One-Hour Postload Hyperglycemia Is a Stronger Predictor of Type 2 Diabetes Than Impaired Fasting Glucose

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Context: Subjects with normal glucose tolerance (NGT) but 1-h postload glucose $\geq$ 155 mg/dL (NGT-1h-high) exhibit an intermediate cardiometabolic risk profile between individuals with NGT and impaired glucose tolerance (IGT).

Objective: This study aimed to evaluate whether NGT-1h-high subjects have different cardiometabolic characteristics and an increased risk of type 2 diabetes compared with individuals with isolated impaired fasting glucose (IFG).

Setting, Design, and Patients: A cross-sectional analysis was performed on 595 nondiabetic subjects who underwent an oral glucose tolerance test and an euglycemic hyperinsulinemic clamp in an ambulatory care setting. In addition, a longitudinal analysis was performed on 392 individuals, who were reexamined after a followup of 5.2 $\pm$ 0.9 y.

Main Outcome Measures: Insulin sensitivity, beta-cell function, and risk of developing diabetes were measured.

Results: Subjects with NGT-1h-high have a significant reduction of peripheral insulin sensitivity and beta-cell function, assessed by the disposition index, compared with either 1-h postload glucose $<$ 155 mg/dL (NGT-1h-low) or IFG individuals, but not compared with IGT. Among the 392 subjects studied in the longitudinal analysis the incidence rate of type 2 diabetes over the follow-up period was 2.9, 16.7, 12.5, and 31.4% for subjects with NGT-1h-low, NGT-1h-high, IFG, and IGT, respectively. In a Cox proportional hazard regression analysis the risk of developing diabetes for NGT-1h-high subjects was 4.02 (95% confidence interval [CI] 1.06–15.26); an even higher risk (6.67; 95% CI, 2.09–21.24) was observed in subjects with IGT, but not in the isolated IFG group (1.91; 95% CI, 0.44–8.29).

Conclusions: NGT-1h-high subjects exhibit a higher risk of developing diabetes than those with IFG or NGT-1h-low, likely due to decreased insulin sensitivity and beta-cell function. **(*J Clin Endocrinol Metab* 100: 3744–3751, 2015)**

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Abbreviations: ADA, American Diabetes Association; AUC, area under the curve; BMI, body mass index; CATAMERI, Catanzaro Metabolic Risk Factors; CI, confidence interval; ΔGluc(AUC), incremental AUC of glucose; ΔIns(AUC), incremental AUC of insulin; EUGENE2, European Network on Functional Genomics of Type 2 Diabetes; FPG, fasting plasma glucose; HbA1c, glycosylated hemoglobin; HDL, high-density lipoprotein; HR, hazard ratio; hsCRP, high-sensitivity C-reactive protein; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; ΔIns30/ΔGluc30, insulinogenic index: Ins_{30}-Ins_0/$Gluc_{30}$-$Gluc_0$; M, glucose disposal; M_{FFM}, glucose disposal in milligrams per minute per kilogram fat-free mass; NGT, normal glucose tolerance; NGT-1h-high, 1-h postload glucose $\geq$ 155 mg/dL; NGT-1h-low, 1-h postload glucose $<$ 155 mg/dL; OGTT, oral glucose tolerance test; WHO, World Health Organization.

The prevalence of type 2 diabetes and related dysglycemic conditions at risk for diabetes (the so-called prediabetes) continues to increase worldwide mostly due to the constantly increasing prevalence of obesity (1). Early detection of individuals at risk for type 2 diabetes is essential not only because the progression to diabetes is largely preventable through lifestyle and/or pharmacologic interventions (2–4), but also to prevent or delay the cardiovascular complications associated with both type 2 diabetes and prediabetes itself (5, 6). Diagnostic criteria for categories of increased risk for type 2 diabetes have changed over time (7–9). Typically, the two dysglycemic conditions, which have been referred to as categories of increased risk for future development of type 2 diabetes, are impaired glucose tolerance (IGT) and impaired fasting glucose (IFG) (7). The two dysglycemic conditions have different underlying pathophysiological abnormalities with IFG individuals exhibiting hepatic insulin resistance and impaired early insulin secretion during an oral glucose tolerance test (OGTT), and IGT individuals having muscle insulin resistance, and an impairment of late-phase insulin secretion (7, 10, 11). Recently, an increasing body of evidence has suggested that a plasma glucose concentration of at least 155 mg/dL (8.6 mmol/l) at 1 hour during an OGTT can identify adults at increased risk for future development for type 2 diabetes among those who have normal glucose tolerance (NGT-1h-high) (12–14). Remarkably, subjects with NGT-1h-high exhibit an intermediate cardiometabolic risk profile between NGT and IGT individuals (15–25). However, it is important to note that previous studies aimed at characterizing the cardiometabolic profile of prediabetic categories have essentially compared subjects with NGT-1h-high with individuals with IGT, not excluding subjects with isolated IFG among those with NGT-1h-high (19, 26). Thus, it is unclear whether the cardiometabolic characteristics of subjects with isolated IFG differ from those of subjects with NGT-1h-high, and whether additional information about the risk for type 2 diabetes is embedded in 1-hour postload glucose levels independently of the isolated IFG state. To address these questions, we assessed insulin sensitivity using the euglycemic hyperinsulinemic clamp and insulin secretion by a validated index to estimate β-cell function obtained during an OGTT in 595 nondiabetic offspring of subjects with type 2 diabetic. Secondly, we investigated whether individuals with NGT-1h-high are at increased risk of developing type 2 diabetes compared with subjects with isolated IFG. To this aim, we assessed the ability of NGT-1h-high category to predict future development of type 2 diabetes compared with isolated IFG or IGT categories in a cohort of 392 adult white individuals participating to the Catanzaro Metabolic Risk Factors (CATAMERI) study, who were reexamined after a mean followup of 5.2 $\pm$ 0.9 years.

