The Natural History of Insulin Sensitivity and Insulin Secretion in the Progression from Normal Glucose Tolerance to Impaired Fasting Glycemia and Impaired Glucose Tolerance – The Inter99 study

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Objective The aim of this study was to describe the natural history of insulin secretion and insulin sensitivity in the development of isolated impaired fasting glycemia (i-IFG), isolated impaired glucose tolerance (i-IGT), and combined IFG/IGT.

Research design and methods Baseline and five-year follow-up data from the Inter99 study were used. Individuals with normal glucose tolerance (NGT) at baseline and i-IFG, i-IGT, combined IFG/IGT or NGT at the five-year follow-up were examined with an OGTT (n=3,145). Insulin sensitivity index (ISI), homeostasis model assessment of insulin sensitivity (HOMA-IS), early-phase insulin release (EPIR), and insulin secretion relative to insulin action (disposition index, DI) were estimated.

Results Five years prior to the pre-diabetic diagnoses (i-IFG, i-IGT and IFG/IGT), ISI, HOMA-IS, EPIR, and DI were lower than in individuals who remained NGT. During the five-year follow-up, individuals developing i-IFG only experienced a significant decline in HOMA-IS, whereas individuals developing i-IGT experienced significant declines in ISI, EPIR, and DI. IFG/IGT individuals exhibited pronounced defects in ISI, HOMA-IS, EPIR, and DI during the five-year follow-up.

Conclusions A stationary reduced insulin secretion followed by a decline in hepatic insulin sensitivity characterizes the transition from NGT to i-IFG. In contrast, low whole-body insulin sensitivity with a secondary lack of beta cell compensation is associated with the development of i-IGT. Thereby, i-IFG and i-IGT appear to result from different underlying mechanisms, which may have implications for the prevention and treatment of the diabetes that succeeds them.

Abbreviations DI, disposition index; FPG, fasting plasma glucose; EPIR, early-phase insulin release; HOMA-IS, homeostasis model assessment of insulin sensitivity; i-IFG, isolated impaired fasting glycemia; i-IGT, isolated impaired glucose tolerance; ISI, insulin sensitivity index; NGT, normal glucose tolerance; 2 h PG, 2 h plasma glucose.
During the past years, it has been established that the pre-diabetic conditions of isolated impaired fasting glycemia (i-IFG), isolated impaired glucose tolerance (i-IGT) and combined fasting and post-challenge hyperglycemia (IFG/IGT) represent distinct pathways to diabetes. These pre-diabetic states are characterized by different degrees of insulin sensitivity, insulin secretion, hepatic glucose output as well as secretion of glucagon and incretin hormones (1-8). Nevertheless, the primary abnormalities inherent in the different pre-diabetic conditions are still unknown.

Randomized trials have shown beneficial effects of lifestyle intervention on diabetes risk in individuals with i-IGT and IFG/IGT (9,10), but whether lifestyle interventions have the same preventive effects in individuals with i-IFG is not known. Indeed, a more profound insight into the pathogenesis of the disease is needed to optimize prevention and treatment of type 2 diabetes. Especially, focus on the initial defects responsible for hyperglycemia in the fasting and post-challenge state is essential for interrupting the progression from normal to abnormal glucose metabolism.

Most previous studies have examined the pathophysiology of pre-diabetes in cross-sectional settings without knowing the time of onset of glycemic abnormalities. However, the observed abnormalities in pre-diabetes may be related to traits already apparent in the normoglycemic state. Prospective studies are therefore needed to clarify whether this is the case or whether the metabolic abnormalities associated with i-IFG, i-IGT and IFG/IGT develop simultaneously with the increases in fasting and/or post-challenge plasma glucose levels.

The aim of this study was to describe the natural history of insulin sensitivity and insulin secretion during the progression from normal glucose tolerance (NGT) to the pre-diabetic states of isolated impaired fasting glycemia (i-IFG), isolated impaired glucose tolerance (i-IGT), and combined IFG/IGT.

