Metabolic syndrome: linking diabetes, cardiovascular disease and non alcoholic fatty liver disease

Christopher D Byrne

University of Southampton & Southampton University Hospitals Trust

www.metabolicsyndrome.org.uk
Content

- Definition in the context of type 2 dm
- Metabolic syndrome and type 2 dm
- Metabolic syndrome and morbidity and mortality
- Insulin resistance and CV risk
- Physical activity
- NAFLD
Changing patterns of CVD risk factors

1984
Cholesterol
Smoking
Hypertension

2011
Central obesity
Diabetes & MetS
What is type 2 diabetes?

a progressive metabolic disorder – linked to beta cell failure and/or insulin resistance

fpg $\geq 7.0$ mmol/l
What is metabolic syndrome?

Ectopic fat accumulation & insulin resistance adversely affecting cardiometabolic risk factors (to increase risk of type 2 diabetes, cardiovascular disease and NAFLD)
Portrait of Daniel Lambert by Benjamin Marshall, 19th Century

-so why do we need to decrease weight in people with MetS?
Metabolic Syndrome

Features 2009

- Waist > 94/80 cm
- BP ≥ 130/85
- TG ≥ 1.7 mmol/l
- Glucose ≥ 5.6 mmol/l
- HDL < 1.0/1.3 mmol/l

↑ Triglyceride
↓ HDL Cholesterol
↑ BP

Fatty liver
Glucose intolerance
Vascular inflammation & procoagulant phenotype

OBESITY
## Criteria for Clinical Diagnosis of the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Measure</th>
<th>Categorical cut points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Elevated waist circumference</td>
<td>Population- and country-specific definitions</td>
</tr>
<tr>
<td>Elevated triglycerides (drug treatment for elevated triglycerides is an alternate indicator)</td>
<td>≥150 mg/dL</td>
</tr>
<tr>
<td>Reduced HDL cholesterol (drug treatment for reduced HDL cholesterol is an alternate indicator)</td>
<td>&lt;40 mg/dL for males and &lt;50 mg/dL for females</td>
</tr>
<tr>
<td>Elevated blood pressure (drug treatment for elevated blood pressure is an alternate indicator)</td>
<td>Systolic ≥130 mm Hg and/or diastolic ≥85 mm Hg</td>
</tr>
<tr>
<td>Elevated fasting glucose (drug treatment for elevated glucose is an alternate indicator)</td>
<td>≥100 mg/dL</td>
</tr>
</tbody>
</table>

Consensus statement **International Diabetes Federation (IDF), the National Heart, Lung, and Blood Institute (NHLBI), the World Heart Federation, the International Atherosclerosis Society, and the American Heart Association (AHA)** *Circulation* 2009; 120:1640-1645
Risk factors for (central) obesity

- Ageing but ? reason
- Sex, men and post menopausal women
- Ethnicity, South Asians – low lean body mass
- Socio-economic status - deprivation
- Low levels of physical activity – work/ leisure/ transport/ central heating
- Excessive calorie intake
- Secondary to e.g. hypothyroidism, glucocorticosteroids
- Smoking cessation/ other lifestyle change / depression
- Rarely genetics –commonest MCR-4R mutations (5% of people BMI > 30 kg/m2 middle aged adults)
Obesity, insulin resistance, type 2 diabetes and metabolic syndrome

Metabolic syndrome: a disorder of ‘ectopic fat’ accumulation, insulin resistance (NAFLD) & cardio-metabolic risk
Diagnosis of diabetes 2010

• ADA for the first time said that HbA1c levels $\geq 6.5\%$ are sufficient for a diagnosis of diabetes, while levels from 5.7\% to 6.4\% are a marker of "prediabetes" and indicate increased risk of both incident diabetes and cardiovascular disease

Survival is worsened with increasing number of features of Metabolic syndrome

P value for trend
P=0.04
HR 4.76; p=0.04
(5 features versus 1)

Gudzer, Gatling, Mullee, Byrne Diabetologia 2006 Jan;49(1):49-55
Association between the metabolic syndrome and cardiovascular events and mortality: meta-analyses of longitudinal studies

