Disclosure

• No conflicts of interest

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Objectives

• Brief introduction
• Discuss impact of OA as a comorbid condition on management & outcomes of other conditions
• Review the evidence linking OA to metabolic syndrome (diabetes, hypertension, hyperlipidemia, obesity)
  • Metabolic OA phenotype
• Globally, aging populations & growing prevalence of obesity → increased population risk for hypertension, dyslipidemia, diabetes, cardiovascular disease…

… & osteoarthritis (OA)

OA is the fastest growing major health condition
Ranking of Major Causes of Death and Disability (%DALYs)

- Cardiovascular / circulatory: 33% average \(\uparrow\) 1990 – 2010
- All neoplasms
- Mental/behavioural
- MSK: 45% \(\uparrow\) 1990 – 2010

Back pain
Neck pain
OA (83% knee OA)

Lancet 15 December 2012
Major Challenges to Dx & Mgmt of OA

• Societal attitudes / beliefs about OA
• Physician knowledge / awareness
• Attitudes and beliefs about ‘pain killers’
• Co-existent medical problems
  – Competing demands
  – Contraindications to OA therapies
Co-Existental Medical Conditions

• 90% of people 65+ years with OA have ≥ 1 other chronic condition (common risk factors: aging, obesity)
  – Most commonly cardiovascular disease (CVD), type 2 diabetes, hypertension
  • + depressed mood (~ 1/3) - impacts adherence / effectiveness of therapies

Nieves Plaza et al J Clin Rheum 2013
K Magnusson et al Arthritis Care & Res 2014
Clustering of Common Chronic Conditions
Potential Explanations - 1

- Aging
- Obesity
- Hypertension
- Hyperglycemia
- Dyslipidemia
- Physical inactivity
- NSAIDS

CVD & Diabetes (complications)

Symptomatic OA
pain + functional limitations
What is the evidence that OA impacts physical activity?

• Surveys
  – US men aged 66-74 years – 60% reported activity limitations due to chronic back, hip or knee pain and most managing their pain with sedentary activities / rest

• Qualitative studies:
  – People with OA frequently manage joint pain by giving up activities (risk of taking pain killers, not offered other options)
  – In setting of multiple health conditions
    • Patients prioritize the condition(s) seen as ‘more severe’ or with worse future implications
    • To balance health care issues, most frequently dropped activity was exercise
  – In patients with diabetes
    • Arthritis cited as a barrier to CVD risk factor control (physical activity self-management)
Impact of OA on outcomes of other common conditions?

Hip and Knee OA

Chronic disease management

Hand OA

Appel et al, JAMA. 2003
Cheraghi-Sohi Arthritis Care & Res 2013

6/8/2015
Walking disability and mortality risk

- Population based cohort 35+ years with symptomatic hip/knee OA recruited 1994-5 from 40 English general practices (n=2,703)
- Examined survival status & cause of death to February 2009 using data from National Statistics
- Controlling for age, sex, diabetes, cancer, CVD, walking disability (1.48, 1.17 to 1.86) predicted ↑ all-cause death (mainly from CVD causes)

Neusch et al BMJ 2011
Grip strength, walking disability and risk for CVD & diabetes complications

• Population cohort 55+ years, symptomatic hip/knee OA recruited 1996-98 using tax records (n=2,156)
  • HAQ walking & grip strength (0-3)

• Whole cohort:
  – Examined hospital admission for CVD (AMI, CABG or PCI, CHF, stroke or TIA) & survival to Feb 2012 using provincial administrative databases

• Subset with diabetes at baseline:
  • Examined hospital admission for diabetes-specific complication (hypoglycemia, soft tissue infection, amputation, end-stage renal disease)

Hawker G et al PLOS ONE 2014
Grip strength, walking disability and risk for CVD & diabetes complications

