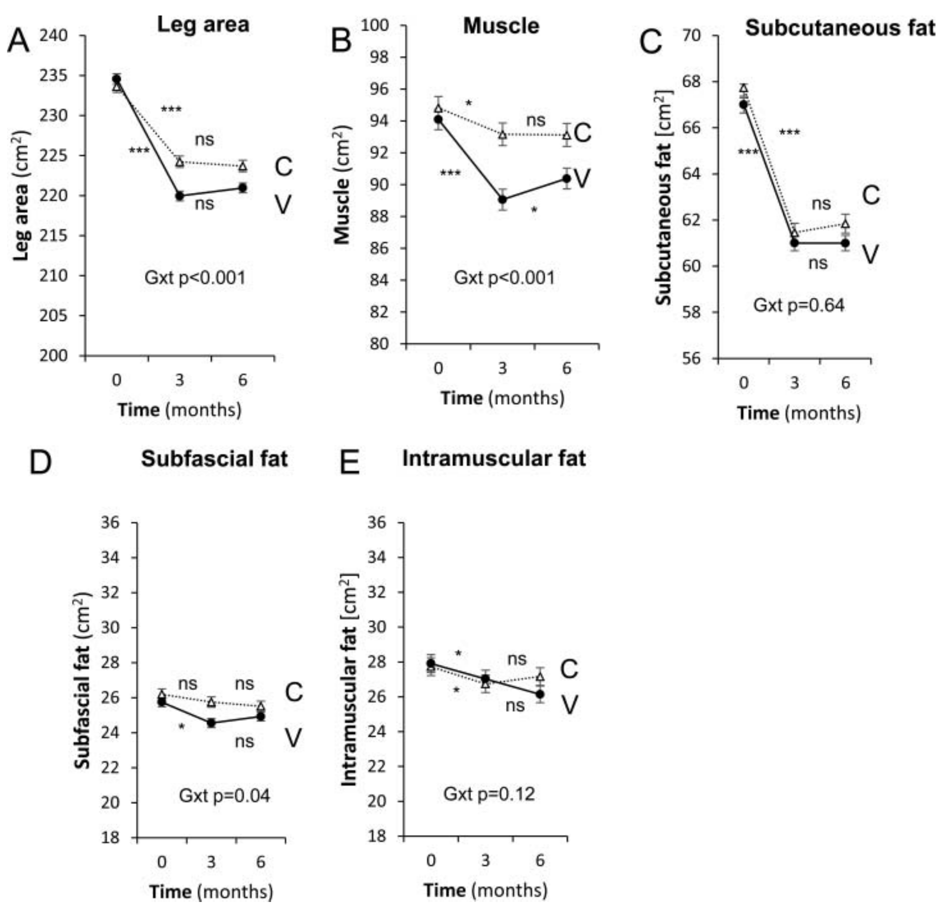

Figure 2. Changes in thigh composition in response to a vegetarian diet (V, full line and circles) and conventional diet (C, dotted line and triangles). Data are means ± 95% confidence intervals. Significant changes from baseline to 3 months and from 3 to 6 months for within-group changes assessed by paired comparison t tests are indicated by * for $p < 0.05$, ** for $p < 0.01$, and *** for $p < 0.001$. Gxt: p value for the interaction between factors group (vegetarian and control group) and time (0, 3, and 6 months) assessed by repeated measures analysis of variance. (A) total leg area, (B) muscle area, (C) subcutaneous fat area, (D) subfascial fat area, and (E) intramuscular fat area.

in intramuscular fat tended to be greater in response to a vegetarian diet (−1.78 cm^2 [95% CI, −2.26 to −1.27] in V vs −0.57 cm^2 [95% CI, −1.06 to −0.09] in C; however, the interaction between group and time was not statistically significant ($p = 0.12$; Fig. 2F).

Metabolic data

HbA1c decreased and MCR increased in both groups in response to the dietary interventions. Parameters of β-cell function improved comparably in response to both diets. For more details we refer to our previously published articles [3,14].

Adherence

The diet adherence was high among 55% of participants in V and 32% in C, medium among 22.5% in V and 39% in C, and low among 22.5% in V and 29% in C. Adherence to the exercise program was 90.3% in V and 80.6 in C.

Correlations

Correlations between changes in the thigh compartments and metabolic data are shown in Table 1. Changes in total leg area and subcutaneous and subfascial fat correlated with changes in HbA1c ($r = 0.34$; $p < 0.05$), fasting plasma glucose ($r = 0.44$; $p < 0.01$), metabolic clearance rate of glucose ($r = -0.24$; $p < 0.05$), resting energy expenditure ($r = 0.30$; $p < 0.05$), and β-cell insulin sensitivity ($r = -0.38$; $p < 0.05$). After adjustment for changes in BMI, correlations of changes in total leg area and subcutaneous and subfascial fat remained significant with changes in fasting plasma glucose ($r = 0.30$; $p < 0.05$) and β-cell insulin sensitivity ($r = -0.34$; $p < 0.05$) and with changes in triglycerides ($r = 0.41$; $p < 0.05$).

