Profiles of Glucose Metabolism in Different Prediabetes Phenotypes, Classified by Fasting Glycemia, 2-Hour OGTT, Glycated Hemoglobin, and 1-Hour OGTT: An IMI DIRECT Study

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Differences in glucose metabolism among categories of prediabetes have not been systematically investigated. In this longitudinal study, participants ($N = 2,111$) underwent a 2-h 75-g oral glucose tolerance test (OGTT) at baseline and 48 months. HbA_{1c} was also measured. We classified participants as having isolated prediabetes defect (impaired fasting glucose [IFG], impaired glucose tolerance [IGT], or HbA_{1c} indicative of prediabetes [IA1c]), two defects (IFG+IGT, IFG+IA1c, or IGT+IA1c), or all defects (IFG+IGT+IA1c). β-Cell function (BCF) and insulin sensitivity were assessed from OGTT. At baseline, in pooling of participants with isolated defects, they showed impairment in both BCF and insulin sensitivity compared with healthy control subjects. Pooled groups with two or three defects showed progressive further deterioration. Among groups with isolated defect, those with IGT showed lower insulin sensitivity, insulin secretion at reference glucose (ISR_r), and insulin secretion potentiation ($P < 0.002$). Conversely, those with IA1c showed higher insulin sensitivity and ISR_r ($P < 0.0001$). Among groups with two defects, we similarly found differences in both BCF and insulin sensitivity. At 48 months, we found higher type 2 diabetes incidence for progressively increasing number of prediabetes defects (odds ratio >2, $P < 0.008$). In conclusion, the prediabetes groups showed differences in type/degree of glucometabolic impairment. Compared with the pooled group with isolated defects, those with double or triple defect showed progressive differences in diabetes incidence.

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PATHOPHYSIOLOGY

The current prediabetes conditions include impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and HbA_{1c} indicative of prediabetes (IA1c) (1). In some studies investigators found that IFG and IGT differ in the mechanisms involved in glucose homeostasis (2); they summarized that, though both individuals with IFG and IGT show reduction in early-phase insulin secretion, those with IGT also have impaired late-phase insulin secretion. Furthermore, individuals with IGT have marked peripheral insulin resistance with only mild hepatic insulin resistance, whereas those with IFG show the opposite condition. However, few studies considered all the prediabetes groups and their combinations, and they suffered from several limitations, especially lack of longitudinal data (3–6).

In this study, we investigated the differences in the main parameters of glucose metabolism in all categories of prediabetes, i.e., IFG, IGT, IA1c, and their combinations. Furthermore, we considered 1-h oral glucose tolerance test (OGTT) glycemia, since increasing consensus is emerging for this criterion to characterize glucose tolerance (7). We also investigated differences between groups in the incidence of type 2 diabetes onset after 48 months. Finally, we briefly investigated reversal to normal glucose tolerance (NGT).

RESEARCH DESIGN AND METHODS

Study Design and Participants

We used data from the Innovative Medicines Initiative (IMI) Diabetes Research on Patient Stratification (DIRECT) European multicenter project, aimed to validate biomarkers of glycemic deterioration before and after type 2 diabetes onset (ClinicalTrials.gov identifier NCT03814915) (8) The present analysis considers a cohort of European adults without diabetes, with focus on data collected at baseline (month 0) and month 48. A screening tool was used to identify, from previous cohort studies, at-risk participants to be recruited into the new study (8). Inclusion criteria were as follows: *1*) no treatment with insulin-sensitizing, glucose-lowering, or other antidiabetes drugs; *2*) fasting capillary blood glucose <10 mmol/L at baseline; *3*) White European ethnicity; and *4*) age ≥35 and <75 years. Exclusion criteria were *1*) diagnosed diabetes of any type; *2*) for women, pregnancy, lactation, or plans to conceive within the study period; and *3*) any significant medical reason for exclusion as determined by the investigators. All participants provided written informed consent, and the study protocol was approved by the regional research ethics review boards. The research conformed to the ethics principles for medical research involving human participants outlined in the Declaration of Helsinki.

Data Collection

Participants underwent a 75-g OGTT at baseline and at 48 months, with measurement of glucose, insulin, and C-peptide at 0, 15, 30, 45, 60, 90, and 120 min. Plasma glucose was analyzed with an enzymatic method and photometric measurement. Plasma insulin and C-peptide were analyzed with chemiluminometric immunoassay. HbA_{1c} was measured by liquid chromatography. Assays were carried out centrally at the University of Eastern Finland for glucose, insulin, and C-peptide (within- and between-run coefficients of variation ≤6.6%) and the University of Exeter (Exeter, U.K.) for HbA_{1c} (coefficients of variation ≤3%). Additional details have previously been reported (8).

Stratification According to the Prediabetes Criteria

Based on the definition of prediabetes of the American Diabetes Association (ADA) (1) we classified the participants as having IFG (fasting glucose ≥5.6 and ≤6.9 mmol/L), IGT (2-h glucose ≥7.8 and ≤11.0 mmol/L), or IA1c (HbA_{1c} ≥39 and ≤47 mmol/mol). We stratified the participants in groups having a single defect (isolated IFG, IGT, or IA1c), two defects (IFG+IGT, IFG+IA1c, or IGT+IA1c), or all three defects (IFG+IGT+IA1c). We also considered participants with NGT (fasting glucose <5.6 and 2-h glucose <7.8 mmol/L and HbA_{1c} <39 mmol/mol). In a separate analysis, we also considered participants having the single defect of 1-h hyperglycemia (7) (I1hG) (1-h glycemia ≥8.6 mmol/L), thus without the defects of fasting glucose, 2-h glucose, and HbA_{1c} (i.e., <5.6 mmol/L, <7.8 mmol/L, and <39 mmol/mol, respectively). In this analysis, the IFG, IGT, IA1c, and NGT groups were redefined by exclusion from each group of the participants with 1-h hyperglycemia.

From the 2,127 participants initially included, 16 were excluded due to lack of data relevant for the analyses; thus, 2,111 participants were studied. The 1,691 participants who completed the final examination at 48 months were analyzed for determination of the incidence of type 2 diabetes, diagnosed according to at least one of the American Diabetes Association criteria (1) or based on records of clinical diagnosis or use of antidiabetes medications.

Parameters of Glucose Metabolism

β-Cell function (BCF) was assessed by mathematical modeling and quantified by glucose sensitivity (G_{SENS})

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(slope of relationship between insulin secretion and glucose concentration), rate sensitivity (R_{SENS}) (index of early secretion), insulin secretion at reference glucose of 6 mmol/L (rounded mean basal glucose in all participants) (ISR_r), potentiation factor ratio (PFR) (index of OGTT insulin secretion potentiation), and basal (ISR_b) and total (ISR_t) insulin secretion (9). Insulin resistance was estimated at fasting by the homeostasis model assessment index of insulin resistance (HOMA-IR) (10) and insulin sensitivity from the OGTT by predicted M (PREDIM) (11), a surrogate of the clamp M value. Insulin clearance (CL_{ins}) was obtained as the ratio between the area under the curve of total insulin secretion and that of plasma insulin (12).

Statistical Analyses

Normality of parameter distributions was tested with the Shapiro-Wilk test. In case of skewed distributions, values were logarithmically transformed. Differences among groups in parameter means were assessed with one-way ANCOVA, with adjustment for sex, age, and BMI. Pairwise comparisons were also performed. In case of inhomogeneity of parameter variances, assessed with the Levene test, heteroscedasticity was addressed by generalized least squares allowing separate variances per group. Moreover, we used Tukey honestly significant difference to adjust for multiple statistical testing. Logistic regression analysis was used to assess differences and odds ratios (ORs) for type 2 diabetes incidence in the studied groups (or similar analyses), with adjustment for sex, age, and BMI. Parameter changes between baseline and follow-up were assessed by paired *t* test, following logarithmic transformation for skewed distributions and assuming inequality of variances if appropriate. Difference in sex distribution among groups was assessed by χ^2 test. Values are presented as mean ± SD unless otherwise specified. Two-sided $P < 0.05$ was considered statistically significant.

Data and Resource Availability

Due to the type of consent provided by study participants and the ethics approvals for this study, individual-level data from IMI DIRECT cohorts cannot be transferred from the centralized IMI DIRECT repository. Requests for access to IMI DIRECT data, including those presented here, can be made to DIRECTdataaccess@Dundee.ac.uk. Requestors will be provided with information and assistance on how data can be accessed via the DIRECT Computerome secure analysis platform following submission of appropriate documentation.

RESULTS

Participants With Single, Double, and Triple Defect

Single Defect Versus NGT

Basic Characteristics. We first compared participants with single defect pooled (1DEF) with the NGT group (Table 1). 1DEF were slightly younger ($P < 0.04$) but had higher BMI ($P < 0.0001$). As expected, glycemia and HbA_{1c} were higher ($P < 0.0001$).

