Establishment of Efficacy of Intervention in those with Metabolic Syndrome

Dr Wendy Russell - ILSI Europe Expert Group
• Conflict of interest regarding this presentation:

I have no conflict of interest to report in relation to this presentation.
Background to Activity

- Approx. 30-40% of the European population suffer from Metabolic Syndrome
- Significant risk factor for Cardiovascular Disease and Type 2 Diabetes Mellitus
- Defined as presenting with 3-5 of the defining criteria
# Metabolic Syndrome - Definition

<table>
<thead>
<tr>
<th></th>
<th>IDF 1</th>
<th>WHO 2</th>
<th>ATPIII 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>triglyderides</td>
<td>≥ 1.7 mmol/L</td>
<td>≥ 1.7 mmol/L</td>
<td>≥ 1.7 mmol/L</td>
</tr>
<tr>
<td>reduced HDL (M)</td>
<td>&lt; 1.03 mmol/L</td>
<td>&lt; 0.9 mmol/L</td>
<td>&lt; 1.04 mmol/L</td>
</tr>
<tr>
<td>reduced HDL (F)</td>
<td>&lt; 1.03 mmol/L</td>
<td>&lt; 1.0 mmol/L</td>
<td>&lt; 1.03 mmol/L</td>
</tr>
<tr>
<td>raised BP (systolic)</td>
<td>≥ 130 mm Hg</td>
<td>≥ 140 mm Hg</td>
<td>≥ 130 mm Hg</td>
</tr>
<tr>
<td>(diastolic)</td>
<td>≥ 85 mm Hg</td>
<td>≥ 90 mm Hg</td>
<td>≥ 85 mm Hg</td>
</tr>
<tr>
<td>fasting pGLC</td>
<td>&gt; 5.6 mmol/L</td>
<td>&gt; 6.1 mmol/L</td>
<td>&gt; 6.1 mmol/L</td>
</tr>
<tr>
<td>waist circumference</td>
<td>&gt; 94 cm</td>
<td></td>
<td>&gt; 102 cm</td>
</tr>
<tr>
<td>(M)</td>
<td>&gt; 80 mm</td>
<td></td>
<td>&gt; 88 mm</td>
</tr>
<tr>
<td>(F)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td></td>
<td>&gt; 30 kg/m²</td>
<td></td>
</tr>
<tr>
<td>waist/hip ratio</td>
<td>&gt; 0.9 (M)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>&gt; 0.85 (F)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>albumin excretion</td>
<td>≥ 20 ug/mol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>albumin/creatinine</td>
<td>≥ 3.4 ug/mol</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ratio</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

However:

- No consensus as to a universal definition of Metabolic Syndrome
- Limited understanding of the pathological impact of the defining criteria
- Dietary interventions target individual criteria
- Observational studies on risk, lack detailed dietary information
- Additional risk factors have not been identified
Metabolic Syndrome - Risk

• Evidence for CVD risk is estimated to be 1.5-3x
• MetS increases risk of T2DM up to approx. 6x
• Predictive of new onset T2DM

Cardiovascular Disease
- Isomaa et al (2001)
- Ford et al (2005)
- Garni et al (2007)

Type 2 Diabetes
- Echel et al (2005)
- Hanson et al (2002)
- Grandy et al (2005)
Objectives

1. Establish the impact of dietary intervention on the currently recognised features of MetS
2. Understand the relative pathological impact of the individual components on CVD and T2DM
3. Utilise a modelling approach, attempt to quantify the importance of diet on disease outcome
4. Identify additional risk factors that are modulated by diet
1. Establish the impact of dietary intervention on the currently recognised features of MetS

Comprehensive literature review (PRISMA), high quality data was obtained from RCTs for dietary interventions (>8 weeks duration) in subjects exhibiting three or more defining features of MetS

**Search Strategy**

Med line Search 1996- current
1. Metabolic syndrome = 59563
2. Metabolic syndrome x = 49947
3. 1 or 2 = 28678 (59563)

