Mechanisms underlying glycemic deterioration in type 2 diabetes: An IMI DIRECT study

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Full title

Processes underlying glycemic deterioration in type 2 diabetes: An IMI DIRECT study

Running title

Glycemic deterioration in type 2 diabetes

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Abstract

Objective

We investigated the processes underlying glycemic deterioration in type 2 diabetes (T2D).

Research Design and Methods

732 recently diagnosed T2D patients from the IMI-DIRECT study were extensively phenotyped over three years, including measures of insulin sensitivity (OGIS), β-cell glucose sensitivity (GS) and insulin clearance (CLIm) from mixed meal tests, liver enzymes, lipid profiles, and baseline regional fat from MRI. The associations between the longitudinal metabolic patterns and HbA_{1c} deterioration, adjusted for changes in BMI and in diabetes medications, were assessed via stepwise multivariable linear and logistic regression.

Results

Faster HbA_{1c} progression was independently associated with faster deterioration of OGIS and GS, and increasing CLIm; visceral or liver fat, HDL-cholesterol and triglycerides had further independent, though weaker, roles (R^2=0.38). A subgroup of patients with a markedly higher progression rate (fast progressors) was clearly distinguishable considering these variables only (discrimination capacity from AUROC=0.94). The proportion of fast progressors was reduced from 56% to 8-10% in subgroups in which only one trait among OGIS, GS and CLIm was relatively stable (odds ratios 0.07 to 0.09). T2D polygenic risk score and baseline pancreatic fat, GLP-1, glucagon, diet, and physical activity did not show an independent role.

Conclusions

Deteriorating insulin sensitivity and β-cell function, increasing insulin clearance, high visceral or liver fat, and worsening of the lipid profile are the crucial factors mediating glycemic deterioration

of T2D patients in the initial phase of the disease. Stabilization of a single trait among insulin sensitivity, β-cell function, and insulin clearance may be relevant to prevent progression.

Maintaining glucose levels within appropriate limits in patients with type 2 diabetes (T2D) is a crucial factor to prevent complications. Effective strategies to slow glycemic progression can be supported by understanding the processes underlying deterioration of glucose control.

Few studies have assessed HbA_{1c} trajectories and the possible determinants of glycemic deterioration. An established finding is that β-cell function decline is an important factor (1,2), while contradictory conclusions were drawn for insulin sensitivity (1,3–7). Whether heterogeneous patterns between patients exist in β-cell function and insulin sensitivity decline has not been clarified, an important question for patient stratification and personalized medicine. Other limitations of previous analyses include the incomplete characterization of the metabolic parameters affecting glucose homeostasis (derived using fasting data only (2,4)), the restricted set of traits investigated together, and the lack of potentially relevant measures such as ectopic fat, insulin clearance, or lifestyle. No study has assessed the relationships between the longitudinal trajectories of HbA_{1c} and those of the other metabolic traits.

In this analysis, we have used data from the cohort of recently diagnosed and extensively phenotyped T2D patients of the DIRECT study (8,9) to elucidate the processes underlying glycemic deterioration. Specific features of the DIRECT study are the detailed assessment of the glucose homeostasis parameters, and patients all being in the initial phase of the disease. We determined the patterns over a 3-year period of HbA_{1c}, β-cell function, insulin sensitivity and other relevant laboratory, clinical and functional parameters, and assessed their relevance in the deterioration of glucose control.

Research Design and Methods

Subjects and protocol

The IMI-DIRECT (Innovative Medicines Initiative - Diabetes Research on Patient Stratification) project is a multicenter prospective study on northern European adults (8,9) (ClinicalTrials.gov identifier NCT03814915). The present analysis considers the DIRECT cohort of recently diagnosed T2D patients, who were recruited according to the following criteria: white race, T2D diagnosis according to the American Diabetes Association 2011 criteria (10) not less than 6 months and not more than 24 months before baseline examination, previous treatment via lifestyle measures with or without metformin therapy, age between 35 and 74 years, BMI between 20 and 50 kg/m^2, estimated glomerular filtration rate >50 ml/min, and HbA$_{1c}$ concentration <7.64 % (60.0 mmol/mol) within the previous 3 months. Participants were studied at baseline (month 0) and at months 9, 18 and 36. Subjects with HbA$_{1c}$ available at least in two visits were included in this analysis (N=750).