**RESEARCH DESIGN AND METHODS**

**Study population:** Individuals from the Danish, population-based study Inter99 (11) were used as study population. The Inter99 study is a five-year non-pharmacological intervention study aiming at reducing the incidence of ischemic heart disease and type 2 diabetes in the Danish population.

All individuals were invited to a screening program at the Research Center for Prevention and Health in Glostrup in 1999-2001. The initial participation rate in the Inter99 study was 52.5% (n = 6,784). After 5 years, all eligible 6,784 individuals were re-invited to a health examination. A total of 4,735 individuals were classified with NGT at baseline, and 68.2% of these (n = 3,229) attended the five-year follow-up examination. Individuals with diabetes at the five-year follow-up (n = 42) or with incomplete measures of fasting plasma glucose (FPG) and 2 h PG (n = 42) were excluded, leaving 3,145 individuals with baseline and five-year follow-up data for analysis.

All participants gave a written consent before taking part in the Inter99 study. The protocol was in accordance with the Helsinki declaration and approved by the local ethical committee (KA 98 155) and registered with ClinicalTrials.gov (reg. no.: NCT00289237). The Inter99 study is described in detail elsewhere (11,12).

**Glucose tolerance status:** After an overnight fast, the participants had a standard 75-g OGTT. Venous samples for measurement of plasma glucose and serum insulin concentrations were taken prior to glucose ingestion, and after 30 and 120 minutes. Glucose was analyzed using the hexokinase/G6P-DH technique (Boehringer Mannheim, Germany) and insulin was
analyzed with fluoro-immunoassay technique (AutoDELFIA, Perkin Elmer-Wallac, Turku, Finland). The participants were classified into categories of glucose tolerance according to the WHO 1999 criteria (13).

**Data collection:** Self-administered general questionnaires were completed before the participants’ first visit to the research center. Family history of diabetes was assessed by asking questions about parents’ and siblings’ history of diabetes. An estimate of physical activity in minutes per week was obtained by combining answers of commuting and leisure time physical activity (14). Smoking status was categorized into daily smokers, occasional smokers, previous smokers and never smokers. A 48-item food-frequency questionnaire was used to assess the participants’ dietary habits. Based on the participants’ intake of vegetables, fruit, fish, and fat, a dietary quality score ranging from one (unhealthy dietary habits) to nine (healthy dietary habits) was developed (15). Measurement of waist circumference was taken to the nearest 0.5 cm half way between the lowest point of the costal margin and highest point of the iliac crest.

**Lifestyle intervention:** All participants received individual lifestyle counseling with a doctor, including a risk assessment based on age, gender, total and HDL cholesterol, systolic blood pressure, smoking, BMI, known diabetes, family predisposition and previous heart disease (16). Individuals at high risk of developing ischemic heart disease were offered a low- or high-intensity lifestyle intervention at baseline. Individuals in the high-intensity intervention group were offered participation in group meetings with a clinical dietician. The meetings aimed at increasing the participants’ knowledge on the importance of smoking, diet and physical activity in the prevention of type 2 diabetes and cardiovascular diseases. Participants in the low-intensity intervention group were only referred to their general practitioner. The randomization and intervention is described in detail elsewhere (11,12). A three-class variable based on the risk and intervention status (low-risk/no intervention, high-risk/low-intensity intervention and high-risk/high-intensity intervention) was together with changes in different lifestyle factors included in the present analyses to adjust for a potential effect of the intervention.

