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Janssen-Cilag Ltd, 50-100 Holmers Farm Way, Buckinghamshire, HP12 4EG, UK

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Managing obesity in patients with diabetes

Dr Matthew S Capehorn
GPwSI and bariatric physician
Clinical Director - National Obesity Forum
Clinical Manager – Rotherham Institute for Obesity
Declaration of interests

Unpaid
- Clinical Director, NOF

Paid
- Medical Director, Lighter Life

Advisory Boards
- BI/Lilly Alliance (national and global)
- Novo Nordisk
- MSD

Speaker fees/travel:
- BI/Lilly, Novo, MSD, Janssen
To discuss:

1) Prevalence of diabetes and obesity and impact on the NHS
2) Why does weight gain (visceral fat) matter
3) Why do we care about obesity?
4) How do we manage obesity?
5) Treatment interventions for managing obesity and diabetes
6) Questions?
Financial Cost of Diabetes – UK

- In 2010, 10% of NHS budget was spent on treating diabetes and its complications

  - £9 Billion per year
  - £173 Million per week
  - £25 Million per day
  - £1 Million per hour
  - £17 000 per minute
  - £286 per second

- 80% of the cost of treating diabetes comes from treating complications

http://www.diabetes.org.uk/Documents/Reports/Diabetes_in_the_UK_2010.pdf:
Prevalence of diabetes in the UK is increasing

<table>
<thead>
<tr>
<th>Year</th>
<th>Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>1940</td>
<td>200,000</td>
</tr>
<tr>
<td>1960</td>
<td>400,000</td>
</tr>
<tr>
<td>1980</td>
<td>800,000</td>
</tr>
<tr>
<td>1996</td>
<td>1,400,000</td>
</tr>
<tr>
<td>2004</td>
<td>1,800,000</td>
</tr>
<tr>
<td>2010</td>
<td>3,000,000</td>
</tr>
</tbody>
</table>


Over 2 million people diagnosed\(^1\)
Approx 4.9% of UK adult population\(^1\)
T2DM accounts for 85-95% of all cases\(^2\)

The total number of people with diabetes in the UK could increase to >5.5 million by 2030\(^3\)

All references accessed in May 2012
Prevalence of overweight and obesity in people with T2DM

Overweight refers to BMI 25–29.9 kg/m²; obese refers to BMI ≥30 kg/m².

Almost two thirds of adults and one third of children have a weight problem

- **67.1% of men and 57.2% of women** are overweight or obese\(^1\)
  - 1 in 4 adults were obese in 2013 (26.0% men and 23.8% women)

- **Children in 2013-14**
  - 22.5% of Reception children were either overweight or obese\(^2\)
  - 33.5% of Year 6 children were either overweight or obese\(^2\)
  - 9.5% of Reception children and 19.1% of Year 6 children were classed as obese, showing a doubling between the two age groups\(^2\)

- **Foresight report (Oct07):**
  - estimates on current trends >\textbf{50}\% of the UK will be obese by \textbf{2050}
  - Currently 2/3 adults and 1/3 children overweight or obese
  - Without action 9/10 adults and 2/3 children overweight or obese by 2050

By 2050 total direct and indirect costs of obesity may increase to **£49.9bn**

Obesity is everywhere!
- and it leads to diabetes
Excess visceral fat promotes insulin resistance and increased CV risk

- Hepatic FFA flux (portal hypothesis)
- Suppression of lipolysis by insulin
- Insulin resistance
- Dyslipidaemia
- Pro-atherogenic

Excess visceral fat

- Secretion of metabolically active substances (adipokines)
- PAI-1
- Adiponectin
- IL-6
- TNFα

Net result:
- Insulin resistance
- Inflammation

FFA = free fatty acids

Visceral Fat

©1994 Mayo Foundation for Medical Education and Research. By permission of Mayo Foundation.
Etiology of Obesity

Energy Intake
- Energy-Dense, High-Calorie Diet
- Genetic Predisposition
- Epigenetic factors

Energy Expenditure
- Sedentary Lifestyle
Figure 8.4: The full obesity system map, which highlights how agents outside conventional mechanisms are key enablers of and barriers to change. Variables outside of coloured areas relate to social trends and interaction or human biology. Variables are represented by boxes, positive causal relationships are represented by solid arrows and negative relationships by dotted lines. The central engine is highlighted in orange at the centre of the map.
How can we solve a problem like obesity?

1) Tackle all 100+ causes

- Nanny state or "nudge"
- Increase physical activity
- Decrease food consumption
- Food tax/subsidy
- Etc

Where is the evidence that we can "prevent" obesity?

