Screen detected subjects with type 2 diabetes and impaired glucose tolerance have more adverse cardiovascular risk than subjects with impaired fasting glucose especially when they are obese

The ADDITION Netherlands study

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Abstract

Aims: To determine cardiovascular risk of screen detected subjects with type 2 diabetes (T2DM), impaired glucose tolerance (IGT) and impaired fasting glucose (IFG). To examine whether BMI is an effect modifier regarding the relation between level of glucose regulation and cardiovascular risk factors.

Methods: From 2002 to 2003, 29,251 persons, aged 50–70 years, participated in a population-based diabetes screening programme. Diagnosis was based on the 1999 WHO criteria. Characteristics were assessed of 285 subjects with T2DM, 175 with IGT and 218 with IFG.

Results: IFG did not resemble IGT and T2DM regarding weight and blood pressure. BMI (kg/m²) was 27.3 ± 4.4, 29.5 ± 5.7, 30.7 ± 5.6 in IFG, IGT, DM, respectively; systolic blood pressure (mmHg) 150 ± 25, 161 ± 24, 162 ± 23; diastolic blood pressure (mmHg) 84 ± 12, 89 ± 12, 90 ± 11.

The poorer the glycaemic control, the worse levels of BMI, blood pressure and lipids. When BMI was higher, cardiovascular risk factors were more adverse, especially in subjects with diabetes.

Conclusions: Subjects with IFG had lower blood pressure and weight than subjects with IGT and T2DM suggesting IFG is a condition with less risk to develop cardiovascular diseases. Effect modification by BMI was found.

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1. Introduction

Type 2 diabetic patients are at increased risk for cardiovascular diseases (CVD). At the time of diagnosis diabetes patients often already have complications [1,2]. From the Dutch Hoorn study we know that screen detected type 2 diabetic patients already have a cardiovascular risk profile typical of diabetes [3]. Furthermore, the prevalence of macrovascular disease...
2. Methods

2.1. Screening procedure

The present study forms a part of the ongoing ADDITION study (Anglo-Danish-Dutch Study of Intensive Treatment in People with Screen-Detected Diabetes in Primary Care). From 2002 to 2003, we carried out a population-based screening programme as the first stage of the ADDITION Netherlands study. The study was approved by the Medical-Ethical Committee of the University Medical Center Utrecht. Participants gave written informed consent.

The screening algorithm is shown in Fig. 1 and has been described elsewhere [16]. The screening algorithm in the three countries was comparable [17]. In brief, the procedure started with a self-completed questionnaire, containing mainly items on cardiovascular risk (scoring range 0–29 points), mailed to 29,251 non-diabetic, predominantly Caucasian registered patients, aged 50–70 years, from 41 general practices in the southwestern region of The Netherlands. Participants with a score ≥4 points were invited for a random blood glucose (RBG) measurement. If RBG ≥5.5 mmol/l a fasting blood glucose (FBG) was measured. Those with FBG > 6.0 mmol/l but RBG < 11.1 mmol/l were invited for further diagnostic testing by means of a (venous) standard 75-g oral glucose tolerance test (OGTT). Participants whose fasting blood glucose concentration was ≥5.2 mmol/l and ≤6.0 mmol/l also underwent an OGTT. If these subjects had a post-load plasma glucose level

![Fig. 1 – Algorithm of the screening procedure and number of patients. RBG, random blood glucose (mmol/l); FBG, fasting blood glucose (mmol/l); FPG, fasting plasma glucose (mmol/l); 2-h PG, two-hour plasma glucose (mmol/l); OGTT, oral glucose tolerance test; NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; epidemiological diabetes, one diabetic glucose value.](image-url)
(2-h FG) $\geq 11.1$ mmol/l in the OGTT (their first diabetic glucose value) or a second OGTT was performed. Participants who had RBG $\geq 11.1$ mmol/l and FGB $> 6.0$ mmol/l did not undergo an OGTT and were directly diagnosed as diabetic patients. All subjects with either an RBG $< 5.5$ mmol/l or FGB $< 5.2$ mmol/l did not undergo further glucose testing and were categorized as having normal glucose tolerance. Participants were classified according to the 1999 WHO diagnostic criteria [18]. Individuals who achieved only one diabetic glucose value were defined as having “epidemiological diabetes”.