**Calculations:** Insulin sensitivity was estimated by use of the insulin sensitivity index (ISI), which is based on plasma glucose and insulin measurements during OGTTs as well as information on body weight (17). The ISI correlates relatively well with the M-value from a euglycemic, hyperinsulinemic clamp (17). HOMA-IS (1/HOMA-IR) was also calculated (18). Early-phase insulin release (EPIR), which correlates with 1st phase insulin release measured during a hyperglycemic, hyperinsulinemic clamp, was estimated from fasting insulin, 30 min insulin and 30 min plasma glucose levels (19). An estimate of disposition index (DI) was calculated by multiplying ISI with EPIR. Hence, DI reflects the ability of the beta cell to compensate for insulin resistance. When ISI was plotted against EPIR, the data points approximated a hyperbolic curve, suggesting that the DI may be a good surrogate measure of beta cell function.

**Statistical methods:** The study population was divided into 4 groups of glucose tolerance based on the classification at the five-year follow up: 1) NGT, 2) incident i-IFG, 3) incident i-IGT and 4) incident IFG/IGT. Estimates of ISI, HOMA-IS, EPIR, and DI were compared among the four groups prior to the diagnosis (baseline, all had NGT) and at the time of diagnosis (five-year follow-up) by use of Wald test from multiple linear regression models. Changes in metabolic characteristics during the five-year follow-up ($\Delta =$ five-year follow-up minus baseline) were also analyzed in
multiple linear regression models. Serum insulin levels, HOMA-IS, ISI, and DI were non-normally distributed, and therefore log-transformed before analysis. SAS version 9.1 (SAS Institute, Cary, USA) was used for statistical analysis.

Even though a relatively large number of statistical comparisons are performed in this study, we have not used \( p \) corrections, since the majority of the tests are pre-defined. Thus, some of the borderline and weakly significant findings may be related to non-causal associations, and should be interpreted with some caution.

**RESULTS**

**Prior to the pre-diabetic diagnosis (baseline):** Five years prior to the development of pre-diabetes, several characteristics differed between the groups (Table 1). The proportion of men and individuals with a family history of diabetes was highest in the groups who later developed i-IFG and IFG/IGT. Physical activity was lower in those who later developed i-IGT, and dietary quality score was lower in all groups progressing to pre-diabetes, but only significant in those with subsequent i-IGT. At baseline, plasma glucose and insulin levels were higher, and ISI, HOMA-IS, EPIR and DI were lower in individuals who progressed to i-IFG, i-IGT or IFG/IGT than in those who maintained NGT status. Those who later progressed to i-IGT had lower baseline ISI than those who subsequently developed i-IFG. In contrast, baseline EPIR was slightly but significantly lower in those with subsequent i-IFG and IFG/IGT than in those who later developed i-IGT (Table 1).

High-intensity lifestyle intervention was offered to 36.6% of those who maintained NGT status, 50.6% of those who developed i-IFG, 39.1% of those who developed i-IGT, and 46.4% of those who developed IFG/IGT (\( p<0.05 \) for i-IFG vs. NGT).

**Time of pre-diabetic diagnosis (five-year follow-up):** At the five-year examination, ISI, HOMA-IS, EPIR and DI were still low in all three pre-diabetic groups (Table 2). However, ISI was lower in those with i-IGT and IFG/IGT compared with i-IFG individuals, whereas HOMA-IS was lower in those with i-IFG and IFG/IGT than in i-IGT individuals. EPIR was equally low in individuals with i-IFG and i-IGT, but lower in those with IFG/IGT. Disposition index was lower in those with i-IGT and IFG/IGT than in individuals with i-IFG.

Cross-sectional data of all individuals with NGT, i-IFG, i-IGT and IFG/IGT at baseline in the Inter99 study (\( n = 6,006 \)) showed the same pattern of insulin sensitivity and insulin secretion (see Table A1 in the online appendix available at [http://care.diabetesjournals.org](http://care.diabetesjournals.org)).