2) Treat the overweight/obese

"Treating" the overweight "prevents" more obesity etc

NICE Recommends (for adults):
- Diet
- Exercise
- Behavioural therapy
- Drug treatment
- Surgery (if BMI >40, or >35 with co-morbidities)

NICE Clinical Guideline 43; Treating people who are overweight or obese. Dec 1996
Does the patient think they have a weight problem?
Diseases related to obesity (*)

Pulmonary disease
- obstructive sleep apnea
- Asthma/COPD

Nonalcoholic fatty liver disease
- steatohepatitis
- cirrhosis

Gall bladder disease

Gynaecologic abnormalities
- abnormal menses
- infertility
- polycystic ovarian syndrome

Osteoarthritis

Hyperuricaemia and Gout

Coronary heart disease
- Dyslipidemia
- Hypertension

Diabetes

Cancer
- breast, uterus, cervix
- colon, esophagus, pancreas
- kidney, prostate

Stroke

Phlebitis
- venous stasis

Stress incontinence

Leg ulcers
- pressure sores

* Speakers own opinion
Relative risk of health problems associated with obesity

<table>
<thead>
<tr>
<th>Disease</th>
<th>Women</th>
<th>Men</th>
</tr>
</thead>
<tbody>
<tr>
<td>T2D</td>
<td>12.7</td>
<td>5.2</td>
</tr>
<tr>
<td>Hypertension</td>
<td>4.2</td>
<td>2.6</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3.2</td>
<td>1.5</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>2.7</td>
<td>3.0</td>
</tr>
<tr>
<td>Angina</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Gall bladder disease</td>
<td>1.8</td>
<td>1.8</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>1.7</td>
<td>-</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>1.4</td>
<td>1.9</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.3</td>
<td>1.3</td>
</tr>
</tbody>
</table>

Risk of Major Depression with Extreme Obesity

Odds ratio

BMI

<18.5: 1.13
25-29.9: 1
35-39.9: 1.9

**Weight Loss Reduces Mortality**

<table>
<thead>
<tr>
<th>Mortality</th>
<th>&gt; 20-25% fall in mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>&gt; 30-40% fall in diabetes-related deaths</td>
</tr>
<tr>
<td></td>
<td>&gt; 40-50% fall in obesity-related cancer deaths</td>
</tr>
<tr>
<td>Blood pressure</td>
<td>Fall of approximately 10 mmHg SBP and DBP</td>
</tr>
<tr>
<td>Diabetes</td>
<td>Fall of 50% in fasting glucose</td>
</tr>
<tr>
<td>Lipids</td>
<td>Fall of 10% in total cholesterol</td>
</tr>
<tr>
<td></td>
<td>Fall of 15% in LDL-C</td>
</tr>
<tr>
<td></td>
<td>Fall of 30% in triglycerides</td>
</tr>
<tr>
<td></td>
<td>Rise of 8% in HDL-C</td>
</tr>
</tbody>
</table>

Weight loss of 10 kg produces a marked improvement in mortality.

So, what works?

**NICE** Recommends (for adults):
- Diet
- Exercise
- Behavioural therapy
- Drug treatment
- Surgery (if BMI >40, or >35 with co-morbidities)

NICE Clinical Guideline 43; Treating people who are overweight or obese. Dec 1996
The eatwell plate

Use the eatwell plate to help you get the balance right. It shows how much of what you eat should come from each food group.
Which is healthiest?

- Big Mac
- Subway Melt
- Tesco BLT

Which has the highest:
- Calories?
- Fat?
- Salt?
# Big Mac vs Subway Melt vs packaged sandwich*

*Reference to manufacturer’s own data (McDonalds, Subway, Tesco)*

<table>
<thead>
<tr>
<th></th>
<th>Big Mac</th>
<th>Subway Melt (6”)</th>
<th>Tesco BLT Packaged sandwich</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calories (kcal)</td>
<td>495</td>
<td>351</td>
<td>520</td>
</tr>
<tr>
<td>Protein (g)</td>
<td>29</td>
<td>27</td>
<td>25.4</td>
</tr>
<tr>
<td>Carbohydrate (g)</td>
<td>41</td>
<td>40</td>
<td>46.4</td>
</tr>
<tr>
<td>Of which sugars (g)</td>
<td>9</td>
<td>3.2</td>
<td>8.3</td>
</tr>
<tr>
<td>Fat (g)</td>
<td>24</td>
<td>11.1</td>
<td>25.8</td>
</tr>
<tr>
<td>Of which saturates (g)</td>
<td>9</td>
<td>5.2</td>
<td>7.1</td>
</tr>
<tr>
<td>Fibre (g)</td>
<td>5.0</td>
<td>4.0</td>
<td>5.5</td>
</tr>
<tr>
<td>Salt (g)</td>
<td>2.0</td>
<td>4.3</td>
<td>3.1</td>
</tr>
</tbody>
</table>
Common mistakes

