How to approach management of the patient with obesity and prediabetes

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Senior Principle Clinical Scientist, Novo Nordisk
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Hon Professor, Dept. Medicine, UCL

SCOPE Summer School 2016
London

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Outline

• Case history
• For and against screening for diabetes and diagnosing prediabetes
• Definitions and prevalence
• Risks of impaired glucose metabolism
• Guidelines for screening and diagnostic criteria
• Lifestyle interventions for prevention
• Pharmacological interventions for prevention
• Case History

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Case History

JG is a 54 yr. old Caucasian commercial airline pilot
He has passed his airline certification 6 months’ ago
He falls and sustains a Colles’ fracture of his left wrist
On admission to the fracture clinic, he has a capillary blood glucose measured
The result is 5.7 mmol/l (104 mg) and he is told that he should see his doctor as he has pre-diabetes
His father and brother both developed type 2 diabetes in their 70’s
He has a BMI of 30 kg.m²
Case History

- Do you agree that he has pre-diabetes?
- If he does will this stop him flying?
- Are there further tests that you would want to do?
- If these confirm a diagnosis of pre-diabetes would you treat him with
  - Advice on diet and exercise
  - Metformin
  - Other hypoglycaemic medication
  - Weight loss medication

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Why diagnose pre-diabetes?

- It might explain a patient’s symptoms?
- It is a risk for ill health in itself
- Early treatment provides benefit
  - Prevents development of diabetes
  - Delays development of diabetes
  - Reduces CV morbidity and mortality
- Unproven benefit but seems logical in the same way that other risk factors lowering (lipids, BP) has been proven to be beneficial

Why not diagnose pre-diabetes?

- Implications for individuals include:
  - the time and other resources necessary to undergo the screening test (or tests) and any subsequent diagnostic test (or tests);
  - the psychological and social effects of the results whether the screening test proves ‘positive’ or ‘negative’ and whether or not the diagnosis of type 2 diabetes is subsequently made and
  - the adverse effects and costs of earlier treatment of type 2 diabetes or any preventive measures instituted as a result of the individual being found to have diabetes. These may include occupational discrimination and/or increased costs or difficulty in obtaining insurance.

Why not diagnose pre-diabetes?

- The effects on the health system and society as a whole:
  - costs and other implications (especially in primary care and support services such as clinical biochemistry) of carrying out the screening test (or tests) and the necessary confirmatory test (or tests);
  - additional costs of the earlier treatment of those at high risk of developing diabetes or cardiovascular disease in the future
  - the implications of false negative and false positive
  - loss of production as a result of the earlier diagnosis of the condition (from absence from work or reduced job opportunities, for example)

Arguments against diagnosing pre-diabetes

- Population measures of glycaemia are continuous, with no inflections to provide obvious cut-off points
- Cut-offs for the diagnosis of diabetes are based on thresholds for risk of retinopathy
- Lesser degrees of hyperglycaemia increase the risk of developing diabetes and maybe arteriolar disease. But in both cases the risk is graded, making any choice of cut-off point purely arbitrary
Arguments against diagnosing pre-diabetes

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Effect of drugs</th>
<th>Effect of lifestyle intervention</th>
<th>Effect of screening tools</th>
<th>Effect of screening tools</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFG</td>
<td>(nominal)</td>
<td>(nominal)</td>
<td>(nominal)</td>
<td>(nominal)</td>
</tr>
<tr>
<td>IGT</td>
<td>(nominal)</td>
<td>(nominal)</td>
<td>(nominal)</td>
<td>(nominal)</td>
</tr>
<tr>
<td>HbA1c</td>
<td>(nominal)</td>
<td>(nominal)</td>
<td>(nominal)</td>
<td>(nominal)</td>
</tr>
</tbody>
</table>

Outline

- Case history
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- lifestyle interventions for prevention
- Pharmaceutical interventions for prevention
- Case History

Cut-points for diagnosing diabetes, impaired glucose tolerance, and impaired fasting

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Venous plasma glucose (mg/dL)</th>
<th>Venous blood glucose (mmol/L)</th>
<th>Capillary blood glucose (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IFG-FG</td>
<td>6.1 (110)</td>
<td>5.0 (90)</td>
<td>5.6 (100)</td>
</tr>
<tr>
<td>IGT-2hG</td>
<td>7.8 (140)</td>
<td>6.5 (117)</td>
<td>7.2 (130)</td>
</tr>
<tr>
<td>Diabetes-FG</td>
<td>10.0 (180)</td>
<td>14.0 (254)</td>
<td>16.0 (285)</td>
</tr>
<tr>
<td>Diabetes-2hG</td>
<td>11.1 (200)</td>
<td>9.4 (169)</td>
<td>10.3 (185)</td>
</tr>
</tbody>
</table>

