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Different Metabolic Responses to Long-Term Weight Loss After Lifestyle Intervention Among Type 2 Diabetes Risk Clusters: Results From the TULIP Study

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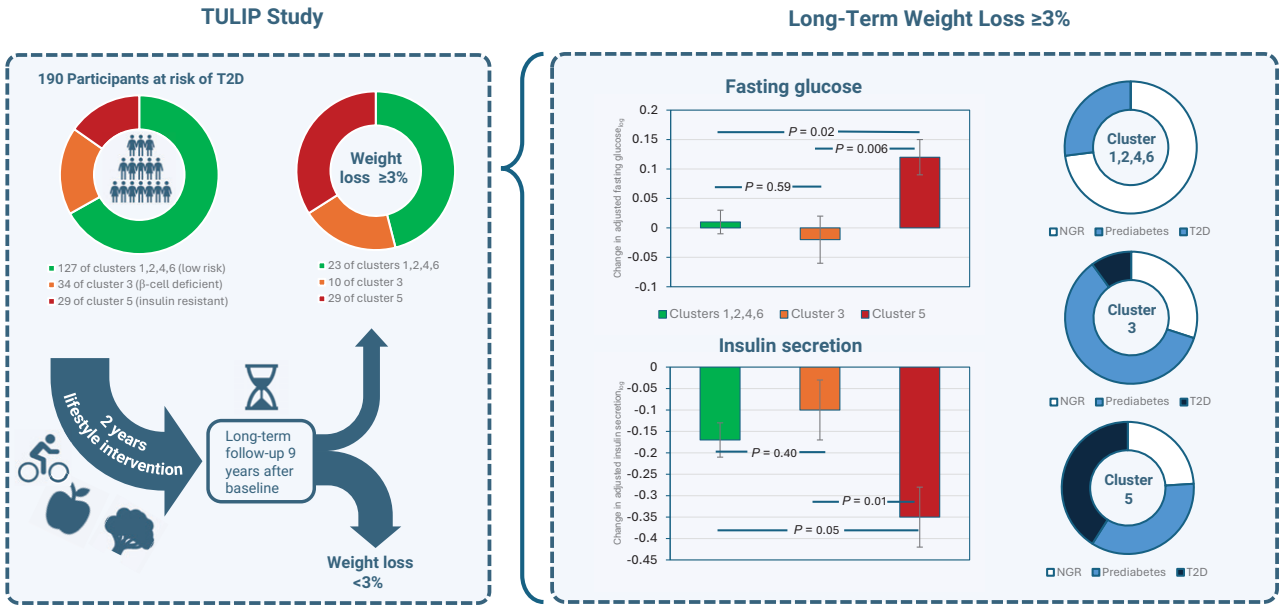

Conclusion: Despite a sustained and large amount of weight loss, people in diabetes risk cluster 5 had deterioration of glycemia, the largest decrease of insulin secretion among the clusters and a high risk of T2D.

NGR, normal glucose range; T2D, type 2 diabetes; TULIP, Tübingen Lifestyle Intervention Program.

Q:0 Different Metabolic Responses to Long-Term Weight Loss After Lifestyle Intervention Among Type 2 Diabetes Q:2 Risk Clusters: Results From the TULIP Study

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We previously identified six clusters of people at different risks of type 2 diabetes and/or comorbidities, of which cluster 3 (β-cell deficient) and 5 (older age, higher BMI, severe insulin resistance) had a high risk of progression to diabetes. We have now investigated whether cluster 3 and 5 individuals differed from those of the other clusters in changes in insulin sensitivity, insulin secretion, and the development of type 2 diabetes during a long-term reduction of body weight. A total of 190 participants completed a 24-month lifestyle intervention in the Tübingen Lifestyle Intervention Program (TULIP) and were followed up for 8.7 ± 1.6 years. Sixty participants had a weight loss ≥3% (mean reduction of 8%) at the long-term follow-up. Of them, cluster 5 participants (*n* = 17) had a larger increase of adjusted fasting glycemia compared with the cluster group 1,2,4,6 (*n* = 33) and cluster 3 (*n* = 10) and a larger increase of adjusted 2-h glucose levels compared with cluster 3 (all *P* < 0.05). In cluster 5, a larger decrease of adjusted insulin secretion compared with cluster 3 (*P* = 0.01) and cluster group 1,2,4,6 (*P* = 0.05) was observed. Forty-one percent of cluster 5 participants (0% in cluster group 1,2,4,6 and 10% in cluster 3) developed type 2 diabetes. In conclusion, despite a sustained and large amount of weight loss, diabetes risk cluster 5 participants had deterioration of glycemia and insulin secretion and a high risk of type 2 diabetes. If this result can be replicated in a prospective study, people of this cluster would need targeted prevention strategies.

ARTICLE HIGHLIGHTS

- There may be heterogeneity in the response to a lifestyle intervention to prevent type 2 diabetes.
- This study investigated whether participants of Tübingen Lifestyle Intervention Program (TULIP) type 2 diabetes risk clusters 3 and 5, who have a very high risk of diabetes, benefit from long-term weight loss following a 2-year lifestyle intervention.
- Diabetes risk cluster 5 participants had an impaired response regarding improvement of glycemia and insulin secretion and a high risk of developing type 2 diabetes, despite a long-term (9-year) mean weight loss of 8%.
- Alternative or intensified interventions should be considered for people in Tübingen type 2 diabetes risk cluster 5.

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Lifestyle intervention is effective in preventing the development of type 2 diabetes in people at high risk for the disease. Furthermore, the effect of a lifestyle intervention for the prevention of type 2 diabetes is sustainable and Q:3 extends beyond the duration of the intervention (1–12).