All participants provided written informed consent and the study protocol was approved by the regional research ethics review boards. The research conformed to the ethical principles for medical research involving human participants outlined in the declaration of Helsinki.

Collected data

Anthropometric data, HbA$_{1c}$, blood lipids and liver enzymes were collected at all visits. A 27-month HbA$_{1c}$ sample was collected in 39 patients. A standardized mixed meal test (8) (MMTT) was performed at months 0, 18 and 36 to calculate indices of insulin sensitivity (in fasting conditions, QUICKI (11), and post-MMTT, OGIS (12)), β-cell function (13) (glucose sensitivity, GS, and rate sensitivity), and insulin clearance (in fasting conditions, and post-MMTT, CLIm). From the baseline visit we collected glucagon, proinsulin and glucagon-like peptide 1 (GLP-1), measures of regional fat from MRI (8) (available in 561 participants), of physical activity from accelerometer (8), and of self-reported 24-hour nutrient intake (8), and we computed the fatty liver index (FLI) (14) and a T2D polygenic risk score (PRS) (15). The whole set of traits considered in this study is described in detail in the Supplemental Material (DATA, METHODS, and Table S2).

Assessment of progression rates

We computed the progression rates for HbA_{1c} and several traits available at follow up (Supplemental Table S4). Each trajectory was described with a conditional linear mixed-effect model (16), in which the longitudinal component of the data was described as a proportional function of time, with normally distributed slopes describing individual progression rates. HbA_{1c} progression was adjusted for changes in BMI and diabetes medications, which were recorded at all visits (as dosage and start and end of treatment). The adjustments were assumed to be 1) proportional to BMI; 2) linearly related to the metformin dose, expressed as percentage of a maximal dose of 3 grams; 3) linearly related to the cumulative dose for the other antidiabetic drugs (insulin excluded), expressed as sum of the percentages of the maximum dose of each drug; 4) constant under insulin treatment. A proportional effect of delay in HbA_{1c} assay, i.e. of the difference between the time of measurement and the time of sample collection, was also introduced. Medications were considered to be effective if taken at least 30 days before HbA1c measurement. OGIS and QUICKI trajectories were adjusted for changes in BMI. Further details about the conditional linear mixed-effect models are provided in the Supplemental Material (METHODS).

Statistical analysis

Results are presented for participants (*N*=732) with GAD <11 U/ml and islet antigen-2 antibodies (IA-2) <7.5 U/ml, to exclude other possible forms of diabetes (17). Distributions are described as mean ± standard deviation. Pairwise associations between continuous variables were assessed using the Spearman correlation coefficient; differences between groups were assessed using the Wilcoxon signed rank test (for two groups) and Kruskal-Wallis test (for three or more groups).

We used stepwise multivariable linear regression to determine the set of variables, as baseline values (Table S2) and progression rates (Table S4), independently associated with the HbA_{1c} progression rate, with adjustment for center, sex and age. For baseline variables, both untransformed and transformed values were considered; transformations were logarithmic, or logit when variables where constrained within an interval. The independent variables were included in the regression model when their effects had $p<0.05$ and produced an increment in the adjusted R^2 value. Two stepwise analyses were performed: one on all participants, excluding MRI variables from the analysis, and one on the subset of participants with MRI data, including this data in the analysis. Standardized coefficients were computed per standard deviation of the underlying data distribution.

Since the distribution of HbA_{1c} progression rates was skewed to the right with a group of patients with high values, we split the subjects into *average* and *fast* progressors according to a progression rate threshold (see Results). We used multivariable logistic regression to assess the odds ratios of average *vs* fast progression, using the independent variables identified in the multiple linear regression analysis of HbA_{1c} progression. The logistic analysis provided values for AUROC, sensitivity, specificity and accuracy, to be used as measures of the discrimination capacity of the investigated independent variables over fast *vs* average progressors. These parameters must not be interpreted as measures of predictive capacity.

Role of the funding source

The funders had no role in study design, in collection, analysis, and interpretation of data, in writing of the report, or in the decision to submit the paper for publication. The corresponding author had full access to all data and had final responsibility for the decision to submit for publication.