Metabolic Parameters. 1DEF had worse insulin sensitivity both at fasting and during the OGTT, as assessed with HOMA-IR and PREDIM ($P < 0.0001$). 1DEF also showed higher insulin secretion, both at fasting, ISR_b, and total during the OGTT, ISR_t ($P < 0.0001$). In contrast, ISR_r was lower ($P < 0.0001$). β-Cell G_{SENS} was impaired ($P < 0.002$). CL_{ins} was lower ($P < 0.0001$). Supplementary Fig. 1*A* shows the model-determined relationship between insulin secretion and glucose concentration (i.e., the dose response, whose average slope is G_{SENS}) for NGT and 1DEF, as well as for other groups, as outlined below.

Double Defect Versus 1DEF

Basic Characteristics. In comparisons of double defect participants pooled (2DEF) with 1DEF (Table 1), 2DEF were slightly older ($P < 0.05$). Both glycemia and HbA_{1c} were higher ($P < 0.0001$).

Metabolic Parameters. 2DEF had worse insulin sensitivity, both HOMA-IR and PREDIM ($P < 0.003$). 2DEF also showed higher ISR_b and ISR_t but lower ISR_r ($P < 0.003$). G_{SENS} was impaired ($P < 0.0001$). Slight impairment was found for the PFR ($P < 0.02$). β-Cell dose response for 2DEF is reported in Supplementary Fig. 1*A*.

Triple Defect Versus 2DEF

Basic Characteristics. In comparisons of the group with all three defects (3DEF) (i.e., IFG+IGT+IA1c) with 2DEF (Table 1), 3DEF were slightly older ($P < 0.05$) and had higher BMI ($P < 0.0006$). Glycemia and HbA_{1c} were higher ($P < 0.0002$).

Metabolic Parameters. 3DEF had both worse HOMA-IR and PREDIM ($P < 0.002$). 3DEF also showed higher ISR_b and ISR_t and lower ISR_r ($P < 0.02$). G_{SENS} and PFR were lower ($P < 0.03$). β-Cell dose response for 3DEF is reported in Supplementary Fig. 1*A*.

The Groups With Single Defect: IFG, IGT, and IA1c

Basic Characteristics

The percentage of participants with single defect, compared with that of participants with double or triple defect, is displayed in Supplementary Fig. 2*A*. In comparison of the single defect groups (Table 2), those with IFG were slightly younger ($P < 0.02$) than those with IGT and those with IA1c. Glycemia was typically lower for the IA1c group, intermediate for IFG, and higher for IGT ($P < 0.0001$).

Metabolic Parameters

The IFG group showed worse HOMA-IR ($P < 0.0001$) compared with IGT and IA1c, whereas PREDIM was lower in IGT, intermediate in IFG, and higher in IA1c ($P < 0.0001$). Those with IFG had higher ISR_b compared with IA1c ($P < 0.002$), whereas ISR_t was higher in IGT ($P < 0.001$). The IGT group also had lower ISR_r compared with

Table 1—Basic characteristics and metabolic parameters for NGT participants and for 1DEF, 2DEF, and 3DEF

	NGT	1DEF	2DEF	3DEF
N (male/female)	665 (477/188)	898 (695/203)*	447 (351/96)	101 (73/28)
Basic characteristics				
Age (years)	62.4 ± 6.2	61.7 ± 6.3*	62.3 ± 5.9†	63.8 ± 6.2‡
BMI (kg/m^2)	27.1 ± 3.7	28.0 ± 3.8*	28.5 ± 4.3	30.0 ± 4.1‡
HbA_{1c} (mmol/mol)	35.3 ± 2.2	36.8 ± 2.4*	39.4 ± 2.7†	40.6 ± 1.6‡
Glucose, insulin, C-peptide plasma concentrations				
G_b (mmol/L)	5.21 ± 0.32	5.74 ± 0.45*	6.00 ± 0.38†	6.15 ± 0.35‡
G_{60} (mmol/L)	7.49 ± 1.86	8.91 ± 2.11*	10.19 ± 2.17†	11.58 ± 1.72‡
G_{120} (mmol/L)	5.23 ± 1.17	5.73 ± 1.40*	6.64 ± 1.83†	8.94 ± 0.78‡
G_m (mmol/L)	6.77 ± 1.09	7.74 ± 1.26*	8.68 ± 1.33†	9.92 ± 1.03‡
I_b (pmol/L)	48.5 ± 29.4	62.4 ± 42.5*	66.9 ± 39.4	86.2 ± 51.3‡
I_m (pmol/L)	305.6 ± 195.6	392.1 ± 250.1*	444.1 ± 305.5†	552.2 ± 334.4‡
CP_b (pmol/L)	723 ± 253	862 ± 307*	934 ± 338†	1,100 ± 415‡
CP_m (pmol/L)	2,503 ± 762	2,840 ± 877*	3,004 ± 970†	3,321 ± 986
Insulin sensitivity/resistance				
HOMA-IR (nondim.)	1.88 ± 1.14	2.68 ± 1.9*	2.99 ± 1.82†	3.96 ± 2.48‡
PREDIM (mg · kg^{-1} · min^{-1})	5.93 ± 1.77	4.94 ± 1.5*	4.39 ± 1.51†	3.17 ± 0.88‡
BCF and insulin secretion				
G_{SENS} (pmol · min^{-1} · m^{-2} · mmol/L^{-1})	124.0 ± 62.4	113.6 ± 53.5*	99.7 ± 48.1†	90.6 ± 28.9‡
R_{SENS} (pmol · m^{-2} · mmol/L^{-1})	1,021 ± 778	918 ± 706	787 ± 543	869 ± 561
PFR (nondim.)	1.74 ± 0.63	1.80 ± 0.66	1.70 ± 0.58†	1.41 ± 0.39‡
ISR_r (pmol · min^{-1} · m^{-2})	277.0 ± 113.4	231.4 ± 98.7*	194.5 ± 85.8†	152.7 ± 62.4‡
ISR_b (pmol · min^{-1} · m^{-2})	90.4 ± 31.2	108.5 ± 38.9*	116.8 ± 42.0†	136.8 ± 51.5‡
ISR_t (nmol · m^{-2})	46.1 ± 14.7	52.7 ± 17.3*	56.7 ± 18.8†	64.4 ± 19.4‡
CL_{ins} (L · min^{-1} · m^{-2})	1.48 ± 0.47	1.32 ± 0.40*	1.28 ± 0.41	1.15 ± 0.38

Data are means ± SD unless otherwise indicated. HbA_{1c} (%): 5.4 ± 0.20 (NGT), 5.5 ± 0.22 (1DEF), 5.8 ± 0.25 (2DEF), 5.9 ± 0.15 (3DEF) (from http://www.ngsp.org/convert1.asp). CP_b, CP_m, basal (fasting) and mean C-peptide, respectively; G_b, G_{60}, G_{120}, G_m, glucose at basal, 60 min, and 120 min and mean glucose; I_b, I_m, basal and mean insulin; nondim., nondimensional. *Significant difference for 1DEF vs. NGT, †2DEF vs. 1DEF, ‡3DEF vs. 2DEF.

IFG and IA1c ($P < 0.002$). In contrast, in the IA1c group, ISR_r was higher than in both IGT and IFG ($P < 0.0001$). PFR was different in the three groups, being lower in IGT, intermediate in IA1c, and higher in IFG ($P < 0.0003$). A summary of the differences among groups for the main parameters of insulin sensitivity/resistance and insulin secretion/BCF is reported in Fig. 1*A*.

The Groups With Double Defect: IFG+IGT, IFG+IA1c, and IGT+IA1c

Basic Characteristics

The percentage of participants with double defect is displayed in Supplementary Fig. 2*A*. In comparisons of the double defect groups (Table 2), IGT+IA1c were somehow older ($P < 0.008$) than the other two groups. Expectedly, the two groups including IFG had higher fasting glycemia than IGT+IA1c ($P < 0.0001$), whereas the two groups including IGT had higher 2-h glycemia than IFG+IA1c ($P < 0.0001$); 1-h glycemia was lower in IFG+IA1c than in the other two groups ($P < 0.003$). Mean glycemia was lower in IFG+IA1c, intermediate in IGT+IA1c, and higher in IFG+IGT ($P < 0.004$), whereas HbA_{1c} was higher in the two groups including IA1c ($P < 0.0001$).