We previously identified six clusters of people at different risks of type 2 diabetes and/or comorbidities (Tübingen type 2 diabetes risk clusters), of which cluster 3 and 5 have a high risk of progression to diabetes (13). While people in cluster 3 mostly have low insulin secretion, those in cluster 5 predominantly have low insulin sensitivity, which is initially compensated by hypersecretion of insulin (13). In the Prediabetes Lifestyle Intervention Study (PLIS), participants in all clusters had improved glycemic traits during the 12-month lifestyle intervention, whereas insulin secretion only increased in clusters 3 and 5. However, high liver fat content in cluster 5 was associated with a failure to improve insulin secretion (14).

In the Diabetes Prevention Program (DPP), short-term (6-month) weight loss was protective against diabetes in people with overweight or obesity, impaired fasting glycemia, and impaired glucose tolerance; however, longer-term weight loss (0–2 years) was more effective in reducing the incidence of the disease (15). Therefore, it is important to promote long-term weight loss in people at risk for type 2 diabetes and to investigate whether those with different risks of type 2 diabetes differ in their response to long-term weight loss regarding improvement in glycemia. In the current study, we addressed this question in the Tübingen Lifestyle Intervention Program (TULIP) (16–19). We investigated whether participants in the Tübingen type 2 diabetes risk clusters differed in changes of glycemia, insulin sensitivity, and insulin secretion; the incidence of diabetes during a long-term follow-up of a sustained weight loss of ≥3%; and the possible mechanisms involved.

RESEARCH DESIGN AND METHODS

Participants and Study Design

A total of 413 participants were enrolled in TULIP, with 357 undergoing 9 months of intensive lifestyle intervention and 300 completing the full intervention after 24 months. We invited these 300 participants via written invitation or telephone call to a long-term follow-up visit; 190 individuals (63.3%) attended this visit after a mean follow-up time (i.e., time between baseline and long-term follow-up) of 8.7 ± 1.6 years. The main reason for not participating in the long-term follow-up was an unknown address (16). Inclusion criteria in TULIP were at least one of the following: family history of type 2 diabetes, BMI >27 kg/m^2, impaired glucose tolerance (blood glucose ≥7.78 mmol/L), or previous diagnosis of gestational diabetes mellitus. A diagnosis of diabetes or a severe, critical mental or physical illness was an exclusion criterion. Before enrollment, participants were given detailed information about the procedure, aims, and risks of the study and were Q:4 informed that they could withdraw voluntarily at any time. Ethical approval was obtained from the Medical Faculty of the Eberhard Karls University Tübingen, Germany, and all participants gave written informed consent. At baseline, anthropometric, medical history, and physical examination data were obtained, and a 2-h 75-g oral glucose tolerance test (OGTT) was performed. These examinations were repeated at 9 and 24 months after the baseline visit and ∼9 years later. During the first 24 months, the participants underwent a lifestyle intervention to improve their glucose metabolism, as assessed by the OGTT. The aim was to reduce fat intake to <30% and saturated fat intake to <10% of total energy intake and to increase fiber intake to 15 g per 1,000 kcal. They were also asked to be physically active for at least 3 h per week, which should result in a weight loss of >5%. To achieve this goal, all participants received standardized and individualized dietary advice from trained diabetes educators throughout 15 sessions, which took place monthly for the first 9 months and then every 3 months until 24 months after the start of the study. This study aimed to investigate whether clusters of people at risk for type 2 diabetes differ in their long-lasting response regarding improvement of glucose metabolism while they maintain a reduced body weight.

Clustering of Participants

Participants were assigned to the Tübingen type 2 diabetes risk clusters based on the criteria developed from the TULIP and Tübingen Diabetes Family Study data and replicated in the London Whitehall II study of 6,810 individuals (13). The clustering procedure is publicly available (20) and requires the following measures: sex, BMI, waist circumference, hip circumference, fasting glucose, 2-h OGTT glucose, fasting insulin, 2-h OGTT insulin, triglycerides, HDL cholesterol, and plasma glucose. The variables used to assign participants to these clusters were those assessed at baseline (before the intervention). We focused on cluster 3 and 5 participants, as they have the highest risk of progression to type 2 diabetes (13), and compared them with participants in the other clusters (hereafter, cluster group 1,2,4,6).

OGTT

Participants underwent a 2-h, five-point, 75-g OGTT at baseline, after 9 and 24 months of the lifestyle intervention, and at the long-term follow-up. Blood samples were taken at 0, 30, 60, 90, and 120 min. Plasma glucose was measured with a bedside glucose analyzer (YSI, Yellow Springs, OH) and in the laboratory with an ADVIA XPT clinical chemistry analyzer (Siemens Healthineers) using the hexokinase method and an immunoturbidimetric assay. Plasma insulin, C-peptide levels, and triglycerides were determined by immunoassay using an ADVIA Centaur XPT chemiluminescence immunoassay system (Siemens Healthineers, Erlangen, Germany). Area under the curve glucose at 0–120 min ($AUC_{0–120}$) was calculated using the trapezoidal method. Prediabetes and type 2 diabetes were diagnosed according to the diagnostic criteria of the American Diabetes Association (21). The estimation of insulin sensitivity proposed by Matsuda