**Transition from normal to abnormal glucose regulation (five-year changes):** During the five-year follow-up, different changes in insulin secretion and action were observed in the groups developing i-IFG, i-IGT and IFG/IGT compared with those who maintained NGT status (Figure 1). ISI decreased significantly in individuals progressing to i-IGT and IFG/IGT, but not in those who developed i-IFG even though ISI tended to fall (\( p=0.227 \) vs. NGT). In contrast, HOMA-IS decreased significantly in individuals with i-IFG and IFG/IGT, but not in those with i-IGT (\( p=0.851 \) vs. NGT). A minor but significant decline in EPIR was observed for i-IGT individuals compared with NGT individuals (\( p<0.001 \)). The change in EPIR did not differ between the other pre-diabetic groups and the NGT group (\( p \geq 0.154 \) for all other comparisons), even though EPIR seemed to increase in the IFG/IGT group during the five-year follow-up (\( p=0.393 \) vs. NGT). However, DI decreased significantly in individuals who progressed to i-IGT and IFG/IGT and tended to decrease in those who developed i-IFG (\( p=0.066 \); Figure 1).
CONCLUSIONS

This study is the first to report abnormalities in insulin secretion and insulin sensitivity prior to the development of i-IFG, i-IGT and IFG/IGT. We found that different disturbances of insulin sensitivity, absolute insulin secretion and disposition index were apparent five years before the pre-diabetic states of i-IFG, i-IGT and IFG/IGT were breached. These findings support the view that i-IFG and i-IGT represent two distinct pathologic mechanisms.

**Progression from NGT to i-IFG:**

Absolute and relative insulin secretion (EPIR and DI) was significantly impaired in normoglycemic individuals who subsequently progressed to i-IFG, but during the development of i-IFG, EPIR and DI did not decrease further, indicating that a progressive loss of the ability to secrete sufficient amounts of insulin is not a major feature in the early states of fasting hyperglycemia. Instead, an underlying more stationary beta cell failure seems to be present in these individuals. Reduced absolute and/or relative insulin secretion has previously been demonstrated in i-IFG individuals (1,2,5,6,20). However, all these studies were cross-sectional, and they were therefore not able to detect whether this feature occurred concomitantly with the development of hyperglycemia, or whether it was manifest years before overt hyperglycemia was present. In this particular study, family history of diabetes was significantly more prevalent in individuals with i-IFG than in those with NGT. This could indicate a role for genetics in the development of i-IFG, which should be examined in future studies.

Prior to the development of i-IFG and at time of diagnosis, ISI was significantly reduced compared to NGT individuals, but ISI did not change significantly during the development of i-IFG. The finding of reduced insulin sensitivity contrasts recent observations in a smaller sub-sample of the Inter99 population studied with euglycemic, hyperinsulinemic clamp technique (1). Also other studies using the euglycemic, hyperinsulinemic clamp technique have reported normal peripheral insulin sensitivity in i-IFG individuals (1,4,6,7), whereas only few studies reported low insulin sensitivity (2,3). Accordingly, the observed low insulin sensitivity in individuals with i-IFG may indicate that estimates of insulin sensitivity derived from OGTTs are not as precise as measures obtained from gold standards like the euglycemic, hyperinsulinemic clamp technique. The clamp technique provides estimates of predominantly peripheral (muscle) insulin action and only to a lesser extent hepatic insulin action. Whether estimates based on glucose and insulin levels during OGTTs also reflect mainly peripheral insulin sensitivity needs to be addressed in future studies. HOMA-IS is based on fasting glucose and insulin levels, and therefore is assumed to reflect hepatic insulin sensitivity (5). The pre-diabetic state i-IFG therefore appears to be caused by stationary abnormalities in beta cell function in combination with a progressive decline in hepatic insulin sensitivity.

In the present study, the proportion of men was 65% higher in the i-IFG group compared to the NGT group. A higher prevalence of i-IFG in men has previously been reported by others (8,20,21). Since men in general have lower serum insulin levels than women (20), the different gender distributions in the i-IFG and i-IGT groups may have contributed to some of the observed differences in insulin secretion between the groups. Further studies are needed to clarify the impact of gender differences on the pathophysiology of i-IFG and i-IGT.