Materials and Methods

Study subjects

Two different samples of white nondiabetic adults (age $\geq$ 18 y) were studied. Sample 1 encompasses 595 nondiabetic offspring subjects participating in the European Network on Functional Genomics of Type 2 Diabetes (EUGENE2) project (11) who had only one parent with type 2 diabetes. Subjects were consecutively recruited at the Department of Medical and Surgical Sciences of the University "Magna Graecia" of Catanzaro and at the Department of Systems Medicine, University of Tor Vergata, Rome, Italy as previously described (19, 22). Participants underwent anthropometrical evaluation including measurements of body mass index (BMI), waist circumference, and body composition evaluated by bioelectrical impedance. A 75-g OGTT was performed with 0-, 30-, 60-, 90-, and 120-minute sampling for plasma glucose and insulin determinations. Insulin sensitivity was assessed by euglycemic hyperinsulinemic clamp study, as previously described (22, 27). Briefly, a priming dose of insulin (Humulin, Eli Lilly & Co.) was administrated during the initial 10 minutes to acutely raise plasma insulin followed by continuous insulin infusion fixed at 40 mU/m^2 $\times$ minutes. The blood glucose level was maintained constant during the 2-hour clamp study by infusing 20% glucose at varying rates according to blood glucose measurements assessed by a glucose analyzer at 5-minute intervals (mean coefficient of variation of blood glucose was $<$ 5%).

Sample 2 includes individuals participating to the CATAMERI study, an ongoing longitudinal observational study recruiting individuals at risk for metabolic and cardiovascular outcomes (15, 24, 25). To date, 436 participants completed a 5-year follow-up visit (mean followup, 5.2 $\pm$ 0.9 y). Here, we analyzed 392 individuals, who were free of type 2 diabetes at baseline, whereas 44 individuals with type 2 diabetes at baseline were excluded from the present analysis. Type 2 diabetes outcome at follow-up visit was determined according to the American Diabetes Association (ADA) criteria (9): glycosylated protein (HbA1c) at least 6.5% (48 mmol/mol), fasting plasma glucose (FPG) at least 126 mg/dL (7 mmol/l), 2-hour postload glucose at least 200 mg/dL (11.1 mmol/l), or use of glucose-lowering medications. The study was approved by the Hospital ethical committee (Comitato Etico Azienda Ospedaliera "Mater Domini") and written informed consent was obtained from all participants in accordance with principles of the Declaration of Helsinki.

Calculation

According to the ADA criteria (9), individuals were classified as having NGT when FPG was less than 100 mg/dL (5.5 mmol/l) and 2-hour postload was less than 140 mg/dL (7.77 mmol/l), isolated IFG when FPG was 100–125 mg/dL (5.5–6.9 mmol/l), and 2-hour postload was less than 140 mg/dL (7.77 mmo/l), and IGT when FPG was less than 126 mg/dL (7 mmol/l) and 2-hour postload was 140–199 mg/dL (7.77–11.0 mmol/l). Glucose tolerance status was evaluated also according to World Health Organization (WHO) criteria (28): individuals were thus classified as NGT when FPG was less than