Table 1—Participant characteristics

Characteristic	Baseline	9 months	24 months	9 years
Sex (female/male), *n*	112/78			
Age (years)	49 ± 10	50 ± 10	51 ± 10	58 ± 10
Body weight (kg)	86.3 ± 17.9	83.3 ± 16.7	84.6 ± 17.8	86.9 ± 19.5
Body height (cm)	170.4 ± 9.1	170.5 ± 9.1	170.4 ± 9.1	169.7 ± 9.3
BMI (kg/m^2)	29.7 ± 5.4	28.6 ± 5.0	29.1 ± 5.5	30.1 ± 5.9
Total fat mass (lb)[a]	30.4 ± 11.6	27.9 ± 10.6	29.2 ± 11.6	34.9 ± 11.5
Visceral fat mass (lb)[b]	3.5 ± 2.1	2.9 ± 1.9	3.2 ± 2.1	4.8 ± 2.7
Subcutaneous fat mass (lb)[c]	9.0 ± 4.7	7.9 ± 4.3	6.8 ± 4.2	12.6 ± 5.4
Liver fat content (%)[d]	6.0 ± 6.9	4.1 ± 4.1	4.8 ± 5.2	6.1 ± 5.5
Fasting blood glucose (mmol/L)	5.3 ± 0.5	5.2 ± 0.5	5.3 ± 0.5	5.7 ± 0.8
2-h Blood glucose (mmol/L)	7.2 ± 1.7	6.8 ± 1.8	7.3 ± 2.0	7.2 ± 2.1
Triglycerides (mg/dL)	129 ± 88	121 ± 83	125 ± 127	133 ± 141
ISI Matsuda	11.9 ± 6.4	13.7 ± 7.1	12.4 ± 7.3	8.4 ± 5.1
$IGI_{0–30}$	132 ± 104	156 ± 338	135 ± 102	163 ± 132
$AUC_{1–120}$ C-peptide to $AUC_{1–120}$ Glc	303 ± 86	302 ± 93	297 ± 87	266 ± 85
Disposition index	1,391 ± 1498	1,921 ± 4350	1,446 ± 1060	1,171 ± 1032

Data are mean ± SD unless otherwise indicated. [a]$n = 104$. [b]$n = 106$. [c]$n = 93$. [d]$n = 99$.

and DeFronzo, based on glucose (Glc) and insulin levels, was used to determine the insulin sensitivity index (ISI) (22). The insulinogenic index ($IGI_{0–30\ min}$), calculated as $(Ins_{30} - Ins_0)/(Glc_{30} - Glc_0)$ (21), and the relative insulin secretion (disposition index), calculated as the product of ISI and $IGI_{0–30\ min}$ (23), were used as proxies for insulin secretion. We focused on the ratio of $AUC_{0–120}$ C-peptide to $AUC_{0–120}$ Glc as an index of insulin secretion, as this index is well suited to assess β-cell secretory function (24) and exhibits low variation and high discriminatory power (25).

Measurement of Body Fat Mass and Distribution and Liver Fat Content by MRI and ^{1}H Magnetic Resonance Spectroscopy

Determination of whole-body fat mass and fat distribution was performed using an axial T1-weighted fast spin echo technique, as previously described, on a 1.5-T whole-body imager (Magnetom Sonata; Siemens Healthineers) (17). Liver fat content was quantified by localized ^{1}H magnetic resonance spectroscopy as previously described (18).

Statistical Analysis

The statistical analysis was performed using the commercial software program JMP (SAS Institute, Inc., Cary, NC). Data are presented as mean ± SD (tables) or mean ± SEM (figures). The Student *t* test was used for statistical comparison and to determine significance differences between two groups with normally distributed parameters. Parameters were tested for normal distribution using the Shapiro-Wilk *W* test, and nonnormally distributed values were logarithmically transformed to approximate a normal distribution. Multivariable linear regression analyses were performed to identify independent relationships. $P \leq 0.05$ was considered statistically significant.

Data and Resource Availability

The data sets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

RESULTS

The baseline characteristics of the participants who attended the long-term follow-up and who were included in this analysis and those who were lost to long-term follow-up are reported in Supplementary Table 1. Among the 190 participants who attended the long-term follow-up, mean body weight decreased by 3% after 9 months of the lifestyle intervention and was similar to the baseline body weight after the long-term follow-up of 9 years (Table 1). Based on the largest mean decrease in body weight, which was observed after 9 months of the lifestyle intervention, participants were divided into those with and without sustained long-term effects of the intervention with regard to decreased body weight (≥3% or <3% weight loss, respectively, from baseline to 9 years of follow-up).

We first investigated whether weight loss was different in the clusters. In all 190 participants analyzed together, weight loss (adjusted for age, sex, and the baseline weight) was largest in cluster 5 ($P = 0.03$ vs. cluster group 1,2,4,6; $P = 0.13$ vs. cluster 3; ANCOVA $P = 0.097$). No differences

in weight loss among the clusters were observed when the participants were divided into those with <3% (ANCOVA $P = 0.44$) and ≥3% (ANCOVA $P = 0.43$) weight loss.

