Diabetes and cancer

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Declaration of interests

- I have no conflicts of interest
- I do not undertake talks / advisory bodies / research for any pharma company
- Consultant in diabetes
  - 1 session per week in primary care
  - Main clinical interest is diabetic renal disease

What I will cover

- The link between diabetes and cancer
  - Two epidemics or one?
- Possible mechanisms
  - Insulin + IGF-1
  - Cancer therapies and diabetes
- Does glucose control matter in cancer patients?
- Practical management of glucose in patients with diabetes and cancer
  - Five case studies

The worlds most populated countries?

1. INDIA
2. CHINA
3. DIABETES
4. USA
5. BRAZIL

Why is diabetes important?

Retinopathy
Commonest cause of blindness in people of working age

Stroke
3x increased risk

Heart Disease
75% of patients with diabetes die of CVD

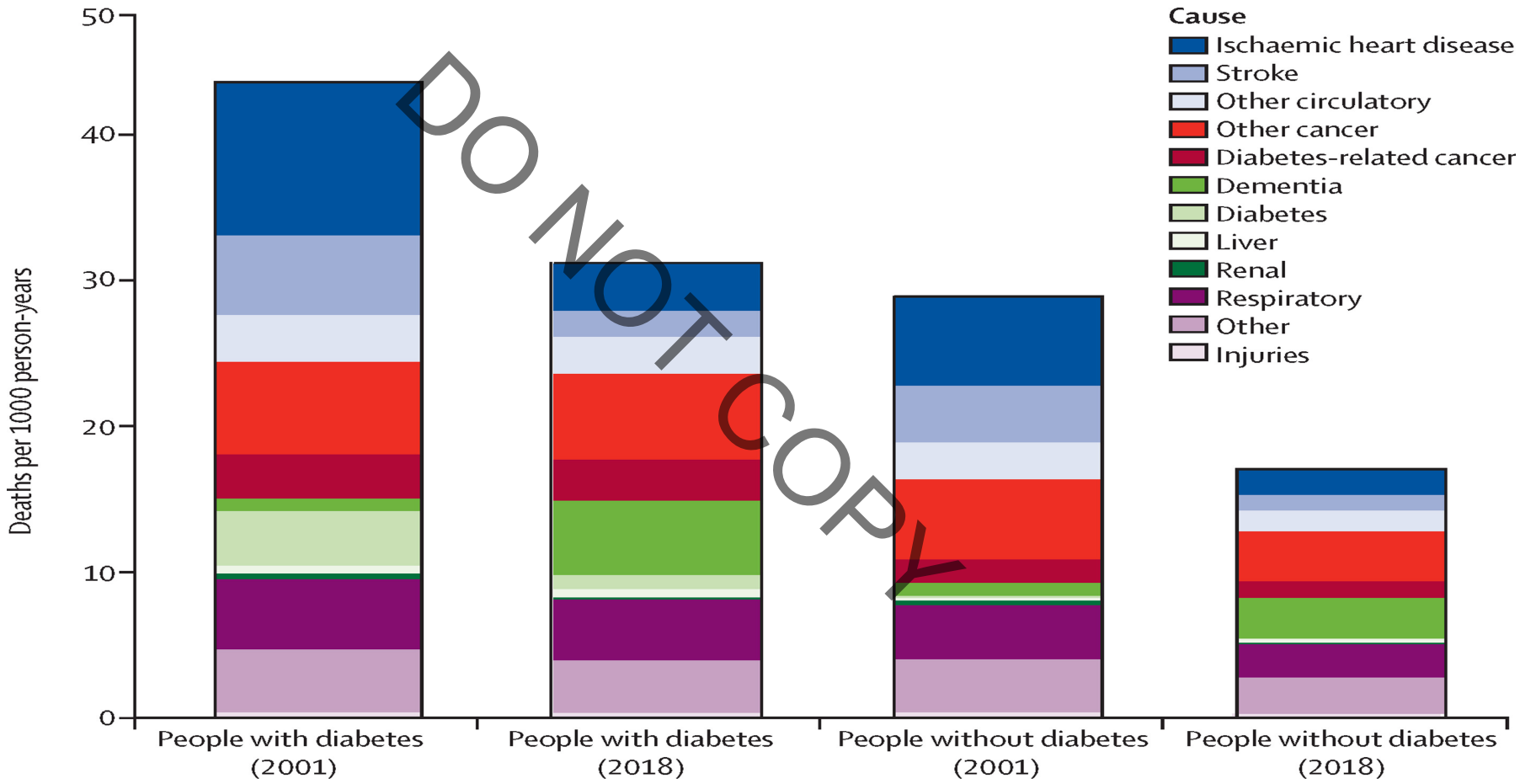
Cirrhosis
Third commonest cause of cirrhosis worldwide