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Median Follow-Up</th>
<th>%</th>
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<tbody>
<tr>
<td>All-cause death (n=2156)</td>
<td>13.2 years</td>
<td>57%</td>
</tr>
<tr>
<td>Composite CVD outcome (n=2156)</td>
<td>9.2 years</td>
<td>38%</td>
</tr>
<tr>
<td>Diabetes complication* (n=357)</td>
<td>6.5 years</td>
<td>37%</td>
</tr>
</tbody>
</table>

*102 experienced at least one infection; 47 hypoglycemia; 10 amputations; 11 hyperglycemia; and 4 initiated chronic dialysis
**Grip strength, walking disability and risk for CVD & diabetes complications**

Walking disability predicted ↑ all-cause death (aHR 1.30, 1.22-1.39, p<0.001) & ↑ CVD events (aHR 1.17, 1.08-1.27, p=0.001)

* Covariates: age, sex, income, diabetes, hypertension, smoking, NSAIDs, frailty, pre-existing CVD

Subgroup OA + DM:
Walking disability and grip strength predicted ↑ diabetes complications: aHR per HAQ walking score 1.25 (1.01-1.55), p=0.04; aHR per HAQ grip strength score 1.21 (1.01-1.45), p=0.04
Survival curves for those who did and did not receive a primary, elective hip or knee replacement

Hazard Ratio 0.56 (0.43-0.74)  
p<0.0001

Number of TJAs Needed to Prevent 1 Death: NNT 8 patients

Ravi B et al BMJ 2014
Comparative Effects: Physical Activity

- **Diabetes**
  - NNT: 7 patients

- **Metabolic syndrome**
  - NNT: 3 patients
Summary

• Large well-controlled observational studies show consistent independent relationship between walking disability and future CVD events, diabetes complications & all cause death
  - Risk for all-cause death:
    • UK study: adj. HR for self-reported walking disability = 1.48 (1.17-1.86)
    • Canadian study: adj. HR for HAQ walking score ≥ 2 = 1.51 (1.34-1.70)

• Possible explanations
  - Unmeasured confounding
  - Physical inactivity due to disabling OA
  - Stress (pain, depressed mood)
  - NSAIDs
  - Systemic inflammation? *Metabolic OA Phenotype*
OA Pathogenesis: Influence of Aging and Obesity

Joint Destruction

Biomechanical Stress

Systemic Factors

Matrix destruction
Aberrant repair response
Mechanical failure

Hand OA 2X more common in obese than non-obese
Yusuf E et al, Ann Rheum Dis 2010
Metabolic syndrome

• Cluster of cardiac risk factors:
  – Abdominal obesity
  – Dyslipidemia
  – Impaired fasting glucose
  – Hypertension (atherosclerosis)

• Visceral adiposity $\rightarrow$ abnormal lipid metabolism + generation of inflammatory mediators (adipokines) $\rightarrow$ activation of renin-angiotensin-aldosterone system, ++ catecholamine production, insulin resistance, endothelial dysfunction

Puenpatom RA Postgraduate Medicine 2009
Adipokines influence all joint tissues
e.g., infra-patellar fat pad

Produces chondrocyte activation similar to that seen with mechanical stress

Conde J et al *Arthritis* 2011
Sellem J & Berenbaum F *Joint Bone Spine* 2013
Clustering of Common Chronic Conditions
Potential Explanations - 2

Aging
Obesity

Hypertension
Hyperglycemia
Dyslipidemia

Physical inactivity
NSAIDS

Symptomatic OA

CVD & Diabetes
(complications)
Metabolic OA: 5th component of MetS?