Discussion

We showed that a vegetarian diet reduced subfascial fat more and tended to also reduce intramuscular fat more than a conventional hypocaloric diabetic diet. These results are in accordance with previous research by Goodpaster et al. demonstrating that subfascial and intramuscular fat are markers of insulin resistance in obesity and T2D [6], suggesting that a decrease in subfascial and intramuscular fat is associated with improvements in insulin resistance.

It appears that there is a regional pattern of thigh adipose tissue distribution, specifically an increased subfascial fat in patients with T2D, that is associated with insulin resistance [6,16]. It seems that reduction in fat content in this specific metabolically adverse depot may have a beneficial effect on glucose metabolism. In addition, Marcus et al. observed that intramuscular fat increased with age and inactivity, and this was associated with a decrease in muscular strength and mobility, particularly in older people with diabetes [17]. The trend toward greater reduction in intramuscular fat in response to a vegetarian diet observed in our study is therefore a very positive finding.

Our data stress the importance of exercise in weight loss programs to preserve lean mass. Thigh muscle mass has been shown to be protective against the risk of diabetes and coronary heart disease in previous research conducted by Eastwood et al. [18]. Exercise might help to prevent muscle loss during a dietary intervention [19], which may play an important role in decreasing cardiometabolic risk.

Table 1. Relationships between Changes in Thigh Compartments and (a) Unadjusted Metabolic Data and (b) after Adjustment for Changes in BMI Evaluated by the O2PLS Model[a].

		Predictive Component		
	Variable	Component Loading	*t* Statistics[b]	*R*[c]
Table 1a				
Relevant predictors (matrix **X**)	Δ leg area	0.366	5.51	0.803**
	Δ subcutaneuos fat	0.300	2.98	0.660*
	Δ subfascial fat	0.344	7.67	0.757**
Explained variables (matrix **Y**)	Δ HbA1c	0.247	2.85	0.341*
	Δ FPG	0.324	3.60	0.437**
	Δ MCR	−0.286	−2.90	−0.239*
	Δ REEm	0.224	2.26	0.296*
	Δ β-cell glucose sensitivity	−0.309	−2.60	−0.384*
Explained variability		49.1% (38.5% after cross-validation)		
Table 1b				
Relevant predictors (matrix **X**)	Δ leg area	0.356	5.13	0.683**
	Δ subcutaneuos fat	0.424	6.08	0.813**
	Δ subfascial fat	0.448	5.52	0.859**
Explained variables (matrix **Y**)	Δ BMI	0.453	9.78	0.879**
	Δ FPG	0.572	2.37	0.303*
	Δ β-cell glucose sensitivity	−0.575	−2.19	−0.338*
	Δ TG	0.412	2.68	0.413*
Explained variability		10.5% (6.3% after cross-validation)		

O2PLS = , HbA1c = glycated hemoglobin, FPG = fasting plasma glucose, MCR = metabolic clearance rate of glucose, REE = resting energy expenditure, BMI = body mass index, FPG = fasting plasma glucose, TG = triglycerides.
aMultivariate regression with reduction of dimensionality (O2PLS) shows how much each variable correlates with the common predictive component.
[b]Component loading of the predictive component divided by the standard error of the component loading.
[c]Component loadings expressed as correlation coefficients with predictive component.
*$p < 0.05$. **$p < 0.01$.

We found an association between changes in total leg area and subcutaneous fat and subfascial fat on the one hand and markers of glucose and lipid metabolism on the other hand, even after adjustments for changes in BMI. Interestingly, no association was found for changes in intramuscular fat. Thigh intramuscular fat has been shown to increase with aging [20]. The association between thigh intramuscular fat and insulin resistance and T2D demonstrated by Goodpaster et al. [6] has not been confirmed in our study.

Conclusion

In conclusion, our data indicate that a vegetarian diet is more effective in reducing subfascial fat and tends to also reduce intramuscular fat more than a conventional hypocaloric diabetic diet. Our data suggest the importance of both subcutaneous and subfascial fat in relationship to glucose and lipid metabolism. Further research is needed to determine how dietary interventions with different diet composition can influence thigh fat distribution in relationship to glucose and lipid metabolism.

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Author contributions

H.K. and T.P. designed the study, wrote the grant application, recruited the participants, collected the data, and wrote the article. M.K., V.H., A.S., S.H., and A.M. were involved in acquisition and analyses of data. M.H. carried out the statistical analyses and interpretation of data. All authors had full access to the data and revised and approved the article for publication. The guarantor is T.P.

