# Potential effects of reduced red meat compared with increased fiber intake on glucose metabolism and liver fat content: a randomized and controlled dietary intervention study

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**ABSTRACT**

**Background:** Epidemiological studies suggest that an increased red meat intake is associated with a higher risk of type 2 diabetes, whereas an increased fiber intake is associated with a lower risk.

**Objectives:** We conducted an intervention study to investigate the effects of these nutritional factors on glucose and lipid metabolism, body-fat distribution, and liver fat content in subjects at increased risk of type 2 diabetes.

**Methods:** This prospective, randomized, and controlled dietary intervention study was performed over 6 mo. All groups decreased their daily caloric intake by 400 kcal. The "control" group ($N = 40$) only had this requirement. The "no red meat" group ($N = 48$) in addition aimed to avoid the intake of red meat, and the "fiber" group ($N = 44$) increased intake of fibers to 40 g/d. Anthropometric parameters and frequently sampled oral glucose tolerance tests were performed before and after intervention. Body-fat mass and distribution, liver fat, and liver iron content were assessed by MRI and single voxel proton magnetic resonance spectroscopy.

**Results:** Participants in all groups lost weight (mean 3.3 ± 0.5 kg, $P < 0.0001$). Glucose tolerance and insulin sensitivity improved ($P < 0.001$), and body and visceral fat mass decreased in all groups ($P < 0.001$). These changes did not differ between groups. Liver fat content decreased significantly ($P < 0.001$) with no differences between the groups. The decrease in liver fat correlated with the decrease in ferritin during intervention ($r^2 = 0.08$, $P = 0.0021$). This association was confirmed in an independent lifestyle intervention study (Tuebingen Lifestyle Intervention Program, $N = 229$, $P = 0.0084$).

**Conclusions:** Our data indicate that caloric restriction leads to a marked improvement in glucose metabolism and body-fat composition, including liver-fat content. The marked reduction in liver fat might be mediated via changes in ferritin levels. In the context of caloric restriction, there seems to be no additional beneficial impact of reduced red meat intake and increased fiber intake on the improvement in cardiometabolic risk parameters. This trial was registered at clinicaltrials.gov as NCT03231839. *Am J Clin Nutr* 2019;109:288–296.

**Keywords:** type 2 diabetes, prevention, randomized controlled intervention study, nutritional factors, fiber, red meat

## Introduction

Weight loss induced by caloric restriction is a major goal in the prevention of type 2 diabetes and cardiovascular disease (1–3). However, for many subjects, it is difficult to lose weight (4). Furthermore, the cardiometabolic risk largely differs between subjects who are at risk of diabetes (5, 6), and there is also a large variability in the beneficial cardiometabolic effects for the same amount of weight loss (7). Furthermore, modification of the diet was also shown to improve the cardiometabolic risk, independent of weight loss (8, 9).

Among several dietary factors that are considered to modulate the risk of type 2 diabetes and cardiovascular disease (10, 11), increased consumption of red meat is associated with an

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Abbreviations used: AUC, area under the curve; IGI, insulinogenic index; ISI, insulin sensitivity index; OGTT, oral glucose tolerance test; TULIP, TUebingen Lifestyle Intervention Program.

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increased risk of type 2 diabetes (12–16), cardiovascular disease, and mortality (17, 18). In contrast, increased intake of fibers and whole grain is associated with a reduced risk of type 2 diabetes and cardiovascular disease (19–23). A high intake of red meat and a low intake of fibers are also associated with an elevated risk of diabetes in the German Diabetes Risk Score, which has been developed in the German European Prospective Investigation into Cancer and Nutrition study (24) and has been validated in other cohorts (11). Therefore, it has been hypothesized that reducing the intake of red meat and/or increasing the intake of fibers may be beneficial for glucose metabolism and body-fat mass and distribution.

Few intervention studies have been performed to investigate the role of whole-grain intake or the consumption of red meat for glucose metabolism and their role in the prevention of diabetes. Those studies yielded contradicting results (25–29). Furthermore, it is unclear whether a reduced intake of red meat and an increased intake of fibers have additional beneficial effects, when added to a calorie-restricted diet, to reduce the cardiometabolic risk. To test this hypothesis, we performed a randomized, controlled intervention study over 6 mo. Subjects were carefully phenotyped in respect of glucose and lipid metabolism, body-fat mass, and distribution as well as hepatic fat and iron load.

## Material and Methods

### Study design and participants

This 6-mo, randomized and controlled dietary intervention trial was conducted at the University Hospital Tübingen, Germany. The protocol was approved by the ethics committees of the Medical Faculty of the University of Tübingen, and informed written consent was obtained from all subjects. The study was conducted in accordance with the principles of the Declaration of Helsinki and Good Clinical Practice.

The study participants were identified by local advertisement (newspaper, e-mail) and by word of mouth. A total of 225 individuals responded, and 183 were screened. All participants originated from south-west Germany including an area of 100 km around the university city of Tübingen, which is economically well developed. The advertisements included the information that a nutritional intervention study to reduce weight and to improve glucose metabolism is conducted at the university hospital. Individuals aged between 18 and 75 y at a high risk of type 2 diabetes (e.g., family history of type 2 diabetes, metabolic syndrome, BMI of >27 kg/m$^2$, diagnosis of impaired glucose tolerance, or previous diagnosis of gestational diabetes) were included in a 6-mo dietary intervention program. The main exclusion criteria were diagnosis of type 1 or type 2 diabetes, a BMI >45 kg/m$^2$, or the presence of serious illness such as cardiovascular, malignant, or psychiatric disease. Extensive phenotyping and metabolic examinations were performed at baseline and after 6 mo of intervention.