**Progression from NGT to i-IGT:**

Five years prior to the i-IGT diagnosis, EPIR was not significantly different from those who maintained NGT status. However, during the
development of i-IGT, small but significant declines in EPIR and DI were observed. This indicates that a progressive – and thereby age-dependent – loss of insulin secretion is involved in the development of post-challenge hyperglycemia. Indeed, age-dependent loss of insulin secretion is a well established feature of overt type 2 diabetes as documented in the U.K. Prospective Diabetes Study (22). The present data indicate that this feature may be more central to patients who have developed type 2 diabetes via i-IGT as compared with via i-IFG, but this remains to be shown in prospective studies including patients with overt type 2 diabetes studied before and after the diabetes diagnosis.

Numerous cross-sectional studies found that i-IGT individuals are insulin resistant (1-7). In this study, we take this finding a step further by documenting that low insulin sensitivity is present already five years prior to the demonstration of i-IGT. The progressive decline of insulin secretion therefore seems to be secondary to the low insulin sensitivity, and thus represent an inadequate compensatory insulin secretory response. This primary decline in insulin sensitivity could be caused by an adverse lifestyle, as indicated by the lower level of physical activity and dietary quality compared to NGT individuals. However, also genetic factors or in utero pre-programmed abnormalities could have contributed.

Progression from NGT to IFG/IGT: Not surprisingly, the IFG/IGT phenotype was characterized by the same defects in insulin sensitivity as those who developed i-IFG (decline in HOMA-IS) and i-IGT (decline in ISI). Interestingly, EPIR tended to increase during the development of IFG/IGT. This finding supports the notion that modest increases in plasma glucose levels may induce beta cell proliferation and survival, while prolonged exposure to significant elevations in plasma glucose levels can cause impaired beta cell proliferation and increased beta cell failure and apoptosis (23). Based on our observations, we suggest that some of the mechanisms leading to an early compensatory increase in beta cell function may be initiated by elevated fasting plasma glucose (i-IFG and IFG/IGT) but not by postprandial plasma glucose levels (i-IGT). In that respect, it was of interest that individuals who developed IFG/IGT had more characteristics in common with those who developed i-IFG as compared to those who developed i-IGT (e.g. gender distribution and family history of diabetes). We therefore suggest that individuals with elevated 2-h plasma glucose levels should be separated into an i-IGT and an IFG/IGT group instead of being classified in one group of IGT individuals as currently suggested by the WHO (13).

Study limitations: Our estimates of insulin secretion and insulin sensitivity were based on OGTTs, and therefore may correlate with the classification of the pre-diabetic groups. Also it should be noted that disposition indices based on estimates of insulin secretion and insulin sensitivity derived from the same test (e.g. an OGTT) may not be as solid and reliable as disposition indices based on independent tests. Ideally, estimates of insulin secretion and action should be based on gold standards like the glucose clamp technique. However, this is not feasible in large-scale epidemiological studies, and we believe that proxy measures are reliable with large data sets such as in this study. However, caution should be taken when comparing estimates of insulin secretion based on intravenous versus oral glucose tolerance tests. In particular, the gut incretin hormones glucagon-like-peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) may influence the results, since the secretion of these hormones seems to differ significantly between individuals with different types of pre-diabetes (1).

The classification of glucose tolerance status was based on single OGTTs.
Accordingly, it is likely that some individuals may have been misclassified due to normal day-to-day variation in plasma glucose. Also, the intra-individual variation in serum insulin levels is large (24), affecting the estimates of insulin secretion and action. Small changes in the estimates would therefore be expected if the same measurements were repeated on a separate day.

In general, the changes in insulin secretion and insulin sensitivity during the five-year follow-up were relatively small. However, since even small changes in plasma glucose and insulin levels may have consequences for glucose homeostasis, we believe our findings are biologically relevant. Nevertheless, the biological significance of such small disturbances needs to be clarified in other studies.