Notes and references:

- DECODE*: fasting plasma glucose and 2 hr blood in 13 European population-based cohorts included.
Effect of Aging on A1C Levels in Individuals Without Diabetes

Overweight and obesity are major risk factors for prediabetes

Obese people with pre-diabetes (Impaired Glucose Regulation*) have 17 times as great a risk of type 2 diabetes

Prevalence of prediabetes* in England from 2003 to 2011: BMI and age

Prevalence of prediabetes in England from 2003 to 2011: Odds Ratios for pre-diabetes

Relative proportions of IGT and IFG in pre-diabetic patients: 2000 and 2010

2000

2010 USA prediabetes estimates: 25% > 20y 50% > 65y 79 million


Data based on American obese pre-diabetic patients aged 45-74 years

IFG only
23.5%
2.8 million

IGT only
51.3%
6.1 million

Combined IFG+IGT
25.2%
3.0 million

2010 USA prediabetes estimates: 25% > 20y 50% > 65y 79 million

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Impact of increased A1C on CV event and mortality in non-diabetic men (EPIC Norfolk)

Average follow-up 6 yr of A1C on EPIC Norfolk men age 45 to 79

Association between A1C, coronary heart disease and mortality


Age Group (Years )

10 year cumulative incidence per 1000 patient years

Pre-diabetes conversion rates

Baseline glucose intolerance

Ryden et al. European Heart Journal (2013) 34, 3035–3087

Hazard ratios for CVD mortality for FPG ( ) and 2hPG ( ) intervals using previously diagnosed DM ( ) as reference category.
Individuals

Screening for Type 2 Diabetes & Prediabetes in Asymptomatic Individuals

- Type 2 diabetes testing
  - Adults of any age who are overweight or obese and who have ≥1 diabetes risk factor
  - Begin testing at age 45
  - Normal test? Repeat at ≥3-year intervals

- Prediabetes testing
  - A1C, FPG, or 2-h PG after 75-g OGGT
  - Identify & treat other CVD risk factors
  - Consider testing in children and adolescents who are overweight or obese and have ≥2 diabetes risk factors

Categories of Increased Risk for Type 2 Diabetes (Prediabetes)

<table>
<thead>
<tr>
<th>FPG</th>
<th>2-h PG*</th>
<th>A1C</th>
</tr>
</thead>
<tbody>
<tr>
<td>100-125 mg/dL</td>
<td>140-199 mg/dL</td>
<td>5.7-6.4%</td>
</tr>
<tr>
<td>5.6-6.9 mmol/L</td>
<td>7.8-11.0 mmol/L</td>
<td>39-46 mmol/mol</td>
</tr>
</tbody>
</table>

Impaired fasting glucose (IFG) tolerance (IGT)

Risk is continuous, extending below lower limit of range and becoming disproportionately greater at higher ends of range

Definition of pre-diabetes

Fasting glucose and 2-h blood glucose (OGGT)

- Pre-diabetes definition (ADA)
  - Impaired fasting glucose (FPG) 5.6-8.9 mmol/L
  - Impaired glucose tolerance (IGT) 2-h glucose at OGGT >7.8-11.0 mmol/L
- Fasting glucose abruptly increases ~3yr and post OGGT ~>5yr before the diagnosis of diabetes
- Annual probability of developing diabetes
  - Both IGT and IFG: 15.8%
  - IGT or IFG (monotherapy): 5.4%
Outline

- Defining obesity, diabetes and pre-diabetes
- Obesity, fat distribution and insulin resistance
- Prevalence of obesity, diabetes and pre-diabetes
- Health risks to the person with pre-diabetes
- Benefits of weight loss

5 yr incidence of type 2 diabetes by quartiles of PAI-1 in subjects with normal (NGT) and impaired (IGT) glucose tolerance at baseline

Association Between Impaired Fasting Glucose (100 to 125 mg/dl) and Cardiovascular Outcomes

Pre-diabetes and cancer mortality - men

Pre-diabetes and cancer mortality - women

Pre-diabetes and cancer mortality - men
Pre-diabetes and cancer mortality - women