<table>
<thead>
<tr>
<th>Study</th>
<th>RR</th>
<th>95% CI</th>
<th>Covariates in risk model</th>
</tr>
</thead>
<tbody>
<tr>
<td>McNeill</td>
<td>1.62</td>
<td>1.41 - 1.87</td>
<td>X X X X X</td>
</tr>
<tr>
<td>Sattar</td>
<td>1.41</td>
<td>1.05 - 1.90</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>Schillaci</td>
<td>1.73</td>
<td>1.25 - 2.38</td>
<td>X X X X X X</td>
</tr>
<tr>
<td>Summary</td>
<td>1.54</td>
<td>1.32 - 1.79</td>
<td></td>
</tr>
</tbody>
</table>

Decreased risk  Increased risk

All studies excluded people with prevalent cardiovascular disease, and 1 study (45) excluded women. "Other" covariates included race (62), study site (in a multicenter study) (62), body mass index (45), C-reactive protein (45), creatinine (60), left ventricular hypertrophy (60), and cigarette smoking (45,60,62). The boxes represent the relative risk (RR) for individual studies and are proportional to their weight in the analysis, and the lines represent their 95% confidence intervals (CIs). The diamond represents the pooled RR, and its width represents its 95% CI. BP = hypertension or elevated systolic or diastolic blood pressure; Glu = fasting hyperglycemia; X = covariate included.

Source: Gami et al J Am Coll Cardiol 2007;49:403-14
Association between the MetS, CV events and mortality: meta-analyses of longitudinal studies

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Studies (N)</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV event</td>
<td>11</td>
<td>2.18</td>
<td>1.63-2.93</td>
</tr>
<tr>
<td>CHD event</td>
<td>18</td>
<td>1.65</td>
<td>1.37-1.99</td>
</tr>
<tr>
<td>CV death</td>
<td>10</td>
<td>1.91</td>
<td>1.47-2.49</td>
</tr>
<tr>
<td>CHD death</td>
<td>7</td>
<td>1.60</td>
<td>1.28-2.01</td>
</tr>
<tr>
<td>Death</td>
<td>12</td>
<td>1.60</td>
<td>1.37-1.92</td>
</tr>
</tbody>
</table>

N=172,573 people

The diamonds represent the pooled relative risk (RR) and 95% confidence interval (CI) for studies that assessed each outcome. Some studies assessed more than 1 outcome. CHD = coronary heart disease; CV = cardiovascular.

Source: Gami et al J Am Coll Cardiol 2007;49:403-14
**ULSAM: *Death and Major Cardiovascular Events (HR, 95% CI) in the Different Groups***

<table>
<thead>
<tr>
<th>End point</th>
<th>Normal weight without metabolic syndrome</th>
<th>Normal weight with metabolic syndrome</th>
<th>Overweight without metabolic syndrome</th>
<th>Overweight with metabolic syndrome</th>
<th>Obese without metabolic syndrome</th>
<th>Obese with metabolic syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total death</td>
<td>Referent</td>
<td>1.28 (0.90–1.82)</td>
<td>1.21 (1.03–1.40)</td>
<td>1.53 (1.19–1.96)</td>
<td>1.65 (1.03–2.66)</td>
<td>2.43 (1.81–3.27)</td>
</tr>
<tr>
<td>CV death</td>
<td>Referent</td>
<td>1.77 (1.11–2.83)</td>
<td>1.44 (1.14–1.83)</td>
<td>2.19 (1.57–3.06)</td>
<td>1.20 (0.49–2.93)</td>
<td>3.20 (2.12–4.82)</td>
</tr>
<tr>
<td>Major CV events</td>
<td>Referent</td>
<td>1.63 (1.11–2.37)</td>
<td>1.52 (1.28–1.80)</td>
<td>1.74 (1.32–2.30)</td>
<td>1.95 (1.14–3.34)</td>
<td>2.55 (1.82–3.58)</td>
</tr>
</tbody>
</table>

*Circulation, Jan 2010; 121: 230 - 236*

*1758 middle-aged individuals without diabetes in the Uppsala Longitudinal Study of Adult Men (ULSAM).

During a median follow-up of 30 years, 788 participants died and 681 developed cardiovascular disease. Hazard models adjusted for age, smoking, and LDL cholesterol, metabolic syndrome
Diagnosis of diabetes 2010

- ADA for the first time said that HbA1c levels $\geq 6.5\%$ are sufficient for a diagnosis of diabetes, while levels from 5.7\% to 6.4\% are a marker of "prediabetes" and indicate increased risk of both incident diabetes and cardiovascular disease.