110 mg/dL (6.1 mmol/l) and 2-hour postload was less than 140 mg/dL (7.77 mmol/l), isolated IFG when FPG was 110–125 mg/dL (6.1–6.9 mmol/l) and 2-hour postload was less than 140 mg/dL (7.77 mmo/l), and IGT when FPG was was less than 126 mg/dL (7 mmol/l) and 2-hour postload was 140–199 mg/dL (7.77–11.0 mmol/l). Individuals in the NGT group were further divided into two subgroups (NGT-1h-low and NGT-1h-high) based upon their 1-hour plasma glucose concentration (below or above 155 mg/dL [8.6 mmol/l], respectively). Glucose disposal (M) was calculated as the mean rate of glucose infusion measured during the last 60 minutes of the clamp examination (steady state) and is expressed as milligrams per minute per kilogram fat-free mass (M_{FFM}) measured with the use of electrical bioimpedance. Early phase of insulin secretion during an OGTT was estimated by the insulinogenic index as follows: Ins_{30}-Ins_0/$Gluc_{30}$-$Gluc_0$ (ΔIns30/ΔGluc30) where Ins_y and $Gluc_y$ represent insulin and glucose values, respectively, at time y minutes during the OGTT. The late phase of insulin secretion was estimated by $\Delta Ins_{0-120}/\Delta Gluc30_{0-120}$, as well as by the incremental area under the curve (AUC) of insulin (ΔIns[AUC]) divided by the incremental AUC of glucose (ΔGluc[AUC]) during the 60- to 120-minute time period of the OGTT using the trapezoid rule. To evaluate β-cell function, the so-called disposition index was calculated as $\Delta Ins30/\Delta Gluc30 \times M_{FFM}$.

Analytical determinations

Glucose, triglycerides, total, and high-density lipoprotein (HDL) cholesterol concentrations were determined by enzymatic methods (Roche). High-sensitivity C-reactive protein (hsCRP) levels were measured with an automated instrument (CardioPhase hsCRP, Siemens Healthcare), and plasma insulin concentration by a chemiluminescence-based assay (Immulite, Siemens Healthcare).

Statistical analyses

To obtain the sample size, a power calculation was performed at http://www.statisticalsolutions.net/pss_calc.php. Variables with skewed distribution including triglycerides, hsCRP, fasting insulin, 30-minute-insulin, 1-hour insulin, 2-hour insulin, $\Delta Ins_{0-120}/\Delta Gluc_{0-120}$, and $AUCIns_{60-120}/AUCGluc_{0-120}$ were natural log–transformed for statistical analyses. After log transformation the variables have a normal distribution, and untransformed data are presented to facilitate interpretation. Continuous variables are expressed as means ± SD. Categorical variables were compared by χ^2 test. A general linear model with post-hoc Bonferroni correction for multiple comparisons was used to compare differences of continuous variables between groups. Partial correlation coefficients adjusted for age, sex, and BMI were computed between variables. A Cox proportional hazard regression analysis including age, sex, and BMI at baseline as covariates was used to determine the association between the study groups and the risk to develop type 2 diabetes. For all analyses, $P \leq .05$ was considered to be statistically significant. All analyses were performed using SPSS software Version 16.0 for Windows (IBM).

Results

Cross-sectional analysis in Sample 1

Plasma glucose concentrations in subjects with NGT-1h-low, NGT-1h-high, isolated IFG, and IGT are shown in Figure 1. Table 1 presents the anthropometric, biochemical, and metabolic characteristics of nondiabetic offspring subjects classified according to ADA criteria.

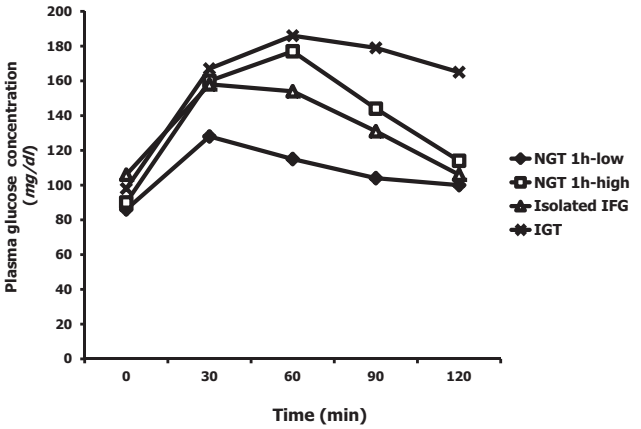

Figure 1. Plasma glucose levels during OGTT in subjects with NGT-1h-low, NGT-1h-high, isolated IFG, and IGT.

As shown in Table 1, there was a significantly higher proportion of males in the NGT-1h-high group compared with NGT-1h-low group ($P = .001$). Moreover, individuals of the NGT-1h-high group were older and exhibited significantly higher FPG, 2-hour postload plasma glucose, fasting, 1-hour and 2-hour postchallenge insulin levels, triglycerides, and hsCRP levels compared with subjects of the NGT-1h-low group, after adjusting for age, sex, and BMI. Individuals of the NGT-1h-high group have a significant reduction in peripheral insulin sensitivity, evaluated by the hyperinsulinemic euglycemic clamp, compared with individuals of the NGT-1h-low group (Table 1). The insulinogenic index (ΔIns30/ΔGluc30) of insulin secretion was significantly lower in individuals of the NGT-1h-high group compared with individuals of the NGT-1h-low group even after adjusting for age, sex, and BMI. By contrast, late insulin secretion during the OGTT, as estimated by $\Delta Ins_{0-120}/\Delta Gluc_{0-120}$ and $AUCIns_{60-120}/AUCGluc_{0-120}$ was significantly higher in individuals of the NGT-1h-high group, compared with individuals of the NGT-1h-low group even after adjusting for age, sex, and BMI. Because insulin secretion is dependent on actual insulin sensitivity, we compared the disposition index, calculated as the product of the insulinogenic index and insulin-stimulated glucose disposal in the two groups of NGT individuals. The disposition index was significantly lower in NGT-1h-high group compared with the NGT-1h-low group.