After screening and meeting inclusion and not meeting exclusion criteria, individuals were randomly assigned (proportion 1:1:1) to 3 intervention groups using computer-generated random numbers. In the "control" group, individuals were instructed to decrease their intake of calories to 400 kcal below their requirements. In addition to the requirement for the control group (decrease in caloric intake by 400 kcal), the "no red meat" group also aimed to avoid the intake of red meat (not including turkey, fish, or chicken), and the "fiber" group aimed to increase intake of fibers to at least 40 g/d. There was no restriction of red meat intake in the "fiber" group. All 3 groups had to reduce their caloric intake by 400 kcal. All 3 groups were initially provided general information that physical activity of at least 3 h/wk should be performed.

After the baseline measurements, individuals underwent dietary counseling and had 6 sessions with a dietician (after 1, 4, 8, 12, 16, and 20 wk). During each visit, participants presented a 4-d food diary and discussed the results with the dieticians. Diet composition was determined with a validated computer program using a 4-d diary (DGE-PC 3·0, Deutsche Gesellschaft für Ernährung).

We additionally analyzed the 9-mo follow-up data of 229 participants who took part in the TUebingen Lifestyle Intervention Program (TULIP) (30). This study includes individuals at increased risk of diabetes. The intervention consists of an increase in physical activity and a dietary intervention to reduce caloric intake. The detailed study design and participants of the TULIP cohort, which was analyzed here specifically regarding ferritin levels and liver fat content, have been described earlier (30). Baseline subject characteristics of the TULIP cohort are provided as Supplemental Table.

### Procedures

#### *Oral glucose tolerance test.*

After an overnight fast, subjects ingested a standard solution containing 75 g of glucose [Accu-Chek Dextro oral glucose tolerance test (OGTT), Roche Diagnostics] at 0800. Plasma glucose and insulin concentrations were determined from venous blood samples that had been obtained at 0, 30, 60, 90, and 120 min.

#### *Total body fat and body-fat distribution.*

Body-fat mass and distribution were assessed using MRI as previously described (31, 32). In brief, a T1-weighed fast spin echo technique was applied on a 1.5Tesla (1.5T) whole-body magnetic resonance imager (Magnetom Sonata; Siemens Healthineers). The entire body was measured with a slice thickness of 10 mm and gaps of 10 mm in between, resulting in approximately 110–120 slices per volunteer. Postprocessing was done by an automatic segmentation procedure based on fuzzy clustering (33). Visceral adipose tissue was quantified between femoral heads and thoracic diaphragm. Abdominal subcutaneous adipose tissue was quantified between femoral heads and humeral heads.

#### *Quantitative analysis of liver fat and liver iron.*

Liver fat content was assessed by single voxel proton magnetic resonance spectroscopy ($^1$H-MRS) in the posterior part of segment 7 as described earlier (34, 35). Signal integrals of the water resonance at 4.7 ppm and lipids (methylene at 1.3 ppm and methyl at 0.9 ppm) were quantified, and intrahepatic lipids (IHL) are given as a percentage by the ratio of lipids/(water + lipids). In order to assess the liver iron content, the effective transverse relaxation time T2∗ was determined, applying a multiecho gradient-echo sequence (36, 37). T2∗ was calculated in a region of interest close to the spectroscopic voxel by monoexponential fitting. Data are given in milliseconds.