### 2.2. Measurements

In all subjects with type 2 diabetes and IGT the following parameters were measured: HbA1c, BMI, waist circumference, blood pressure, cholesterol, HDL-cholesterol, LDL-cholesterol and triglycerides. Capillary blood glucose values were measured with a HemoCue B-Glucose Analyser based on the glucose-dehydrogenase method. Plasma glucose was determined using a peroxidase method. HbA1c was assessed with high-performance liquid chromatography (160 Menarini). Cholesterol, HDL-cholesterol and triglycerides were determined with enzymatic techniques (LX20 Beckman). Blood pressure was measured using an Omron device. In subjects with IFG only HbA1c, BMI, waist circumference, and blood pressure were determined. In addition, the algorithm of the screening procedure enabled us to assess the last men-

### 2.3. Data analysis

Data were analysed applying the SPSS statistical package (Version 11.0). Clinical characteristics of subjects in different categories of glucose regulation were compared using ANCOVA with adjustment for age and gender. In addition, we studied the age and gender adjusted relationships between diagnostic category and clinical characteristics using linear regression analysis to test for trend. Subsequently, we repeated this analysis separately in subjects with BMI $> 27$ kg/m$^2$ and $< 27$ kg/m$^2$.

### 3. Results

The study population included 285 detected diabetic patients, 175 subjects with IGT and 218 with IFG.

Table 1 shows a comparison of clinical characteristics of subjects in different diagnostic categories after adjustment for age and gender. Blood pressure was similar in subjects with IGT and diabetes. BMI, waist circumference and systolic and diastolic blood pressure were significantly different between people with IFG on the one hand and those with IGT and diabetes on the other. When the 72 subjects with NGT were also taken into the analysis, BMI, waist circumference and systolic and diastolic blood pressure were found to be similar in subjects with NGT and IFG (NUT: BMI (kg/m$^2$) 26.7 $\pm$ 3.7 S.D., systolic blood pressure (mmHg) 150 $\pm$ 25, diastolic blood pressure (mmHg) 84 $\pm$ 10). The HbA1c level (7.5% $\pm$ 1.8) in type 2 diabetic patients was much higher than in the other diagnostic categories.

In addition, Table 1 shows that (after adjustment for age and gender) BMI, waist circumference and blood pressure were more adverse when glucose metabolism was more disturbed. Plasma lipid levels proved to be more unfavourable in type 2 diabetic patients compared with subjects with IGT. Subsequently, these analyses were repeated

| Table 1 - Clinical characteristics of subjects in different categories of glucose regulation adjusted for age and gender |
|---|---|---|---|---|
| | IFG | IGT | Type 2 diabetes | P for trend |
| n | 218 | 175 | 285 | |
| Gender (% male) | 52.3 | 49.7 | 56.8 | |
| Age (years) | 59.6 $\pm$ 5.2 | 60.4 $\pm$ 5.4 | 60.2 $\pm$ 5.2 | |
| HbA1c (%) | 6.0 $\pm$ 0.4 | 6.0 $\pm$ 0.4 | 7.5 $\pm$ 1.8<sup>a</sup> | <0.001 |
| BMI (kg/m$^2$) | 27.3 $\pm$ 4.4<sup>b</sup> | 29.5 $\pm$ 5.7 | 30.7 $\pm$ 5.6<sup>a</sup> | <0.001 |
| Waist circumference (cm) | 97 $\pm$ 13<sup>b</sup> | 102 $\pm$ 12 | 105 $\pm$ 13<sup>a</sup> | <0.001 |
| SBP (mmHg) | 150 $\pm$ 25<sup>b</sup> | 161 $\pm$ 24 | 162 $\pm$ 23 | <0.001 |
| DBP (mmHg) | 84 $\pm$ 12<sup>b</sup> | 89 $\pm$ 12 | 90 $\pm$ 11 | <0.001 |
| Cholesterol (mmol/l) | 5.5 $\pm$ 1.0 | 5.7 $\pm$ 1.1 | 0.073 |
| HDL-cholesterol (mmol/l) | 1.3 $\pm$ 0.3 | 1.1 $\pm$ 0.4 | <0.001 |
| LDL-cholesterol (mmol/l) | 3.5 $\pm$ 0.8 | 3.8 $\pm$ 0.9 | <0.001 |
| Triglycerides (mmol/l) | 1.7 $\pm$ 1.0 | 2.1 $\pm$ 1.7 | 0.013 |

Data are means ± S.D. unless otherwise indicated. SBP, systolic blood pressure; DBP, diastolic blood pressure.