Nephropathy
Commonest cause of ESRF

Cancer
X2 increased risk of breast, liver, colon and pancreas cancer

Foot Problems
Commonest cause of amputation

What is the commonest cause of death in people with diabetes?



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Association of cancers (classified by site) with obesity, diabetes and treatments

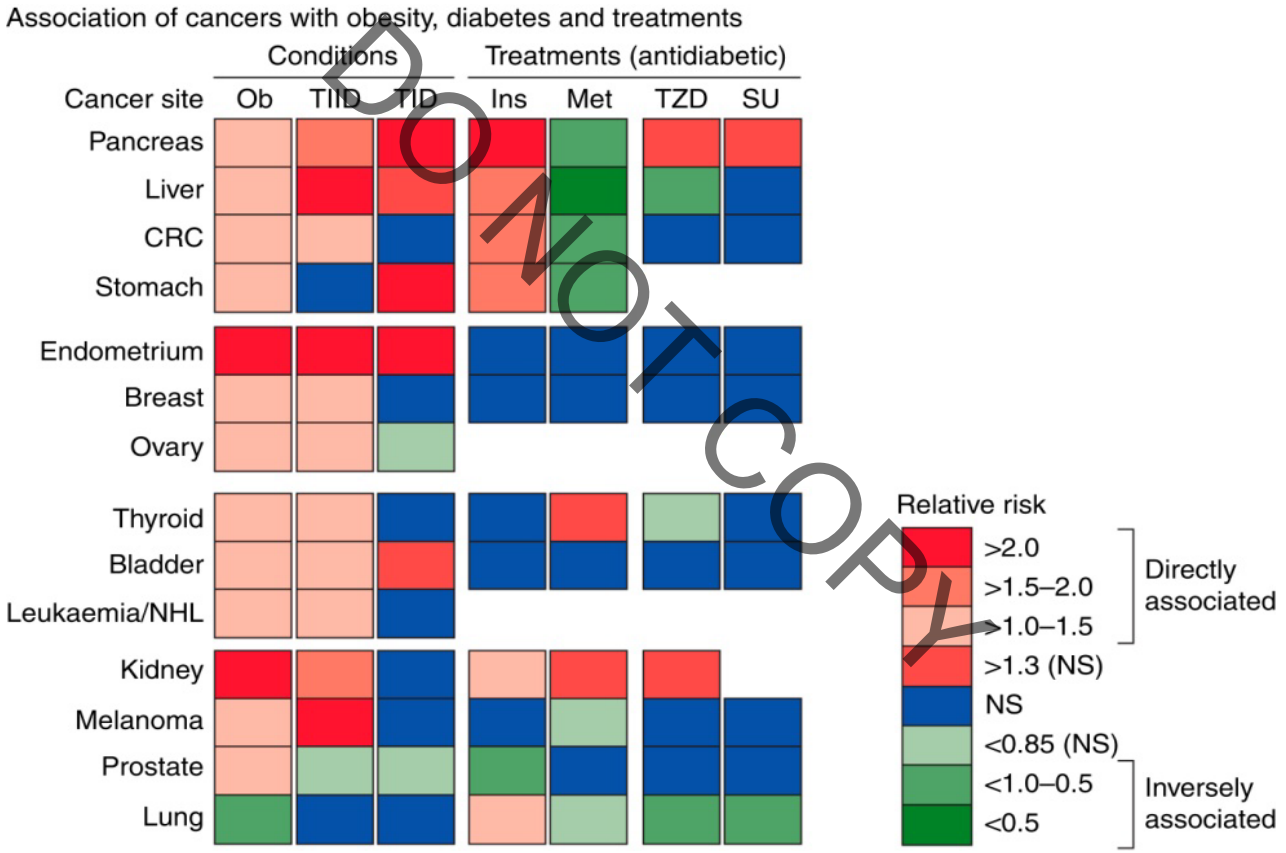
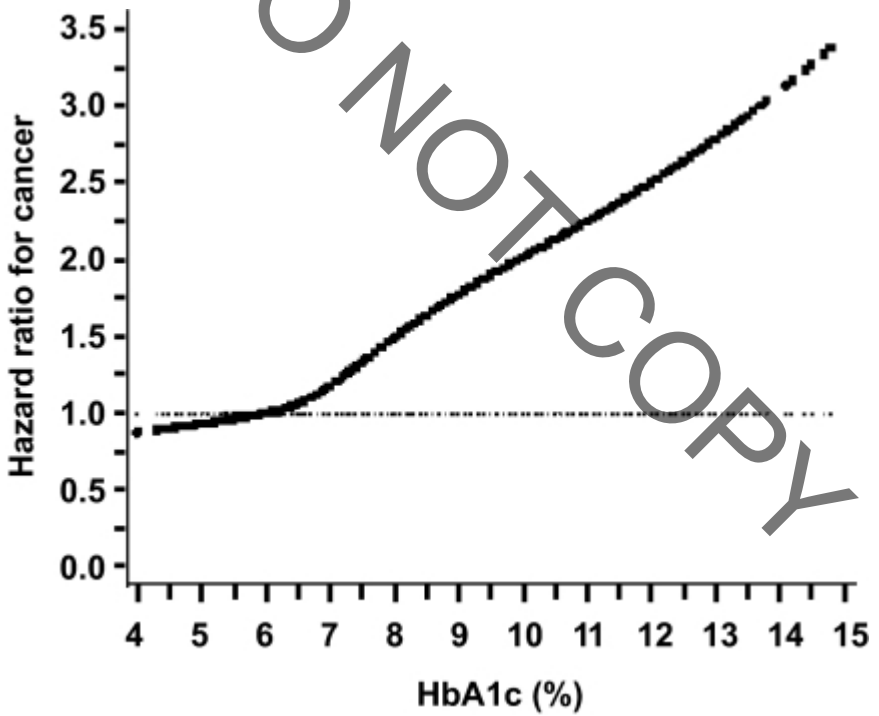