References

1. American Diabetes Association: Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. Diabetes Care 31(Suppl 1):S61–S78, 2008.
2. Barnard ND, Cohen J, Jenkins DJA, Turner-McGrievy G, Gloede L, Jaster B, Seidl K, Green AA, Talpers S: A low-fat vegan diet improves glycemic control and cardiovascular risk factors in a randomized clinical trial in individuals with type 2 diabetes. Diabetes Care 29:1777–1783, 2006.
3. Kahleova H, Matoulek M, Malinska H, Oliyarnik O, Kazdova L, Neskudla T, Skoch A, Hajek M, Hill M, Kahle M, Pelikanova T: Vegetarian diet improves insulin resistance and oxidative stress markers more than conventional diet in subjects with type 2 diabetes. Diabet Med J Br Diabet Assoc 28:549–559, 2011.
4. Nicholson AS, Sklar M, Barnard ND, Gore S, Sullivan R, Browning S: Toward improved management of NIDDM: a randomized, controlled, pilot intervention using a lowfat, vegetarian diet. Prev Med 29:87–91, 1999.
5. Goff LM, Bell JD, So P-W, Dornhorst A, Frost GS: Veganism and its relationship with insulin resistance and intramyocellular lipid. Eur J Clin Nutr 59:291–298, 2005.
6. Goodpaster BH, Thaete FL, Kelley DE: Thigh adipose tissue distribution is associated with insulin resistance in obesity and in type 2 diabetes mellitus. Am J Clin Nutr 71:885–892, 2000.
7. Ferrannini E: The theoretical bases of indirect calorimetry: a review. Metabolism 37:287–301, 1988.
8. Mann JI, De Leeuw I, Hermansen K, Karamanos B, Karlström B, Katsilambros N, Riccardi G, Rivellese AA, Rizkalla S, Slama G, Toeller M, Uusitupa M, Vessby B; Diabetes and Nutrition Study Group (DNSG) of the European Association: Evidence-based nutritional approaches to the treatment and prevention of diabetes mellitus. Nutr Metab Cardiovasc Dis 14:373–394, 2004.
9. Pelikánová T, Kohout M, Válek J, Base J, Kazdová L: Insulin secretion and insulin action related to the serum phospholipid fatty acid pattern in healthy men. Metabolism 38:188–192, 1989.
10. Pelikánová T, Kazdová L, Chvojková S, Base J: Serum phospholipid fatty acid composition and insulin action in type 2 diabetic patients. Metabolism 50:1472–1478, 2001.
11. Van Cauter E, Mestrez F, Sturis J, Polonsky KS: Estimation of insulin secretion rates from C-peptide levels. Comparison of individual and standard kinetic parameters for C-peptide clearance. Diabetes 41:368–377, 1992.
12. Mari A, Tura A, Gastaldelli A, Ferrannini E: Assessing insulin secretion by modeling in multiple-meal tests: role of potentiation. Diabetes 51(Suppl 1):S221–S226, 2002.
13. Mari A, Schmitz O, Gastaldelli A, Oestergaard T, Nyholm B, Ferrannini E: Meal and oral glucose tests for assessment of beta-cell function: modeling analysis in normal subjects. Am J Physiol Endocrinol Metab 283:E1159–E1166, 2002.
14. Kahleova H, Mari A, Nofrate V, Matoulek M, Kazdova L, Hill M, Pelikanova T: Improvement in β-cell function after diet-induced weight loss is associated with decrease in pancreatic polypeptide in subjects with type 2 diabetes. J Diabetes Complications 26:442–449, 2012.
15. Trygg J, Holmes E, Lundstedt T: Chemometrics in metabonomics. J Proteome Res 6:469–479, 2007.
16. Uhthoff HK, Matsumoto F, Trudel G, Himori K: Early reattachment does not reverse atrophy and fat accumulation of the supraspinatus—an experimental study in rabbits. J Orthop Res Off Publ Orthop Res Soc 21:386–392, 2003.
17. Marcus RL, Addison O, Kidde JP, Dibble LE, Lastayo PC: Skeletal muscle fat infiltration: impact of age, inactivity and exercise. J Nutr Health Aging 14:362–366, 2010.
18. Eastwood SV, Tillin T, Wright A, Mayet J, Godsland I, Forouhi NG, Whincup P, Hughes AD, Chaturvedi N: Thigh fat and muscle each contribute to excess cardiometabolic risk in South Asians, independent of visceral adipose tissue. Obesity (Silver Spring) 22:2071–2079, 2014.
19. Aoi W, Naito Y, Yoshikawa T: Dietary exercise as a novel strategy for the prevention and treatment of metabolic syndrome: effects on skeletal muscle function. J Nutr Metab 2011:676208, 2011.
20. Hogrel JY, Barnouin Y, Azzabou N, Butler-Browne G, Voit T, Moraux A, Leroux G, Behin A, McPhee JS, Carlier PG: NMR imaging estimates of muscle volume and intramuscular fat infiltration in the thigh: variations with muscle, gender, and age. Age (Dordr) 37:9798, 1–11, 2015.