## Incidence of New Diabetes and Hazard Ratio (95% CI) for Diabetes and Other Clinical Outcomes (14-Year Median Follow-Up), by Baseline Glycated Hemoglobin Level, in Nondiabetics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>&lt;5.0%</th>
<th>5.0% to &lt;5.5%&lt;sup&gt;c&lt;/sup&gt;</th>
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<th>≥6.5%</th>
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<tbody>
<tr>
<td>Diabetes incidence (%)</td>
<td>6</td>
<td>12</td>
<td>21</td>
<td>44</td>
<td>79</td>
</tr>
<tr>
<td>Diabetes&lt;sup&gt;b&lt;/sup&gt;</td>
<td>0.52 (0.40–0.69)</td>
<td>1.00</td>
<td>1.86 (1.67–2.08)</td>
<td>4.48 (3.92–5.13)</td>
<td>16.47 (14.22–19.08)</td>
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<td>CHD</td>
<td>0.96 (0.74–1.24)</td>
<td>1.00</td>
<td>1.23 (1.07–1.41)</td>
<td>1.78 (1.48–2.15)</td>
<td>1.95 (1.53–2.48)</td>
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<tr>
<td>Ischemic stroke</td>
<td>1.09 (0.67–1.76)</td>
<td>1.00</td>
<td>1.17 (0.89–1.53)</td>
<td>2.22 (1.60–3.08)</td>
<td>3.16 (2.15–4.64)</td>
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<td>Mortality</td>
<td>1.48 (1.21–1.82)</td>
<td>1.00</td>
<td>1.18 (1.04–1.35)</td>
<td>1.59 (1.34–1.89)</td>
<td>1.65 (1.31–2.08)</td>
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a. Adjusted for age, sex, race, low-density and high-density cholesterol levels, triglyceride level, body-mass index, waist-to-hip ratio, hypertension, family history of diabetes, education level, alcohol use, physical activity, and smoking status
b. Defined as self-reported diagnosis of diabetes or use of antidiabetic medications
c. Reference for hazard ratios

• What is the relationship between insulin resistance and CV outcome?
Measures of tissue insulin sensitivity

• 75g Oral Glucose Tolerance Test
  -NEFA suppression – to derive a measure of fat insulin sensitivity
  Belfiore F et al. Insulin sensitivity indices calculated from basal and OGTT-induced insulin, glucose, and FFA levels. Mol Genet Metab. 1998 Feb;63(2):134-41

• Euglycaemic Hyperinsulinaemic Clamp
  -Whole body glucose uptake & suppression of glucose production
Kaplan–Meier survival curves for subjects free from subsequent CHD events during 10.4 years of follow-up, for a) tertiles of insulin sensitivity index ($S_i$), and b) tertiles of intact proinsulin at baseline.
How can we improve insulin sensitivity?

• Which aspect of ‘insulin sensitivity’ are we trying to improve?
  – regulation of glucose metabolism?
    • Decrease hepatic glucose output, promote skm & adipose glucose uptake
  
  – regulation of vascular function?
    • Increase vasodilatation?
    • Increase microvascular nutrient exchange
  
  – regulation of triglyceride metabolism?
    • Decrease VLDL secretion
    • Decrease lipolysis of adipose TG to release free fatty acids?
Tissue microvascular dysfunction and metabolic syndrome

- Obesity
- Insulin Resistance
- Hyperglycemia
- Dyslipidemia
- Inflammation

Haemodynamics
- Vasodilatation
  - ↓NO/AA Metabolism
- ↑Myogenic Response

Endothelial Integrity
- ↓Microvascular Density
- Cytoskeletal Contraction
- Junctional Disorganisation

Impaired Microvascular Perfusion
- Inflammation and atherothrombosis
- Impaired Microvascular Solute/water Exchange

Clough et al Diabetes 2009
Turzyniecka et al Diabetic Med 2010
Turzyniecka et al J Appl Physiol 2010
Clough et al Microcirculation 2010
How can we improve insulin sensitivity?

• ‘Lifestyle’ treatment
  – What is it, how does it work & what exactly should we be recommending?

• Drugs
  – What drugs, how do they work & what should we be recommending?