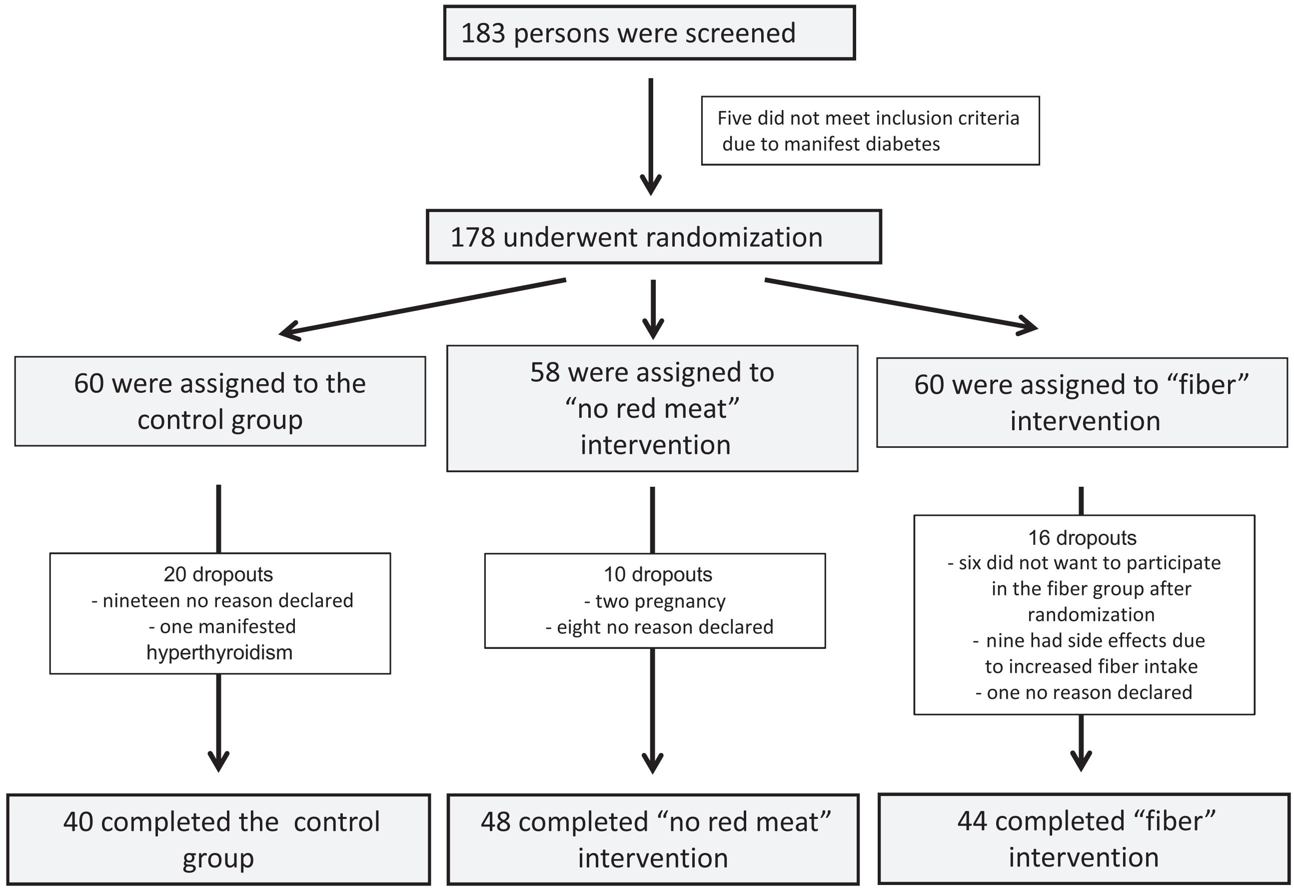


**FIGURE 1** Enrollment of the participants and completion of the study.

***Glucose metabolism.***

Plasma insulin was determined on an ADVIA Centaur XP (Siemens Healthcare Systems). Blood glucose was measured using a bedside glucose analyzer (Yellow Springs Instruments).

The area under the curve (AUC) glucose during the OGTT was calculated by the trapezoid method for all 5 time-points. The insulinogenic index (IGI) was calculated as (Ins30 – Ins0) / (Glc30 – Glc0), where Ins0 and Glc0 represent fasting insulin and fasting glucose, and Ins30 and Glc30 represent insulin and glucose levels 30 min after glucose ingestion during OGTT. The OGTT-derived insulin sensitivity index (ISI) was estimated as $ISI = 10,000 \times \sqrt{[(Glu_0 \times Ins_0 \times Glu_{mean} \times Ins_{mean})]}$ (38). The disposition index was calculated as ISI × IGI.

### Outcomes and statistical analyses

The primary outcome was the change in glucose metabolism measured during the OGTT. Secondary outcomes were changes in body weight, body-fat distribution measured by MRI, and liver fat and liver iron content. Furthermore, blood lipids (triglycerides and cholesterol levels) were assessed.

Changes in the primary and secondary endpoints in response to the 6-mo intervention in all groups as a whole were studied using a 2-sided Wilcoxon signed rank test.

Differences in the change in primary and secondary outcome variables between the groups ("control," "no red meat," "fiber") were tested using an analysis of covariance (ANCOVA). The terms "intervention group" ("control," "no red meat," "fiber") and the baseline values of the tested variables were used as covariates. Furthermore, an ANCOVA in addition adjusted for sex and age was performed for all variables. The variables of body-fat distribution and glucose metabolism were in addition adjusted for baseline BMI and change in BMI, respectively.

Unless otherwise stated, data are given as means ± SEM. Non-normally distributed variables were transformed to their natural logarithm before statistical analysis. Differences with a $P$ value $<0.05$ were considered to indicate nominal associations.

For statistical analysis, the JMP 10.0 statistical software package (SAS Institute) was used.

## Results

### Subjects and baseline characteristics

A total of 183 subjects were screened for this study (**Figure 1**). Five individuals could not participate in the trial because of newly diagnosed diabetes at screening. The remaining 178 subjects were randomly assigned to the "control," the "no red meat," or the increase in "fiber" groups. A total of 46 subjects dropped out, resulting in 132 subjects that completed the intervention (Figure 1).

Subject characteristics are shown in **Table 1**. Subjects had a mean age of 42 ± 1 y and a mean BMI of 31.2 ± 0.4 kg/m$^2$ at baseline. The groups did not differ in their baseline anthropometric and metabolic parameters. From the 132 participants that

