

Limited Overlap Between Intermediate Hyperglycemia as Defined by A1C 5.7–6.4%, Impaired Fasting Glucose, and Impaired Glucose Tolerance

TUULA SAUKKONEN, MD^{1,2}
HENNA CEDERBERG, MD¹
JARI JOKELAINEN, MSc^{1,3}
MAURI LAAKSO, MD^{1,3}

PIRJO HÄRKÖNEN, MNSC⁴
SIRKKA KEINÄNEN-KIUKAANNIEMI, MD, PHD^{1,3,5}
ULLA RAJALA, MD, PHD¹

RESEARCH DESIGN AND METHODS

—Between 1996 and 1998, 593 subjects (245 men, 348 women) born in 1935 were enrolled a longer follow-up study evaluating IH among inhabitants of Oulu, Finland (5,6). The study excluded 87 participants with previously known or screen-detected diabetes according to OGTT or A1C $\geq 6.5\%$, leaving 486 with complete data for analysis in the present report (5). The study protocol was approved by the ethics committee of the Faculty of Medicine, University of Oulu, Finland. Clinical data collection and anthropometric and glucose measurements are described in detail elsewhere (5,6).

Standardized 75-g OGTT was performed according contemporary World Health Organization guidelines with fasting whole-blood glucose and 2-h glucose from a capillary sample (7,8). A1C was analyzed with the Bayer DCA 2000 Analyzer (Bayer Healthcare, Tarrytown, NY), calibrated to the Diabetes Control and Complications Trial standard (9).

IH was classified as IFG (fasting blood glucose 5.6–6.0 mmol/L), IGT (2-h glucose ≥ 7.8 and < 11.1 mmol/L), and elevated A1C (5.7–6.4%) (1,7,8). Isolated forms of IH are referred to as i-IGT, i-IFG, and i-A1C 5.7–6.4%.

Differences in continuous variables were analyzed with two-way ANOVA and Kruskal-Wallis, as appropriate, and *P* values were adjusted for sex. Values of *P* < 0.05 were considered statistically significant. SAS software (SAS Institute, Cary, NC) was used for statistical analysis.

RESULTS—Characteristics of the participants have been presented previously (5). Prevalence of IH (IFG, IGT, or A1C 5.7–6.4%) was 34% (*n* = 165). Prevalences of i-A1C 5.7–6.4%, i-IGT, and i-IFG were 8.0, 13.2, and 4.5%, respectively. Overlap between these three markers was limited. Only 5 individuals (1%) fulfilled all three criteria (IFG, IGT, and A1C 5.7–6.4%), and 9 (2%), 8 (2%), and 17 (4%) subjects were included in the combination

OBJECTIVE—We compared the prevalences and overlap between intermediate hyperglycemia (IH), defined by a hemoglobin A_{1c} (A1C) 5.7–6.4%, impaired fasting glucose (IFG), and impaired glucose tolerance (IGT).

RESEARCH DESIGN AND METHODS—Oral glucose tolerance test results and A1C measurements were evaluated as markers of IH in an unselected cohort of 486 nondiabetic adults from Finland.

RESULTS—The overall prevalence of IH was 34%. Prevalences of isolated A1C 5.7–6.4%, IGT, and IFG were 8.0, 13.2, and 4.5%, respectively. Overlap between these three markers was uncommon. Isolated A1C 5.7–6.4% was associated with a higher BMI compared with isolated IFG and IGT and with a more adverse lipid profile compared with isolated IFG.

CONCLUSIONS—Prevalence of isolated IH was high, with limited overlap between the definitions. Differences in cardiovascular disease risk factors were observed among the groups. This study demonstrates that an A1C of 5.7–6.4% detects, in part, different individuals with IH compared with IFG and IGT.

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Hemoglobin A_{1c} (A1C) at a range of 5.7–6.4% was proposed as an indicator of increased risk for type 2 diabetes (1) in addition to the currently used criteria of intermediate hyperglycemia (IH) as follows: impaired fasting glucose (IFG) and impaired glucose tolerance (IGT).

The use of A1C in a nondiabetic range may detect a different prevalence of IH compared with IFG or IGT (2). However, the degree of overlap between these markers is not well reported. Recent studies from diabetic populations have yielded conflicting data regarding differences in cardiovascular disease (CVD) risk factor profiles among those diagnosed by A1C $\geq 6.5\%$

and oral glucose tolerance test (OGTT) (3,4). Studies comparing CVD risk factor profiles among individuals with IH diagnosed by A1C 5.7–6.4% and OGTT are lacking.

We hypothesized that these three different markers of IH, in part, detect different individuals and that individuals with A1C 5.7–6.4% would be characterized by a more unfavorable CVD risk profile than individuals diagnosed by OGTT. To this aim, we conducted a population-based observational study to compare 1) diagnosis of IH based on A1C 5.7–6.4% with OGTT and 2) differences in CVD risk factors among the three groups.

From the ¹Institute of Health Sciences, Faculty of Medicine, University of Oulu, Oulu, Finland; the ²Oulu Occupational Health Centre, Hallituskatu, Oulu, Finland; the ³Unit of General Practice, Oulu University Hospital, Oulu, Finland; the ⁴Oulu Deaconess Institute/Diapolis Oy Research Unit, Oulu, Finland; and the ⁵Oulu Health Centre, Diabetes Unit, Saaristonkatu, Oulu, Finland.