As compared with individuals with isolated IFG defined by ADA criteria, subjects in the NGT-1h-high group exhibited significantly higher 2-hour postload plasma glucose, 1-hour and 2-hour postchallenge insulin levels, hsCRP and triglycerides levels. Insulin-stimulated glucose disposal was significantly lower in individuals of the

Table 1. Anthropometric and Metabolic Characteristics of the Study Subjects Stratified According to the Glucose Tolerance Defined by ADA Criteria

Variable	NGT With 1-h Glucose <155 mg/dL (1)	NGT With 1-h Glucose ≥155 mg/dL (2)	Isolated IFG (3)	IGT (4)	*P*	*P* 1 vs 2	*P* 1 vs 3	*P* 1 vs 4
n (Male/Female)	344 (119/225)	101 (54/47)	70 (46/24)[b]	80 (38/42)	<.0001	.001	<.0001	.04
Age, y	36 ± 10	40 ± 9[a]	42 ± 9	44 ± 9	<.0001[g]	.003[g]	<.0001[g]	<.0001[g]
BMI, kg/m^2	28.6 ± 7.1	30.1 ± 6.7[a]	29.1 ± 5.7[c]	33.9 ± 6.6	<.0001[h]	.09[h]	.84[h]	<.0001[h]
Waist circumference, cm	92 ± 15	97 ± 14[a,f]	94 ± 14[c]	104 ± 14	.0001[h]	.10[h]	.33[h]	<.0001[h]
Fat mass, %	32 ± 12	34 ± 14[b]	33 ± 11	37 ± 11	.01[h]	.62[h]	.20[h]	.001[h]
SBP, mm Hg	124 ± 16	125 ± 13	122 ± 13[b]	134 ± 17	.02	.09	.06	.09
DBP, mm Hg	79 ± 11	78 ± 10[a]	78 ± 10[b]	86 ± 10	.001	.10	.12	.15
Fasting glucose, mg/dL	86 ± 7	90 ± 7[c,d]	106 ± 5[c]	98 ± 15	<.0001	.004	<.0001	<.0001
30-min glucose, mg/dL	128 ± 22	160 ± 24	158 ± 28[b]	167 ± 32	<.0001	<.0001	<.0001	<.0001
1-h glucose, mg/dL	115 ± 22	177 ± 20[d]	154 ± 39[c]	186 ± 38	<.0001	<.0001	<.0001	<.0001
2-h glucose, mg/dL	100 ± 19	114 ± 18[c,d]	106 ± 21[c]	164 ± 17	<.0001	<.0001	.09	<.0001
Fasting insulin, μU/mL	10 ± 7	12 ± 6[c]	13 ± 8[a]	19 ± 14	<.0001	.006	.04	<.0001
30 min insulin, μU/mL	72 ± 49	82 ± 51	69 ± 49	82 ± 53	.47	.30	.38	.78
1-h insulin, μU/mL	73 ± 55	119 ± 79[a,e]	96 ± 84	105 ± 77	<.0001	<.0001	.08	.04
2-h insulin, μU/mL	55 ± 46	79 ± 52[a,e]	66 ± 62[d]	129 ± 83	<.0001	<.0001	.37	<.0001
Total cholesterol, mg/dL	193 ± 38	196 ± 36	201 ± 36	209 ± 42	.71	.62	.79	.33
HDL, mg/dL	54 ± 14	51 ± 14	48 ± 11	46 ± 12	.19	.86	.55	.03
Triglycerides, mg/dL	102 ± 48	125 ± 60[b,f]	111 ± 50[c]	156 ± 75	<.0001	.12	.14	<.0001
hsCRP, mg/L	2.0 ± 1.9	3.1 ± 3.0[e]	1.4 ± 1.3[a]	3.2 ± 2.4	.02	.03	.13	.05
$\Delta Ins_{30}/\Delta Gluc_{30}$	28.2 ± 13.5	18.1 ± 12.2[f]	22.5 ± 13.4[b]	17.7 ± 11.6	<.0001	<.0001	.04	<.0001
$\Delta Ins_{0-120}/\Delta Gluc_{0-120}$	59 ± 131	81 ± 166[b]	89 ± 168[b]	38 ± 34	.04	.32	.28	.05
$AUCIns_{60-120}/AUCGluc_{0-120}$	0.58 ± 0.38	0.72 ± 0.44	0.64 ± 0.49	0.73 ± 0.54	.03	.003	.63	.65
Insulin-stimulated glucose disposal, mg/min × kg FFM	10.4 ± 4.9	8.5 ± 4.0[f]	10.1 ± 4.3[c]	6.8 ± 3.8	<.0001	.02	.31	<.0001
Disposition index, ΔIns30/ ΔGluc30 × M_{FFM}	263 ± 169	141 ± 103[e]	211 ± 158[c]	108 ± 75	<.0001	<.0001	.23	<.0001

Abbreviations: DBP, diastolic blood pressure; FFM, fat-free mass; M_{FFM}, glucose disposal; SBP, systolic blood pressure.