**TABLE 1** Subject characteristics at baseline[1]

| | Control ($n = 40$) | No red meat ($n = 48$) | Fiber ($n = 44$) | $P$ |
|---|---|---|---|---|
| Gender, female/male | 25/15 | 34/14 | 27/17 | 0.6 |
| Age, y | 42 ± 13 | 42 ± 13 | 42 ± 11 | 0.9 |
| BMI, kg/m$^2$ | 31.7 ± 5.4 | 30.8 ± 3.9 | 30.8 ± 3.8 | 0.5 |
| Habitual physical activity, AU | 7.68 ± 0.18 | 7.89 ± 0.18 | 7.78 ± 0.19 | 0.7 |
| Fasting glucose, mmol/L | 5.42 ± 0.49 | 5.33 ± 0.43 | 5.35 ± 0.53 | 0.4 |
| Glucose, 120-min OGTT, mmol/L | 6.79 ± 1.7 | 6.47 ± 1.3 | 6.71 ± 1.4 | 0.4 |
| Fasting insulin, pmol/L | 79.6 ± 42.5 | 73.0 ± 42.8 | 77.0 ± 46.3 | 0.3 |
| Insulin, 30-min OGTT, pmol/L | 652 ± 361 | 681 ± 367 | 634 ± 363 | 0.6 |

[1]Data are given as means ± SDs. Habitual physical activity was assessed using the HPA score according to Baecke et al. (39). OGTT, oral glucose tolerance test



completed the intervention program, a total of 107 individuals were found to have normal glucose tolerance and 23 to have impaired glucose tolerance according to the 1999 World Health Organization diagnostic criteria at the baseline visit.

### Nutrient factors and compliance during diet intervention

The caloric intake decreased in all groups by a mean of 450 ± 45 kcal/d during the intervention with no significant differences between the groups (**Table 2**). As an index for reduced red meat consumption, iron intake was significantly lower in the "no red meat" group ($P = 0.0018$). Fiber intake in the "fiber" group increased by 9.4 ± 1.1 g/d ($P < 0.0001$). Apart from the differences between groups in iron and fiber intake, all other nutritional components (protein, carbohydrate, fat intake) did not differ between groups (all $P > 0.05$). For detailed information on intake of different nutritional components during intervention, see Table 2.

### Changes in glucose metabolism

Fasting glucose, 120-min glucose, and AUC glucose levels during the OGTT decreased significantly during the interventions when all treatment groups are analyzed together (**Table 3**). Furthermore, insulin sensitivity, as well as insulin secretion relative to insulin sensitivity, increased significantly by 23% and 25%, respectively. ANCOVA revealed that the changes in glucose (fasting and 120-min) levels, as well as of insulin sensitivity and insulin secretion, did not differ between the groups (**Table 4**). However, there was a trend (ANCOVA, $P = 0.07$) for a difference in the change in AUC glucose between the groups. This is illustrated in the post hoc analysis where the "no red meat" group tended to have the strongest decrease in AUC glucose levels compared with the "control" and "increase in fiber" groups. In the "no red meat" group there was also a strong increase in insulin secretion (disposition indexes; from 1474 ± 131 AU to 2763 ± 490 AU, $P < 0.0001$).

### Changes in body weight, body-fat mass and distribution, and liver fat content

During the intervention, body weight decreased when all groups were analyzed together (mean reduction of 3.3 ± 0.5 kg; $P < 0.0001$) (Table 3). There was no significant difference in the changes in body weight between the groups ($P = 0.55$, Table 4).

There was also a significant decrease in total body-fat mass, as well as of visceral and subcutaneous fat mass, when all groups were analyzed together, by approximately 7% (all $P < 0.0001$, Table 3). There were no significant differences with regard to the changes in these parameters between the groups (all $P \geq 0.46$, Table 4).

Liver fat content decreased by 23% from baseline when all groups were analyzed together ($P < 0.0001$, Table 3). However, no significant differences between the groups were found ($P = 0.72$, Table 4).

### Changes in iron metabolism and liver iron content

To investigate the changes in iron metabolism, the iron content of the liver measured by MRI and the plasma iron and ferritin levels were determined. The iron content in the liver, as well as the plasma iron level, did not change significantly during the intervention in any of the groups (Table 4). However, there was a significant mean decrease of 17% in the ferritin levels in all 3 groups (Tables 3 and 4). Here, the ANCOVA revealed a significant difference between groups. In post hoc analyses, the most pronounced decrease in ferritin level was found in the "no red meat" group (22%) compared with the "fiber" (12%) and "control" group (15%) ($P < 0.0001$; Table 4). The reduction in ferritin was correlated to the improvement in liver fat content ($r^2 = 0.08$, $P = 0.0021$). In a multivariate model including baseline BMI and baseline ferritin levels, we tested whether this association was independent of body weight loss. Both change in BMI ($\beta = 7.07 \pm 0.74$, $P < 0.0001$) and change in ferritin levels ($\beta = 0.46 \pm 0.11$, $P < 0.0001$) were independently associated with the reduction in liver fat.

For replication of the finding in a different cohort, we also analyzed whether there was an association of the change in liver fat with the change in ferritin after lifestyle intervention in 229 participants of the TULIP study. In this cohort, we also found that the reduction in serum ferritin levels is correlated with a reduction in liver fat ($r^2 = 0.03$, $P = 0.0084$) (**Figure 2**).