Metabolic Parameters

Insulin sensitivity during the OGTT was lower in IFG+IGT, intermediate in IGT+IA1c, and higher in IFG+IA1c (PREDIM, $P < 0.03$), whereas HOMA-IR was only slightly higher in IFG+IGT than in IGT+IA1c ($P < 0.05$). ISR_t was higher in IFG+IGT compared with IFG+IA1c ($P < 0.0001$). ISR_r was lower in IFG+IGT than the other two groups ($P < 0.005$). PFR was different in the three groups, being lower in IGT+IA1c, intermediate in IFG+IGT, and higher in IFG+IA1c ($P < 0.0001$ for the difference between IFG+IA1c and the other two groups; $P < 0.05$ for the difference between IFG+IGT and IGT+IA1c). A summary of the differences among groups for the main parameters of insulin sensitivity/resistance and insulin secretion/BCF can be found in Fig. 1*B*.

Adding 1-Hour Hyperglycemia

I1hG Versus NGT

Basic Characteristics. The percentage of participants with 1-h hyperglycemia, compared with that of participants with a traditional single defect, is displayed in Supplementary Fig. 2*B*. Of note, the number of participants in the groups is different from that in the previous analyses, as we have now considered one additional criterion. We first compared I1hG with NGT (Table 3). Expectedly, glycemia was higher in I1hG ($P < 0.0001$).

Table 2—Basic characteristics and metabolic parameters for the different groups of participants with single and with double defect

	IFG	IGT	IA1c	IFG+IGT	IFG+IA1c	IGT+IA1c
N (males/females)	643 (540/103)	57 (39/18)*	198 (116/82)†	96 (79/17)	327 (262/65)	24 (10/14)‖¶
Basic characteristics						
Age (years)	60.9 ± 6.0	63.1 ± 7.1*	63.8 ± 6.5†	62.5 ± 6.4	62.0 ± 5.6	66.2 ± 5.9‖¶
BMI (kg/m^2)	28.1 ± 3.6	28.8 ± 3.7	27.7 ± 4.5‡	28.8 ± 4.0	28.3 ± 4.5	28.8 ± 3.4
HbA_{1c} (mmol/mol)	35.9 ± 1.9	35.8 ± 1.8	39.9 ± 1.2†‡	35.6 ± 2.3	40.5 ± 1.6§	40.4 ± 1.4‖
Glucose, insulin, C-peptide plasma concentrations						
G_b (mmol/L)	5.95 ± 0.29	5.22 ± 0.37*	5.21 ± 0.33†	6.07 ± 0.32	6.04 ± 0.32	5.16 ± 0.30‖¶
G_{60} (mmol/L)	8.99 ± 2.11	10.44 ± 1.63*	8.21 ± 1.93‡	11.51 ± 1.92	9.79 ± 2.13§	10.35 ± 1.65‖¶
G_{120} (mmol/L)	5.56 ± 1.17	8.72 ± 0.73*	5.44 ± 1.26‡	9.09 ± 0.87	5.75 ± 1.17§	8.91 ± 0.70¶
G_m (mmol/L)	7.81 ± 1.2	8.99 ± 0.98*	7.16 ± 1.17†‡	9.96 ± 1.14	8.28 ± 1.16§	8.91 ± 0.94‖¶
I_b (pmol/L)	65.3 ± 45.6	59.5 ± 34.5*	53.7 ± 31.7†	73.1 ± 40.1	65.2 ± 39.5	64.4 ± 32.5
I_m (pmol/L)	393.6 ± 245.6	487.3 ± 328.9	359.5 ± 231.8‡	524.9 ± 316.4	419.7 ± 303.6§	452.0 ± 234.0
CP_b (pmol/L)	880 ± 306	844 ± 295	810 ± 311†	992 ± 359	919 ± 332	908 ± 310
CP_m (pmol/L)	2,849 ± 848	3,128 ± 1,033	2,730 ± 903‡	3,271 ± 968	2,920 ± 955§	3,079 ± 1,018
Insulin sensitivity/resistance						
HOMA-IR (nondim.)	2.89 ± 2.05	2.32 ± 1.37*	2.08 ± 1.26†	3.30 ± 1.84	2.94 ± 1.84	2.48 ± 1.31‖
PREDIM (mg · kg^{-1} · min^{-1})	4.84 ± 1.39	3.93 ± 1.11*	5.55 ± 1.71†‡	3.47 ± 1.14	4.71 ± 1.52§	3.78 ± 0.90‖¶
BCF and insulin secretion						
G_{SENS} (pmol · min^{-1} · m^{-2} · mmol/L^{-1})	114.1 ± 53.6	98.4 ± 37.4	116.2 ± 56.2	94.2 ± 44.6	101.7 ± 49.8	94.5 ± 36.5
R_{SENS} (pmol · m^{-2} · mmol/L^{-1})	917 ± 688	967 ± 554	906 ± 798	907 ± 504	744 ± 551	893 ± 516
PFR (nondim.)	1.88 ± 0.63	1.23 ± 0.30*	1.71 ± 0.73†‡	1.37 ± 0.35	1.83 ± 0.59§	1.21 ± 0.31‖¶
ISR_r (pmol · min^{-1} · m^{-2})	222.3 ± 90.1	183.6 ± 67.0*	274.8 ± 117.6†‡	143.7 ± 62.7	208.8 ± 87.2§	202.4 ± 70.3‖
ISR_b (pmol · min^{-1} · m^{-2})	111.3 ± 38.6	104.9 ± 37.7	100.7 ± 39.1†	123.7 ± 45.3	115.1 ± 41.0	112.3 ± 40.0
ISR_t (nmol · m^{-2})	52.5 ± 16.4	62.0 ± 21.0*	50.8 ± 18.1‡	64.5 ± 19.3	54.1 ± 17.9§	60.7 ± 20.8
CL_{ins} (L · min^{-1} · m^{-2})	1.30 ± 0.39	1.29 ± 0.43	1.39 ± 0.42†	1.23 ± 0.41	1.29 ± 0.41	1.30 ± 0.44

Data are means ± SD unless otherwise indicated. HbA_{1c} (%): 5.4 ± 0.17 (IFG), 5.4 ± 0.16 (IGT), 5.8 ± 0.11 (IA1c), 5.4 ± 0.21 (IFG+IGT), 5.9 ± 0.15 (IFG+IA1c), 5.8 ± 0.13 (IGT+IA1c) (from http://www.ngsp.org/convert1.asp). CP_b, CP_m, basal (fasting) and mean C-peptide, respectively; G_b, G_{60}, G_{120}, G_m, glucose at basal, 60 min, and 120 min and mean glucose; I_b, I_m, basal and mean insulin; nondim., nondimensional. *Significant difference for IGT vs. IFG, †IA1c vs. IFG, ‡IA1c vs. IGT, §IFG+IA1c vs. IFG+IGT, ||IGT+IA1c vs. IFG+IGT, ¶IGT+IA1c vs. IFG+IA1c.