<sup>a</sup> Type 2 diabetes significantly different from IGT and IFG.

<sup>b</sup> IFG significantly different from IGT and type 2 diabetes.
separately in subjects with BMI $\geq 27$ kg/m$^2$ and $< 27$ kg/m$^2$.

In subjects with BMI $> 27$ kg/m$^2$, we found that the age and gender adjusted association between glycaemic control and systolic blood pressure was still significant (in subjects with IFG, IGT and type 2 diabetes, SBP (mean ± S.D.) was 153 ± 25 mmHg, 162 ± 24 mmHg, 164 ± 24 mmHg, respectively ($P$ for trend <0.001)). In those with BMI $< 27$ kg/m$^2$, this association was not significant (SBP was 148 ± 25 mmHg (IFG), 157 ± 24 mmHg (IGT) and 156 ± 19 mmHg (type 2 diabetes) ($P$ for trend = 0.090)). Such effect modification by BMI was not found with regard to the diastolic blood pressure.

The significant associations between glycaemic control and HDL-cholesterol, LDL-cholesterol and triglycerides remained significant in subjects with BMI $> 27$ kg/m$^2$, but not in those with BMI $< 27$ kg/m$^2$. Effect modification by BMI was also found regarding the relationship between glycaemic control and total cholesterol: in subjects with BMI $> 27$ kg/m$^2$ a significant association appeared while in those with BMI $< 27$ kg/m$^2$ the association remained insignificant.

In Table 2 age and gender adjusted clinical characteristics of subjects with BMI $> 27$ kg/m$^2$ and $< 27$ kg/m$^2$ are compared. Blood pressure, HDL-cholesterol, and triglycerides were significantly more adverse in overweight people than in those with BMI $< 27$ kg/m$^2$. Effect modification by BMI was also found regarding the relationship between glycaemic control and total cholesterol: in subjects with BMI $> 27$ kg/m$^2$ a significant association appeared while in those with BMI $< 27$ kg/m$^2$ the association remained insignificant.

In Table 2 age and gender adjusted clinical characteristics of subjects with BMI $> 27$ kg/m$^2$ and $< 27$ kg/m$^2$ are compared. Blood pressure, HDL-cholesterol, and triglycerides were significantly more adverse in overweight people than in those with BMI $< 27$ kg/m$^2$. Effect modification by BMI was also found regarding the relationship between glycaemic control and total cholesterol: in subjects with BMI $> 27$ kg/m$^2$, BMI values of 13 persons were not available.

In stratified analyses per glucose regulation category (Table 3), we found that in diabetic patients with BMI $> 27$ kg/m$^2$ systolic and diastolic blood pressure, HDL-cholesterol and triglycerides were significantly more unfavourable than in those with BMI $< 27$ kg/m$^2$. HbA1c, total cholesterol and LDL-cholesterol were higher in diabetic patients in the high BMI category compared with patients in the low BMI category but these differences were not significant. Persons in the IGT group with BMI $> 27$ kg/m$^2$ had lower HDL-cholesterol than those with BMI $< 27$ kg/m$^2$, whereas differences were not significant with regard to the other characteristics. Overweight subjects with IGT had higher diastolic blood pressure than subjects with IFG in the lower BMI category.

### Table 2 – Clinical characteristics of subjects in different categories of BMI adjusted for age and gender

<table>
<thead>
<tr>
<th>n</th>
<th>BMI $\leq 27$ kg/m$^2$</th>
<th>BMI $&gt; 27$ kg/m$^2$</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender (% male)</td>
<td>230</td>
<td>435</td>
<td>52.2</td>
</tr>
<tr>
<td>Age (years)</td>
<td>60.1 ± 5.3</td>
<td>60.0 ± 5.2</td>
<td>0.080</td>
</tr>
<tr>
<td>HbA1c (%)</td>
<td>6.5 ± 1.5</td>
<td>6.7 ± 1.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>SBP (mmHg)</td>
<td>152 ± 23</td>
<td>161 ± 24</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DBP (mmHg)</td>
<td>85 ± 12</td>
<td>89 ± 12</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Cholesterol (mmol/l)</td>
<td>5.7 ± 1.1</td>
<td>5.6 ± 1.0</td>
<td>0.612</td>
</tr>
<tr>
<td>HDL-cholesterol (mmol/l)</td>
<td>1.4 ± 0.6</td>
<td>1.1 ± 0.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LDL-cholesterol (mmol/l)</td>
<td>3.7 ± 0.9</td>
<td>3.6 ± 0.9</td>
<td>0.964</td>
</tr>
<tr>
<td>Triglycerides (mmol/l)</td>
<td>1.6 ± 1.0</td>
<td>2.0 ± 1.6</td>
<td>0.017</td>
</tr>
</tbody>
</table>

Data are means ± S.D. unless otherwise indicated. SBP, systolic blood pressure; DBP, diastolic blood pressure.