All sugars are the same (4kcal/g) i.e., sucrose = fructose etc
- Coco pop straws 34g/100g = 2 finger kitkat
- Fruit juice approx 9g/100mls

All fats (satd/polyunsatd/monounsatd) are the same (9kcal/g)
- Jordan’s Country Crisp Cereal: 28.5g/100g = McDonalds McBacon Roll
- Thick pork sausages: 20.3g/100g

Alcohol (think of each drink as a chocolate bar!)

High fat foods vs Low fat foods

Premium vs Economy ranges vs Home cooked food:
- Premium - likely to have high fat and high sugar (high calories)
- Economy - likely to have high salt
- Home cooked - likely to have high fat (depends on how it is cooked) ?better
The role for Meal Replacement

Meal Replacement Systems:

- Eg, SlimFast, Celebrity Slim, The Biggest Loser, many “own brands”
  - Most MRs aim for 1200-1400
  - Replace 2 meals (breakfast/lunch) + nutritional meal in evening
  - European Directive gives nutritional composition (NOT complete)

  - Products must contain 200-400 kcal, >25% protein, 23 vitamins and minerals, 5-6g fibre

VLCDs (VLEDs):

- Eg, Lighter Life, Cambridge Weight Plan, Lipotrim
  - Defined as < 800 kcal (3,300 kJ) per day or less
  - Nutritionally complete (normally liquid) meals
  - Carbohydrate may be entirely absent (although mostly > 50g)
Explaining calories

2000 kcal (energy requirements)
1500 kcal (intended calorie intake)

Daily calorie deficit 500 kcal
Weekly calorie deficit = 7 * 500 = 3500 kcal = 1 lb FAT

1 lb/week = 4 lb/month = 1 st/3 m = 4 st/year

one night off 4000 x kcal
= >1 lb fat
= >1 week of dedicated dieting

6000 kcal
The role of Exercise

- Isolated exercise is an inefficient way of burning calories and losing weight
- 1 mile (15 mins) burns up 100 kcals
- Regular exercise has a huge effect on burning calories and losing weight

Energy expenditure = BMR x PAL (modified Harris Benedict equation)

- BMR (kcal/day):
  - Age (yrs) | Men | Women
  - 10-18 | 17.5 x Kg + 651 | 12.2 x Kg + 746
  - 18-30 | 15.3 x Kg + 679 | 14.7 x Kg + 496
  - 31-60 | 11.6 x Kg + 879 | 8.7 x Kg + 829
  - >60 | 13.5 x Kg + 487 | 10.5 x Kg + 696

- PAL (Patient Activity Level)
  - Activity level | Men | Women
  - Inactive | 1.3 | 1.3
  - Light | 1.55 | 1.56
  - Moderate | 1.78 | 1.64
  - Heavy | 2.1 | 1.82

Rotherham Institute for Obesity protocol for calorie estimation 2015

eg,
24yr old man 80kg
BMR = 1903
PAL = 1.3
energy = 2474

PAL = 1.55
energy = 2950
Relationship between Physical Activity & Health

Figure *. The dose-response curve demonstrating the relationship between physical activity and risk of chronic disease – The more you exercise the less likely you are to develop a chronic disease

Physical
- Metabolic Syndrome
  - Insulin resistance
  - Type II Diabetes
- CVD
- Stroke
- Cancer
- Asthma (pulmonary disease)
- Hypertension
- Hyperlipidemia
- Orthopaedic incl.
  - abnormal bone growth,
  - degenerative disease,
  - pain

Psychological
- Low Self-Esteem
- Depression
- Substance abuse
Physical Inactivity

Risk of CVD mortality by CV fitness and BMI, 2,316 men with Type 2 diabetes

Church et al. Arch Int Med 2005;165:2114-20
COMFORT EATING AND BINGE EATING
Behaviour change:

- Talking Therapies:
  - Life coaching
  - Cognitive Behavioural Therapy (CBT)
  - Neurolinguistic Programming (NLP)
  - Emotional Freedom Techniques (EFT)
  - Hypothesis
  - Hypnobotbanding
  - etc
Can we ever control appetite?
Pharmaceutical Strategies