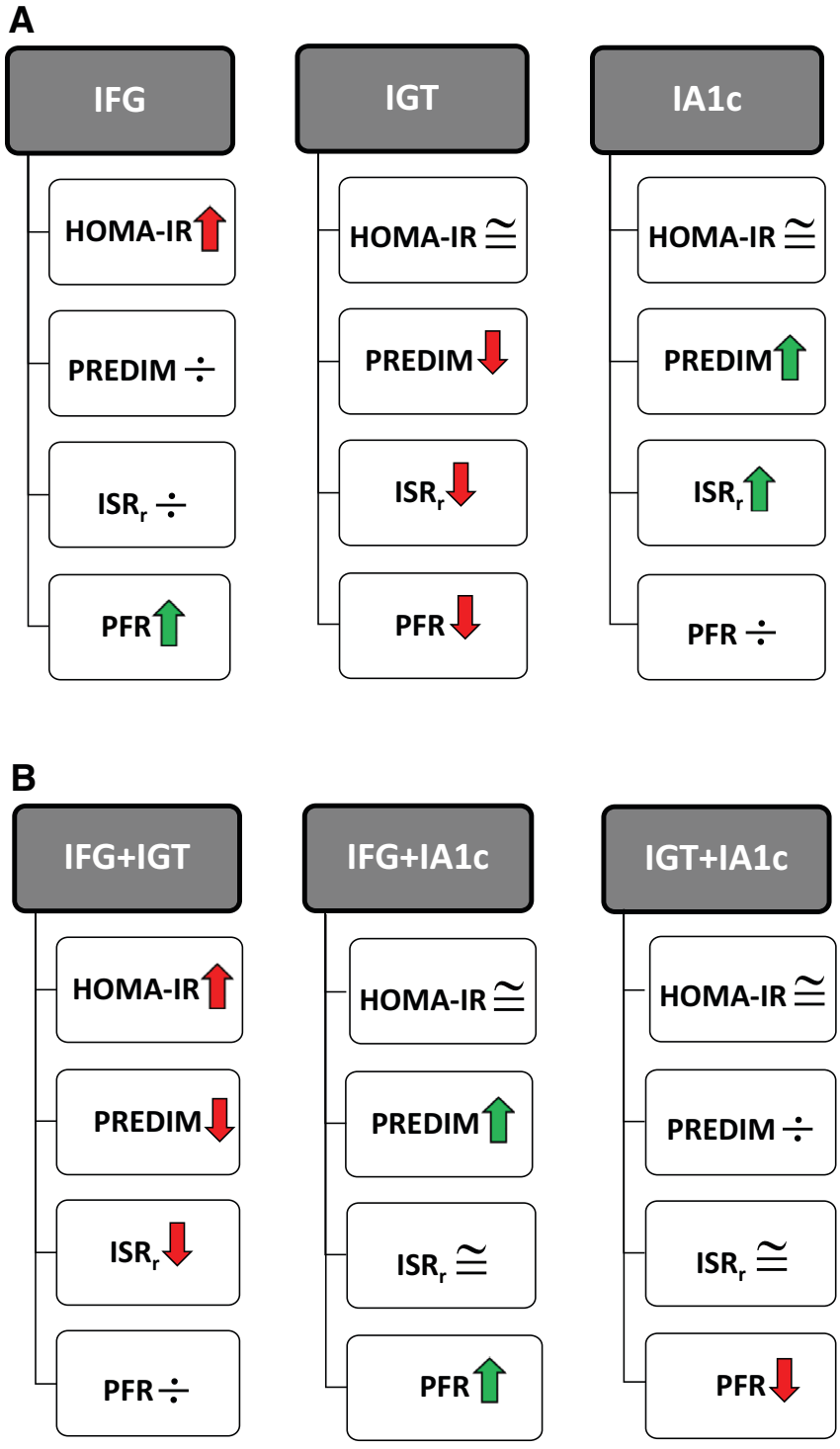

Figure 1—Summary of the main differences among groups with prediabetes with an isolated defect (*A*) and with a double defect (*B*) for the parameters of insulin sensitivity/resistance and insulin secretion/BCF. For ISR_r, reference glucose value is 6 mmol/L. ⇑, higher parameter value; ⇓, lower parameter value; ÷, intermediate parameter value; ≅, similar parameter values (in two groups); green, better condition; red, worse condition.

Metabolic Parameters. I1hG had worse PREDIM ($P < 0.0001$). I1hG also showed higher ISR_t and lower ISR_r ($P < 0.0001$). G_{SENS} was impaired in I1hG ($P < 0.0001$). CL_{ins} was lower ($P < 0.02$).

I1hG, IFG, and IA1c

Basic Characteristics. We then compared I1hG with the other single defect groups (Table 3) excluding IGT, due to low number of participants (N = 5). I1hG were

Table 3—Basic characteristics and metabolic parameters in the analysis including 1-h hyperglycemia for the different groups of participants with a single defect and for NGT

	NGT	IFG	IA1c	I1hG
N (males/females)	491 (324/167)	275 (210/65)	112 (53/59)	173 (152/21)*†‡
Basic characteristics				
Age (years)	62.6 ± 6.2	60.8 ± 6.2	64.1 ± 6.8	61.8 ± 6.0‡
BMI (kg/m^2)	27.1 ± 3.8	27.7 ± 3.3	27.2 ± 3.9	27.2 ± 3.4
HbA_{1c} (mmol/mol)	35.2 ± 2.2	35.9 ± 1.8	39.9 ± 1.2	35.5 ± 2.2‡
Glucose, insulin, C-peptide plasma concentrations				
G_b (mmol/L)	5.17 ± 0.34	5.86 ± 0.22	5.14 ± 0.34	5.31 ± 0.22*†‡
G_{60} (mmol/L)	6.62 ± 1.14	7.04 ± 1.07	6.87 ± 1.12	9.94 ± 1.17*†‡
G_{120} (mmol/L)	5.01 ± 1.08	5.14 ± 1.15	5.10 ± 1.15	5.85 ± 1.21*†‡
G_m (mmol/L)	6.30 ± 0.76	6.78 ± 0.67	6.41 ± 0.77	8.09 ± 0.74*†‡
I_b (pmol/L)	48.0 ± 29.6	64.7 ± 44.2	49.9 ± 24.6	49.8 ± 28.7†
I_m (pmol/L)	280.3 ± 167.4	329.9 ± 177.0	294.2 ± 178.9	375.7 ± 246.1*‡
CP_b (pmol/L)	715 ± 252	853 ± 309	757 ± 245	743 ± 255†
CP_m (pmol/L)	2,408 ± 708	2,608 ± 750	2,470 ± 790	2,766 ± 845*‡
Insulin sensitivity/resistance				
HOMA-IR (nondim.)	1.85 ± 1.14	2.82 ± 1.96	1.91 ± 0.97	1.96 ± 1.13†
PREDIM (mg · kg^{-1} · min^{-1})	6.11 ± 1.79	5.21 ± 1.39	5.86 ± 1.53	5.42 ± 1.60*‡
BCF and insulin secretion				
G_{SENS} (pmol · min^{-1} · m^{-2} · mmol/L^{-1})	133.8 ± 66.4	131.2 ± 63.4	124.3 ± 60.1	95.9 ± 37.1*†‡
R_{SENS} (pmol · m^{-2} · mmol/L^{-1})	1,080 ± 823	1,064 ± 804	1,006 ± 941	853 ± 609
PFR (nondim.)	1.83 ± 0.59	1.86 ± 0.66	1.76 ± 0.84	1.66 ± 0.51†
ISR_r (pmol · min^{-1} · m^{-2})	301.9 ± 115.5	260.4 ± 93.3	304.5 ± 126.4	206.4 ± 69.1*†‡
ISR_b (pmol · min^{-1} · m^{-2})	89.4 ± 30.9	107.9 ± 38.4	93.9 ± 30.6	92.9 ± 32.0†
ISR_t (nmol · m^{-2})	43.8 ± 13.4	46.4 ± 14.0	45.1 ± 15.8	52.4 ± 16.4*†‡
CL_{ins} (L · min^{-1} · m^{-2})	0.09 ± 0.03	0.08 ± 0.02	0.09 ± 0.02	0.08 ± 0.03*

Data are means ± SD unless otherwise indicated. IGT was excluded because of low sample size. HbA_{1c} (%): 5.4 ± 0.20 (NGT), 5.4 ± 0.16 (IFG), 5.8 ± 0.11 (IA1c), 5.4 ± 0.20 (I1hG) (from http://www.ngsp.org/convert1.asp). CP_b, CP_m, basal (fasting) and mean C-peptide, respectively; G_b, G_{60}, G_{120}, G_m, glucose at basal, 60 min, and 120 min and mean glucose; I_b, I_m, basal and mean insulin; nondim., nondimensional. *Significant difference for I1hG vs. NGT, †I1hG vs. IFG, ‡I1hG vs. IA1c.

younger than IA1c ($P < 0.005$). Glycemia was higher in I1hG ($P < 0.0002$) than in the other two groups, except for fasting glycemia compared with IFG, as expected; HbA_{1c} was obviously lower than in IA1c ($P < 0.0001$) but was similar to that in IFG.

Metabolic Parameters. I1hG had better HOMA-IR compared with IFG ($P < 0.0001$) but lower PREDIM compared with IA1c ($P < 0.0009$). I1hG also showed higher ISR_t ($P < 0.0001$) but lower ISR_b compared with IFG ($P < 0.0001$). Also, in I1hG, ISR_r was lower ($P < 0.0001$). G_{SENS} was impaired ($P < 0.0008$) in I1hG, who also showed lower PFR compared with that in the IFG group ($P < 0.005$). The β-cell dose response for the groups of this analysis is reported in Supplementary Fig. 1*B*. A summary of the differences among groups for the main parameters of insulin sensitivity/resistance and insulin secretion/BCF is reported in Fig. 2.

Incidence of Type 2 Diabetes and Parameters at Follow-up

We evaluated how many participants developed type 2 diabetes by the 48-month follow-up visit. Among the 1,691 participants studied, the percentage who developed diabetes in each group is shown in Fig. 3. According to logistic regression analysis, 1DEF showed higher percentage of diabetes compared with NGT ($P < 0.0002$), with OR much higher than 1 (OR 6.23, 95% CI 2.45–15.87). However, among the three groups with single defect there were no differences in the percentage of participants developing diabetes ($P \geq 0.64$).

Similarly, in comparisons of 2DEF with 1DEF, 2DEF showed a higher percentage of participants with diabetes ($P < 0.0001$, OR 3.03, 95% CI 1.99–4.61). However, there were no differences in the percentage of participants with diabetes among the three groups with double defect ($P \geq 0.59$). In comparison of 3DEF with 2DEF, the former had a higher percentage of participants developing diabetes ($P < 0.008$, OR 2.18, 95% CI 1.23–3.88).