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Effect of interventions on weight change in pre-diabetes

Lifestyle intervention studies to lose weight and prevent type 2 diabetes

- Diabetes Prevention Program\(^1\)
  - US, 3,234 over-weight men and women with IGT and IFG
  - diet plus exercise vs. lifestyle interventions vs. placebo (4-year follow-up)
- Diabetes Prevention Study (DPS)\(^2\)
  - Finland, 522 overweight men and women with IGT
  - diet plus exercise vs. lifestyle interventions vs. placebo (6-year follow-up)
- Da Qing IGT and Diabetes Study (Da Qing)\(^3\)
  - China, 530 men and women with IGT
  - diet, exercise, and diet plus exercise lifestyle interventions vs. placebo (20-year follow-up)

The Diabetes Prevention Study\(^1,2\)
- 5 centres across Finland in men and women
  - Ages: 40-65 years
  - BMI ≥25 kg/m\(^2\)
  - IGT: Defined as a 2-h plasma glucose 7.8-11.0 mmol/l following OGTT (75 g)
- 523 subjects were randomly assigned to either:
  - Lifestyle modification (n=265)
  - Control (n=257)
- Interventions:
  - Control: initial general information on lifestyle changes and annual follow-up
  - Interventions: 7 sessions with a nutritionist during year 1 and a visit every 3 months thereafter aimed at reducing weight (target ≤25 kg/m\(^2\)), and dietary modification (<30% energy intake from fat). Individual guidance to increase physical activity.
- Mean subject disposition:
  - Age, 55 years; BMI, 31.0 kg/m\(^2\); gender, 67% female
- Average follow-up: 3.2 years

Diabetes Prevention Study showed that weight loss reduced risk of type 2 diabetes by 58%
The Diabetes Prevention Program

- 27 centres across the US in men and women
  - aged ≥25 years
  - BMI ≥24 (≥22 in Asians) kg/m²
  - ADA 1997 criteria for prediabetes
- 3234 subjects were randomly assigned to either:
  - Intensive lifestyle modification (n=1078)
  - Standard lifestyle recommendations plus metformin (850 mg BID) (n=1073)
  - Standard lifestyle recommendations plus placebo (BID) (n=1082)
- Lifestyle interventions:
  - Intensive: target ≥7% weight loss; ≥150 min weekly exercise; 16 lessons; individual and group sessions
  - Standard: written information; annual 30 min counselling
- Mean subject disposition:
  - age, 51 years; BMI, 34.0 kg/m²; gender, 68% female; race, 45% non-Caucasian
- Average follow-up (initial): 2.8 years


Change in weight (kg)

Time (months)

Diabetes Prevention Program: Effect of Interventions on Weight

Placebo    Metformin    Lifestyle

Change in weight (kg)

Time (months)

Diabetes Prevention Program: Cumulative incidence of diabetes

Placebo    Metformin    Lifestyle

Cumulative risk of diabetes (%)

Time (months)

Contribution of weight loss following lifestyle intervention to the risk of developing diabetes in DPP

For every 1 kg of weight loss, the risk of developing diabetes was reduced by 16%


Baseline factors predicting restoration of normal glucose regulation (NGR) in pre-diabetic subjects in the DPP

<table>
<thead>
<tr>
<th>Predictor of interest</th>
<th>OR 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age in years</td>
<td>1.04 (1.02–1.06)</td>
<td>0.003</td>
</tr>
<tr>
<td>Diabetes vs. placebo</td>
<td>2.25 (1.89–2.68)</td>
<td>0.001</td>
</tr>
<tr>
<td>Male vs. female sex</td>
<td>1.77 (1.38–2.27)</td>
<td>0.001</td>
</tr>
<tr>
<td>Black vs. non-Caucasian</td>
<td>2.93 (1.37–6.27)</td>
<td>0.006</td>
</tr>
<tr>
<td>Baseline fasting plasma glucose</td>
<td>1.31 (1.08–1.60)</td>
<td>0.006</td>
</tr>
<tr>
<td>Overall baseline plasma glucose</td>
<td>1.28 (1.13–1.45)</td>
<td>0.001</td>
</tr>
<tr>
<td>Baseline total cholesterol</td>
<td>1.07 (1.00–1.16)</td>
<td>0.052</td>
</tr>
<tr>
<td>Baseline triglycerides</td>
<td>1.01 (0.92–1.11)</td>
<td>0.802</td>
</tr>
<tr>
<td>Baseline weight loss</td>
<td>1.34 (1.21–1.49)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Baseline height</td>
<td>1.01 (0.92–1.11)</td>
<td>0.802</td>
</tr>
</tbody>
</table>