Data are Means ± SD.

Triglycerides, hsCRP, fasting, 1-h and 2-h insulin, $\Delta Ins_{0-120}/\Delta Gluc_{0-120}$, and $AUCIns_{60-120}/AUCGluc_{0-120}$ were log transformed for statistical analysis, but values in the table represent a back transformation to the original scale.

Categorical variables were compared by χ^2 test. Comparisons between the four groups were performed using a general linear model with post-hoc Bonferroni correction for multiple comparisons.

P values refer to results after analyses with adjustment for age, sex, and BMI.

[a] $P < .001$ vs IGT.

[b] $P < .05$ vs IGT.

[c] $P < .0001$ vs IGT.

[d] $P < .0001$ vs IFG.

[e] $P < .001$ vs IFG.

[f] $P < .05$ vs IFG.

[g] *P* values refer to results after analyses with adjustment for sex.

[h] *P* values refer to results after analyses with adjustment for sex, and age.

NGT-1h-high group compared with individuals of the isolated IFG group even after adjusting for age, sex, and BMI. The insulinogenic index of insulin secretion and the disposition index were significantly lower in individuals of the NGT-1h-high group, compared with individuals of the isolated IFG group, whereas late insulin secretion during the OGTT did not differ (Table 1).

As compared with individuals with IGT, subjects in the NGT-1h-high group exhibited significantly lower adiposity, FPG, fasting and 2-hour postchallenge insulin levels, and triglycerides levels. Insulin-stimulated glucose disposal, the $\Delta Ins_{30}/\Delta Gluc_{30}$ and $AUCIns_{60-120}/AUCGluc_{0-120}$ indices of insulin secretion, and the disposition index did not differ between the two groups, after adjusting for age, sex, and BMI (Table 1).

We next examined whether anthropometric, metabolic, and cardiovascular risk factor profiles differ between subjects stratified according to the glucose tolerance defined by WHO criteria (Table 2). All the differences in insulin-stimulated glucose disposal, indices of early and late insulin secretion, and disposition index between the NGT-1h-low and NGT-1h-high groups remained significant after adjusting for age, sex, and BMI. Compared with individuals of the NGT-1h-low group, individuals with isolated IFG according to WHO criteria exhibited significantly higher late phase of insulin secretion, whereas the index of early phase insulin secretion and the disposition index did not differ between the two groups after adjusting for age, sex, and BMI (Table 2).

Age-, sex-, and BMI- adjusted univariate correlations between fasting, 1-hour and 2-hour postchallenge glucose

Table 2. Anthropometric and Metabolic Characteristics of the Study Subjects Stratified According to the Glucose Tolerance Defined by WHO Criteria