Reduced blood flow in subchondral vessels may reduce nutrient/O\textsubscript{2} supply and/or accelerate apoptosis of subchondral osteocytes → subchondral bone remodeling

Deleterious effects of lipid and glucose abnormalities on cartilage homeostasis

Zhuo, Q. et al. (2012) Metabolic syndrome meets osteoarthritis
Metabolic syndrome and OA

• Adjusting for age and BMI:
  – ~ 3X > MetS in OA vs general population; relationship stronger in < 65 years
  – OA patients more sedentary (accelerometers), > more MetS
  – Number of MetS components predicted risk of development & progression of knee OA, hand OA

NHANES III: Puenpatom RA et al Postgrad Med 2009
Liu et al, Arthritis Care Res
Yoshimura N et al OA&C 2012 – ROAD study
Sowers M et al Arthritis Rheum 2009
Relationship stronger for knees and hands than hips

Metabolic syndrome = 2+ of hypertension, diabetes, obesity, hyperlipidemia
OA = pain, swelling, stiff in hips/knees or hands for at least 6 weeks in past 3 months
Severe OA = OA with functional limitations, e.g. difficulty walking

Prevalence of metabolic syndrome by affected joint in subjects without OA, with OA, and with severe OA

n~ 24,000 55+ years
Metabolic OA: 5th component of MetS?

Atherosclerosis (carotid intima media thickness, carotid plaque) independently associated with knee & hand, not hip OA

Hypertension associated with bilateral knee OA

Glucose intolerance & diabetes predicted development and progression of knee OA

Hoeven TA et al BMJ 2014
Yoshimura N et al OA&C 2012
Eymard et al, OA&C
Nieves Plaza et al J Clin Rheum 2013
Schett G et al Diabetes Care 2013
Magnusson N Arthritis Care & Res 2015
Summary

• Independent associations between MetS and its components with OA (knee, hand, women, younger adults > hip, men, older adults?)

• Symptomatic OA associated with walking disability, reduced grip strength, which increases risk for CVD and diabetes events

• Limitations:
  – Variable definitions of MetS and OA
  – Variable control for key confounders (age, obesity, smoking, alcohol, etc)

What is the relative contribution of disability versus systemic inflammation?
Interactions Between OA & Other Common Conditions

CLINICAL IMPLICATIONS
Pivotal role of physical activity
combination of aerobic, resistance, balance + flexibility exercises

• ↓ Metabolic Alterations
  – accumulation of advanced glycation end-products [AGEs]
  – lipid metabolism
  – excess adipose tissues/fatty acids
  – hyperglycemia
  – systemic inflammation
    • Walking + weight loss in OA reduced IL-6 levels – Messier et al JAMA 2013

• ↓ Physical Impairments
  – activity/mobility limitations
  – deconditioning
  – excess body weight/joint loads
  – joint stiffness
  – muscle weakness/loss of lean muscle mass
  – poor balance/falls

Positive effect of PA on depressed mood…sleep

Clinical Implications

- OA is a risk factor for CVD?
- Impact on treatment decisions (e.g. NSAIDs)

<table>
<thead>
<tr>
<th>Core treatments</th>
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<tbody>
<tr>
<td>Appropriate for all individuals</td>
<td></td>
</tr>
<tr>
<td>Land-based exercise</td>
<td>Water-based exercise</td>
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<tr>
<td>Weight management</td>
<td>Self-management &amp; education</td>
</tr>
<tr>
<td>Strength training</td>
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**Knee OA with other health problems**
- Biomechanical interventions
- Intra-articular corticosteroids
- Topical NSAIDs

**Multi-joint OA with other health problems**
- Biomechanical interventions
- Intra-articular corticosteroids
- Oral Cox-2 inhibitors (selective NSAIDs)
- Duloxetine
Future directions

• Larger, prospective studies to confirm/examine temporal relationships & elucidate mechanisms beyond age & BMI
  – OA incidence and progression
  – Structure versus symptoms
  – Weight-bearing vs non weight-bearing joints

• Clinical trials of impact of Rx of metabolic syndrome / components on OA incidence and progression
  – Modifiable risk factors for OA?

• Clinical trials of impact of Rx of OA disability on outcomes for other conditions associated with MetS
Thanks

AND DON'T LET HIM SWEET-TALK YOU ABOUT DIET AND EXERCISE. I WANT PILLS!