The Diabetes Prevention Program Outcomes Study (DPPOS)

- Long-term follow-up of the Diabetes Prevention Program (DPP)
- To investigate whether the delay in development of diabetes seen during the DPP can be sustained
- To assess long-term effects of the interventions on health
  - diabetes incidence
  - weight change
  - cardiovascular
  - disease risk

The Diabetes Prevention Program Outcomes Study (DPPOS)

- Participants informed of the main results from DPP
- Metformin and placebo groups entered into a 1–2 week drug washout study to identify whether treatment of fasting glucose accounted for the diabetes risk reduction with metformin
- Unmasked to their treatment assignments and placebo stopped
- All participants, including the original lifestyle group and those who had developed diabetes, offered a group-administered version of the 16-session lifestyle curriculum as a bridge protocol
- DPPOS follow-up protocol was started in September, 2002
- Lifestyle sessions (HELP) were offered to all participants every 3 months
- Primary outcome, as in the DPP, was development of diabetes

Weight changes and diabetes incidence from Diabetes Prevention Program randomisation and enrolment in the DPPOS

Undiscounted, per capita, direct medical costs of care outside the DPP/DPPOS

The Da Qing Study – description and interventions

- 33 centres across Da Qing, China
- Men and women
- Aged ≥25 years
- IGT defined as 2-h plasma glucose 7.8–11.1 mmol/l following OGGT (75 g)
- 577 subjects were randomly assigned to either:
  - age: 55 years; BMI: 31.0 kg/m²; gender: 46% female
  - Control (n=138)
  - Interventions: diet, exercise or both (n=438)
- Interventions:
  - Control: general info on diabetes and IGT; general brochures on diet & exercise but no individual sessions.
  - Diet only: for BMI >25 reduce calorie intake to achieve weight losses of 0.5–1.0 kg per month until BMI=23. Dietary recommendations were individually tailored.
  - Exercise only: 1 exercise unit ranged gentle (30 mins) to very strenuous (5 mins). Age <50 increase 2 units/day, >50 1 unit/day.
  - Diet & exercise: Instructions and counselling similar to those described above
- Intervention and follow-up: 6 years and 20 years

The Da Qing Study — patient disposition

Da Qing study participants by group at baseline (1986), end of the 6-year active intervention (1992), and end of follow-up (2006)

Da Qing study, intervention and incidence of type 2 diabetes

Cumulative incidence of all-cause and cardiovascular mortality during follow-up in Da Qing Diabetes Prevention Outcome Study

Findings of four lifestyle intervention studies that aimed at preventing type 2 diabetes in subjects with impaired glucose tolerance

Baseline factors predicting restoration of normal glucose regulation (NGR) in pre-diabetic subjects in the Diabetes Prevention Program

<table>
<thead>
<tr>
<th>Study</th>
<th>Cohort Size</th>
<th>Mean BMI (kg/m²)</th>
<th>Duration (years)</th>
<th>RRR (%)</th>
<th>ARR (%)</th>
<th>NNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Malmo</td>
<td>217</td>
<td>26.6</td>
<td>5</td>
<td>63</td>
<td>18</td>
<td>28</td>
</tr>
<tr>
<td>DPS</td>
<td>323</td>
<td>31.0</td>
<td>3</td>
<td>58</td>
<td>22</td>
<td>22</td>
</tr>
<tr>
<td>DPP</td>
<td>346</td>
<td>34.0</td>
<td>3</td>
<td>58</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Da Qing</td>
<td>1000</td>
<td>25.0</td>
<td>6</td>
<td>46</td>
<td>27</td>
<td>25</td>
</tr>
</tbody>
</table>

RRR = relative risk reduction; ARR = absolute risk reduction; NNT = number needed to treat.