Finally, it is possible that individuals who participated in group lifestyle counseling (high-intensity intervention) may have changed their physical activity level, smoking status, diet, and body composition more than those who were not included in the high-intensity intervention during the five-year follow-up. However, by adjusting for intervention status as well as for changes in body composition and lifestyle factors, we believe that our results are reliable and can be generalized to other white Caucasian populations.

In summary, this study showed that impairments in glucose metabolism occur many years before it is possible to classify individuals as abnormally hyperglycemic either in the fasting or post-challenge state. Hyperglycemia in the fasting state (i-IFG) seems primarily to be caused by an inherent insulin secretory dysfunction followed by a decline in hepatic insulin sensitivity. In contrast, the development of post-challenge hyperglycemia (i-IGT) mainly seems to be caused by low whole-body insulin sensitivity followed by a progressive decline in beta cell function, indicating a loss of beta cell compensation.

This study supports the notion that the pre-diabetic states i-IFG and i-IGT may have different etiological and pathophysiological origins, which in turn may have implications for future prevention and treatment of overt type 2 diabetes.

ACKNOWLEDGMENTS

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Disclosure: K. Borh-Johansen is head of the Steno Diabetes Center, a hospital integrated in the Danish National Healthcare Service, but owned by Novo Nordisk. K. Borh-Johansen holds shares in Novo Nordisk Inc. The other authors declare that they have no duality of interest associated with this manuscript.
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Figure legend

Figure 1 Baseline and five-year values of insulin sensitivity index (A), homeostasis model assessment of insulin sensitivity (B), early-phase insulin release (C), and disposition index (D) in 3,145 individuals developing i-IFG (square), i-IGT (triangle) or IFG/IGT (circle), or maintaining NGT status (diamond). Data are presented as medians. P values for differences in changes (five-year minus baseline) between groups are adjusted for age, gender, family history of diabetes, risk/intervention group as well as changes in BMI, smoking, physical activity, and dietary quality during the five years of follow-up. Wald test from linear models: a) i-IFG vs. NGT, b) i-IGT vs. NGT, c) IFG/IGT vs. NGT, d) i-IGT vs i-IFG, e) IFG/IGT vs. i-IFG, f) IFG/IGT vs. i-IGT.
Table 1 Characteristics of individuals with NGT prior to the development of i-IFG, i-IGT or IFG/IGT or maintenance of NGT status (baseline, n = 3,145).