Variable	NGT With 1-h Glucose <155 mg/dL (1)	NGT With 1-h Glucose ≥155 mg/dL (2)	Isolated IFG (3)	IGT (4)	*P*	*P* 1 vs 2	*P* 1 vs 3	*P* 1 vs 4
n (Male/Female)	370 (133/237)	123 (72/51)	22 (14/8)	80 (38/42)	<.0001	<.0001	.01	.07
Age, y	36 ± 10	41 ± 10[a]	43 ± 9	44 ± 9	<.0001[d]	<.0001[d]	.004[d]	<.0001[d]
BMI, kg/m^2	28.6 ± 7.1	30.1 ± 6.4[a]	29.4 ± 4.7[a]	34 ± 6.6	<.0001[e]	.06[e]	.73[e]	<.0001[e]
Waist circumference, cm	92 ± 15	97 ± 14[b]	95 ± 13[b]	104 ± 14	<.0001[e]	.05[e]	.77[e]	<.0001[e]
Fat mass, %	33 ± 12	33 ± 13[a]	36 ± 15	38 ± 10	.004[e]	.48[e]	.04[e]	.001[e]
SBP, mm Hg	124 ± 16	125 ± 14[b]	127 ± 14	134 ± 17	.02	.03	.42	.09
DBP, mm Hg	79 ± 11	79 ± 10[b]	80 ± 9[a]	86 ± 10	.02	.07	.2	.13
Fasting glucose, mg/dL	87 ± 8	92 ± 8[c]	113 ± 4[c]	98 ± 15	<.0001	.001	<.0001	<.0001
30-min glucose, mg/dL	129 ± 22	161 ± 24	181 ± 21[a]	167 ± 32	<.0001	<.0001	<.0001	<.0001
1-h glucose, mg/dL	116 ± 23	179 ± 20	170 ± 36[a]	186 ± 38	<.0001	<.0001	<.0001	<.0001
2-h glucose, mg/dL	100 ± 20	114 ± 19[c]	107 ± 19[c]	164 ± 17	<.0001	<.0001	.24	<.0001
Fasting insulin, μU/mL	10 ± 7	12 ± 8[c]	14 ± 5	19 ± 14	<.0001	.03	.004	<.0001
30-min insulin, μU/mL	71 ± 48	80 ± 55	79 ± 50	82 ± 53	.66	.3	.5	.89
1-h insulin, μU/mL	73 ± 54	120 ± 87[a]	113 ± 68	105 ± 77	<.0001	<.0001	.008	.01
2-h insulin, μU/mL	54 ± 45	83 ± 64[c]	68 ± 57[b]	129 ± 83	<.0001	<.0001	.09	<.0001
Total cholesterol, mg/dL	193 ± 38	200 ± 37	189 ± 23	209 ± 42	.26	.74	.14	.25
HDL, mg/dL	54 ± 14	50 ± 13	46 ± 9	46 ± 12	.08	.64	.18	.02
Triglycerides, mg/dL	102 ± 48	124 ± 63[b]	112 ± 48[b]	156 ± 75	<.0001	.2	.43	<.0001
hsCRP, mg/L	2.1 ± 2.0	2.8 ± 2.9[a]	1.0 ± 0.7[b]	3.2 ± 2.5	.001	.001	.77	.04
ΔIns30/ΔGluc30	28.1 ± 19	18 ± 12	21.5 ± 13	17.7 ± 11.6	<.0001	<.0001	.15	<.0001
$\Delta Ins_{0-120}/\Delta Gluc_{0-120}$	48 ± 129	78 ± 158	106 ± 240	38 ± 34	<.0001	.04	<.0001	.01
$AUCIns_{60-120}/AUCGluc_{0-120}$	0.57 ± 0.38	0.73 ± 0.49	0.74 ± 0.43	0.73 ± 0.54	.004	.05	.001	.44
Insulin-stimulated glucose disposal, mg/min × kg FFM	10.5 ± 4.9	8.7 ± 4.2[a]	9.3 ± 3.5[a]	6.8 ± 3.8	<.0001	.04	.73	<.0001
Disposition index, ΔIns30/ΔGluc30 × M_{FFM}	265 ± 177	142 ± 99	185 ± 130[a]	108 ± 75	<.0001	<.0001	.09	<.0001

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; FFM, fat-free mass; M_{FFM}, glucose disposal.

Data are Means ± SD.

Triglycerides, hsCRP, fasting, 1-h and 2-h insulin, $\Delta Ins_{0-120}/\Delta Gluc_{0-120}$, and $AUCIns_{60-120}/AUCGluc_{0-120}$ were log transformed for statistical analysis, but values in the table represent a back transformation to the original scale.

Categorical variables were compared by χ^2 test.

Comparisons between the four groups were performed using a general linear model with post-hoc Bonferroni correction for multiple comparisons.

P values refer to results after analyses with adjustment for age, sex, and BMI.

[a] $P < .05$ vs IGT.

[b] $P < .001$ vs IGT.

[c] $P < .0001$ vs IGT.

[d] *P* values refer to results after analyses with adjustment for sex.

[e] *P* values refer to results after analyses with adjustment for sex, and age.

levels and insulin-stimulated glucose disposal in the whole study group showed that both 1-hour (r = −0.21; $P < .0001$) and 2-hour (r = −0.22; $P < .0001$) postchallenge glucose levels exhibited a stronger inverse correlation with insulin-stimulated glucose disposal compared with fasting glucose levels (r = −0.07; $P = .11$). Accordingly, both 1-hour (r = −0.45; $P < .0001$) and 2-hour (r = −0.31; $P < .0001$) postchallenge glucose levels exhibited a stronger inverse correlation with the disposition index compared with fasting glucose levels (r = −0.03; $P = .54$). Similar results were observed when the IGT group was excluded from the analyses. Thus, both 1-hour (r = −0.19; $P < .0001$) and 2-hour (r = −0.18; $P < .0001$) postchallenge glucose levels exhibited a stronger inverse correlation with insulin-stimulated glucose disposal compared with fasting glucose levels (r = −0.04; $P = .41$). In addition, both 1-hour (r = −0.44; $P < .0001$) and 2-hour (r = −0.23; $P < .0001$) postchallenge glucose levels exhibited a stronger inverse correlation with the disposition index compared with fasting glucose levels (r = −0.03; $P = .54$).