We then studied whether changes in our main parameters of interest (i.e., insulin sensitivity, insulin secretion, the development of type 2 diabetes) differed between the groups with <3% and ≥3% weight loss from baseline to 9 years of follow-up within clusters. Data for all 190 participants are shown in the Supplementary Table 2, for those who lost <3% weight in Supplementary Table 3, and for those who lost ≥3% weight in Table 1. As expected, in multivariable linear regression analyses within the clusters, insulin sensitivity (adjusted for age, sex, and baseline insulin sensitivity [least squares mean]) decreased less or increased more in the groups with ≥3% versus those with <3% weight loss (cluster group 1,2,4,6 $P = 0.0005$; cluster 3 $P = 0.003$; cluster 5 $P = 0.14$), and there was no statistically significant cluster × weight loss group interaction for change in insulin sensitivity ($P = 0.28$). Furthermore, in multivariable linear regression analyses, the change in insulin secretion ($AUC_{0–120}$ C-peptide to $AUC_{0–120}$ Glc, adjusted for age, sex, insulin secretion at baseline, and insulin sensitivity at baseline and follow-up) was not different between the weight loss groups within the clusters (cluster group 1,2,4,6 $P = 0.25$; cluster 3 $P = 0.64$; cluster 5 $P = 0.32$), and there was no statistically significant cluster × weight loss group interaction for change in insulin secretion ($P = 0.25$). In addition, in nominal logistic regression models, the development of type 2 diabetes (adjusted for age, sex, and baseline presence of prediabetes or normal glucose regulation) was not statistically different between the weight loss groups within the clusters. However, after adjustment for age, sex, and the baseline presence of prediabetes or normal glucose regulation, the clusters × weight loss group interaction for development of type 2 diabetes was statistically different ($P = 0.01$). Diabetes tended to be higher in weight loss group <3% in cluster group 1,2,4,6 ($P = 0.07$); was not different between weight loss groups in cluster 3 ($P = 0.26$); and tended to be lower in weight loss group <3% in cluster 5 ($P = 0.08$). We then analyzed these two weight loss groups separately by cluster group 1,2,4,6; cluster 3; and cluster 5 and henceforth, focus on the group of participants with a sustained weight loss of ≥3% during the long-term follow-up.

Short-Term Effects of the Lifestyle Intervention

The group that lost ≥3% body weight from baseline to 9 years of follow-up consisted of 60 participants, of whom 33 were in cluster group 1,2,4,6; 10 in cluster 3; and 17 in cluster 5 (Table 2). The highest baseline weight (93.7 ± 15 kg) and the largest weight loss (8.8%) within the first 9 months of the study were observed in cluster 5 participants (Fig. 1). Weight loss from baseline to 9 years of follow-up was not different among the clusters (cluster group 1,2,4,6, –8.9%; cluster 3, –8.9%; cluster 5, –8.0%; ANOVA $P = 0.80$). In both high-risk clusters (3 and 5), the baseline fasting glucose level was 5.9 mmol/L and decreased by 8.5% during the first 9 months, while the baseline level in cluster group 1,2,4,6 was 5.2 mmol/L and decreased by 1.9%. The mean baseline 2-h glucose level during the OGTT was highest in cluster 5 (9.3 mmol/L) and decreased more at 9 months (16.1%) compared with cluster 3 (6.9%) and cluster group 1,2,4,6 (1.6%). Two cluster 3 participants had mild diabetes (for both, only based on elevated 2-h glucose values of 11.86 and 11.89 mmol, respectively, during the OGTT) after 9 months from the start of the intervention and did not have diabetes at the end of the active phase of the intervention (24 months). The baseline ISI was lowest in cluster 5 (4.7 arbitrary units), only increased to 8.3 arbitrary units after 9 months, and, thereby, was only half as high as the ISIs of the other clusters after 9 months of the lifestyle intervention. Liver fat content and fasting blood triglycerides, which are strongly associated with insulin sensitivity, were highest in cluster 5 and largely decreased after 9 months of the lifestyle intervention, indicating an adequate response of triglyceride metabolism in cluster 5. The ratio of $AUC_{0–120}$ C-peptide to $AUC_{0–120}$ Glc decreased by 6.8% in cluster 5 and increased by 1.5% in cluster 3 (Table 2).

Long-Term Effects of the Lifestyle Intervention

In the group that lost ≥3% body weight from baseline to 9 years of follow-up, the mean weight loss was similar among the clusters (−7 to −8% compared with the baseline body weight) (Table 2 and Fig. 1). An improvement of fasting glucose levels was observed in cluster 3, and a moderate increase of fasting glucose levels was found in cluster group 1,2,4,6 (Table 2). In contrast, cluster 5 participants had an increase in fasting glucose levels. Subsequently, multivariable linear regression analysis was performed, with change in fasting glucose as the dependent variable and cluster allocation as the explanatory variable of interest. The model was adjusted for age, sex, and baseline fasting glucose level. A significant difference between high-risk clusters 3 and 5 ($P = 0.006$), with a decrease of fasting glucose in cluster 3 and an increase of fasting glucose in cluster 5, was observed (Fig. 2*A*). This increase of fasting glucose in cluster 5 was also larger than in cluster group 1,2,4,6 ($P = 0.02$).

Regarding 2-h glucose, cluster group 1,2,4,6 participants had a small increase, and both high-risk clusters had a decrease (Table 2). In multivariable linear regression analysis, the changes of 2-h glucose levels (adjusted for age, sex, and baseline 2-h glucose levels) were significantly different between the high-risk clusters ($P = 0.02$), with an increase in cluster 5 (Fig. 2*B*).