<table>
<thead>
<tr>
<th></th>
<th>NGT → NGT</th>
<th>NGT → i-IFG</th>
<th>NGT → i-IGT</th>
<th>NGT → IFG/IGT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 2,842)</td>
<td>(n = 83)</td>
<td>(n = 192)</td>
<td>(n = 28)</td>
</tr>
<tr>
<td>Male (%)</td>
<td>46.8 (45.0-48.7)</td>
<td>77.1 (66.6-85.6)</td>
<td>53.1 (45.8-60.3)</td>
<td>67.9 (47.6-84.1)</td>
</tr>
<tr>
<td>Family history of diabetes (%)</td>
<td>14.4 (13.2-15.8)</td>
<td>22.9 (14.4-33.4)</td>
<td>18.2 (13.0-24.4)</td>
<td>39.3 (21.5;59.4)</td>
</tr>
<tr>
<td>Age (years)</td>
<td>45.4 (45.2;45.7)</td>
<td>48.6 (47.0;50.2)</td>
<td>47.7 (46.6;48.7)</td>
<td>49.0 (46.2;51.8)</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>25.2 (25.1;25.3)</td>
<td>27.2 (26.4;28.1)</td>
<td>26.4 (25.9;27.0)</td>
<td>28.2 (26.7;29.6)</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>83.4 (82.9;83.8)</td>
<td>92.3 (89.8;94.8)</td>
<td>87.6 (85.9;89.2)</td>
<td>95.4 (91.1;99.7)</td>
</tr>
<tr>
<td>Physical activity (min/week)</td>
<td>305 (299;312)</td>
<td>295 (260;331)</td>
<td>275 (251;298)</td>
<td>336 (276;396)</td>
</tr>
<tr>
<td>Dietary Quality Score (points)</td>
<td>4.08 (4.03;4.14)</td>
<td>3.69 (3.37;4.00)</td>
<td>3.84 (3.63;4.04)</td>
<td>3.64 (3.11;4.17)</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>5.3 (5.3;5.3)</td>
<td>5.7 (5.6;5.8)</td>
<td>5.4 (5.3;5.4)</td>
<td>5.8 (5.6;5.9)</td>
</tr>
<tr>
<td>2 h plasma glucose (mmol/l)</td>
<td>5.4 (5.4;5.5)</td>
<td>5.8 (5.6;6.0)</td>
<td>6.2 (6.0;6.3)</td>
<td>6.4 (6.0;6.8)</td>
</tr>
<tr>
<td>Fasting serum insulin (pmol/l)*</td>
<td>30 (21;43)</td>
<td>38 (26;48)</td>
<td>35 (24;56)</td>
<td>34 (24;59)</td>
</tr>
<tr>
<td>2 h serum insulin (pmol/l)*</td>
<td>131 (83;196)</td>
<td>148 (77;266)</td>
<td>188 (124;284)</td>
<td>161 (86;341)</td>
</tr>
<tr>
<td>Insulin sensitivity index (ISI)*</td>
<td>3.03 (2.96;3.10)</td>
<td>2.62 (2.23;3.02)</td>
<td>2.37 (2.11;2.64)</td>
<td>2.36 (1.67;3.04)</td>
</tr>
<tr>
<td>HOMA-IS*</td>
<td>0.99 (0.67;1.42)</td>
<td>0.74 (0.58;1.08)</td>
<td>0.81 (0.51;1.20)</td>
<td>0.78 (0.48;1.11)</td>
</tr>
<tr>
<td>Early-phase insulin release (EPIR)*</td>
<td>755 (559;973)</td>
<td>637 (449;912)</td>
<td>689 (494;1014)</td>
<td>503 (364;936)</td>
</tr>
<tr>
<td>Disposition index (DI)*</td>
<td>2037 (1464;2728)</td>
<td>1507 (1053;2175)</td>
<td>1586 (1112;2182)</td>
<td>1209 (699;1620)</td>
</tr>
</tbody>
</table>

Data are unadjusted means and proportions (95% CI). *: Unadjusted medians (interquartile range). $P$ values are adjusted for age and gender. $P$ values for BMI were further adjusted for baseline physical activity level. $P$ values for HOMA-IS, ISI, EPIR, and DI were further adjusted for family history of diabetes as well as baseline values of BMI, smoking, physical activity, and dietary quality. HOMA-IS, homeostasis model assessment of insulin sensitivity. Wald test from linear models: a) i-IFG vs. NGT, b) i-IGT vs. NGT, c) IFG/IGT vs. NGT, d) i-IGT vs. i-IFG, e) IFG/IGT vs. i-IFG, f) IFG/IGT vs. i-IGT.
**Table 2** Characteristics of individuals with incident i-IFG, i-IGT, IFG/IGT or NGT (five-year follow-up, n = 3,145).