Results

Subjects' baseline characteristics

At baseline, the participants had age of 62±8 years, were moderately obese (30.4±4.9 kg/m^2 BMI), and had HbA_{1c} of 6.41±0.53 % (46.5±5.8 mmol/mol) and fasting glucose of 7.1±1.4 mmol/l. (Table S2). 34% of the subjects were treated with metformin at baseline, the rest was treatment naïve.

Progression rates of HbA_{1c} and other traits

The individual HbA_{1c} progression rates (Supplemental Figure S1), adjusted for changes in BMI and in diabetes medications, were on average only slightly positive and mostly distributed close to their median (median, first and ninth deciles were 0.041, -0.038 and 0.185 %/year (0.45, -0.41 and 2.02 mmol mol^{-1} $year^{-1}$), respectively). However, the distribution showed a heavy right tail with values up to 0.897 %/year (9.8 mmol mol^{-1} $year^{-1}$). The adjustment of progression rates for BMI changes implied a standardized coefficient for the BMI effect of 0.37.

All the other investigated traits had a mean progression rate per year smaller, in absolute value, than 5% of the corresponding baseline average (see Table S5 for details). On average, waist circumference, but not BMI, increased very slightly. Insulin sensitivity (as OGIS) and most of the β-cell function parameters decreased. Fasting, but not post-meal, insulin clearance decreased. Total cholesterol did not change, while its fractions showed opposite changes, with HDL increasing and LDL decreasing; TG increased. Creatinine and ALT did not change, while AST and AST/ALT increased.

Several pairwise associations were observed between HbA_{1c} progression rate and laboratory, clinical, and functional parameters (Supplemental Figure S2). In particular, HbA_{1c} progression rate was clearly associated ($p<0.01$) with some baseline traits (positively with BMI, waist circumference, triglycerides, glucagon, liver and visceral fat; inversely with age, HDL, insulin sensitivity, and β-cell function) and some progression rates (positively with those of triglycerides and liver enzymes; inversely with those of insulin sensitivity, β-cell function, AST/ALT ratio, and HDL).

Several pairwise associations were also observed between the progression rates of the investigated traits (Figure S2, panel B). GS and OGIS progression rates were independent of one another despite HbA_{1c} progression rate being associated with both of them.

Variables associated with HbA_{1c} progression rate: multivariable linear analysis

In multivariable linear analysis of HbA_{1c} progression rate in all patients, the baseline values and the progression rates of several traits provided an independent contribution (adjusted R^2 0.38; Figure 1, panel A). Faster HbA_{1c} progression was independently associated with lower baseline values and faster deterioration of insulin sensitivity (as OGIS) and β-cell function (mostly as glucose sensitivity, GS), with higher baseline values of MMTT insulin clearance, CLIm, and with its increase (all p-values <0.001). Faster HbA_{1c} progression was also independently associated with lower baseline HDL ($p<0.05$) or its slower increase ($p<0.001$), with a quicker increase of TG ($p<0.001$), as well as with higher baseline values of BMI ($p<0.01$) and lower baseline values of HbA_{1c} ($p<0.001$). The variables with strongest effects were the baseline OGIS value and the progression rates of OGIS, GS and CLIm (standardized coefficients, in absolute value, between 0.24 and 0.57).

In multivariable analysis of the subset of patients with baseline MRI measurements (adjusted R^2 0.40; Figure 1, panel B), baseline visceral fat was positively and independently correlated with HbA_{1c} progression rate; moreover, female sex and younger age independently predicted faster HbA_{1c} progression. The role of the other key metabolic parameters, OGIS, GS and CLIm, remained similar. Replacing visceral fat with liver fat produced similar results (standardized coefficient equal to 0.15 for visceral fat, to 0.11 for liver fat); when both visceral and liver fat were included in the model, the latter was not independently associated with HbA_{1c} progression.

No independent effects were detected for smoking status, family history, T2D polygenic risk score, baseline values of diet, physical activity, pancreatic fat, GLP-1 (total and intact at fasting, total at 60 min), glucagon, and 60-min proinsulin, baseline values and progression rates of AST and ALT.

Further details on the multivariable linear analysis are reported in the Supplemental Material (RESULTS).