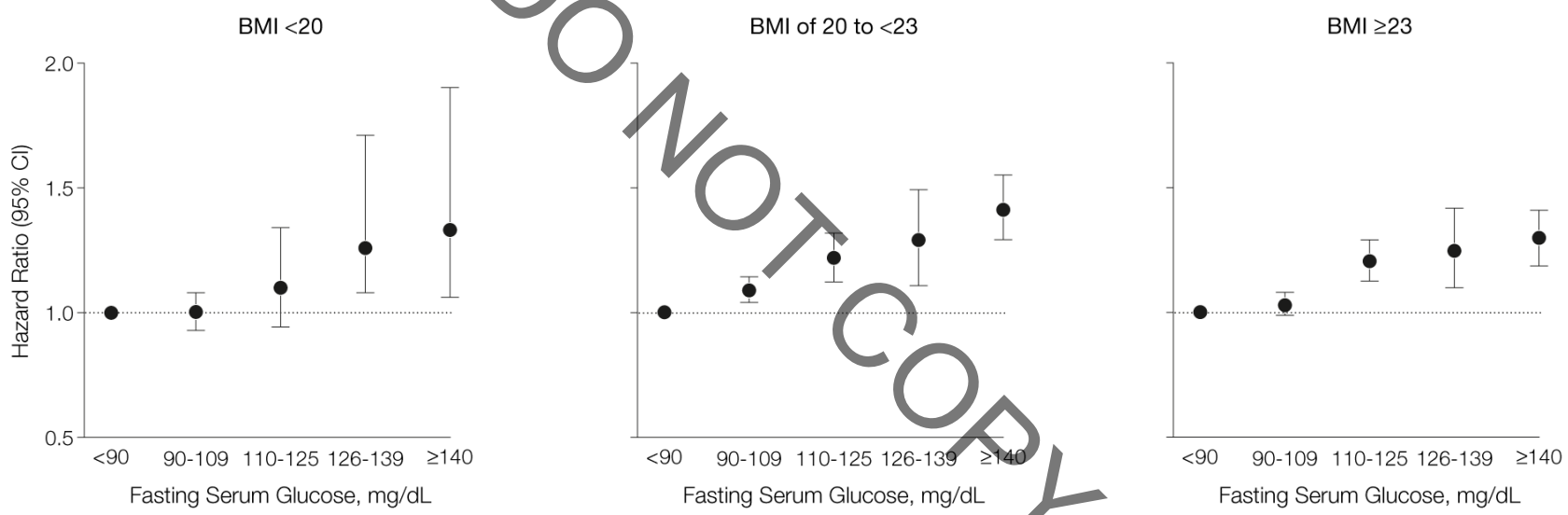
Figure 1 from García-Jiménez *et al.* *British Journal of Cancer* doi:10.1038/bjc.2016.37