Old Medications:
- Am-Bar (amphetamine + barbiturate)
- Phentermine,
- Rimonabant,
- Sibutramine

Current licensed medications:
- Pancreatic lipase inhibitors – Orlistat (Xenical/Alli)

Weight friendly diabetic medications:
- Metformin
- DPP4 inhibitors (“gliptins”)
- SGLT2 inhibitors (“flozins”) eg Canagliflozin
- GLP1 analogues

Coming soon? (all available in the US)
- Liraglutide 3.0mg
- Lorcaserin
- Qnexa/Qsymia (Phentermine + Topiramate)
- Contrave (Naltrexone SR + Bupropion SR)
National Institute for Health and Clinical Excellence (NICE): T2D treatment algorithm

**MET**
- HbA1c ≥6.5%

**MET + SU**
- HbA1c ≥7.5%

**Insulin + MET + SU**
- HbA1c ≥7.5%

**Consider substituting DPP-4 or TZD for SU if:**
- Risk of hypoglycaemia or SU is contraindicated or not tolerated

**Consider SU if:**
- Not overweight
- MET not tolerated or is contraindicated
- Rapid response needed because of hyperglycaemic symptoms

**MET + DPP-4 or TZD**
- HbA1c ≥7.5%

**Insulin + MET + SU**
- HbA1c ≥7.5%

**MET + DPP-4, or MET + SU + TZD, or MET + SU + exenatide**

**HbA1c ≥6.5%**

**Start insulin**
- HbA1c ≥7.5%

**Insulin + MET + SU**
- HbA1c ≥7.5%

**Increase insulin dose and intensify regimen over time. Consider adding pioglitazone with insulin if:**
- A TZD has previously had marked glucose-lowering effect or blood glucose control is inadequate with high-dose insulin

**MET = metformin, SU = sulphonylureas, TZD = thiazolidinedione, DPP-4= dipeptidyl peptidase-4 inhibitor**

# Treatment options in T2D*

<table>
<thead>
<tr>
<th>Drug/Class</th>
<th>Effect on</th>
<th>Adverse effects4*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Weight1,2,5</td>
<td>Lipids1,2</td>
</tr>
<tr>
<td>Metformin</td>
<td>↔/↓</td>
<td>✔</td>
</tr>
<tr>
<td>Acarbose</td>
<td>↓?</td>
<td>?</td>
</tr>
<tr>
<td>Meglitinides</td>
<td>↔?</td>
<td>?</td>
</tr>
<tr>
<td>Sulphonylureas</td>
<td>↑</td>
<td>✔</td>
</tr>
<tr>
<td>Pioglitazone</td>
<td>↑</td>
<td>✔</td>
</tr>
<tr>
<td>DPP-4 inhibitors</td>
<td>↔</td>
<td>?</td>
</tr>
<tr>
<td>GLP-1 receptor agonists</td>
<td>↓</td>
<td>✔</td>
</tr>
<tr>
<td>SGLT2 inhibitors</td>
<td>↓</td>
<td>?</td>
</tr>
<tr>
<td>Insulin</td>
<td>↑</td>
<td>✔</td>
</tr>
</tbody>
</table>

Case Study:

49 year old woman, who has 3 children and works as a teacher. Diagnosed as having T2DM 6 years ago. She has attended DESMOND but her control is worsening. Rarely has time to monitor her blood sugars.

BMI 36kg/m2 (increasing over time)
HbA1c 65mmol/mol (8.1%) when last checked
BP 130/85, Egfr 48ml/min/1.73m2 (stable)

Current medication:

- Ramipril 10mg od
- Metformin 1g bd
- Gliclazide 160 mg bd
- Linagliptin 5mg od

What would you consider next?
Things to consider:

- Is she a driver?
- She doesn’t test BM’s often
- Is she getting hypos?
- Her weight is going up – why?
- Renal function stable but needs monitoring

- Could consider reducing/stopping gliclazide (but HbA1c may go up)
- Could consider SGLT2i eg Canagliflozin (but egfr < 60)
- Could consider replacing linagliptin with GLP1 analogue

**Should** consider referral to weight management clinic
- Talking Therapy
- Orlistat
- VLCD
- Bariatric Surgery??
The next surgical frontier

1995

Who Would Have Thought It?
An Operation Proves to Be the Most Effective Therapy for Adult-Onset Diabetes Mellitus

Walter J. Porjes, M.D., Melvin S. Swanson, Ph.D., Kenneth G. MacDonald, M.D., Stuart B. Long, M.S., Patricia G. Morisse, B.S.N., Brenda M. Brown, M.R.A., Hisham A. Barakat, Ph.D., Richard A. deRamon, M.D., Gay Israel, Ed.D., Jeannette M. Doleazol, Ph.D., and Lynis Dorn, Ph.D.