Regarding insulin sensitivity, cluster 5 participants had not only the lowest insulin sensitivity at baseline but also the smallest improvement of insulin sensitivity compared with the other clusters. In multivariable linear regression analysis, insulin sensitivity (adjusted for age, sex, and baseline insulin sensitivity) increased in cluster 3 ($P = 0.05$ vs. cluster group 1,2,4,6; $P = 0.04$ vs. cluster 5), and the change in insulin

Table 2—Characteristics of participants in the type 2 diabetes risk clusters who lost ≥3% of their body weight after 9 years compared with baseline

	Follow-up											
	Cluster group 1,2,4,6				Cluster 3				Cluster 5			
Characteristic	Baseline	9 Months	24 Months	9 Years	Baseline	9 Months	24 Months	9 Years	Baseline	9 Months	24 Months	9 Years
Sex (female/male), *n*	18/15				5/5				14/3			
Age (years)	47 ± 11	47 ± 11	49 ± 11	56 ± 10	54 ± 9	55 ± 9	57 ± 9	63 ± 9	53 ± 7	53 ± 7	55 ± 7	62 ± 8
Body weight (kg)	90.3 ± 22	85.2 ± 21	84.1 ± 22	82.2 ± 20	82.9 ± 8	77.6 ± 10	77.8 ± 10	75.5 ± 9	93.7 ± 15	85.5 ± 12	88.9 ± 14	85.9 ± 13
Body height (cm)	172.2 ± 9.8	172.3 ± 9.8	172.2 ± 9.7	171.7 ± 10.2	170.8 ± 8.1	170.8 ± 8.1	170.8 ± 8.1	169.7 ± 7.6	163.7 ± 8.4	163.7 ± 8.4	163.8 ± 8.4	162.8 ± 8.6
BMI (kg/m^2)	30.2 ± 5.3	28.5 ± 5.0	28.1 ± 5.5	27.6 ± 4.7	28.5 ± 2.6	26.7 ± 3.5	26.7 ± 3.4	26.2 ± 2.7	34.9 ± 5.0	32.0 ± 4.4	33.3 ± 5.3	32.5 ± 4.5
Total fat mass (lb)[a]	34.5 ± 14.3	30.3 ± 13.3	30.7 ± 16.3	32.3 ± 11.9	24.9 ± 3.8	18.9 ± 8.4	21.5 ± 6.2	23.5 ± 5.5	42.0 ± 13.3	36.7 ± 12.4	39.8 ± 12.6	43.0 ± 13.1
Visceral fat mass (lb)[b]	3.4 ± 2.3	2.7 ± 1.9	2.8 ± 2.4	3.8 ± 2.8	3.4 ± 1.8	2.4 ± 2.0	2.7 ± 1.7	3.8 ± 2.8	4.6 ± 1.8	4.1 ± 1.9	3.9 ± 2.4	5.3 ± 2.4
Subcutaneous fat mass (lb)[c]	11.0 ± 6.6	9.6 ± 6.0	7.7 ± 6.2	11.5 ± 6.8	7.5 ± 2.3	4.1 ± 2.7	4.2 ± 2.4	7.5 ± 2.2	15.0 ± 5.7	13.2 ± 2.8	9.6 ± 2.9	17.4 ± 5.7
Liver fat content (%)[d]	5.4 ± 5.8	2.9 ± 3.3	2.7 ± 3.5	3.2 ± 2.5	7.7 ± 7.6	7.4 ± 4.0	3.2 ± 3.1	6.7 ± 4.0	13.1 ± 10.4	5.6 ± 4.2	8.0 ± 8.8	7.9 ± 6.4
Fasting blood glucose (mmol/L)	5.2 ± 0.5	5.1 ± 0.4	5.1 ± 0.5	5.4 ± 0.5	5.9 ± 0.5	5.4 ± 0.6	5.6 ± 0.9	5.6 ± 0.8	5.9 ± 0.4	5.4 ± 0.4	5.7 ± 0.6	6.4 ± 1.2
2-h Blood glucose (mmol/L)	6.3 ± 1.3	6.2 ± 1.4	6.5 ± 1.5	6.4 ± 1.2	8.6 ± 1.5	8.0 ± 2.3	7.9 ± 2.1	7.1 ± 2.3	9.3 ± 1.5	7.8 ± 2.5	9.5 ± 2.3	8.8 ± 2.5
Triglycerides (mg/dL)	110 ± 47	103 ± 57	90 ± 38	92 ± 34	168 ± 135	115 ± 58	116 ± 72	112 ± 55	172 ± 119	131 ± 52	170 ± 128	135 ± 71
Prediabetes, % of participants	24	24	24	27	70	40	60	60	100	47	65	35
Type 2 diabetes, % of participants	0	0	0	0	0	20	0	10	0	6	24	41
ISI Matsuda	14.2 ± 6.8	16.1 ± 7.2	15.7 ± 8.8	11.2 ± 5.3	9.3 ± 2.8	15.1 ± 6.4	15.2 ± 9.6	12.4 ± 7.9	4.7 ± 1.7	8.3 ± 3.7	6.7 ± 4.4	5.7 ± 3.4
IGI_{0-30}	140 ± 90	292 ± 784	125 ± 84	129 ± 90	81 ± 36	80 ± 48	82 ± 46	106 ± 91	122 ± 82	106 ± 53	123 ± 79	114 ± 83
Ratio of AUC_{0-120} C-peptide to AUC_{0-120} Glc	306 ± 97	307 ± 104	293 ± 89	242 ± 90	269 ± 84	273 ± 110	251 ± 77	235 ± 102	322 ± 83	300 ± 64	289 ± 68	248 ± 72
Disposition index	1,676 ± 1,039	4,100 ± 1,0059	1,718 ± 1,225	1,326 ± 1,312	728 ± 356	1,098 ± 755	1,110 ± 706	956 ± 469	470 ± 222	880 ± 778	739 ± 462	688 ± 904

Data are mean ± SD unless otherwise indicated. [a]$n = 43$. [b]$n = 35$. [c]$n = 31$. [d]$n = 31$.