Baseline factors predicting restoration of normal glucose regulation (NGR) in pre-diabetic subjects in the Diabetes Prevention Program

| Factor                         | Odds Ratio (95% CI) | p  
|--------------------------------|---------------------|-----
| Age < 45 yrs                  | 2.9 (1.6-5.3)       | <0.0005 |
| Hypertension                  | 1.23 (0.83-1.83)    | 0.268 |
| Diabetes                      | 1.67 (1.05-2.64)    | 0.040 |
| Family history of diabetes    | 0.80 (0.50-1.30)    | 0.406 |
| Cigarette use                 | 1.17 (0.88-1.57)    | 0.300 |
| Low-normal fasting glucose    | 1.00 (0.98-1.03)    | 0.654 |
| Low-normal HbA1c              | 0.80 (0.67-0.97)    | 0.026 |
| Low-normal fb glucose         | 0.93 (0.84-1.04)    | 0.153 |
| High-normal blood pressure    | 0.94 (0.87-1.02)    | 0.137 |
| Low-normal HDL cholesterol    | 1.07 (0.99-1.16)    | 0.113 |
| Low-normal triglycerides      | 0.76 (0.65-0.89)    | 0.0003 |
| Low-normal ALT               | 1.02 (0.93-1.11)    | 0.691 |
| Low-normal PLT               | 0.87 (0.78-0.98)    | 0.029 |
| Low-normal WBC               | 0.95 (0.88-1.03)    | 0.191 |
| Low-normal CRP               | 0.88 (0.76-1.01)    | 0.077 |

Combined numbers for placebo and diet-exercise groups.

Findings of four lifestyle intervention studies that aimed at preventing type 2 diabetes in subjects with impaired glucose tolerance

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Trial design: SCALE Obesity and Prediabetes.
Liraglutide 3.0 mg in weight management (160 weeks)

XENDOS trial (orlistat + very low calorie diet): Weight loss and diabetes incidence

Proportion of subjects diagnosed with T2DM over time
0–172 weeks

Regression to normoglycaemia.
Measured at OGTT visits: 0–172 weeks

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• He has passed his airline certification 6 months ago.
• He falls and sustains a Colles’ fracture of his left wrist.
• On admission to the fracture clinic, he has a capillary blood glucose measured.
• The result is 5.7 mmol/l (104 mg) and he is told that he should see his doctor as he has pre-diabetes.
• His father and brother both developed type 2 diabetes in their 70’s.
• He has a BMI of 30 kg.m².

Case History

• Do you agree that he has pre-diabetes?

Yes

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>Venous phlebotomy (mmol/l)</th>
<th>Venous blood glucose (mmol/l)</th>
<th>Capillary blood glucose (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>HG—FS</td>
<td>5.1 (18)</td>
<td>5.0 (97)</td>
<td>5.2 (196)</td>
</tr>
<tr>
<td>OGT—HG</td>
<td>7.6 (16)</td>
<td>6.6 (107)</td>
<td>7.7 (166)</td>
</tr>
<tr>
<td>Diabetes—FS</td>
<td>10.5 (33)</td>
<td>9.5 (164)</td>
<td>10.3 (195)</td>
</tr>
</tbody>
</table>

But this was taken under conditions of stress, so probably not valid.

Case History

• If he does will this stop him flying?

Yes:
  – OGTT
  – HbA1c

Case History

• Are there further tests that you would want to do?

Yes:
Case History

• If these confirm a diagnosis of pre-diabetes would you treat him with
  – Advice on diet and exercise
  – Metformin
  – Other hypoglycaemic medication
  – Weight loss medication
• Let’s discuss!!

What to discuss with patients with pre-diabetes

• A diagnosis of pre-diabetes does not mean that you will develop diabetes. In fact, of 100 people like you, fewer than 50 are likely to develop diabetes in the next 10 years
• There are ways of reducing your risk of developing diabetes that involve changing your diet and being active. These can result from efforts you make as well as changes in your environment (food supply, workplace conditions, education, and other social determinants of health)
• There are drugs to delay diabetes, but these are the same drugs you will need if you do develop diabetes, and the value of starting them before you have developed diabetes is unknown

Recommendations for Preventing or Delaying Type 2 Diabetes

Individuals with prediabetes:
  – IFG, IGT, or A1C 5.7% - 6.4%
  – Refer to intensive diet & physical activity behavior counseling program targeting

Consider metformin therapy for type 2 diabetes prevention in individuals with prediabetes

Especially in presence of:
  – BMI >35 kg/m²
  – Age <60 years
  – Women with prior GDM

At least annual monitoring of individuals with prediabetes

Screen for and treat modifiable CVD risk factors: obesity, hypertension, dyslipidemia

ADA DSG Guidelines

Screen on Diabetes Mellitus. Diabetes Care 2015;38:S10–S42.