### Changes in lipids and liver parameters

During the intervention, total- and LDL-cholesterol levels decreased when all groups were analyzed together, whereas HDL-cholesterol levels remained unchanged (Table 3). The transaminases (glutamic oxaloacetic transaminase, glutamic pyruvic transaminase) and $\gamma$-glutamyl transferase also decreased

**TABLE 2** Intake of nutrients in the intervention groups[1]

| | Control ($n = 40$) | | | | | No red meat ($n = 48$) | | | | | Fiber ($n = 44$) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline (V0) | | During intervention (V1–V6) | | | Baseline (V0) | | During intervention (V1–V6) | | | Baseline (V0) | | During intervention (V1–V6) | | |
| | Mean | SEM | Mean | SEM | *P* | Mean | SEM | Mean | SEM | *P* | Mean | SEM | Mean | SEM | *P* |
| Caloric intake, kcal | 2323 | 75 | 1942 | 41 | <0.0001 | 2441 | 90 | 1878 | 40 | <0.0001 | 2391 | 82 | 1894 | 53 | <0.0001 |
| Iron intake, mg | 13.71 | 0.43 | 13.51 | 0.32 | 0.7 | 14.8 | 0.54 | 12.69 | 0.32 | 0.0001 | 14.62 | 0.43 | 15.56 | 0.33 | 0.0092 |
| Fiber intake, g | 22.53 | 1.11 | 24.03 | 0.89 | 0.05 | 24.4 | 1.2 | 24.07 | 0.88 | 0.8 | 23.73 | 0.81 | 32.55 | 0.94 | <0.0001 |
| Carbohydrates, g | 254.3 | 10 | 220.34 | 6.89 | 0.0003 | 261 | 11 | 215.44 | 6.07 | <0.0001 | 253.90 | 9.3 | 219.82 | 6.68 | <0.0001 |
| Protein, g | 85.7 | 3.3 | 77.17 | 2.25 | 0.0016 | 93.4 | 3.9 | 76.57 | 2.09 | <0.0001 | 89.75 | 3.16 | 78.92 | 2.08 | <0.0001 |
| Fat, g | 92.7 | 4.0 | 73.45 | 2.19 | <0.0001 | 103 | 4.5 | 69.83 | 1.91 | <0.0001 | 97.4 | 4.3 | 68.32 | 2.63 | <0.0001 |

[1]Intake of nutrients before and during intervention in the different intervention groups.

(Table 3). There were no significant differences in the changes in lipids, transaminases, or the $\gamma$-glutamyl transferase between the groups (Table 4).

## Discussion

In the present study, we investigated the effects of a diet avoiding the intake of red meat and a diet consisting of an increased intake of fibers, both compared with a control diet, all under a calorie-restricted regimen, on glucose and lipid metabolism, body-fat mass, and distribution and on liver fat content in subjects who were at increased risk of type 2 diabetes. Body weight and fat mass in all body compartments decreased in all 3 dietary intervention arms. This resulted in marked improvements in glucose tolerance and insulin sensitivity. These beneficial effects occurred to a comparable extent in all 3 intervention groups. These data suggest that regardless of a reduced intake of red meat or an increased intake of fibers, caloric restriction, as achieved in our study, was sufficient to result in an improved cardiometabolic risk profile.

These data may seem to be in contrast to data from several dietary observation studies where a reduced intake of red meat and an increased intake of fibers were associated with a beneficial cardiometabolic outcome and a decreased risk of type 2 diabetes (5–16). However, in those studies, the consumption of fiber and red meat mostly was not associated with a reduction in calorie intake and body weight. In contrast, in our present intervention study during a period of 6 mo of intervention, there was an intended decrease in calorie intake on average by $450 \pm 45$ kcal/d in all groups, which resulted in a mean decrease in body weight of 3.5%. This caloric restriction seems to be the main determinant for the success of the intervention. This is supported by the classic POUNDS LOST (Preventing Overweight Using Novel Dietary Strategies) trial, which found that "reduced-calorie diets result in clinically meaningful weight loss, regardless of which macronutrients they emphasize" (40).

Our study might indicate that the dietary modification that was chosen in our trial, in addition to caloric restriction, has an effect on specific secondary endpoints. We detected 1 parameter that was significantly different between the intervention groups, namely, ferritin. Ferritin levels decreased in all groups but to a different extent in the specific groups, with the most pronounced reduction in the "no red meat" group (−22%), followed by the "control" group (−15%) and the "fiber" group (−12%) ($P = 0.02$, ANCOVA). This could have a major clinical impact because the change in ferritin levels was correlated with the improvement in liver fat when all 3 intervention groups were analyzed together. Of note, this association was independent of weight reduction. We were able to replicate this finding by analyzing the TULIP cohort of 229 participants; the reduction in ferritin was associated with the reduction in liver fat in both study cohorts (Figure 2).

Because the decrease in ferritin was most pronounced in the "no red meat" group, one could presume that the reduction in red meat with a consecutively lower iron intake may also lead to a significantly better reduction in liver fat. Accordingly, the association of high red meat consumption with nonalcoholic fatty liver disease and insulin resistance has been reported most recently (41). However, in our study, we were able to detect a reduction in liver fat in all study groups ("control" −10%,