*Combination of keyword and mesh terms did not increase the number of recoveries*

4. ‘Metabolic Syndrome’ and ‘randomised control trial’ = 1224
5. ‘Metabolic syndrome’ and ‘multi centre study’ = 199
6. 4 or 5 = 1224
7. ‘Metabolic syndrome’ and ‘comparative study’ = 224
8. 4 and 7 = 1224

*Metabolic Syndrome and RCT captures all multicentre and comparative studies*

Total studies to be checked = 1224

Abstracts to be screened = 1224

All abstracts screened by at least two individuals to ascertain that they met study criteria

Manuscripts to be screened = 212

Data exported for model construction
1. Establish the impact of dietary intervention on the currently recognised features of MetS

**Dietary Components Included**

- Complete Dietary Regimes
- Macronutrients (Carbohydrate, Protein and Fat)
- Micronutrient Vitamins and Minerals
- Non-nutrient Phytochemicals
- Food/Health Supplements

**Not Included**

- Physical Activity
- Drugs
2. Understand the relative pathological impact of the individual components on CVD and T2DM

Data on disease outcome from observational studies (>5 years) Subjects also exhibiting three or more defining features of MetS

Search Strategy
Defining Criteria
Data Extraction
Data Exported

as before
3. Utilise a modelling approach, attempt to quantify the importance of diet on disease outcome

<table>
<thead>
<tr>
<th>Details</th>
<th>Study Design</th>
<th>Impact on MetS Criteria</th>
<th>Additional Information</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>TG Units</td>
<td>DBP Units</td>
</tr>
<tr>
<td>ORN</td>
<td>Treatment</td>
<td></td>
<td></td>
</tr>
<tr>
<td>UI</td>
<td>Form of Treatment</td>
<td>TG Baseline</td>
<td>DBP Baseline</td>
</tr>
<tr>
<td>Author</td>
<td>Dose mg if supplement</td>
<td>TG SE Baseline</td>
<td>DBP SE Baseline</td>
</tr>
<tr>
<td>TI</td>
<td>Details if dietary intervention</td>
<td>TG After</td>
<td>DBP After</td>
</tr>
<tr>
<td>SO</td>
<td>Study Design</td>
<td>TG SE After</td>
<td>DBP SE After</td>
</tr>
<tr>
<td>YR</td>
<td>Blinding</td>
<td>TG Change</td>
<td>DBP Change</td>
</tr>
<tr>
<td>Length in Days</td>
<td></td>
<td>TG SE Change</td>
<td>DBP SE Change</td>
</tr>
<tr>
<td>Sample size</td>
<td></td>
<td>TG p value</td>
<td>DBP p value</td>
</tr>
<tr>
<td>Ethnicity of study population</td>
<td></td>
<td>TG significance y n</td>
<td>DBP significance y n</td>
</tr>
<tr>
<td>MetS criteria</td>
<td></td>
<td>HDL Units</td>
<td>SBP Units</td>
</tr>
<tr>
<td>MetS population (y/n)</td>
<td></td>
<td>HDL Baseline</td>
<td>SBP Baseline</td>
</tr>
<tr>
<td>Other relevant study characteristics</td>
<td></td>
<td>HDL SE Baseline</td>
<td>SBP SE Baseline</td>
</tr>
<tr>
<td>Proportion of male subjects</td>
<td></td>
<td>HDL After</td>
<td>SBP After</td>
</tr>
<tr>
<td>Analysis Type</td>
<td></td>
<td>HDL SE After</td>
<td>SBP SE After</td>
</tr>
<tr>
<td>Baseline Average weight kg</td>
<td></td>
<td>HDL Change</td>
<td>SBP Change</td>
</tr>
<tr>
<td>Baseline Average BMI (kg /m2 )</td>
<td></td>
<td>HDL SE Change</td>
<td>SBP SE Change</td>
</tr>
<tr>
<td>Baseline Average Age</td>
<td></td>
<td>HDL p value</td>
<td>SBP p value</td>
</tr>
<tr>
<td></td>
<td></td>
<td>HDL significance y n</td>
<td>SBP significance y n</td>
</tr>
</tbody>
</table>
3. Utilise a modelling approach, attempt to quantify the importance of diet on disease outcome