• Bariatric surgery
  – What is it, how does it work and what should we be recommending?
How can we improve insulin sensitivity?

• ‘Lifestyle’ treatment
  – Physical activity/exercise
  – Diet & good nutrition
Energy balance

- 50 extra calories a day leads to 2.4kg weight gain per year
- Losing 1kg requires a deficit of about 7000 calories
- Losing 0.5-1kg/week requires a deficit of 500-1000 calories/day
Definitions:
Physical activity/exercise
We know that physical activity is beneficial but..............

1 person on the stairs!
What is wrong with this picture – why are they not on the stairs?
Managing CV risk

• High absolute risk
  – Aggressive CV risk reduction treatment
    • LDLc treatment – statins targets QoF/NICE
    • Bp treatment ‘ABCD’ - targets
  – Good nutrition – 5-10 fruits & veg
  – Tackling obesity – consider bariatric surgery
  – Improving PAEE – accumulation of 1 h ‘brisk walking’ daily
Where else to intervene to reduce CV mortality?

- Try and prevent/slow the progression of Type 2DM.
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b. Defined as self-reported diagnosis of diabetes or use of antidiabetic medications

c. Reference for hazard ratios

Glycaemic control and CV Mortality

– Fasting glycaemic control reduces microvascular complications, and does not appear to contribute to reducing CV mortality.

– Metformin reduces CV mortality (by improving endothelial function) and not by improving glycaemic control.

– German Diabetes Intervention Study – the only interventional study to show improved CVD and all-cause mortality by controlling post-prandial glycaemia.
Ectopic fat accumulation: a link between insulin resistance, type 2 DM and vascular disease

Lipid metabolism: NAFLD, insulin resistance and type 2 DM

↑ NEFA oxidation
↓ Glucose production

↑ Glucose uptake
↑ NEFA oxidation
↑ Insulin sensitivity

Triglyceride: obesity, insulin resistance and risk of type 2 DM

↓ NFκB
↓ Foam cell formation
↓ Neointimal proliferation

Triglyceride accumulation: insulin resistance and risk of type 2 DM
Non-alcoholic Fatty Liver Disease (NAFLD)
….significant lipid deposition in the hepatocytes of the liver parenchyma in a patient without a history of excessive alcohol consumption
Non-alcoholic fatty liver disease (NAFLD) definition

• Liver injury – fat accumulation exceeding 5-10% by weight – fat laden hepatocytes by light microscopy
• Similar to alcohol-induced liver injury
• NAFLD
  • Steatosis
  • Steatohepatitis (NASH)
  • NASH + extensive fibrosis
  • NASH-induced cirrhosis
NAFLD: Spectrum of disease

Non alcoholic fatty liver disease

- Steatosis (fatty liver) (20-30% of total)
- Steatohepatitis (NASH) (fatty liver + inflammation) (2-3% of total)
- Cirrhosis
- Hepatocellular carcinoma
What causes/contributes to NAFLD?

• Age
• Smoking
• Diabetes
• Met S/central obesity
• Altered early development
  (Bruce et al Hepatology 2009)
What is the relationship between physical activity, hepatic insulin sensitivity and hepatic fat?

Physical activity

Insulin sensitivity

Hepatic fat

$r = 0.55, p = 0.01$

$r = -0.51, p = 0.05$ (liver)

$r = -0.53, p = 0.04$ (muscle)

$r = -0.52, p = 0.04$ (fat)

Holt H et al.  
Diabetologia 2006  
49:141-148

Holt HB et al.  
Diabetologia 2007;  
50: 1698–1706;

Holt HB et al.  
Diabetologia 2007;  
50: 1024–1032.
Association between NAFLD and prevalent CVD in type 2 diabetic adults with and without NAFLD

Data are expressed as odds ratios (±95% confidence intervals).

*The multiple adjustment reported in the third and fourth bars was as follows: age, sex, BMI, smoking status, diabetes duration, HbA1c, LDL cholesterol and current use of medications (hypoglycaemic, anti-hypertensive, lipid-lowering or anti-platelet drugs).