From the Departments of Surgery and Biochemistry o Performance Laboratory of East Carolina University, G

1995

2006

Surgery as an Effective Early Intervention for Diabesity

Why the reluctance?

2006

The Early Effect of the Roux-en-Y Gastric Bypass on Hormones Involved in Body Weight Regulation and Glucose Metabolism

Francisco Rubino, M.D.,* Michel Gagner, M.D., F.A.C.S.,† Paolo Gertler, M.D., slab, Schapira, Kao, M.D.,§ Shoji Fukayama, M.D.,§ John Feng, M.D.,§ and Ed L. B. Quinones, M.D.,§

2004

Objective: To examine the early effect of Roux-en-Y (RYGB) gastric bypass on hormones involved in body weight regulation and glucose metabolism.

1995

2004

Methods

Objective: To examine the early effect of Roux-en-Y (RYGB) gastric bypass on hormones involved in body weight regulation and glucose metabolism.

1995

Summary Background Data

Obesity and diabetes, both notoriously resistant to medical treatment, is thus an important factor in the current epidemic of obesity and diabetes.

2004

Results: In the first 14 years, 49% of the obese patients were treated with gastric bypass surgery. The early effect of Roux-en-Y (RYGB) gastric bypass on hormones involved in body weight regulation and glucose metabolism.

1995

Conclusions: Roux-en-Y gastric bypass reduces BMI changes before significant MOD changes take place. These results support the hypothesis of an endocrine effect as the possible mechanism of action of RVG.

1995

Obesity Surgical Interventions

- **Technical Complexity**
  - Low
  - Medium
  - High

- **Efficacy**
  - Low
  - Medium
  - High

- **Surgical Procedures**
  - Gastric Balloon
  - Gastric Band
  - Gastric Bypass
  - Sleeve Gastrectomy
  - Duodenal Switch
  - Sleeve Gastrectomy
Surgery – a cure for T2DM?

ECO 2009 Metanalysis Presentation:

- Laparoscopic Band Surgery  56.7%
- Roux-En-Y Gastric Bypass  80.3%
- Biliopancreatic Duodenal Switch  95.1%

NHS Commissioning Board (2013)
Clinical Commissioning Policy: Complex and Specialised Obesity Surgery

Intended to address the postcode lottery of availability for bariatric surgery
Address “perverse incentives” of gaining weight to meet NHS criteria for surgery
Address the findings of the NCEPOD Report findings (2012)

Key changes:
- Nationwide BMI criteria meeting NICE recommendations (BMI 40 or 35 with comorbidity)
- BMI > 50 still needing to meet other criteria
- 4 surgical procedures available on NHS (band, bypass, sleeve, switch)
- Revisional procedures only considered for clinical reasons due to complications
- Surgical team post-op care for 2 years and lifelong in tier 3
- 12-24m (*6m) in a tier 3 non-surgical MDT for intensive medical management

Problem:
- Highlighted the postcode lottery regarding the availability of tier 3 services
NHS Rotherham Healthy Weight Framework
(locally referred to as “Weigh Up”)

(< £1m per year)

TIER 4
More Life
Residential Weight Management Camps

TIER 3
MDT Obesity Service
More Life
(SELF REFERRAL)

TIER 2
Community Weight Management Service
e.g. diet/nutrition/lifestyle/exercise education
More Life Clubs via Places For People Leisure
(SELF REFERRAL)

TIER 1
Primary Activity
Population wide basic intervention & prevention
e.g. School nurse, GP, Health Visitor

TIER 4
Specialist Tertiary service
e.g. Bariatric surgery

TIER 3
Specialist MDT Obesity Service
Rotherham Institute for Obesity (RIO)
(REFERRAL ONLY)

TIER 2
Community Weight Management Service
e.g. diet/nutrition/lifestyle/exercise education
SHAPE UP
(SELF REFERRAL)

TIER 1
Primary Activity
Population wide basic intervention & prevention
e.g. GP, Health Visitor, Leisure Services

WHOLE POPULATION PREVENTION ACTIVITY
e.g., Maternal Matters, UNICEF Baby Friendly, Early Years, Play Path Finder, Healthy Schools, Ministry Of Food, Leisure and Green Spaces, Transport and Planning, Workplaces, Built Environment, etc