Variables associated with HbA_{1c} progression rate: multivariable logistic analysis

The threshold selected to separate the heavy right tail of the distribution of HbA_{1c} progression rates was 0.255 %/year (2.79 mmol mol^{-1} $year^{-1}$). This threshold split the subjects into average progressors (N=699), with a progression rate of 0.044±0.076 %/year (0.48±0.83 mmol mol^{-1} $year^{-1}$), and fast progressors (N=33), with a ~10-fold mean progression rate (0.460±0.185 %/year, 5.03±2.02 mmol mol^{-1} $year^{-1}$) (Figure 2).

We found that the trajectories of most variables independently affecting HbA_{1c} progression as from the linear analysis were clearly different ($p<0.001$) in the two groups (Figure 2): in fast progressors, OGIS and GS strongly declined and TG and CLIm markedly increased. At baseline, fast progressors had lower OGIS ($p<0.05$), CLIm ($p<0.01$) and HDL ($p<0.001$), and higher BMI ($p<0.01$).

Logistic analysis substantially confirmed the results of linear regression (Figure 1), with half the investigated variables still contributing ($p<0.05$) to distinguish average and fast progressors (Figure 3): fast HbA_{1c} progression independently associated with stronger deterioration and a lower baseline value of OGIS and GS, CLIm increase, and HDL reduction. The discrimination capacity of the logistic model, computed as AUROC, was 0.94 (95% CI between 0.86 and 0.98).

Similar outcomes were obtained using lower HbA_{1c} progression rate thresholds, which resulted in larger numbers of patients classified as fast progressors (Supplemental Material - RESULTS, Figures S1 and S3).

At baseline, the percentage of patients treated with metformin were not different between fast progressors (39.4% [24.7-56.3%, 95% CI]) and average progressors (33.9% [30.5-37.5%], p = 0.64). At the last visit, the percentage of patients treated with any diabetes medication was somewhat higher in fast progressors, as expected (p = 0.048, details provided in the Supplemental Material - RESULTS). Only 7 average progressors were on insulin at the last visit.

Impact of stable OGIS, GS or CLIm on proportion of fast HbA_{1c} progressors

Because HbA_{1c} progression was associated with worsening of three main factors, OGIS, GS and CLIm, we have evaluated the possible importance of maintaining one of these key traits relatively stable in order to avoid fast progression. For this purpose, we considered each trait as deteriorating if its progression rate fell within its worst tertile (the bottom tertile for OGIS and GS, the top one for CLIm), and as stable if it fell in the other two tertiles. We examined the subgroups of patients in which none or only one of these key traits was relatively stable (Table 1).

We found that the proportion of fast progressors was 56% in the patient subgroup where GS, OGIS and CLIm were all deteriorating, and decreased to 8-10% in the subgroups where a single trait, either GS, OGIS or CLIm, was stable. All proportions were different from 0 at 90% confidence level, stressing that fast progression did not imply quick changes for each of the three considered traits. All differences in proportions (one stable trait *vs* none) had $p<0.001$, and were associated to odds ratio for fast *vs* average progression below 0.1 (Table 1); thus, relatively stable progression rate of one single trait among GS, OGIS and CLIm was strongly associated to reduced glycemic deterioration.

Conclusions

Leveraging on the detailed participant characterization of the DIRECT study, we have been able to elucidate the processes underlying glycemic deterioration in T2D patients in the initial phase of the disease. We found that HbA_{1c} deterioration was independently associated with 1) a decrease in insulin sensitivity; 2) a decrease in β-cell function (primarily β-cell glucose sensitivity); 3) an increase in insulin clearance; 4) lower values of insulin sensitivity and glucose sensitivity and higher values of insulin clearance at baseline. Further variables independently associated with faster HbA_{1c} progression were declining HDL, increasing TG and high baseline visceral or liver fat.

The variables identified by multivariable linear analysis also explained the rapid HbA_{1c} deterioration detected in a subset of patients (identified as fast progressors), the strongest predicting variables of the multivariable linear model being significant also with logistic analysis. Clear differences were evident between fast and average HbA_{1c} progressors (Figure 2), consistent with the associations derived from the multivariable linear analysis. The high discrimination capacity of the logistic analysis suggests that the selected variables capture the most relevant pathophysiological factors underlying glycemic deterioration.

The independent associations with HbA_{1c} progression of several variables, in particular the progression rates of insulin sensitivity, β-cell function and insulin clearance, and the existence of fast HbA_{1c} progressors with relatively stable conditions for any of these three traits (Table 1), indicates 1) that the processes of glycemic deterioration are heterogeneous in this population of T2D patients; 2) that fast progression does not imply quick deterioration of a specific trait, e.g. insulin sensitivity or β-cell function.