**TABLE 3** Anthropometric parameters, parameters of glucose metabolism, body-fat composition and iron metabolism before and after intervention[1]

| | Baseline | After 6-mo intervention | $P$ |
|---|---|---|---|
| Weight, kg | 91.9 ± 1.4 | 88.6 ± 1.40 | <0.0001 |
| BMI, kg/m$^2$ | 31.22 ± 0.37 | 30.12 ± 0.37 | <0.0001 |
| Fasting glucose, mmol/L | 5.4 ± 0.04 | 5.1 ± 0.1 | <0.0001 |
| Glucose, 120-min OGTT, mmol/L | 6.7 ± 0.1 | 6.3 ± 0.1 | 0.0015 |
| AUC glucose, mmol × h/L | 943 ± 16 | 872 ± 16 | <0.0001 |
| Fasting insulin, pmol/L | 76 ± 4 | 63 ± 3 | <0.0001 |
| Insulin sensitivity ISI, AU | 10.61 ± 0.52 | 13.06 ± 0.57 | <0.0001 |
| Insulin secretion, insulinogenic index, AU | 195 ± 15 | 195 ± 15 | 0.9 |
| Insulin secretion, disposition index, AU | 1924 ± 193 | 2398 ± 205 | <0.0001 |
| Total body fat, L ($n$ = 124) | 41.6 ± 1 | 38.6 ± 1 | <0.0001 |
| Visceral fat, L ($n$ = 124) | 4.2 ± 0.2 | 3.8 ± 0.2 | <0.0001 |
| Liver fat, percentage signal ($n$ = 122) | 7.1 ± 0.7 | 5.5 ± 0.6 | <0.0001 |
| Abdominal subcutaneous fat, L ($n$ = 124) | 15.6 ± 0.5 | 14.3 ± 0.5 | <0.0001 |
| Liver iron content, ms ($n$ = 124) | 28.8 ± 0.7 | 29.1 ± 0.7 | 0.82 |
| Ferritin, $\mu$g/dL ($n$ = 70) | 9.4 ± 1 | 7.8 ± 0.8 | <0.0001 |
| Iron, $\mu$g/dL | 98 ± 3 | 94 ± 3 | 0.37 |
| Glutamic oxaloacetic transaminase, U/L | 23.9 ± 0.7 | 22.3 ± 1 | 0.0002 |
| Glutamic pyruvic transaminase, U/L | 30.3 ± 1.7 | 28.3 ± 1.4 | 0.0257 |
| $\gamma$-Glutamyl transferase, U/L | 25.3 ± 2 | 24.2 ± 3 | <0.0001 |
| Cholesterol, mg/dL | 197 ± 3 | 187 ± 3 | <0.0001 |
| HDL, mg/dL | 53 ± 1 | 52 ± 1 | 0.4 |
| LDL, mg/dL | 123 ± 3 | 118 ± 3 | 0.0033 |
| Triglycerides, mg/dL | 120 ± 5 | 108 ± 5 | 0.0022 |

[1]Anthropometric parameters, parameters of glucose metabolism, body-fat composition and iron metabolism before and after intervention for all participants ($n$ = 132). Data are given as means ± SEM. $P$ values for changes in parameters in each group were determined using the Wilcoxon test. OGTT, oral-glucose-tolerance test.

"fiber" −26%, and "no red meat" −29%). The reduction in ferritin, e.g., by avoiding red meat consumption, but also by other ferritin-reducing mechanisms such as venesection, as has been proposed before (42), might have beneficial effects for the prevention of diabetes and of cardiometabolic diseases, especially in individuals with high liver fat content.

Because a higher hepatic iron content is associated with insulin resistance and dysglycemia (37), one could argue that specific changes in liver metabolism due to a subsequent hepatic iron deduction could be a plausible explanation for association of liver fat reduction and lower ferritin levels (43). Of note, hepatic iron content in the present study did not change in either intervention group. This rather indicates that the improvement in liver fat content is primarily linked to a reduction in the ferritin level as a marker of whole-body iron storage.

Regarding the increase in whole-grain intake, we could not detect any specific effects of increased whole-grain intake on glucose metabolism beyond those induced by caloric restriction and weight loss. Several intervention studies on that topic yielded conflicting results. One main difference of our study to several other studies is the longer duration of intervention. A short 3-d intervention study with fiber-enriched diets found better insulin sensitivity, measured using a euglycemic, hyperinsulinemic clamp, in the fiber group (44). Accordingly, whole-grain intake over 6 wk was found to decrease fasting insulin levels and to improve insulin sensitivity in overweight and hyperinsulinemic subjects (45)—which, however, is in contrast to a very similar study with the same duration of intervention where no positive effects could be detected (46). Interestingly, a high-fiber diet compared with a high-protein diet resulted in improved insulin sensitivity after 6 wk in the fiber group—after 18 wk, however, the effect was attenuated (47). Our present study was conducted with a significantly longer intervention time of 26 wk; thus, adaptive processes, as suggested by Weickert et al. (47), might also have occurred in our study. In line with our findings, a recently published study, which lasted over 2 y, postulated that there is no strong evidence for beneficial effects of insoluble fiber intake on glycemic control (48). This study was similar to ours in design and resulted in a relatively large weight loss.

In an interventional study in patients with type 2 diabetes, the beneficial nutritional factors identified in the German Diabetes Risk Score for diabetes prevention (higher fiber intake, less red meat intake, and lower coffee consumption) were combined in 1 intervention group, and this group was compared with a control weight loss diet over a period of 8 wk (26). Interestingly, even the combination of these potentially beneficial dietary factors did not result in a significantly better outcome in terms of glycemic markers, independent of weight loss. These data support the hypothesis that caloric restriction appears to be the major driver of metabolic health.

In summary, shifts in nutritional factors, such as the increase in whole-grain consumption or the reduction in red meat consumption, in addition to a calorie-restricted diet, may have small effects on metabolic parameters, especially on liver fat content. However, caloric restriction and accompanying significant reduction in body weight seem to override these effects. Therefore, caloric restriction remains the main goal in prevention programs targeting cardiometabolic diseases and diabetes.