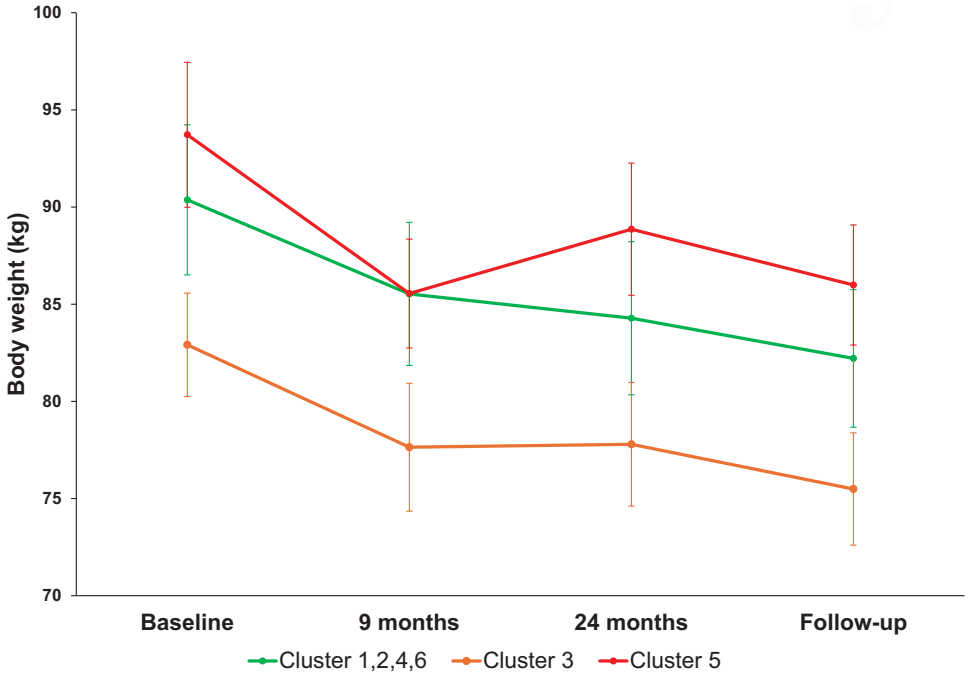

Figure 1—Course of weight from baseline to follow-up by cluster for participants with weight loss ≥3% at 9 years of follow-up. Data are mean ± SEM.

sensitivity was not different between cluster group 1,2,4,6 and cluster 5 (Fig. 2*C*).

In all clusters, liver fat content and fasting blood triglycerides were lower after 9 years of follow-up compared with baseline but were still highest in cluster 5 compared with the other clusters (Table 2). In multivariable linear regression analysis, changes in circulating triglycerides and liver fat content (adjusted for age, sex, and baseline triglyceride levels or liver fat content) were not different among the clusters.

Based on the mean ratio of $AUC_{0–120}$ C-peptide to $AUC_{0–120}$ Glc, insulin secretion was found to be similar in all clusters (Table 1). However, in the multivariable regression analysis, the decrease of insulin secretion (adjusted for age, sex, baseline insulin secretion, and insulin sensitivity at baseline and follow-up) was greatest in cluster 5 and statistically different from cluster 3 ($P = 0.01$) and cluster group 1,2,4,6 ($P = 0.05$) (Fig. 2*D*). Importantly, 41% of cluster 5 participants, but 0% of cluster group 1,2,4,6 participants and only 10% of cluster 3 participants developed type 2 diabetes (Table 2). No distinct differences among the clusters were observed for changes in fasting and 2-h glucose levels and insulin sensitivity and insulin secretion in the participants who did not achieve a long-term weight loss of at least 3% (Supplementary Material).

DISCUSSION

The beneficial effects of a lifestyle intervention to prevent type 2 diabetes in people at high risk of the disease have been well documented (1–12). However, its long-term effects on glycemia, insulin sensitivity, and insulin secretion among distinct pathophysiological subgroups of people at risk for type 2 diabetes remain unclear. We investigated the long-lasting effects of a lifestyle intervention on these parameters and the incidence of type 2 diabetes in people characterized by the Tübingen type 2 diabetes risk clusters. Because sustained weight loss during a lifestyle intervention is considered an important target to prevent type 2 diabetes (15), we focused on people who achieved sustained weight loss after a mean follow-up of nearly 9 years.

In cluster 3, which is characterized by impaired insulin secretion with only mild insulin resistance, participants experienced improvements of both fasting glucose and, more strongly, 2-h glucose levels, and most cluster 3 participants reverted to normoglycemia. In these individuals, we also found an increase in insulin sensitivity. The decrease in insulin secretion in cluster 3 participants was smallest compared with the other clusters, indicating a favorable long-term response in most individuals in this cluster. Nevertheless, 10% of cluster 3 participants still progressed to type 2 diabetes, despite a sustained mean weight loss of 7% after 9 years of follow-up.

In contrast, in cluster 5, which is characterized by severe insulin resistance with initially compensatory hypersecretion of insulin, participants experienced deterioration of glycemia. This occurred despite achieving the greatest initial weight loss of all clusters within the first 9 months and a mean weight loss of 8% after 9 years of follow-up. Unexpectedly, despite this large amount of weight loss, 41% of cluster 5 participants developed type 2 diabetes. In cluster 5, we also found the largest decrease of insulin sensitivity and,