Longitudinal analysis in Sample 2

Table 3 shows the anthropometric and metabolic characteristics of the Sample 2 subjects. The incidence rate to type 2 diabetes over the follow-up period (mean followup, 5.2 ± 0.9 y) was 2.9, 16.7, 12.5, and 31.4% for NGT-1h-low, NGT-1h-high, isolated IFG, and IGT groups, respectively. A Cox proportional hazard regression analysis including age, sex, and BMI at baseline as covariates was used to estimate the hazard ratio (HR) to develop type 2 diabetes of NGT-1h-high, isolated IFG, and IGT groups, compared with the NGT-1h-low group (the reference category) (Table 3). The HR for the development of diabetes of NGT-1h-high subjects was 4.02 (95% confidence interval [CI], 1.06–15.26); an even higher HR (6.67; 95% CI, 2.09–21.24), was observed in subjects with IGT, but

Table 3. Anthropometric and Metabolic Characteristics of the Study Subjects Stratified According to the Glucose Tolerance Defined by ADA Criteria

Variable	NGT With 1-h Glucose <155 mg/dL (1)	NGT With 1-h Glucose ≥155 mg/dL (2)	Isolated IFG (3)	IGT (4)	*P*
n (Male/Female)	174 (67/107)	60 (33/27)	72 (50/22)	86 (42/44)	<.0001
Age, y	41 ± 11	44 ± 10	50 ± 11	50 ± 11	<.0001[a]
BMI, kg/m^2	28.4 ± 6.3	29.4 ± 4.4	29.2 ± 4.6	31.8 ± 5.3	.002
Fasting glucose, mg/dL	86 ± 7	90 ± 8	105 ± 5	98 ± 12	<.0001
1-h glucose, mg/dL	113 ± 22	180 ± 19	161 ± 46	187 ± 33	<.0001
2-h glucose, mg/dL	98 ± 19	112 ± 20	111 ± 19	164 ± 17	<.0001
Subjects converted to type 2 diabetes	5	10	9	27	<.0001
Hazard ratio (95% CI) of developing type 2 diabetes	1 (Reference)	4.02 (1.06–15.26)	1.91 (0.44–8.29)	6.67 (2.09–21.24)	<.0001

Data are Means ± SD.

Categorical variables were compared by χ^2 test.

Comparisons between the four groups were performed using a general linear model.

P values refer to results after analyses with adjustment for age, sex, and BMI.

[a] *P* values refer to results after analyses with adjustment for sex.

not in the isolated IFG group (1.91; 95% CI, 0.44–8.29) (Table 3). We next examined the HR for the development of diabetes when isolated IFG subjects were further divided into two subgroups (isolated IFG-1h-low [n = 37] and isolated IFG-1h-high [n = 35]) based upon their 1-hour plasma glucose concentration (below or above 155 mg/dL, respectively). The HR for the development of diabetes of isolated IFG-1h-low subjects was 0.95 (95% CI, 0.10–8.68) but a higher HR (3.07; 95% CI, 0.62–15.28) was observed in subjects with isolated IFG-1h-high although it did not reached the threshold of significance.

Discussion

Longitudinal epidemiological studies have shown that a subgroup of subjects with NGT whose plasma glucose value at 1 hour during an OGTT is at least 155 mg/dL (8.6 mmol/l) (NGT-1h-high), are at elevated risk for the development of type 2 diabetes compared with NGT subjects with a 1-hour value below 155 mg/dL (NGT-1h-low) (13, 14, 29). Several reports have shown that individuals with NGT-1h-high exhibit impaired insulin sensitivity and β-cell dysfunction, associated with an intermediate cardiovascular risk profile between NGT-1h-low and IGT individuals (15–26). However, these studies did not exclude subjects with isolated IFG among those with NGT-1h-high (20, 27), and the contributory role of isolated IFG to the metabolic phenotype of subjects with NGT-1h-high has thus not been investigated. These observations coupled with the accessibility of carefully characterized cohorts of nondiabetic subjects prompted us to compare insulin sensitivity and β-cell function in individuals with NGT-1h-high or isolated IFG, and to examine the risk of developing type 2 diabetes in different dysglycemic conditions. Our analysis of cross-sectional data from the EUGENE2 study showed that individuals with NGT-1h-high exhibit reduced insulin sensitivity, assessed by euglycemic-hyperinsulinemic clamp technique, and impaired early- but not late-phase insulin secretion, estimated by OGTT-derived indices compared with NGT, whose 1-hour postchallenge glucose is less than 155 mg/dL (NGT-1h-high). When insulin secretion was adjusted for the prevailing degree of insulin sensitivity using the disposition index (insulin sensitivity × insulin secretion), β-cell function was significantly impaired in NGT-1h-high individuals compared with the NGT-1h-low group even after adjusting for age, sex, and BMI. Remarkably, NGT-1h-high individuals have a significantly lower insulin sensitivity and impaired β-cell function compared with subjects with isolated IFG defined by ADA criteria, but not compared with subjects with IGT. These differences between isolated IFG and NGT-1h-high individuals were not observed when subjects were stratified according to the WHO criteria of glucose tolerance. The idea that hyperglycemia at 1 hour during an OGTT may be a useful tool to identify a subgroup of subjects with reduced insulin sensitivity and β-cell dysfunction is consistent with previous studies in adults (20, 27, 30). However, these studies have focused on the comparison between NGT (1h-low or 1h-high) and IGT. Our study is unique in that we have compared the metabolic characteristics of subjects with NGT-1h-high with those of subjects with isolated IFG in addition to the IGT group.