Of note, when analyzing progression to the triple prediabetes defect rather than to overt diabetes, we found higher incidence in IGT than in IFG and IA1c (9 of 43 vs. 42 of 538 and 11 of 157 participants; $P < 0.007$, OR 3.10, 95% CI 1.37–7.04, and $P < 0.008$, OR 3.84, 95% CI 1.43–10.31, respectively), as well as in IGT+IA1c than in IFG+IA1c ($P < 0.02$, OR 4.46, 95% CI 1.31–15.12).

In the analysis including I1hG, 2 of 381 participants developed diabetes in NGT, 7 of 231 in IFG, 4 of 86 in

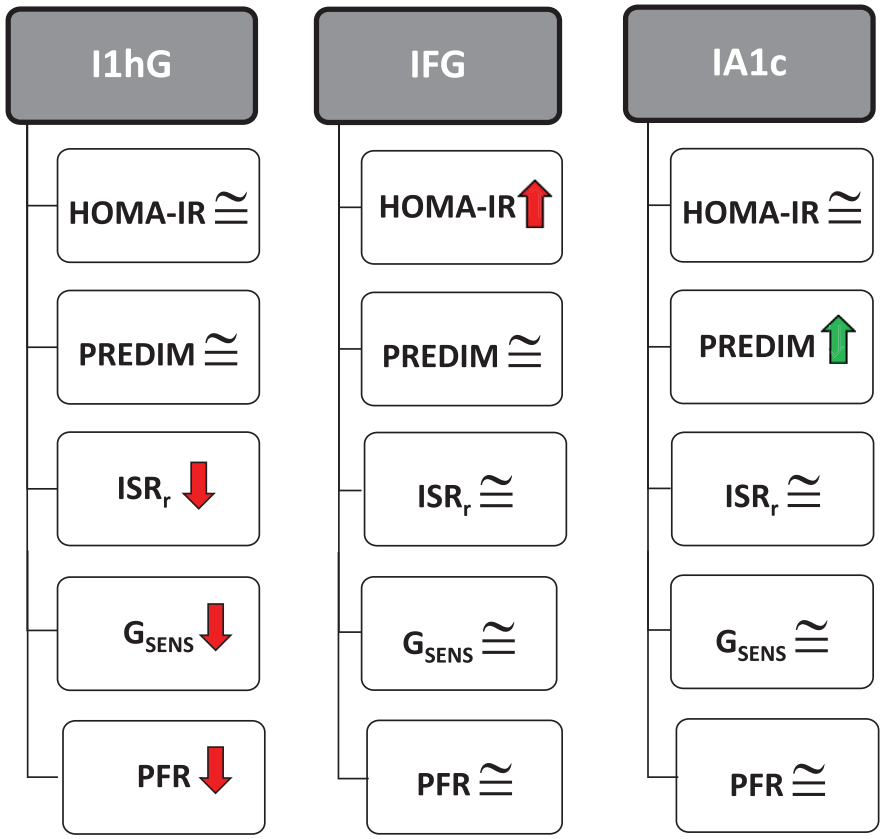

Figure 2—Summary of the main differences among I1hG, IFG, and IA1c for the parameters of insulin sensitivity/resistance and insulin secretion/BCF. For ISR_r, reference glucose value is 6 mmol/L. ⇑, higher parameter value; ⇓, lower parameter value; ÷, intermediate parameter value; ≅, similar parameter values (in two groups); green, better condition; red, worse condition.

IA1c, and 3 of 150 in I1hG. There were no differences in the percentage of participants developing diabetes in I1hG compared with the other two groups with single defect, i.e., IFG and IA1c ($P > 0.13$). However, single defect groups pooled (i.e., IFG, IA1c, I1hG grouped) showed higher percentage of diabetes onset compared with NGT ($P < 0.03$, OR 5.71, 95% CI 1.29–25.29), consistent with previous findings.

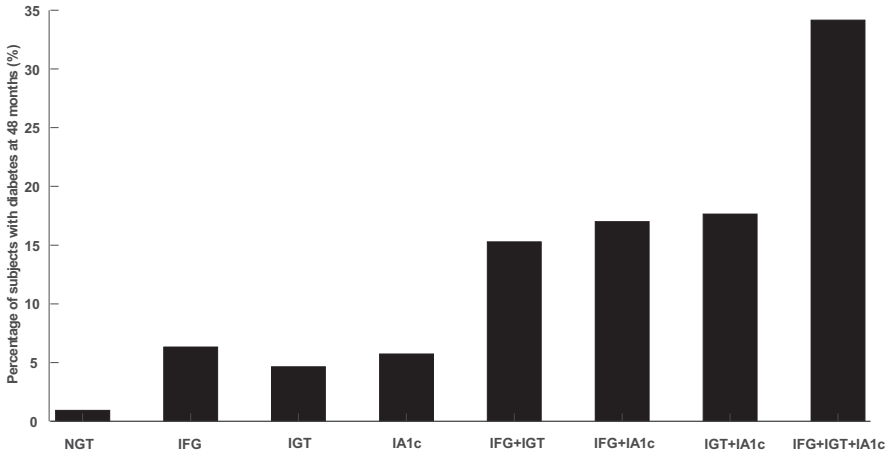

Figure 3—Percentage of participants with type 2 diabetes at 48 months in the different groups. The number of participants developing diabetes out of the total of each glucose tolerance group was 5 of 532 NGT, 34 of 538 IFG, 2 of 43 IGT, 9 of 157 IA1c, 11 of 72 IFG+IGT, 43 of 253 IFG+IA1c, 3 of 17 IGT+IA1c, and 27 of 79 IFG+IGT+IA1c (i.e., 3DEF).

Table 4—Basic characteristics and metabolic parameters for NGT participants and for the different groups of participants with single, double, and triple defect (i.e., IFG+IGT+IA1c) who completed the follow-up