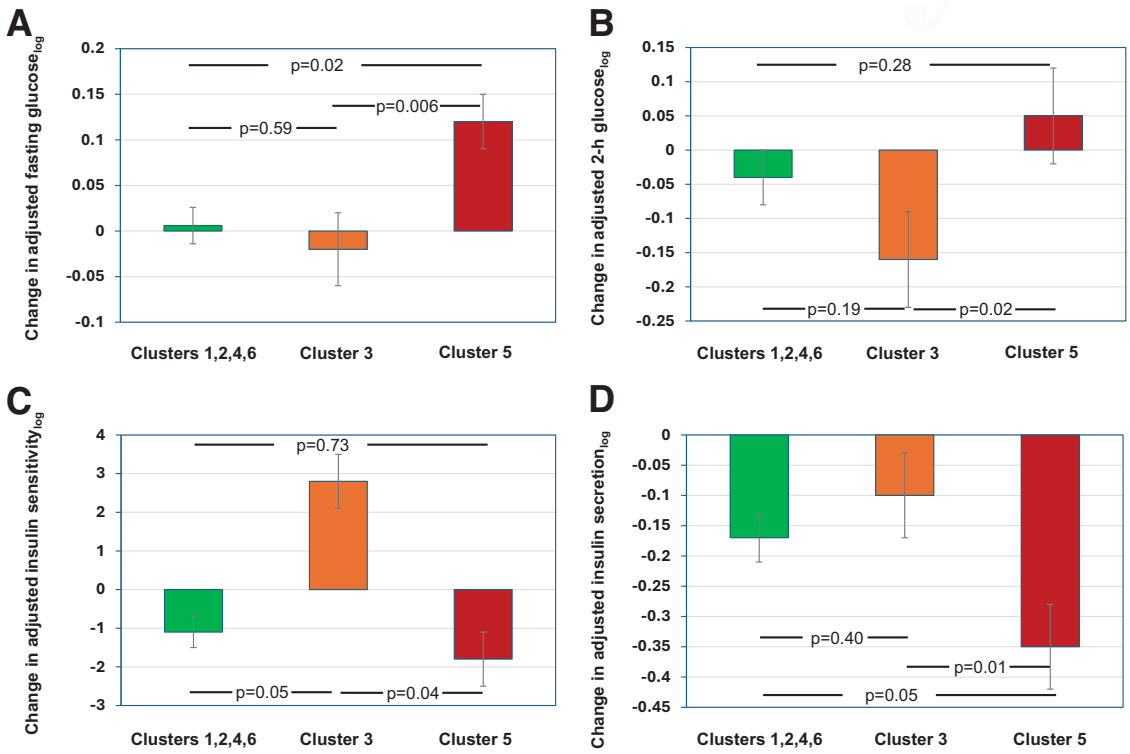

Figure 2—Change (from baseline to 9 years of follow-up) in adjusted (for age, sex, and baseline level) logarithmic fasting plasma glucose (*A*), logarithmic 2-h plasma glucose (*B*), and logarithmic insulin sensitivity (*C*) and of adjusted (for age, sex, insulin sensitivity at baseline and follow-up, and baseline level) logarithmic $AUC_{1-,20}$ C-peptide to AUC_{1-120} Glc (*D*) by cluster for participants with weight loss ≥3%. Data are mean ± SEM.

more importantly, the largest decrease of insulin secretion after the long-term follow-up. These findings suggest that sustained moderate to large weight loss alone may be insufficient to counteract the progressive deterioration of glucose metabolism in this high-risk group. Furthermore, impaired triglyceride metabolism (liver and circulating triglycerides) may not improve as expected in cluster 5 individuals, although the changes in these parameters were not statistically significant among the clusters. Although percentage weight loss was almost identical among the three clusters, cluster 5 participants had the highest body weight at baseline and at the 9 year follow-up visit. Thus, a larger weight loss may be necessary to improve glucose and lipid metabolism in cluster 5 individuals.

The focus of the analyses on participants who achieved a large and sustained mean weight loss of 8% after a very-long follow-up of 9 years is limited by the sample Q:9 size becoming small for statistical analyses. Therefore, we also performed analyses in all 190 participants. In these analyses, a larger weight loss (as a continuous parameter) during 9 years of follow-up was also associated with a larger adjusted increase of insulin sensitivity but not with improvement of adjusted insulin secretion within all clusters. Furthermore, in these participants, a larger weight loss (as a continuous parameter) during 9 years of follow-up was only associated with a lower adjusted incidence of diabetes within cluster group 1,2,4,6 but not in clusters 3 or 5. These data support that people with more severe impairment of glucose metabolism, particularly as observed in cluster 5 participants with low insulin sensitivity and low insulin sensitivity-corrected insulin secretion, may need more intensified interventions.

The different responses of the parameters of glucose metabolism to the lifestyle intervention in the diabetes risk clusters may have resulted from the distinct pathophysiological phenotypes that prevail in participants in the respective clusters. The main metabolic characteristic of cluster 3 is a deficient β-cell function in the presence of mild insulin resistance. The decrease in the ratio of AUC_{0-120} C-peptide to AUC_{0-120} Glc during the first 9 months of the lifestyle intervention indicates that the moderate compensatory insulin hypersecretion decreased, likely due to improvement of insulin action in peripheral tissues during weight loss. This may have resulted in relieving β-cells from stress that is brought about by the need of hypersecretion of insulin (26). This observation is important, considering that β-cell function was already impaired at baseline. Reduction of β-cell stress may delay or even prevent the development of type 2 diabetes, which occurs when poor β-cell function can no longer compensate for insulin resistance (27–29).