<table>
<thead>
<tr>
<th></th>
<th>NGT → NGT (n = 2,842)</th>
<th>NGT → i-IFG (n = 83)</th>
<th>NGT → i-IGT (n = 192)</th>
<th>NGT → IFG/IGT (n = 28)</th>
<th>p &lt; 0.05</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI (kg/m²)</td>
<td>25.6 (25.5;25.8)</td>
<td>28.2 (27.4;29.1)</td>
<td>27.4 (26.8;27.9)</td>
<td>29.1 (27.6;30.6)</td>
<td>a, b, c</td>
</tr>
<tr>
<td>Waist circumference (cm)</td>
<td>86.5 (86.1;86.9)</td>
<td>95.9 (93.4;98.5)</td>
<td>91.8 (90.1;93.5)</td>
<td>98.5 (94.1;102.9)</td>
<td>a, b, c, f</td>
</tr>
<tr>
<td>Physical activity (min/week)</td>
<td>301 (296;307)</td>
<td>299 (265;333)</td>
<td>256 (233;279)</td>
<td>309 (250;368)</td>
<td>b</td>
</tr>
<tr>
<td>Dietary Quality Score (points)</td>
<td>4.60 (4.54;4.65)</td>
<td>4.37 (4.06;4.69)</td>
<td>4.25 (4.04;4.46)</td>
<td>4.46 (3.89;5.03)</td>
<td>b</td>
</tr>
<tr>
<td>Fasting plasma glucose (mmol/l)</td>
<td>5.2 (5.2;5.2)</td>
<td>6.4 (6.3;6.6)</td>
<td>5.4 (5.1;5.4)</td>
<td>6.4 (6.2;6.6)</td>
<td>a, b, c, d, f</td>
</tr>
<tr>
<td>2 h plasma glucose (mmol/l)</td>
<td>5.2 (5.2;5.3)</td>
<td>5.8 (5.6;6.0)</td>
<td>8.6 (8.5;8.8)</td>
<td>8.5 (8.1;8.9)</td>
<td>a, b, c, d, e</td>
</tr>
<tr>
<td>Fasting serum insulin (pmol/l)*</td>
<td>27 (20;39)</td>
<td>48 (34;67)</td>
<td>37 (25;54)</td>
<td>56 (37;91)</td>
<td>a, b, c, d, f</td>
</tr>
<tr>
<td>2 h serum insulin (pmol/l)*</td>
<td>139 (85;211)</td>
<td>202 (103;292)</td>
<td>365 (231;560)</td>
<td>361 (246;571)</td>
<td>a, b, c, d, e</td>
</tr>
<tr>
<td>Insulin sensitivity index (ISI)*</td>
<td>2.68 (2.19;3.43)</td>
<td>1.99 (1.69;2.54)</td>
<td>1.47 (1.27;1.67)</td>
<td>1.36 (1.20;1.58)</td>
<td>a, b, c, d, e</td>
</tr>
<tr>
<td>HOMA-IS</td>
<td>1.11 (0.75;1.54)</td>
<td>0.51 (0.36;0.73)</td>
<td>0.79 (0.54;1.17)</td>
<td>0.45 (0.33;0.67)</td>
<td>a, b, c, d, f</td>
</tr>
<tr>
<td>Early-phase insulin release (EPIR)*</td>
<td>746 (569;978)</td>
<td>639 (380;960)</td>
<td>670 (447;903)</td>
<td>586 (365;1001)</td>
<td>a, b, c, f</td>
</tr>
<tr>
<td>Disposition index (DI)*</td>
<td>2084 (1514;2864)</td>
<td>1325 (918;1949)</td>
<td>1047 (656;1312)</td>
<td>815 (516;1185)</td>
<td>a, b, c, d, e</td>
</tr>
</tbody>
</table>

Data are unadjusted means and proportions (95% CI). *: Unadjusted medians (interquartile range). P values are adjusted for age, gender and risk/intervention group. P values for BMI were further adjusted for five-year physical activity level. P values for ISI, HOMA-IS, EPIR, and DI were further adjusted for family history of diabetes as well as five-year values of BMI, smoking, physical activity, and dietary quality. HOMA-IS, homeostasis model assessment of insulin sensitivity. Wald test from linear models: a) i-IFG vs. NGT, b) i-IGT vs. NGT, c) IFG/IGT vs. NGT, d) i-IGT vs i-IFG, e) IFG/IGT vs. i-IFG, f) IFG/IGT vs. i-IGT.
Progression from NGT to IFG and IGT

A. Insulin sensitivity index

B. HOMA-IS

C. Early-phase insulin release

D. Disposition index