Construct a model based on the data collection

- Multivariate Model (at least five responses; MetS defining criteria)
- Large number of different diets

Two approaches:

1) Define groups of diets and then compare their response patterns

2) Unsupervised clustering of dietary treatments based on the observed responses
In addition to the currently accepted defining parameters, data on potential novel risk factors has also been captured. These include:

- several indices of inflammation
- adiposity and renal function,
- additional markers of lipid, glucose and insulin dysregulation
Additional Risk Factors Identified

1. abdominal adiposity, visceral fat, central obesity, waist/hip ratio, visceral adipose tissue

2. HbA1c, glucose at 120 min after 75 g-OGTT, HOMA-IR, fasting plasma insulin, plasma glucose AUC, plasma insulin AUC, matsuda index, insulin sensitivity index, disposition index,

3. Inflammation, CRP, IL-6, TNF (TNF-α), adiponectin, ICAM-1, e-selectin, IL-1 (IL -1β), leptin, MCP-1, PAI-1, fibrinogen, IL-18, F2-isoprostane, IL-8, 8-epiPGFα,

4. estimated glomerular filtration rate, glomerular filtration rate, hypertension, systolic blood pressure, diastolic blood pressure, urinary microalbumin:creatinin ratio, 24 h urinary albumin excretion, microalbuminuria, albuminuria, macroalbuminuria, HbA1C, 24h urine sodium excretion, cystatin C, diabetic retinopathy, plasma renin activity, 24h proteinuria,

5. Total cholesterol (TC), LDL-C, ApoA, ApoB, Non-HDL-C, Prevalence of MetS/Change in MetS score, TC:HDL-C ratio, LDL particle/subfraction size or quantity, ApoB/ApoAI ratio, HDL particles/subfractions sizes or quantity, VLDL-C, ApoB100, LDL- or VLDL-ApoB or B48, ApoCIII, Free fatty acids, LDL-C:HDL-C ratio, NEFA, VLDL particles/ subfractions , sizes or quantity, Remnant-like particle cholesterol OR remnant lipoprotein cholesterol, Oxidised LDL, ApoB48, hypertriglyceridaemia, hypercholesterolaemia
Model Overview

**Dietary Intervention**
- Comparative RCT multi-centre
- > 8 weeks
- 1996-2014

**MetS Population > 3**
- Triglycerides ≥ 1.7 mmol/L
- Red-HDL ≤ 1.03/1.04 mmol/L
- Blood pressure ≥ 85/130 mm HG
- F-GLC ≥ 6.1 mmol/L
- Waist circ. ≥ 102/88 cm

**Novel hallmarks identified by EG (sig. modulated by intervention)**

**T2DM**
- Observational
- 5-10 years
- 1996-2014

**CVD**
Outcomes

- Comprehensive review on the ‘Efficacy of Intervention in those with MetS’
- Consensus Report on ‘Novel Risk Factors and Disease Outcome’
- Fit-for-purpose model linking Diet and Disease
Expert Group Members

Professor Julie Lovegrove; University of Reading
Professor Ronald Mensink; Maastcht University
Dr Herve Nordmann; Ajinomoto Europe
Dr Katerina Vafeiadou; University of Hertfordshire
Dr Hanna Koutnikova; Danone
Dr Julie-Ann Nazare; University of Lyon
Professor Jogchum Plat; Maastricht University
Professor Bart Staels; Institut Pasteur de Lille
Dr Claus Mayer; Biomathematics & Statistics Scotland
Professor Massimo Massi-Benedetti; Hub for International Health Research
Dr Luc Sterkman; Newtricious
Dr Harry Peters; Unilever
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Dr Wendy Russell; Rowett Institute of Nutrition and Health

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