The dichotomous analysis shows that the odds for fast *vs* average progression are substantially reduced when either glucose sensitivity, insulin sensitivity or insulin clearance is relatively stable. Although these findings do not demonstrate causality, they suggest that preventing either high degradation rates of glucose sensitivity or insulin sensitivity, or high increase rates of insulin clearance, may be an effective strategy to slow down glycemic deterioration in the initial phase of the disease. This reemphasizes the importance of lifestyle interventions aiming at controlling insulin resistance, as preventing deterioration of the other traits currently appears more difficult.

This study also shows that insulin resistance plays a major role in glycemic deterioration in these T2D patients. In particular, we show associations of glycemic deterioration with baseline insulin sensitivity and its longitudinal change that the Belfast Diet Study (1), UKPDS (4,18) and ADOPT (6) could not identify, possibly due to differences in subject selection or to the use of post-MMTT *vs* fasting insulin sensitivity indices. We also demonstrate that the associations between glycemic deterioration and insulin sensitivity are independent from both the baseline value and the progression rate of the *β*-cell function, and that insulin resistance progresses independently from *β*-cell glucose sensitivity. Since in our analysis both HbA_{1c} and insulin sensitivity trajectories were adjusted for BMI changes and BMI did not increase on average, we can conclude that worsening of insulin resistance in T2D and the associated glycemic deterioration are partly independent from BMI changes. Whether the observed average increases in TG and AST (whose progression rates were inversely correlated with OGIS progression rate) have a role in insulin sensitivity deterioration (19), and whether this is mediated by ectopic fat accumulation (20), deserves further study.

UKPDS 25 and 26 (4,18), the Belfast Diet Study (1) and the ADOPT study (6) identified baseline HOMA-%B as a predictor of glycemic deterioration (insulin requirement within 6 years for UKPDS, time of failure to dietary therapy for the Belfast Diet Study, and monotherapy failure before 4 years for ADOPT). Our study confirms the role of β-cell dysfunction as driver of glycemic deterioration using a dynamic β-cell function assessment based on a glucose challenge, rather than on fasting data only. We show that both baseline β-cell dysfunction (especially β-cell glucose sensitivity) and its deterioration over time are independently associated with HbA$_{1c}$ worsening. Moreover, we demonstrate that patients with limited or absent deterioration in β-cell function have considerably lower odds of rapid glycemic deterioration.

Another novel finding is the strong and independent association between HbA$_{1c}$ progression and insulin clearance during the MMTT, CLIm. To our knowledge, this is the first study examining insulin clearance trajectories after T2D onset. We found that higher baseline CLIm and faster CLIm increase over time independently associate with faster HbA$_{1c}$ progression. This is consistent with the glucose homeostasis mechanisms, as higher CLIm reduces the average insulin levels. Notably, we found a positive correlation between insulin sensitivity and insulin clearance, considering both the baseline values of the two traits, in agreement with previous findings (21), and their progression rates (Figure S2). However, on average, in spite of a decrease in insulin sensitivity, insulin clearance did not decrease. These findings show that, while in pre-diabetic subjects insulin clearance reduction may be a way to mitigate the effects of insulin resistance (22), in T2D patients this compensation appears present but impaired and contributing to glycemic deterioration. The reasons underlying these results remain elusive. The lack of decrease in insulin clearance may be explained by the decrease of total MMTT insulin secretion and consequent desaturation of insulin utilization (23) only in fast progressors, as in average progressors total insulin secretion slightly increased (Figure 2). Whether hepatic or extrahepatic mechanisms underlie these findings cannot be determined from this study and deserves further investigation.