4. Discussion

This study evaluates the cardiovascular risk profiles of subjects in different categories of glucose regulation detected in a screening programme. Subjects with IFG were characterized by more favourable anthropometric measures than subjects with type 2 diabetes and IGT. These findings give support to the idea that the impact of fasting non-diabetic hyperglycaemia on CVD risk should not be overestimated. Moreover, we found no differences in blood pressure, BMI and waist circumference between subjects with IFG and normal glucose tolerance. Both type 2 diabetic patients and subjects with IGT identified by screening already have an unfavourable cardiovascular risk profile and can be considered as being at increased risk for cardiovascular disease.

This study further revealed that weight, blood pressure and lipids were more adverse when glucose metabolism was more disturbed. However, poorer glycaemic control was only associated with higher systolic blood pressure and more adverse lipids levels in overweight subjects. When BMI was higher, cardiovascular risk factors were more adverse, especially in subjects with diabetes.

A limitation of our study is the lack of information on plasma lipids in subjects with IFG (and NGT). This restricts the comparison of CVD risk of IFG with the other diagnostic categories. We should realize that the 72 subjects with normal glucose regulation in our study had $5.2$ mmol/l $\leq$ FBG $\leq 6.0$ mmol/l. Therefore, these subjects cannot simply be considered as representative for normal glucose tolerant subjects. So it might not be allowed to conclude that anthropometric measures in subjects with NGT and IFG are similar. Furthermore, the comparison of characteristics in Table 2 between individuals in both BMI categories is distorted in a certain extent because not all BMI values were available.

Our findings are relevant in terms of screening strategies. A question raised by our study results is whether screening for abnormal glucose metabolism should be targeted any longer on IFG. On the other hand, Heldgaard et al. found similar cardiovascular risk profiles in subjects with IGT and IFG and stated that screening initiatives should take into account both categories of impaired glucose metabolism [20]. The differences found in this Danish study and ours are not well understood. A partial explanation might be the fact that in our study 45% of the subjects with IGT fulfilled the criteria for both IGT and IFG (‘combined IGT’) whereas in the Danish study only 13% could be classified as having combined IGT. Since it has been shown that the risk for CVD is higher when...
IGT and IFG coexist, the differences in clinical characteristics between the IGT category as a whole and the IFG category in our study may be bigger than in the Danish study. In any case, our findings stress the importance of further research on the impact of IFG on CVD risk. For the time being, our data do not support the proposal of the American Diabetes Association to lower the diagnostic threshold for IGT [21–23]. Another question is whether screening for individuals at high risk for developing diabetes and CVD could be restricted to the overweight population. It has been demonstrated that people with overweight and obesity are at significantly increased risk for cardiovascular diseases [24]. The effect of weight on cardiovascular mortality is partly mediated through other known cardiovascular risk factors [25,26], but even in the absence of other risk factors obese people may be at a higher risk for CVD [27]. Our data show the BMI to be an effect modifier in the associations of glycaemic control with blood pressure and lipids. Moreover, we found that blood pressure, lipids and HbA1c were more adverse in overweight subjects. Given the decreasing prevalence of undiagnosed diabetes in The Netherlands, due to intensified case-finding in general practice in the last decade, the yield of population-based screening for diabetes is low [16]. Furthermore, it may be of greater benefit to screen for an unfavourable cardiovascular risk profile rather than only for hyperglycaemia [28,29]. In this context, our study findings suggest that screening in overweight people might be preferable to a stepwise population-based screening in order to detect people with increased CVD risk.

In conclusion, not only type 2 diabetic patients but also subjects with IGT identified in a screening programme have an unfavourable cardiovascular risk profile. Blood pressure, BMI and waist circumference in subjects with IFG were significantly lower than in subjects with IGT and type 2 diabetes [24]. The increased CVD risk of hyperglycaemia [30] suggests IFG is a condition with less risk to develop cardiovascular diseases. The increased CVD risk of hyperglycaemia is notably present in overweight persons.

### Conflict of interest statement

None declared.

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