Cardiometabolic syndrome

Paul Dromgoole

RGN, RNMH, MSc Diabetes, PGCert Ed

Independent Lecturer Practitioner
What is Type 2 diabetes?

A progressive metabolic disorder characterised by:

- Insulin resistance
- Type 2 diabetes
- β-cell dysfunction

Type 2 diabetes Diagnostic criteria

<table>
<thead>
<tr>
<th>Fasting</th>
<th>non-fasting</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.1</td>
<td>T2DM</td>
</tr>
<tr>
<td>7.8</td>
<td>Impaired glucose tolerance (IGT)</td>
</tr>
<tr>
<td>7.0</td>
<td>T2DM</td>
</tr>
<tr>
<td>6.1</td>
<td>Normal</td>
</tr>
<tr>
<td>6.1</td>
<td>Normal</td>
</tr>
</tbody>
</table>

2 hours post OGTT
Insulin resistance and insulin hypersecretion precede Type 2 diabetes

<table>
<thead>
<tr>
<th>Insulin sensitivity</th>
<th>Insulin secretion</th>
<th>Macrovascular disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>30%</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>50%</td>
<td>70–100%</td>
<td>40%</td>
</tr>
<tr>
<td>70%</td>
<td>150%</td>
<td>10%</td>
</tr>
<tr>
<td>100%</td>
<td>100%</td>
<td></td>
</tr>
</tbody>
</table>

Why does Type 2 diabetes if not effectively managed, lead to such macrovsacular disease?
Obesity and Increasing Age in UK

![Bar chart showing percent of population with BMI >30 kg/m² by age group and gender.]

Waist circumference
Type 2 Diabetes and visceral fat or …

The perils of the pot belly!

… but what’s the connection with cardiovascular risk?
Visceral Fat – metabolically active!!

Cytokines

- FFA’s
- TNF α
- IL - 6
- PAI – 1
- Leptin
- RAS
- Adiponectin

Dyslipidaemia
Insulin signalling
Endothelial dysfunction
Pro-inflammatory (CRP’s)
Pro-thrombosis
SNS (>BP)
Angiotensin II (>BP)
Insulin sensitising
Anti-inflammatory
Anti-atherromatic
Type 2 Diabetes and visceral fat

Visceral fat becomes metabolically active in obesity, leading to increased FFA’s and increased production of a range of inflammatory agents, adipokines and cytokines.

Leading to insulin resistance, hyperglycaemia, increased cardiovascular risk and leading to the term ‘cardiometabolic state’
Race-ethnicity specific waist circumference cut offs for identifying CVD risk factors

Odds ratio and WC in men

- Black
- Hispanic
- White
Race-ethnicity specific waist circumference cut offs for identifying CVD risk factors

Odds ratio and WC in women

Interheart Study: Waist circumference a much better predictor of CV risk than BMI.

## Waist circumference ‘targets’

<table>
<thead>
<tr>
<th></th>
<th>Increased risk</th>
<th>Substantially increased risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men</td>
<td>&gt;= 94 cm</td>
<td>&gt;= 102 cm</td>
</tr>
<tr>
<td>Asian men *</td>
<td></td>
<td>&gt;= 90 cm</td>
</tr>
<tr>
<td>Women</td>
<td>&gt;= 80 cm</td>
<td>&gt;= 88 cm</td>
</tr>
<tr>
<td>Asian women *</td>
<td></td>
<td>&gt;= 80 cm</td>
</tr>
</tbody>
</table>

*Cut off values of risk for individuals of Asian origin have been set at a lower waist measurement (WHO available at [www.diabetes.com.au/pdf](http://www.diabetes.com.au/pdf))*
Waist measurement risk
What’s in a name?

Reaven’s syndrome; Syndrome X; Cardiometabolic syndrome; Insulin Resistance Syndrome.
Metabolic syndrome (IDF definition)

Central obesity plus and 2 of the following:

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Requirement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trigs</td>
<td>$\geq 1.7$ mmols/L</td>
</tr>
<tr>
<td>HDL</td>
<td>$&lt; 1.03$ males</td>
</tr>
<tr>
<td></td>
<td>$&lt; 1.29$ females</td>
</tr>
<tr>
<td></td>
<td>Or on lipid lowering agents</td>
</tr>
<tr>
<td>BP</td>
<td>$\geq 130 / 85$</td>
</tr>
<tr>
<td></td>
<td>Or present / previous treatment of hypertension</td>
</tr>
<tr>
<td>FPG</td>
<td>$&gt; 5.6$ mmols/l</td>
</tr>
<tr>
<td></td>
<td>Or previously treated T2DM</td>
</tr>
<tr>
<td></td>
<td>FPG $&gt; 5.6$ mmols/L OGTT strongly recommended</td>
</tr>
</tbody>
</table>
San Antonio Heart Study
(Metabolic Syndrome as Predictor of Type 2 Diabetes)