	NGT	IFG	IGT	IA1c	IFG+IGT	IFG+IA1c	IGT+IA1c	IFG+IGT+IA1c
N (males/females)	532 (400/132)	538 (471/77)	43 (32/11)	157 (97/60)	72 (64/8)	253 (215/38)	17 (10/7)	79 (56/23)
Basic characteristics								
Age (years)	62.0 ± 6.1	60.5 ± 5.9	63.0 ± 6.6	63.3 ± 6.5	62.1 ± 6.0	61.6 ± 5.6	64.8 ± 6.0	63.6 ± 6.3
	66.1 ± 6.1	64.6 ± 5.9	67.1 ± 6.6	67.5 ± 6.5	66.2 ± 5.9	65.8 ± 5.5	68.9 ± 5.9	67.7 ± 6.3
	↑	↑	↑	↑	↑	↑	↑	↑
BMI (kg/m^2)	27.1 ± 3.6	28.1 ± 3.5	28.6 ± 3.6	27.5 ± 4.4	28.8 ± 3.9	28.1 ± 4.0	28.2 ± 3.2	29.9 ± 3.8
	27.4 ± 3.9	28.1 ± 3.8	28.5 ± 4.1	27.8 ± 4.6	28.3 ± 3.9	28.1 ± 4.3	27.9 ± 3.2	29.8 ± 3.6
	↑	n.s.	n.s.	n.s.	↓	n.s.	n.s.	n.s.
HbA_{1c} (mmol/mol)	35.2 ± 2.2	35.9 ± 1.9	35.9 ± 1.9	39.8 ± 1.2	35.7 ± 2.2	40.5 ± 1.6	40.2 ± 1.1	40.5 ± 1.5
	38.7 ± 2.8	39.3 ± 2.5	39.0 ± 3.1	42.6 ± 2.3	39.1 ± 2.4	43.3 ± 2.5	43.5 ± 1.8	43.6 ± 2.9
	↑	↑	↑	↑	↑	↑	↑	↑
Glucose, insulin, C-peptide plasma concentrations								
G_b (mmol/L)	5.23 ± 0.30	5.95 ± 0.29	5.30 ± 0.24	5.24 ± 0.30	6.08 ± 0.32	6.06 ± 0.33	5.27 ± 0.23	6.11 ± 0.32
	5.62 ± 0.48	6.12 ± 0.49	5.69 ± 0.53	5.71 ± 0.51	6.21 ± 0.46	6.32 ± 0.60	5.64 ± 0.61	6.44 ± 0.65
	↑	↑	↑	↑	↑	↑	↑	↑
G_{60} (mmol/L)	7.57 ± 1.88	9.00 ± 2.13	10.61 ± 1.67	8.32 ± 1.91	11.72 ± 1.87	9.83 ± 2.06	10.76 ± 1.61	11.58 ± 1.59
	8.28 ± 2.26	9.52 ± 2.49	10.32 ± 2.36	9.11 ± 2.26	11.36 ± 2.11	10.63 ± 2.56	11.08 ± 1.79	11.86 ± 2.03
	↑	↑	n.s.	↑	n.s.	↑	n.s.	n.s.
G_{120} (mmol/L)	5.21 ± 1.17	5.56 ± 1.15	8.72 ± 0.73	5.44 ± 1.26	9.05 ± 0.89	5.72 ± 1.22	8.97 ± 0.80	8.89 ± 0.74
	5.88 ± 1.57	6.23 ± 1.64	7.89 ± 2.54	6.17 ± 1.73	7.93 ± 2.24	6.79 ± 1.97	8.51 ± 2.36	9.03 ± 2.26
	↑	↑	↓	↑	↓	↑	n.s.	n.s.
G_m (mmol/L)	6.82 ± 1.11	7.81 ± 1.21	9.07 ± 1.04	7.24 ± 1.12	10.08 ± 1.09	8.29 ± 1.15	9.14 ± 0.98	9.90 ± 0.94
	7.45 ± 1.40	8.27 ± 1.56	8.87 ± 1.73	7.98 ± 1.52	9.61 ± 1.47	9.00 ± 1.67	9.37 ± 1.29	10.16 ± 1.52
	↑	↑	n.s.	↑	↓	↑	n.s.	n.s.
I_b (pmol/L)	47.2 ± 26.9	64.9 ± 41.8	58.9 ± 35.5	53.2 ± 32.1	72.5 ± 38.2	63.9 ± 39.0	61.4 ± 34.9	84.1 ± 40.5
	59.5 ± 37.1	68.1 ± 45.9	71.8 ± 34.3	65.6 ± 37.4	72.0 ± 39.2	67.7 ± 46.3	71.4 ± 35.7	91.9 ± 46.0
	↑	n.s.	↑	↑	n.s.	n.s.	n.s.	↑
I_m (pmol/L)	302.0 ± 190.7	396.6 ± 245.1	498.4 ± 351.2	352.6 ± 220.7	528.4 ± 309.9	416.8 ± 305.1	427.1 ± 257.7	535.9 ± 270.5
	377.0 ± 283.7	450.1 ± 319.8	485.7 ± 330.7	430.1 ± 261.3	516.5 ± 285.7	4,54.4 ± 288.7	485.3 ± 269.4	554.5 ± 281.0
	↑	↑	n.s.	↑	n.s.	↑	n.s.	n.s.
CP_b (pmol/L)	715 ± 239	873 ± 305	824 ± 276	800 ± 301	1,001 ± 346	906 ± 317	868 ± 329	1,089 ± 374
	826 ± 326	921 ± 385	962 ± 302	919 ± 348	1,008 ± 319	971 ± 409	987 ± 343	1,162 ± 364
	↑	↑	↑	↑	n.s.	↑	↑	↑
CP_m (pmol/L)	2,489 ± 742	2,836 ± 855	3,151 ± 1,079	2,700 ± 838	3,318 ± 976	2,910 ± 972	2,898 ± 1,074	3,297 ± 896
	2,755 ± 930	2,984 ± 997	3,177 ± 1,064	2,969 ± 935	3,264 ± 838	3,084 ± 1,011	3,199 ± 1,014	3,393 ± 876
	↑	↑	n.s.	↑	n.s.	↑	↑	n.s.

Continued on p. 2101

Table 4—Continued

	NGT	IFG	IGT	IA1c	IFG+IGT	IFG+IA1c	IGT+IA1c	IFG+IGT+IA1c
Insulin sensitivity/resistance								
HOMA-IR (nondim.)	1.84 ± 1.07	2.87 ± 1.88	2.32 ± 1.42	2.08 ± 1.31	3.28 ± 1.74	2.89 ± 1.84	2.42 ± 1.45	3.83 ± 1.96
	2.51 ± 1.63	3.15 ± 2.30	3.06 ± 1.53	2.81 ± 1.67	3.36 ± 1.98	3.26 ± 2.46	3.04 ± 1.67	4.47 ± 2.49
	↑	↑	↑	↑	n.s.	↑	n.s.	↑
PREDIM ($mg \cdot kg^{-1} \cdot min^{-1}$)	5.94 ± 1.72	4.82 ± 1.39	3.91 ± 1.01	5.58 ± 1.68	3.45 ± 1.06	4.78 ± 1.55	3.90 ± 0.95	3.16 ± 0.77
	5.19 ± 1.72	4.55 ± 1.59	3.92 ± 1.18	4.71 ± 1.58	3.87 ± 1.46	4.39 ± 1.71	3.80 ± 1.10	3.12 ± 0.93
	↓	↓	n.s.	↓	↑	↓	n.s.	n.s.
BCF and insulin secretion								
G_{SENS} ($pmol \cdot min^{-1} \cdot m^{-2} \cdot mmol/L^{-1}$)	122.5 ± 63.5	113.7 ± 53.8	99.3 ± 38.5	112.3 ± 48.0	91.8 ± 44.2	101.8 ± 51.1	86.6 ± 38.5	87.6 ± 25.6
	123.2 ± 59.8	115.8 ± 58.9	107.9 ± 40.4	116.3 ± 59.0	98.8 ± 48.5	101.6 ± 47.5	83.5 ± 19.8	92.9 ± 35.6
	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
R_{SENS} ($pmol \cdot m^{-2} \cdot mmol/L^{-1}$)	987 ± 720	911 ± 690	1,030 ± 544	876 ± 753	947 ± 530	739 ± 553	832 ± 509	887 ± 555
	932 ± 634	865 ± 677	1,040 ± 632	812 ± 565	865 ± 479	700 ± 512	1,000 ± 652	748 ± 448
	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.	n.s.
PFR (nondim.)	1.75 ± 0.64	1.86 ± 0.60	1.25 ± 0.27	1.71 ± 0.77	1.38 ± 0.35	1.85 ± 0.61	1.24 ± 0.34	1.46 ± 0.38
	1.83 ± 0.74	1.94 ± 0.70	1.56 ± 0.46	1.90 ± 0.69	1.78 ± 0.66	2.05 ± 0.86	1.65 ± 0.81	1.54 ± 0.49
	↑	↑	↑	↑	↑	↑	↑	n.s.
ISR_r ($pmol \cdot min^{-1} \cdot m^{-2}$)	271.2 ± 109.2	221.9 ± 92.0	178.1 ± 63.2	264.3 ± 106.2	144.5 ± 64.6	206.1 ± 85.8	178.6 ± 55.4	157.4 ± 61.4
	240.8 ± 106.9	202.2 ± 97.1	193.7 ± 85.3	236.0 ± 101.1	167.5 ± 84.9	193.4 ± 111.0	191.8 ± 80.0	159.8 ± 77.9
	↓	↓	n.s.	↓	↑	↓	n.s.	n.s.
ISR_b ($pmol \cdot min^{-1} \cdot m^{-2}$)	89.6 ± 29.7	110.7 ± 38.7	102.6 ± 35.5	99.4 ± 37.7	125.3 ± 44.4	113.9 ± 39.6	108.9 ± 44.2	135.5 ± 46.1
	102.2 ± 39.8	114.5 ± 47.3	118.7 ± 37.9	112.7 ± 43.0	124.6 ± 40.4	120.3 ± 50.4	121.3 ± 44.4	143.2 ± 44.5
	↑	n.s.	↑	↑	n.s.	↑	↑	↑
ISR_t ($nmol \cdot m^{-2}$)	45.8 ± 14.3	52.3 ± 16.6	62.8 ± 21.9	50.3 ± 16.7	65.5 ± 19.2	54.1 ± 18.4	57.5 ± 22.2	64.0 ± 17.9
	50.8 ± 18.0	55.3 ± 19.4	61.3 ± 21.3	55.3 ± 18.7	62.5 ± 16.2	57.8 ± 19.5	62.9 ± 20.8	65.4 ± 18.1
	↑	↑	n.s.	↑	n.s.	↑	↑	n.s.
CL_{ins} ($L \cdot min^{-1} \cdot m^{-2}$)	1.48 ± 0.47	1.29 ± 0.39	1.31 ± 0.46	1.39 ± 0.41	1.23 ± 0.42	1.29 ± 0.41	1.33 ± 0.46	1.12 ± 0.34
	1.35 ± 0.41	1.25 ± 0.41	1.24 ± 0.39	1.26 ± 0.40	1.20 ± 0.40	1.25 ± 0.39	1.25 ± 0.42	1.10 ± 0.32
	↓	↓	n.s.	↓	n.s.	↓	n.s.	n.s.