Corresponding author: Tuula Saukkonen, tuula.saukkonen@oulu.fi.
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Table 1—Cardiovascular risk factors of participants with i-A1C 5.7–6.4%, i-IFG, i-IGT, and normoglycemia

Variable	i-A1C 5.7–6.4%	i-IFG	i-IGT	NG	P value*		
	n = 39	n = 22	n = 64	n = 322	i-A1C vs. i-IFG	i-A1C vs. i-IGT	i-IGT vs. i-IFG
Women	56.4	45.5	60.9	61.5			
BMI (kg/m ²)	29.7 (5.97)	27.5 (3.00)	27.9 (4.01)	27.1 (3.61)	0.034	0.022	0.686
Waist (cm)	94.6 (13.9)	91.5 (10.3)	89.6 (12.0)	86.9 (11.6)	0.164	0.056	0.995
BP (mmHg)							
Systolic	136 (16.9)	145 (23.2)	145 (18.4)	141 (16.0)	0.071	0.020	0.954
Diastolic	77.1 (6.69)	79.5 (9.17)	80.1 (5.89)	78.6 (8.03)	0.290	0.067	0.727
Triglycerides (mmol/L)	1.38 (1.2–1.98)	1.17 (0.76–1.64)	1.34 (1–1.62)	1.12 (0.88–1.5)	0.008	0.183	0.073
Cholesterol (mmol/L)							
HDL	1.33 (0.31)	1.54 (0.38)	1.45 (0.40)	1.53 (0.38)	0.010	0.168	0.096
LDL	4.01 (0.65)	3.74 (0.73)	3.73 (0.88)	3.72 (0.80)	0.233	0.055	0.771
Total	5.21 (0.94)	5.34 (0.89)	5.12 (1.02)	5.28 (0.99)	0.542	0.679	0.313
A1C (%)	5.8 (5.8–6)	5.2 (5.1–5.4)	5.35 (5.1–5.5)	5.2 (5–5.4)	<0.0001	<0.0001	0.215
FG (mmol/L)	5.1 (4.8–5.3)	5.7 (5.6–5.8)	4.8 (4.65–5.2)	4.8 (4.5–5.1)	<0.0001	0.066	<0.0001
2-h Glucose (mmol/L)	6.5 (5.8–7.3)	6.5 (5.6–7.2)	8.5 (8–9.4)	6.2 (5.6–6.9)	0.955	<0.0001	<0.0001

Data are presented as medians (interquartile range) and means (SD). BP, blood pressure; FG, fasting glucose; NG, normoglycemia. *P values are adjusted for sex.

of IFG/IGT, IFG/A1C 5.7–6.4%, and IGT/A1C 5.7–6.4%, respectively.

Mean BMI was higher in subjects with i-A1C 5.7–6.4% (29.7 kg/m²) compared with i-IFG (27.5 kg/m², $P = 0.034$) and i-IGT (27.9 kg/m², $P = 0.022$; Table 1). A trend was observed for higher waist circumference in the i-A1C 5.7–6.4% group compared with i-IGT (94.6 vs. 89.6 cm, $P = 0.056$).

Systolic blood pressure was lower in i-A1C 5.7–6.4% than in the i-IFG (136 vs. 145 mmHg, $P = 0.071$) and i-IGT (136 vs. 145 mmHg, $P = 0.020$) groups. Only 30.8% of subjects with i-A1C 5.7–6.4% were taking antihypertensive medication, compared with 48.4% in the i-IGT and 31.8% in the i-IFG groups. Values for HDL cholesterol were lower ($P = 0.010$) and triglycerides were higher ($P = 0.008$) in the i-A1C 5.7–6.4% group compared with the i-IFG group.

CONCLUSIONS—Comparison of the prevalences of IH as diagnosed by A1C 5.7–6.4%, IFG, and IGT, showed that isolated forms of prediabetes are common at the population level. Differences in CVD risk factors were observed between the i-A1C, i-IFG, and i-IGT groups. Individuals with A1C 5.7–6.4% with normal OGTT were characterized by higher BMI, central obesity, and a more adverse lipid profile.

The comparability of A1C 5.7–6.4% with IFG and IGT as a marker of IH, particularly regarding associated CVD risk factors, is not well known (10). Data from previous studies using A1C and

OGTT for the diagnosis of type 2 diabetes have been controversial regarding cardiovascular risk profile (3,4). In the Telde Study, Spanish subjects diagnosed with A1C were characterized by a higher BMI and waist circumference and lower levels of HDL cholesterol compared with the OGTT group (4). In contrast, in the Danish Inter99 study population, with a high prevalence of male smokers, individuals with A1C-defined diabetes were leaner and had a higher prevalence of lipid abnormalities compared with the OGTT group (3). Our results are in agreement with those of the Telde Study, showing that individuals classified with a prediabetic A1C of 5.7–6.4% were characterized by higher BMI, waist circumference, and triglycerides and lower HDL cholesterol levels. Further studies in different populations are required to evaluate the finding that the different markers seem to identify in part different individuals.

The advantage of using A1C is less day-to-day variability compared with OGTT. The 2-h glucose levels have higher variability than fasting glucose levels, but both have higher variability than A1C (11,12). The day-to-day variability of the OGTT is a limitation that must be considered when interpreting these results, because OGTT was performed only once in this epidemiological study.

Our study has several strengths. It was performed in an unselected nondiabetic population. We showed that differences in CVD risk profiles of type 2 diabetes are already present in the prediabetic stages of A1C 5.7–6.4%, IFG,

and IGT. The study is limited because the OGTT was performed only once, and capillary samples were used for the 2-h glucose measurement, which may have given slightly higher values than venous plasma samples (7,8,13); however, this effect at the population level is marginal. Findings from our study are also limited to an aging white population.

In conclusion, one in three participants in this population had a form of IH, with limited overlap between the three current definitions. Individuals with IH diagnosed by A1C 5.7–6.4% were characterized by higher BMI, central obesity, and a more adverse lipid profile compared with the OGTT groups.

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