Fatty acid exposures could affect:

- Insulin sensitivity
- Hepatic fat metabolism (synthesis/oxidation) – via SREBP1c,

-> Fatty acids could affect the risk, severity and progression of NAFLD
Saturated fatty acids appear to:

- Insulin sensitivity
- Hepatic fat synthesis
- Hepatic inflammation

-> Saturated fatty acids could increase the risk, severity and progression of NAFLD
Much recent interest in the possible protective effects of omega-3 (ω-3; n-3) fatty acids

‘fish oils’
Found in seafood, especially oily (fatty) fish, fish oils, liver oils, algal oils, pharmaceutical preparations (Omacor) .. ...
‘Fish oil fats’……..these 2 fatty acids are present in ‘fish oil’ and are present in very high concentration in OMACOR

NB. Fish oils may contain other unfavourable compounds e.g. mercury
Fish oils are not pure preparations but OMACOR is just EPA and DHA
Marine ω-3 fatty acids (contained in fish oils)

- Insulin sensitivity (some studies only)
- Hepatic TAG synthesis – via SREBP1c
- Hepatic fatty acid oxidation – via PPAR-α
- Systemic inflammation – via NFκB and PPAR-γ (? Hepatic inflammation) – also eicosanoid and resolvin mediated effects

→ ω-3 fatty acids could decrease the risk, severity and progression of NAFLD
Wessex Evaluation of fatty Liver and Cardiovascular markers in NAFLD with OMacor thErapy:

WELCOME study

funded by the National Institute for Health Research (UK) and Diabetes UK
The WELCOME Study evaluates the effects of purified ω-3 fatty acids (OMACOR 4 g/d) on serum biomarkers, cardiovascular risk markers and liver fat in a randomized placebo controlled trial in patients with NAFLD.
Schedule, visits and timescale

Visits 1 & 2

4

5

6 & 7 (+/- 8)

Purified ω-3 fatty acid EEs 4 g daily (n =50)

Placebo n=50

-4 0 4-6 10-12 15-18 Months
Ongoing RCTs of LC-ω3s in NAFLD.

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>n=</th>
<th>Intervention</th>
<th>Primary outcome</th>
<th>NCT* number</th>
</tr>
</thead>
<tbody>
<tr>
<td>NASH</td>
<td>64</td>
<td>Fish oil 3 gm/day for 12 months</td>
<td>NASH Activity Score</td>
<td>00681408</td>
</tr>
<tr>
<td>NAFLD</td>
<td>58</td>
<td>Fish oil 5 gm/day (3.5 g EPA and DHA) for 3 months</td>
<td>Steatosis (MRS)</td>
<td>00819338</td>
</tr>
<tr>
<td>NASH</td>
<td>24</td>
<td>Lovaza 4 gm/day for 24 weeks</td>
<td>Steatosis (MRI)</td>
<td>00845845</td>
</tr>
<tr>
<td>NASH or NAFLD</td>
<td>30</td>
<td>&quot;Omega-3 fatty acid&quot; 4 gm/day for 2 months</td>
<td>Steatosis (MRS)</td>
<td>00230113</td>
</tr>
<tr>
<td>NASH</td>
<td>100</td>
<td>Lovaza 4 gm/day for 18 months</td>
<td>Serum biomarkers of liver fibrosis</td>
<td>00760513</td>
</tr>
<tr>
<td>NASH, DM-type II</td>
<td>60</td>
<td>&quot;Opti- EPA&quot; (360 mg EPA and 240 DHA) × 6/day for 48 weeks</td>
<td>NASH Activity Score</td>
<td>00323414</td>
</tr>
<tr>
<td>Adolescent NAFLD</td>
<td>8</td>
<td>Fish oil 4 gm/day for 6 months</td>
<td>ALT, safety</td>
<td>00694746</td>
</tr>
<tr>
<td>Child and adolescent NAFLD (per biopsy)</td>
<td>45</td>
<td>DHA 250 or 500 mg/kg/day for 24 months</td>
<td>1*: ALT, 2*: Steatosis (US), fibrosis (Fibroscan)</td>
<td>00885313</td>
</tr>
<tr>
<td>Metabolic syndrome and transaminases &gt; 3 times normal</td>
<td>720</td>
<td>Fish oil 2 gm/day for 30 months</td>
<td>1*: Coronary arteries plaque volume 2*: ALT</td>
<td>00624923</td>
</tr>
</tbody>
</table>
Acknowledgements

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Sanchia Triggs

Bridget Clancy  
Keith McCormick  
Kate Nash

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Collaborator in University of Nottingham

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