Our results on TG and HDL effects were partially anticipated by a study of the Genetics of Diabetes Audit and Research (GoDARTS) (24), where the outcome was the risk of progression to insulin treatment. The study identified baseline TG and HDL (besides BMI, sex, and age, year and $\mathrm{HbA_{1c}}$ at diagnosis) as independent determinants. A later study on the same data (25), investigating the baseline determinants of $\mathrm{HbA_{1c}}$ progression rate over about 9 years, confirmed an independent effect of HDL (together with age, BMI and year at diagnosis) but not of TG. The FIELD study in T2D patients on lifestyle measures only revealed that the HDL effect on initiation of oral hypoglycemic agents survives the adjustment for HOMA-IR (26). Compared to previous studies (24–26) our analysis includes the progression rates of plasma lipid components and baseline MRI assessment of regional fat. We show that baseline HDL and BMI, and the progression rates of TG and HDL are associated with $\mathrm{HbA_{1c}}$ progression, even after accounting for the effects of the three main determinants of glucose homeostasis, i.e. insulin sensitivity, β-cell function and insulin clearance. In the subset of participants with MRI data, baseline visceral fat or liver fat was independently correlated with $\mathrm{HbA_{1c}}$ progression rate, a further novel observation. These findings suggest that additional lipid-dependent factors contribute to $\mathrm{HbA_{1c}}$ deterioration, possible candidates being fat accumulation in the viscera (with excessive supply of fatty acids to the liver (27)), liver fat and consequent hepatic insulin resistance (28), or glucose overproduction (29). The role of visceral/liver fat supports interventions to reduce ectopic fat as a possible way for slowing future glycemic progression.

Previous studies have reported an inverse correlation between baseline age and HbA_{1c} progression (1,4,6,24,25,30). In our analysis, baseline age does not have a clear independent role in the multivariable model, most likely because the age range is relatively narrow relative to other studies, or because the stronger predictors of HbA_{1c} progression are correlated with age. The latter explanation would suggest that the age univariate effect on glycemic deterioration is indirect. We do not find a clear sex effect in glycemic deterioration, in agreement with most previous studies (1,4,6,24,25).

In the multivariable model, baseline HbA_{1c} was independently and inversely correlated with HbA_{1c} progression rate, in contrast with previous findings (1,4,6,24,30). However, baseline HbA_{1c} was not significant in the logistic model. The most likely explanation of this finding is regression to the mean: indeed, a random decrease in baseline HbA_{1c} can produce a higher estimate of HbA_{1c} progression rate, particularly when the follow-up period is not long, as in our study. Tight glycemic control, an inclusion criterion, may have enhanced this effect.

This study does not find a relevant role of other variables often associated with glucose control. In particular, we did not find an effect of smoking status (reported in GPRD (30)), T2D polygenic risk score (in agreement with GoDARTS (24)), baseline values of diet, physical activity, pancreatic fat, GLP-1, and glucagon. Several of these variables were not associated with HbA_{1c} progression rate even in simple correlation analysis (Figure S2). The lack of association for pancreatic fat is particularly relevant, and contributes to the ongoing discussion on the role of pancreas fat in T2D management (31).

In spite of the unique extensive phenotyping of our study and the consistent results, a significant limitation is the relatively short follow-up period (3 years). The accuracy of the estimated HbA_{1c} progression rate over this time frame may be limited, and in a longer time period the factors contributing to progression may differ. In this study, we could not assess the changes over time of relevant variables such as regional fat by MRI, diet and physical activity. MRI measurements were available only for a subset of subjects. Insulin sensitivity was not derived from the gold standard euglycemic clamp. As the cohort included only patients of white race, our findings are not generalizable to other racial/ethnic groups. Causal relationships could not be inferred from our regression analyses. The study of the mechanisms underlying the deterioration of the factors affecting HbA_{1c} progression, an important aspect to envisage optimal treatment strategies, also requires further investigation.

In summary, based on the extensively phenotyped cohort of white European diabetic patients of the DIRECT study, we identified decreasing insulin sensitivity, deteriorating β-cell function, increasing insulin clearance, high liver or visceral fat, and worsening of the lipid profile as the most important factors independently associated with HbA_{1c} deterioration in the early phase of the disease. We also showed that patients with a relatively stable value over time of at least one of insulin sensitivity, β-cell glucose sensitivity, or insulin clearance have considerably reduced odds of fast HbA_{1c} increase. This study contributes to the understanding of the factors underlying diabetes progression, elucidating the processes that might be targeted for personalized treatments.

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Duality of Interest.

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Author Contributions.

R.B. and A.M. designed the analysis, analyzed the data, and wrote the manuscript. R.B., C.J., A.G.J., M.W., E.R.P. and A.M. interpreted the results. E.R.P. and A.M. supervised the analysis. C.J., A.G.J., A.K., M.W. and E.R.P. reviewed the manuscript. All authors were involved in the DIRECT study at different levels, and were essential for the production, release and management of the data analyzed here. R.B. is the guarantor of this work and, as such, takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript.