**TABLE 4** Anthropometric parameters, parameters of glucose metabolism, body-fat composition and iron metabolism before and after intervention separated by groups[1]

| | Control ($n = 40$) | | | No red meat ($n = 48$) | | | Fiber ($n = 44$) | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Baseline | 6 mo | *P* | Baseline | 6 mo | *P* | Baseline | 6 mo | *P* | *P* ANCOVA | *P* ANCOVA adjusted |
| Weight, kg | 94.2 ± 3.1 | 91.0 ± 3.3 | 0.0002 | 91.7 ± 1.8 | 87.7 ± 1.6 | <0.0001 | 90.2 ± 2.3 | 87.5 ± 2.2 | 0.0003 | 0.55 | 0.5 |
| BMI, kg/m$^2$ | 31.88 ± 0.86 | 30.75 ± 0.89 | 0.0003 | 30.95 ± 0.52 | 29.64 ± 0.5 | <0.0001 | 30.92 ± 0.55 | 30.02 ± 0.53 | 0.0003 | 0.55 | 0.52 |
| Fasting glucose, mmol/L | 5.5 ± 0.1 | 5.2 ± 0.7 | 0.0046 | 5.4 ± 0.1 | 5 ± 0.1 | <0.0001 | 5.3 ± 0.1 | 5.1 ± 0.1 | <0.0001 | 0.23 | 0.15 |
| Glucose, 120-min OGTT, mmol/L | 6.9 ± 0.3 | 6.4 ± 0.3 | 0.0394 | 6.7 ± 0.2 | 6.1 ± 0.2 | 0.0024 | 6.5 ± 0.2 | 6.4 ± 0.2 | 0.7 | 0.22 | 0.36 |
| AUC glucose, mmol × h/L | 973 ± 33 | 921 ± 31 | 0.01 | 955 ± 25 | 852 ± 28 | <0.0001 | 907 ± 24 | 850 ± 26 | 0.0033 | 0.07 | 0.09 |
| Fasting insulin, pmol/L | 80 ± 7 | 69 ± 6 | 0.06 | 77 ± 7 | 59 ± 5 | 0.0003 | 73 ± 6 | 62 ± 5 | 0.0006 | 0.42 | 0.53 |
| Insulin sensitivity index, AU | 9.39 ± 0.8 | 11.42 ± 1 | 0.03 | 10.8 ± 0.9 | 14.17 ± 1 | <0.0001 | 11.41 ± 0.9 | 13.41 ± 1.0 | 0.0027 | 0.13 | 0.15 |
| Insulin secretion, insulinogenic index, AU | 207 ± 32 | 189 ± 18 | 0.84 | 158 ± 14 | 202 ± 36 | 0.24 | 218 ± 26 | 195 ± 18 | 0.43 | 0.76 | 0.16 |
| Insulin secretion, disposition index, AU | 1961 ± 433 | 1939 ± 225 | 0.038 | 1474 ± 132 | 2763 ± 491 | <0.0001 | 2304 ± 366 | 2452 ± 287 | 0.26 | 0.22 | 0.3 |
| Total body fat, L, $n = 37/43/44$ | 43.5 ± 2.1 | 39.4 ± 2.2 | <0.0001 | 40.1 ± 1.4 | 37.2 ± 1.4 | 0.0006 | 41.5 ± 1.5 | 39.2 ± 1.5 | 0.0005 | 0.46 | 0.26 |
| Visceral fat, L, $n = 37/43/44$ | 4.7 ± 0.5 | 4.4 ± 0.5 | 0.0018 | 4.1 ± 0.3 | 3.7 ± 0.3 | 0.0064 | 3.8 ± 0.3 | 3.6 ± 0.3 | 0.0292 | 0.51 | 0.64 |
| Liver fat, percentage signal $n = 37/41/44$ | 7.6 ± .1.3 | 6.8 ± 1.5 | 0.2 | 7.2 ± 1.2 | 5.1 ± 1 | <0.0001 | 6.6 ± 1 | 4.9 ± 0.8 | 0.014 | 0.72 | 0.94 |
| Abdominal subcutaneous fat, L, $n = 37/43/44$ | 16.3 ± 1 | 14.4 ± 1 | <0.0001 | 14.8 ± 0.7 | 13.7 ± 0.7 | 0.0074 | 15.7 ± 0.8 | 14.8 ± 0.8 | 0.01 | 0.61 | 0.46 |
| Liver iron content, ms, $n = 20/27/23$ | 28.9 ± 1.4 | 29.4 ± 1.3 | 1 | 29.3 ± 1.2 | 29 ± 1.2 | 0.46 | 28.2 ± 1.2 | 29 ± 1.1 | 0.11 | 0.76 | 0.77 |
| Ferritin, $\mu$g/dL | 10.4 ± 1.7 | 8.8 ± 1.4 | 0.0018 | 8.9 ± 1.5 | 6.9 ± 1.1 | <0.0001 | 9.1 ± 1.8 | 8 ± 1.4 | 0.0437 | 0.038 | 0.0207 |
| Iron, $\mu$g/dL | 100 ± 6 | 92 ± 4 | 0.24 | 97 ± 5 | 94 ± 5 | 0.92 | 100 ± 5 | 97 ± 5 | 0.74 | 0.94 | 0.84 |
| Glutamic oxaloacetic transaminase, U/l | 24.9 ± 1.7 | 22.1 ± 1.2 | 0.05 | 23.7 ± 1.1 | 24 ± 2.6 | 0.1 | 23.2 ± 1 | 20.8 ± 0.8 | 0.002 | 0.78 | 0.83 |
| Glutamic pyruvic transaminase, U/l | 32.5 ± 3.3 | 28.7 ± 2.4 | 0.1 | 30.5 ± 2.3 | 30.4 ± 2.58 | 0.5 | 28.2 ± 2.9 | 26.2 ± 2.3 | 0.1 | 0.65 | 0.68 |
| $\gamma$-Glutamyl transferase, U/l | 34.1 ± 5.4 | 33.9 ± 9.2 | 0.03 | 22.6 ± 2.6 | 20.1 ± 2.5 | 0.0051 | 20.6 ± 1.7 | 19.9 ± 2.2 | 0.0061 | 0.75 | 0.72 |
| Cholesterol, mg/dL | 197 ± 6 | 187 ± 6 | 0.02 | 195 ± 4 | 186 ± 4 | 0.01 | 198 ± 4 | 188 ± 4 | 0.001 | 0.9 | 0.92 |
| HDL, mg/dL | 52 ± 2 | 51 ± 2 | 0.55 | 53 ± 2 | 53 ± 2 | 0.93 | 53 ± 2 | 53 ± 2 | 0.4 | 0.7 | 0.7 |
| LDL, mg/dL | 129 ± 6 | 124 ± 6 | 0.06 | 120 ± 4 | 115 ± 4 | 0.18 | 122 ± 4 | 117 ± 4 | 0.06 | 1 | 1 |
| Triglycerides, mg/dL | 115 ± 9 | 98 ± 8 | 0.02 | 124 ± 8.94 | 111 ± 7.48 | 0.02 | 122 ± 9.6 | 113 ± 8.16 | 0.07 | 0.31 | 0.25 |