Cluster 5, on the other hand, is dominated by severe insulin resistance, which causes a very high glycemic load to the β-cells. Hyperglycemia, brought about by insulin

resistance and increased circulating free fatty acids (30), may have resulted in severe hypersecretion of insulin. This may have promoted the decrease of glucose-stimulated insulin secretion that occurred during the long-term follow-up and the development of type 2 diabetes in 41% of cluster 5 participants. Severe and long-existing hypersecretion of insulin very likely was already present at the beginning of the lifestyle intervention because all cluster 5 participants had prediabetes at baseline. Unfortunately, adjusted insulin sensitivity in cluster 5 only improved in the short term, not in the long-term follow-up. Importantly, this decrease of adjusted insulin sensitivity in the long-term follow-up occurred despite a relatively large and sustained weight loss. Thus, in cluster 5 individuals, pathomechanisms promoting both severe insulin resistance and impairment of β-cell function may be operative. Evidence from our studies in people with prediabetes (PLIS) suggests that the main driver for the decrease of insulin secretion in cluster 5 is high liver fat content (14). In the current study, liver fat content at baseline (adjusted for age, sex, and total body fat mass) was much higher in cluster 5 participants compared with those in cluster group 1,2,4,6 (2.4-fold higher, $P = 0.002$) and cluster 3 (1.7-fold higher, $P = 0.018$). The fatty liver, for example, releases the hepatokine fetuin-A (31), which together with palmitate, induces proinflammatory responses in human adipocytes and mouse macrophages, thereby promoting insulin resistance in animals (32,33) and most probably in humans as well (34). In addition, fetuin-A, together with palmitate, promotes the production of the proinflammatory and cytotoxic cytokine interleukin-1β in macrophages within the isolated islets, and fetuin-A impairs glucose-induced insulin secretion (35). Interestingly, baseline fetuin-A levels (34), which were available in 50 of the 60 participants with long-term weight loss ≥3%, were highest in cluster 5 participants (mean values: 262 ± 40 μg/mL for cluster group 1,2,4,6; 246 ± 53 μg/mL for cluster 3; and 290 ± 29 μg/mL for cluster 5; $P = 0.01$ for cluster 5 vs. cluster group 1,2,4,6 and $P = 0.06$ for cluster 5 vs. cluster 3 after adjustment for age, sex, and the adipose tissue–related insulin sensitivity marker adiponectin). These findings suggest that for people in type 2 diabetes risk cluster 5, it may be more important to focus on interventions that specifically reduce liver fat content rather than body weight. Nevertheless, we recently found that cluster 5 individuals largely benefited from substantial weight loss brought about by bariatric surgery in terms of improvement of insulin resistance, insulin secretion, and prediabetes remission (36).

A limitation of our study is that the group of people who were able to decrease their body weight over a long follow-up is relatively small. Furthermore, although the whole study group ($N = 190$) had a BMI of ≥35.1 kg/m^2, cluster 5 participants had the highest BMI, and nearly all (97%) had prediabetes at baseline. The timing of onset of diabetes may have impacted weight measures, as a higher percentage of cluster 5 participants than those in other clusters may have tried hard to maintain a large decrease of body weight over the long follow-up. This may have resulted in a selection of high-risk people with long-term weight loss ≥3% in the cluster 5. Nevertheless, in our analyses, we adjusted for the baseline levels of insulin sensitivity, insulin secretion, and hyperglycemia, indicating that the observed metabolic risk of people in cluster 5 is most probably pathophysiologically determined. To corroborate our conclusions, prospective studies aimed at maintaining a relatively large amount of weight loss over a long period in all participants (e.g., using pharmacotherapy) are needed.

A strength of our study is that we performed precise phenotyping at four time points during 9 years of follow-up, which enabled us to investigate parameters determining changes of glycemia in our study. Another strength was that we were able to analyze both short-term and long-term effects of a lifestyle intervention in people within different type 2 diabetes risk clusters. This is particularly important considering that, as of today, several effective weight loss strategies (e.g., bariatric surgery, incretin-based pharmacotherapy) are being increasingly used to achieve long-term weight loss.

In conclusion, cluster 3 participants benefited well from long-term and sustained weight loss following a lifestyle intervention, especially in terms of improvement of insulin sensitivity. Insulin secretory function was preserved, which is important as cluster 3 participants already had reduced insulin secretion before the lifestyle intervention. Unfortunately, cluster 5 participants did not benefit as much as those in other clusters from the lifestyle intervention with regard to improvement in glucose metabolism, despite a marked sustained weight loss. If this result can be replicated in a prospective study, there is a need for a more tailored approach to diabetes prevention in which high-risk phenotypes, such as cluster 5, may require more intensive or targeted interventions.

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AUTHOR QUERIES

AUTHOR PLEASE ANSWER ALL QUERIES

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Q1: In the graphical abstract, please confirm/edit the definition of "NGR."

Q2: Please review the edits made to the article title and approve or suggest additional changes.

Q3: Original reference 10 was a duplicate of reference 9 and was therefore deleted; the remaining references were renumbered, both in the text and in the reference list. Please verify changes.

Q4: In the sentence beginning "Before enrollment, participants were given detailed information," do the edits preserve your intent?

Q5: Please verify edits to the insulinogenic index equation.

Q6: In the sentence beginning "Based on the largest mean decrease in body weight," do the edits preserve your intent?

Q7: In the sentence beginning "As expected, in multivariable linear regression analyses," do the edits preserve your intent?

Q8: In the sentence beginning "The baseline ISI was lowest in cluster 5," are the edits correct?

Q9: In the sentence beginning "The focus of the analyses on participants," do the edits preserve your intent?

Q10: In the sentence beginning "Interestingly, baseline fetuin-A levels," do the edits preserve your intent?

Q11: In the sentence beginning "Furthermore, although the whole study group" and the next, do the edits preserve your intent?

Q12: Please indicate whether "This may have resulted in a selection bias of high-risk people" is meant.

Q13: Please check the "Funding" section carefully to confirm the correct presentation of all organization names, institution names, grant numbers, contract numbers, and/or project numbers.

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