• 2,569 patient epidemiological study looking at DM diagnostic criteria on prediction of DM and prediction of CV risk.
• Participants who did not have T2DM at entry to study but went on to develop T2DM by end of 8 years follow up had:
  • Substantially higher total cholesterol LDL and trigs and lower HDL
  • Increased BMI
  • Hypertension …
  • Than those who did not go on to develop T2DM.
  • This led to the ‘ticking click’ hypothesis for CHD

Botnia Study
(Metabolic consequences of a family history of NIDDM)

- 3,606 first degree relatives of T2DM patients in Western Finland
- Follow-up period 7 years
- Cardiovascular mortality was 12% in individuals with metabolic syndrome (MetS) (defined by WHO criteria) compared with 2.2% in individuals without.
- In all subjects, a history of CHD, MI, and stroke was more common in those with the MetS than it was in those without ($P < 0.001$).
- In IFG/IGT, the prevalence of CHD was increased even further in patients with the MetS (35% vs. 8%, $P < 0.001$).
- A history of MI was increased in T2DM with MetS compared with those without (11.2 vs. 4.7%; $P = 0.007$).
- Similarly, a history of stroke was more common in IFG/IGT subjects clear MetS than it was in those without (3.6 vs. 0.9%; $P = 0.05$).

Groop et al., Diabetes (1996) vol., 11, 1585-93
Type 2 Diabetes Prevention

• Note – the 2 big diabetes prevention programmes (DPP and DPS) reduced the progression from IGT to T2DM by 58% in the lifestyle arm, 33% in the Metformin arm.

• This by 5% body weight loss over 4-5 year course of study and engagement in 150 mins exercise per week (multiples of 10 mins upwards).

• 53% of subjects reached a definition of the Metabolic syndrome at baseline:

• This was reduced at 4 years by 41% ($p<0.001$) in lifestyle and 17% ($p=0.03$) in Metformin arm
T2DM: The risks
Type 2 Diabetes: The Risks

- 2-4 fold risk of CVD
- Risk of MI equivalent to that on someone with DM who has already suffered an MI
- 2-5 fold risk of stroke
- Even higher CV risks in South Asian patients
- The leading cause of non-traumatic limb amputation
- Leading cause of end-stage renal failure
- Higher rates of depression over general population
- Shortened life expectancy of 8-12 years – what does this mean for those diagnosed increasingly younger?

Unless aggressive clinical risk management and educational strategies in place
Type 2 Diabetes – reducing the risks
Risk reduction for each 1% reduction in HbA$_{1c}$ in T2DM

Epidemiological extrapolation showing benefit of a 1% reduction in mean HbA$_{1c}$ at 12 years

Risk reduction (%) associated with a 1% lower HbA$_{1c}$

Any diabetes-related endpoint
-20
-10
0
21%
*  
Microvascular complications
-30
-20
-10
0
37%
*  
Cataract extraction
-40
-30
-20
-10
0
19%
*  
Amputation or death due to peripheral vascular disease
-40
-30
-20
-10
0
43%
*  

* *p < 0.0001

The need for regular surveillance and regular treatment increase deterioration of glycaemic control in the UKPDS.

What the evidence shows …….

Hyperglycaemia + time = complications

Early intervention: Avoiding glycaemic burden and microvascular complications

- **Diet**
- **Metformin**
- **Combination therapy**
- **No combination therapy**

<table>
<thead>
<tr>
<th>Time since diagnosis</th>
<th>HbA1c (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6.5%</td>
</tr>
<tr>
<td></td>
<td>7.5%</td>
</tr>
<tr>
<td></td>
<td>7.5%</td>
</tr>
<tr>
<td></td>
<td>Treatment goal</td>
</tr>
</tbody>
</table>

- **Diet** and **Metformin** can lower HbA1c initially.
- **Combination therapy** maintains lower HbA1c levels longer, followed by rebound.
- **No combination therapy** leads to a steady increase in HbA1c.
63% of patients are not at ADA goal of $\text{HbA}_1^c \leq 7.0\%$

Saydah SH et al. JAMA, 2004; 291:335-42
An important diabetes drug ...

- No weight gain
- No hypoglycaemia
- Significant reduction in HbA$_{1c}$
- Cardiovascular protection in overweight patients over and above glucose lowering effect
- Cheap
- Around for 50 years
- Documented use in 1652 (Culpepper)
The reduction in risk with metformin in overweight T2DM patients


*p values in comparison to conventional treatment group

Glucophage SR – superior GI tolerability to Glucophage IR

With Glucophage SR there are fewer than half the gastrointestinal side effects during the first year of treatment compared with Glucophage IR.