[1]Anthropometric parameters, parameters of glucose metabolism, body-fat composition and iron metabolism before and after intervention separated by the different intervention groups. Data are given as means ± SEM. *P* values for changes in variables in each group were determined using the Wilcoxon test. ANCOVA was used to test differences between the groups. All variables were adjusted for sex and age. The variables of body-fat distribution and glucose metabolism were also adjusted for baseline BMI and change in BMI, respectively.

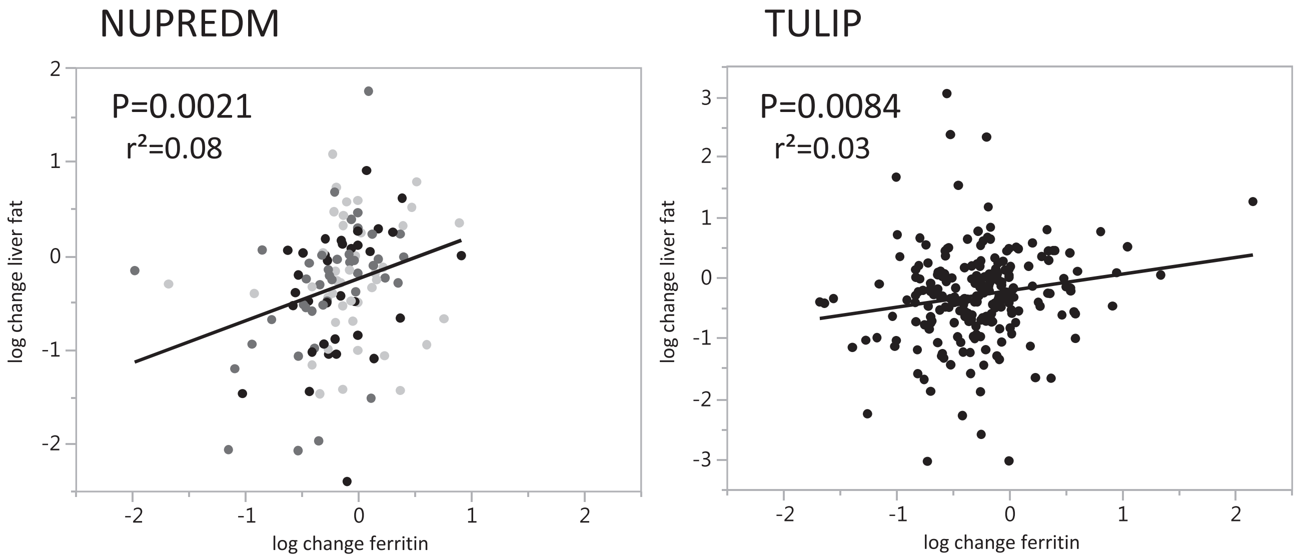


**FIGURE 2** Correlation of change in liver fat with change in ferritin during intervention in the NUPREDM cohort (left panel: black circles denote the control group; dark gray circles denote the "no red meat" group; and light circles denote the "fiber" group) as well as the correlation of change in liver fat with change in ferritin in the TULIP cohort (right panel). NUPREDM cohort $n = 122$; TULIP cohort $n = 229$. NUPREDM, Nutritional Prevention of Diabetes Mellitus Type 2; TULIP, TUebingen Lifestyle Intervention Program.

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