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Table 1. Proportion of fast HbA1c progressors with different combinations of stable/deteriorating conditions for GS, OGIS and CLIm progression rates.

Condition[*]			**Average progressors (*N*)**	**Fast progressors (*N*)**	**Fast progressors (%) [95% CI]**	**Odds ratio [95% CI]**	**p-value**[†]
GS	**OGIS**	**CLIm**					
Deteriorating	Deteriorating	Stable	47	5	9.6 [4.2,20.6]	0.09 [0.02,0.32]	2E-4
Deteriorating	Stable	Deteriorating	56	6	9.7 [4.5,19.5]	0.09 [0.02,0.30]	8E-5
Stable	Deteriorating	Deteriorating	34	3	8.1 [2.8,21.3]	0.07 [0.02,0.32]	4E-4
Deteriorating	Deteriorating	Deteriorating	8	10	55.6 [33.7,75.4]	-	-

[*] The progression rate thresholds dividing stable and deteriorating traits for OGIS, GS and CLIm are -16.68 ml min^{-1} m^{-2} year^{-1}, -4.07 pmol min^{-1} m^{-2} mmol^{-1} l year^{-1} and 0.0184 l min^{-1} m^{-2} year^{-1}, respectively.

[†] Two-sided Chi-square test (α=0.05), with Yates continuity correction, on the proportion of fast progressors in the row compared to the same proportion in the last row.

GS: β-cell glucose sensitivity; OGIS: oral insulin sensitivity; CLIm: mixed meal test insulin clearance.

Figure legends

Figure 1. Variables independently associated with HbA_{1c} progression rate from multivariable linear analysis. Panel A: all subjects are included in the analysis (625 with all variables), and MRI measurements are not considered; panel B: only subjects with MRI are included in the analysis (374 with all variables), and MRI measurements are taken into consideration. For each variable, the figure shows the standardized coefficients ± 95% CI of the effect. Age and HDL were log-transformed. OGIS: oral insulin sensitivity; CLIm: mixed meal test insulin clearance; GS: β-cell glucose sensitivity; TG: fasting triacylglycerol; HDL: fasting HDL-cholesterol; RS: β-cell rate sensitivity; progr: progression rate; bas: baseline value; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.

Figure 2. Temporal trajectories or baseline values (bar graphs) of HbA_{1c} and other key traits in fast (red lines) and average (blue lines) progressors. Data are mean ± standard error. Simple comparisons between fast and average progressors (Wilcoxon rank sum test) are shown for baseline values (asterisks at month 0) and progression rates (asterisks at month 18). These comparisons may differ from the results of the multivariable analyses (Figures 2 and 4). Sex is not included in the figure: males were 42% and 36% in average and fast progressors, respectively (non-significant, Chi-squared test). HbA_{1c} values at 27 months are not displayed as they were collected in a subgroup of individuals. In average progressors, HbA_{1c} increases from 46.4±0.2 mmol/mol to 46.7±0.3 mmol/mol; in fast progressors, from 48.9±1.21 mmol/mol to 75.7±2.5 mmol/mol. OGIS: insulin sensitivity; CLIm: mixed meal test insulin clearance; GS: β-cell glucose sensitivity; RS: β-cell rate sensitivity; TG: fasting triacylglycerol; HDL: fasting HDL-cholesterol; ISRtot: total mixed meal test insulin secretion; bas: baseline value; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.

Figure 3. Odds ratios ± 95% CI from the multivariable logistic analysis of fast *vs* average HbA_{1c} progressors. The independent variables are those identified by multivariable linear analysis of HbA_{1c} progression, excluding MRI variables (N=625, with 32 fast progressors and 593 average progressors). Age and HDL were log-transformed. Values for sensitivity, specificity and accuracy

were derived via maximization of balanced accuracy. OGIS: insulin sensitivity; CLIm: mixed meal test insulin clearance; GS: β-cell glucose sensitivity; TG: fasting triacylglycerol; HDL: fasting HDL-cholesterol; RS: β-cell rate sensitivity; progr: progression rate; bas: baseline value; AUROC: area under the receiver operating characteristics; *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.