- Tight control vs less tight control = 144/82 mmHg vs 154/87 mmHg

- % Risk reduction associated with tighter blood pressure control:
  - Any diabetes-related endpoint: -24% (p = 0.0046)
  - Diabetes-related and all-cause mortality: -32% (p = 0.019)
  - Stroke: -44% (p = 0.013)
  - Heart failure: -56% (p = 0.0043)

*=Tight control vs less tight control = 144/82 mmHg vs 154/87 mmHg*

UKPDS: Tight blood pressure control reduces cardiovascular risk in T2DM
Multiple risk-factor management for Type 2 Diabetes
Change in T2DM management strategies

1980’s
Mild diabetes
“Touch of sugar”

Early 1990’s
Not ‘mild’
Manage the blood glucose

Present
T2DM is CVD
Manage multiple risk factors

How do we get out management messages across?
How do we impact on ‘concordance’?
NNT to prevent one event

<table>
<thead>
<tr>
<th>Risk level: 5-year CV risk (fatal and non-fatal)</th>
<th>Benefits: NNT for 5 years to prevent one event (CVD events prevented per 100 people treated for 5 years)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1 intervention (25% risk reduction)</td>
</tr>
<tr>
<td>30%</td>
<td>13 (7.5 per 100)</td>
</tr>
<tr>
<td>20%</td>
<td>20 (5 per 100)</td>
</tr>
<tr>
<td>15%</td>
<td>27 (4 per 100)</td>
</tr>
<tr>
<td>10%</td>
<td>40 (2.5 per 100)</td>
</tr>
<tr>
<td>5%</td>
<td>80 (1.25 per 100)</td>
</tr>
</tbody>
</table>

Based on the conservative estimate that each intervention: aspirin, blood pressure treatment (lowering systolic blood pressure by 10 mm Hg) or lipid modification (lowering LDL-C by 20%) reduces CV risk by about 25% over 5 years.
Multiple Risk Factor Intervention: The Steno-2 Study

Multiple Risk Factor Intervention: Risk reduction in the Steno-2 Study

Cardiovascular events

- Autonomic Neuropathy: 67%
- Amputations: 50%
- Nephropathy: 61%
- Retinopathy: 58%
- Stroke: 85%
Case studies
Case study - Joan

• Joan (64). Diagnosed with T2DM 5 years ago.
• Ex-smoker – gave up 6 years ago
• BMI 34.2 kg/m².
• Blood pressure 155/88.
• Cholesterol is raised at 6.4 mmols/L, HDL 0.9 mmols/L.
• Home blood sugars generally 12–16 mmols. HbA₁c 9.2%. On Metformin 6 tabs day Glic 4 tabs day
• States she generally feels very well.
• Action?
Case study - Sid

- Sid - 56 yrs. T2DM.
- HbA$_{1c}$ never below 7.3% since diagnosis 8yrs ago. Latest value 9.2%.
- BMI 34.6 kg/m$^2$, BP 155/82, Cholesterol 6.4, HDL 0.9
- Urine microalbuminuria +ve. Background retinopathy *(left)* Pre-prolifative *(right)*
- Current smoker.
- Dislikes taking his tablets. Complains of ‘tummy ache’
- Drug history: Metformin 500mg tds, Rosiglitazone 4mg od, Gliclazide 160mg bd, Aspirin 75mg od, Atorvastatin 40mg nocte

- **What is his 10 year cardiovascular risk?**
- **How *(on earth)* are you going to engage him with his health and future risks?**
10 year Coronary Heart Disease Risk

Before

After

UKPDS Risk Engine v1.1

Input

Age now: 56 years
Hba1c: 9.2%
Diabetes duration: 8 years
Systolic BP: 155 mm Hg
Sex: Male
Total cholesterol: 6.4 mmol/l
Atrial fibrillation: No
HDL cholesterol: 0.9 mmol/l
Ethnicity: White
Smoking: Current smoker

Output

Coronary heart disease: 45.6%
Stroke: 11.8%

UKPDS Risk Engine v1.1

Input

Age now: 56 years
Hba1c: 7.0%
Diabetes duration: 8 years
Systolic BP: 130 mm Hg
Sex: Male
Total cholesterol: 5.0 mmol/l
Atrial fibrillation: No
HDL cholesterol: 1.1 mmol/l
Ethnicity: White
Smoking: Ex-smoker

Output

Coronary heart disease: 16.6%
Stroke: 5.2%
Cardiometabolic Disease Key Points

• It is now recognised that adipose tissue synthesises and releases many factors which influence the body’s metabolic actions.
• Increased visceral fat has an important role to play in metabolic and vascular risk.
• Body mass index is often used as a marker of obesity but gives a limited indication of body composition and so cardiometabolic risk.
• Measuring waist circumference is a more discriminative predictor.
• Rising visceral fat mass predicts worsening insulin resistance - changes in subcutaneous fat are not correlated.
Cardiometabolic Disease Key Points

• Early, aggressive multi-risk management is required from diagnosis of T2DM but probably before.
• Given it’s cardio-protective benefits of Metformin in overweight patients and lack of weight gain, is is a key drug in our armoury.
• Revisiting patients previously unable to tolerate the immediate release form will help cardiovascular risk reduction.
• Increasingly the challenge is in persuading the patient to ‘buy-into’ an ever more aggressive treatment regime …
• Particularly when they are unlikely to have expected (or wanted) their diabetes diagnosis and perhaps have never experienced any of the physical symptoms of diabetes or the cardio-metabolic syndrome.
Central obesity can be dangerous