Data are means ± SD unless otherwise indicated. For each parameter, we report baseline value (top), value at 48 months (middle), and indication of significant variation (↑ or ↓ for significant increase or decrease, respectively, and n.s. [not significant] otherwise) (bottom). HbA_{1c} (%) value at baseline and 48 months, respectively: 5.4 ± 0.20, 5.7 ± 0.26 (NGT); 5.4 ± 0.17, 5.7 ± 0.23 (IFG); 5.4 ± 0.17, 5.7 ± 0.28 (IGT); 5.8 ± 0.11, 6.0 ± 0.21 (IA1c); 5.4 ± 0.20, 5.7 ± 0.22 (IFG+IGT); 5.9 ± 0.15, 6.1 ± 0.23 (IFG+IA1c); 5.8 ± 0.10, 6.1 ± 0.16 (IGT+IA1c); 5.9 ± 0.14, 6.1 ± 0.27 (IFG+IGT+IA1c) (from http://www.ngsp.org/convert1.asp). CP_b, CP_m, basal (fasting) and mean C-peptide, respectively; G_b, G_{60}, G_{120}, G_m, glucose at basal, 60 min, and 120 min and mean glucose; I_b, I_m, basal and mean insulin; nondim., nondimensional.

Table 5—Basic characteristics and metabolic parameters in the analysis including 1-h hyperglycemia for participants who completed the follow-up in the groups with a single defect and in NGT

	NGT	IFG	IA1c	I1hG
N (males/females)	381 (267/114)	231 (181/50)	86 (43/43)	150 (132/18)
Basic characteristics				
Age (years)	62.2 ± 6.3	60.5 ± 6.0	63.6 ± 7.0	61.7 ± 5.6
	66.3 ± 6.3	64.6 ± 5.9	67.7 ± 7.0	65.9 ± 5.6
	↑	↑	↑	↑
BMI (kg/m^2)	27.1 ± 3.7	27.6 ± 3.3	27.3 ± 3.8	27.2 ± 3.4
	27.5 ± 4.1	27.7 ± 3.6	27.6 ± 3.9	27.1 ± 3.3
	↑	n.s.	n.s.	n.s.
HbA_{1c} (mmol/mol)	35.1 ± 2.1	35.8 ± 1.9	39.8 ± 1.3	35.5 ± 2.3
	38.7 ± 2.7	39.0 ± 2.4	42.6 ± 2.3	38.7 ± 3.0
	↑	↑	↑	↑
Glucose, insulin, C-peptide plasma concentrations				
G_b (mmol/L)	5.19 ± 0.32	5.85 ± 0.22	5.17 ± 0.29	5.32 ± 0.21
	5.60 ± 0.50	6.00 ± 0.43	5.68 ± 0.54	5.67 ± 0.42
	↑	↑	↑	↑
G_{60} (mmol/L)	6.64 ± 1.16	7.04 ± 1.09	6.96 ± 1.06	9.94 ± 1.14
	7.64 ± 1.88	8.04 ± 1.95	8.26 ± 1.99	9.89 ± 2.33
	↑	↑	↑	n.s.
G_{120} (mmol/L)	4.97 ± 1.06	5.11 ± 1.11	5.16 ± 1.17	5.82 ± 1.22
	5.68 ± 1.38	5.85 ± 1.34	5.78 ± 1.35	6.39 ± 1.88
	↑	↑	↑	↑
G_m (mmol/L)	6.31 ± 0.77	6.77 ± 0.67	6.50 ± 0.75	8.10 ± 0.76
	7.08 ± 1.16	7.44 ± 1.18	7.43 ± 1.21	8.38 ± 1.54
	↑	↑	↑	n.s.
I_b (pmol/L)	45.9 ± 26.2	64.9 ± 46.4	50.0 ± 24.6	50.2 ± 28.5
	60.5 ± 38.3	65.7 ± 44.9	61.9 ± 27.4	56.8 ± 33.5
	↑	n.s.	↑	↑
I_m (pmol/L)	273.1 ± 159.3	334.4 ± 185.5	294.1 ± 168.3	373.4 ± 238.7
	363.1 ± 280.9	404.8 ± 268.9	391.6 ± 217.8	410.9 ± 289.1
	↑	↑	↑	↑
CP_b (pmol/L)	704 ± 234	844 ± 312	751 ± 233	744 ± 249
	827 ± 336	877 ± 399	882 ± 287	825 ± 300
	↑	n.s.	↑	↑
CP_m (pmol/L)	2,385 ± 695	2,599 ± 778	2,453 ± 752	2,749 ± 792
	2,711 ± 947	2,848 ± 986	2,866 ± 896	2,864 ± 881
	↑	↑	↑	↑
Insulin sensitivity/resistance				
HOMA-IR (nondim.)	1.78 ± 1.05	2.83 ± 2.07	1.92 ± 0.99	1.98 ± 1.12
	2.55 ± 1.69	2.97 ± 2.14	2.64 ± 1.26	2.41 ± 1.47
	↑	n.s.	↑	↑
PREDIM (mg · kg^{-1} · min^{-1})	6.15 ± 1.73	5.21 ± 1.39	5.81 ± 1.47	5.42 ± 1.59
	5.27 ± 1.76	4.85 ± 1.60	4.91 ± 1.45	5.01 ± 1.61
	↓	↓	↓	↓
BCF and insulin secretion				
G_{SENS} (pmol · min^{-1} · m^{-2} · mmol/L^{-1})	133.1 ± 68.9	130.4 ± 64.9	121.7 ± 53.4	95.2 ± 35.0
	131.9 ± 63.4	134.9 ± 69.0	125.9 ± 64.6	101.4 ± 42.6
	n.s.	n.s.	n.s.	n.s.
R_{SENS} (pmol · m^{-2} · mmol/L^{-1})	1,039 ± 748	1,058 ± 821	975 ± 883	854 ± 628
	974 ± 643	1,006 ± 788	892 ± 625	820 ± 600
	n.s.	n.s.	n.s.	n.s.
PFR (nondim.)	1.79 ± 0.67	1.84 ± 0.63	1.74 ± 0.90	1.65 ± 0.53
	1.85 ± 0.72	1.89 ± 0.60	2.01 ± 0.68	1.78 ± 0.78
	n.s.	n.s.	↑	n.s.
ISR_r (pmol · min^{-1} · m^{-2})	297.8 ± 111.7	261.7 ± 96.6	290.3 ± 111.5	203.8 ± 65.4
	256.9 ± 110.1	224.5 ± 107.2	254.7 ± 106.2	200.0 ± 86.1
	↓	↓	↓	n.s.
ISR_b (pmol · min^{-1} · m^{-2})	88.2 ± 28.9	107.0 ± 39.0	93.0 ± 29.2	93.0 ± 31.4
	102.1 ± 40.7	109.1 ± 48.4	107.7 ± 35.2	102.5 ± 37.5
	↑	n.s.	↑	↑

Continued on p. 2103

Table 5—Continued

	NGT	IFG	IA1c	I1hG
ISR_t (nmol · m^{-2})	43.3 ± 13.2	46.3 ± 14.6	44.9 ± 15.2	52.0 ± 15.2
	49.6 ± 18.2	51.5 ± 18.6	52.8 ± 18.1	53.9 ± 17.4
	↑	↑	↑	n.s.
CL_{ins} (L · min^{-1} · m^{-2})	1.52 ± 0.45	1.32 ± 0.37	1.45 ± 0.41	1.40 ± 0.52
	1.36 ± 0.40	1.27 ± 0.40	1.29 ± 0.35	1.32 ± 0.45
	↓	↓	↓	↓

Data are means ± SD unless otherwise indicated. For each parameter, we report baseline value (top), value at 48 months (middle), and indication of significant variation (↑ or ↓ for significant increase or decrease, respectively, and n.s. [not significant] otherwise) (bottom). IGT was excluded because of low sample size. HbA_{1c} (%) at baseline and 48 months, respectively: 5.4 ± 0.19, 5.7 ± 0.25 (NGT); 5.4 ± 0.17, 5.7 ± 0.22 (IFG); 5.8 ± 0.12, 6.0 ± 0.21 (IA1c); 5.4 ± 0.21, 5.7 ± 0.27 (I1hG) (from http://www.ngsp.org/convert1.asp). CP_b, CP_m, basal (fasting) and mean C-peptide, respectively; G_b, G_{60}, G_{120}, G_m, glucose at basal, 60 min, and 120 min and mean glucose; I_b, I_m, basal and mean insulin; nondim., nondimensional.

For participants who completed the follow-up, we also compared the parameters value at baseline and 48 months. All groups, including NGT, showed deterioration of several metabolic parameters (Table 4 and Table 5).