Our analysis of longitudinal data from the CATAMERI study showed that subjects with NGT-1h-high, who would otherwise be considered as a group at low risk of type 2 diabetes by current definitions (9) have an increased risk of developing type 2 diabetes. In fact, although as a whole individuals with NGT had a relatively low incidence rate of type 2 diabetes (6.4%),

subjects with NGT-1h-high exhibited a significantly higher incidence rate of type 2 diabetes (16.7%) compared with subjects with NGT-1h-low (2.9%) (P = .001). More importantly, individuals with NGT-1h-high have a significantly higher risk of developing type 2 diabetes compared with subjects with isolated IFG, but a lower risk compared with IGT individual. Interestingly, when isolated IFG individuals were further divided into two subgroups (isolated IFG-1h-low and isolated IFG-1h-high) based upon their 1-hour plasma glucose concentration (below or above 155 mg/dL, respectively), a tendency toward a higher HR was observed in subjects with isolated IFG-1h-high.

Overall, these results are consistent with those of two longitudinal studies in Mexican-American (13) and Scandinavian Caucasian (15) populations and with a retrospective study carried out in Asian Indians (14). Accordingly, a recent study, which compared the separate and combined performance of 14 OGTT glucose–derived indices in incident type 2 diabetes prediction using the date of the Botnia and Malmö Prevention Project longitudinal studies, has shown that, of all the OGTT indices analyzed, 1-hour postload glucose and total $AUC_{glucose}$ were the best single predictors of future type 2 diabetes (31). Taken together, the present and previous results suggest that 1-hour glucose concentration at least 155 mg/dL during an OGTT may identify a subgroup of NGT individuals at increased risk for developing type 2 diabetes, likely due to decreased insulin sensitivity and β-cell dysfunction. This dysglycemic subgroup is distinct from individuals with isolated IFG or IGT.

The concept that 1-hour hyperglycemia is a useful tool to identify individuals with metabolic derangements is well accepted for the screening of gestational diabetes mellitus (9); however, further prospective studies recruiting larger cohorts followed over longer periods of time are needed to conclusively test the utility of 1-hour glucose concentrations to predict the development of type 2 diabetes. Clinical trials have convincingly demonstrated that lifestyle interventions decrease the incidence of type 2 diabetes in high-risk subjects (32). Most studies have recruited individuals with IGT to test the efficacy of interventions aimed at preventing or delaying the development of type 2 diabetes. The only study aimed at demonstrating the effect of intensive lifestyle modification on prevention of type 2 diabetes in a Japanese cohort of subjects with IFG showed that individuals with isolated IFG did not benefit from lifestyle intervention (33). The reason for these unexpected findings remained unclear. However, it is interesting to note that subgroup analyses showed that lifestyle modifications were effective in isolated IFG individuals with FPG at least 110 mg/dL, but not in the isolated IFG group with FPG no greater than 110 mg/dL, suggesting that the difference in the efficacy of lifestyle changes on type 2 diabetes prevention might be related to the presence of more pronounced derangements in insulin sensitivity and secretion (33). Whether individuals with NGT-1h-high may benefit from lifestyle (and possibly pharmacological) interventions analogously to subjects with IGT is unknown, but it is highly plausible.

Our study has several strengths including the combination of a cross-sectional and a longitudinal design, the recruitment of both men and women, the collection of data by a trained staff, following a standardized protocol, the assays of insulin performed in a centralized laboratory in fresh blood samples rather than in stored samples, and the use of state-of-the-art techniques for assessment of insulin sensitivity. Nevertheless, the present study has some limitations that should be considered. First, we analyzed the data on the basis of a single OGTT at baseline. Although such an approach is common in clinical practice, intra-individual variation in glucose levels cannot be taken into account, and some participants might have been misclassified. The euglycemic clamp was done without tracers; therefore, hepatic glucose output during the clamp was not assessed. Moreover, it can be debated that results of cross-sectional derived from the EUGENE2 study might have been biased by the presence of a family history of diabetes. However, type 2 diabetes has a strong genetic component, and many individuals who develop the disease have a family history of diabetes. Finally, the present results are based on white individuals, and generalizing them to other ethnic groups should be done with cautiousness because differences in the risk of type 2 diabetes have been reported among different ethnic groups. Nonetheless, an increased risk for future type 2 diabetes in individuals with NGT and 1-hour postload glucose at least 155 mg/dL (8.6 mmol/l) has been observed in Mexican-American (13), Scandinavian Caucasian (14), and Asian Indian populations (15), suggesting that 1-hour hyperglycemia during an OGTT is a useful tool to identify subjects at risk for future type 2 diabetes across racial/ethnic groups.

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