Reverting to NGT

We also investigated the incidence of reversal to NGT at follow-up. In the groups with single defect, the fraction of participants reverting to NGT was 26 of 538 in IFG, 4 of 43 in IGT, and 2 of 157 in IA1c. The percentage was lower in IA1c than in IFG and IGT ($P < 0.03$, OR 0.18, 95% CI 0.04–0.80 vs. IFG and $P < 0.01$, OR 0.08, 95% CI 0.01–0.54 vs. IGT), whereas there was no difference between IFG and IGT ($P > 0.34$). In groups with double or triple defect, reversal was negligible (2 of 421 participants in total). In the analysis with 1-h hyperglycemia, there was no difference between I1hG and the other groups with single defect ($P > 0.08$).

DISCUSSION

In this study, we investigated the differences in the main parameters of glucose metabolism in the prediabetes categories according to all established criteria, i.e., defect in fasting glycemia, 2-h OGTT glycemia, and glycated hemoglobin (1). We also investigated the differences among groups in the incidence of type 2 diabetes. To our knowledge, this is the first study presenting the analysis of glucose metabolism profiles in groups identified by all prediabetes criteria, in isolation and combination. Thus, even for the widely studied IFG and IGT populations, previous investigations typically did not analyze the "pure," single metabolic defects (at basal or at 2 h), since they rarely accounted for the third possible defect, i.e., IA1c. Furthermore, none of the previous studies comparing the different prediabetes defects reported longitudinal data.

Among the groups with isolated prediabetes defect, we found differences in the type or degree of impairment for both insulin sensitivity and BCF. Similar results were found for the groups with double defect. In line with the concepts of precision medicine in diabetes (13), our findings indicate the potential clinical benefit of treating each category of prediabetes with optimized strategies, the success of which in preventing or delaying type 2 diabetes appears enhanced with interventions designed to correct the underlying pathophysiological disturbances (14).

In comparisons of the groups with isolated defect, in IFG and IGT our findings confirmed the known notions on fasting insulin resistance in IFG (partly reflecting hepatic insulin resistance [15]) and OGTT insulin resistance in IGT (2). In IGT we also found lower ISR_r and lower PFR, which is related to the enhancing incretin effect on insulin secretion (16), though this cannot be investigated in detail in this analysis. In fact, incretin effect alterations were observed in IGT (16,17). In summary, IGT appears to be the worst phenotype among the three phenotypes with isolated defect.

In IA1c, we found fasting insulin resistance similar to that of IGT, but lower than that of IFG, whereas OGTT insulin sensitivity was higher than for both IFG and IGT. IA1c also had ISR_r higher than both IFG and IGT. Glucose and rate sensitivities were similar to those of IFG and IGT, whereas PFR was somehow lower than in IFG but higher than in IGT. Thus, among the three groups with isolated defect, IA1c showed overall less severe impairment in glucose metabolism. Notably, to our knowledge only one study reported detailed (i.e., model-derived) information on BCF in isolated HbA_{1c}-based prediabetes (18), and comparison with other groups with prediabetes was limited.

In comparisons of the groups with two defects, our findings are consistent with those in the groups with isolated defect, where the metabolic impairment appears more severe in IGT and, in contrast, less severe in IA1c. Thus, IFG+IGT was the worst phenotype, with more severe impairment in both fasting and OGTT insulin sensitivity and partly in BCF.

One-hour hyperglycemia has been proposed as a possible additional marker indicating abnormal glucose metabolism (7,19–22). In our analysis, I1hG showed differences in both insulin sensitivity and BCF compared with the other groups with isolated defect, though comparison

with IGT was not possible. Interestingly, I1hG showed impairment in both G_{SENS} (typically the most important BCF parameter) and potentiation factor, as well as in ISR_r. Thus, 1-h hyperglycemia may identify a prediabetes phenotype with specific metabolic defects (especially, possibly, greater β-cell dysfunction). To our knowledge, no previous studies compared isolated 1-h hyperglycemia with isolated IFG and isolated IA1c.

We also studied the incidence of type 2 diabetes within 4 years from baseline. We did not find differences in the diabetes incidence among the groups with isolated defect (despite our findings suggesting more severe metabolic impairment in IGT) or among the double defect groups. These findings, which partly differ from those of some previous studies in prediabetes (23), may be due to the follow-up duration, which could have been insufficient to disclose possible differences in diabetes incidence among groups with equal number of defects. This is in fact suggested by the observation that, when comparing IFG, IGT, and IA1c in terms of progression to the triple prediabetes defect rather than to overt diabetes, we found higher incidence for IGT compared with both IFG and IA1c and for IGT+IA1c compared with IFG+IA1c. Thus, it can be hypothesized that with longer follow-up duration some differences may emerge in diabetes incidence, among both the groups with isolated defect and those with double defect (with IGT phenotype possibly more prone to development of diabetes, both as isolated defect and in combination with a second defect). On the other hand, 4 years of follow-up was sufficient to reveal differences in diabetes incidence for progressively higher number of prediabetes defects, i.e., from NGT to triple defect. In the context of precision diagnostics (13), this suggests that people known to be at risk for type 2 diabetes should ideally be tested to disclose the possible presence of all three prediabetes defects, as this appears relevant for determination of the actual risk of developing diabetes.

Recent studies suggest that CL_{ins} is an independent process that can adapt to the metabolic demand to maintain glucose homeostasis (24). Of note, one study reported that both increase in insulin secretion and decrease in CL_{ins} may compensate for insulin resistance, but CL_{ins} decrease may be the first mechanism providing adaptation to insulin resistance (25). In our study, we found that CL_{ins} was similar among groups with equal number of defects, but it showed a tendency to progressive decline, ranging from NGT to triple defect. This appears consistent with what was reported in some studies (24,26), though other studies reported different findings (27,28). The RISE Consortium (27) reported no difference in CL_{ins} between participants with and without diabetes. Ohashi et al. (28) found an increased hepatic component in type 2 diabetes but decreased extrahepatic component. In a previous study, we found increased CL_{ins} in women with former gestational diabetes mellitus progressing to type 2 diabetes compared with women remaining diabetes free (12), possibly explained by the role of the SLC30A8 gene (29,30).

Few previous studies analyzed the glucose metabolism profile, including both insulin sensitivity and BCF, in several different groups with prediabetes. In one study (3), participants were stratified into groups of isolated IFG, IGT, and IA1c and further into two groups, with HbA_{1c} combined with IFG and IGT, but IFG+IGT and triple defect were not considered. Nonetheless, similar to our findings, fasting insulin resistance was higher in IFG and in IFG plus IA1c. BCF results of this study were limited by the lack of C-peptide. This may explain the partial disagreement with our findings, as the worse IGT condition, in BCF, was observed in comparisons with IA1c but not IFG. Furthermore, 1-h glycemia defect was not considered and longitudinal data were not provided. Similar limitations hold for other studies (4,5). In our previous study (6), due to limitations in the data set, we analyzed only IFG and IGT combined, plus one group with added 1-h hyperglycemia and another group with additional HbA_{1c} defect. In agreement with the present findings, we found progressive deterioration for both insulin sensitivity and BCF for increasing number of defects. However, similarly to the other previously published studies (3–5), C-peptide was not measured and longitudinal data were not available. Other studies reported separate analyses for some prediabetes categories (31–36). However, the focus was typically not on the assessment of glucose metabolism; thus, the analysis of insulin sensitivity and BCF was limited or absent. Another study focused on the definition of prediabetes phenotypes with different metabolic abnormalities and risk for type 2 diabetes (37). Specifically, several variables were considered (glycemia, insulin sensitivity and secretion, lipids, tissue fat content, anthropometry, polygenic diabetes risk score), yielding the definition of six prediabetes phenotypes at different risk for type 2 diabetes. However, direct comparison with our findings is difficult, due to the peculiar definition of the different prediabetes phenotypes (37).

Some studies, e.g., 38–43, focused on reversal from prediabetes to NGT. Interestingly, in our study we found somehow lower reversal in IA1c compared with IFG and IGT, which may be partly due to greater stability of HbA_{1c} compared with glycemia. This, however, requires further investigations.

Our study has some limitations. The prevalence of the different prediabetes conditions is likely not representative of that among the general population, as it appears from the disparity in IFG and IGT proportions. This is due to the recruitment process (see the study inclusion criteria). However, the size of the study allowed recruitment of a sufficient number of participants even in the less represented prediabetes categories, thus allowing appropriate analyses. Another limitation concerning diabetes incidence may be the duration of the follow-up.

In conclusion, we investigated the differences in several parameters of glucose metabolism in all groups with prediabetes, and we assessed the incidence at 48

months of type 2 diabetes onset in each group. Heterogeneity in the level of impairment of the metabolic parameters suggests that the different prediabetes phenotypes may benefit from specific treatment approaches. Furthermore, our findings indicate that people known to be at risk for diabetes should be tested to disclose the possible presence of all three prediabetes defects, as this appears relevant for determination of the actual risk of developing the disease.

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