Risk of Cancer and HbA1c



Yang et al, Diabetes 2010

Effect appears to be independent of BMI



Jee et al, JAMA 2005

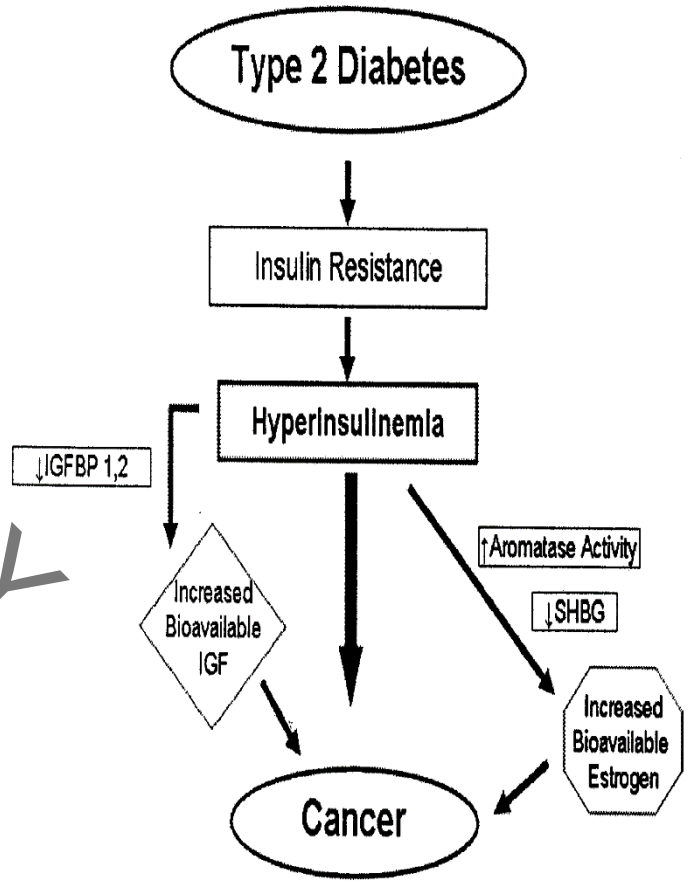
Clinical Message

- The co-diagnosis of cancer and diabetes is much greater than would be expected by chance
- Adjusted excess cancer risk of ~ 30% (Adjusted for BMI, Age, Other cancer risk factors)
- Strongest associations seen with breast, colorectal, liver and pancreatic cancer

How are diabetes and cancer linked?

- **Hyperinsulinaemia**

- Evidence:
  - In vitro, insulin is mitogenic
  - Breast cancer
    - Insulin induces aromatase and reduced SHBG, hence increasing free oestrogen
    - Breast cancer cells have insulin receptors
  - Patients with cancer have higher levels of C-peptide and insulin compared to patients without



How are diabetes and cancer linked?

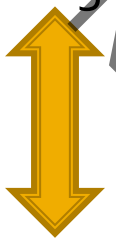
- **IGF-1**
  - Insulin action on IGF-1 receptors may be mitogenic
  - Prospective data shows that baseline IGF-1 is directly correlated with cancer incidence
  - Hyperinsulinaemia results in lower levels of IGFBP-3 – hence increased free IGF-1

Cancer therapies and hyperglycaemia

- Systemic anti-cancer therapies (SACT) that cause hyperglycaemia include:
  - Glucocorticoids
  - Hormonal Therapies
    - LHRH analogues (Goserelin) – 44% increased risk of diabetes
    - Tamoxifen
  - Oxaliplatin
  - 5-fluorouracil
  - mTOR kinase inhibitors (everolimus)
  - ABL kinase inhibitors (nilotinib)
  - Immune checkpoint inhibitors (pembrolizumab, ipilimumab, nivolumab, atezolizumab)

Clinical Message

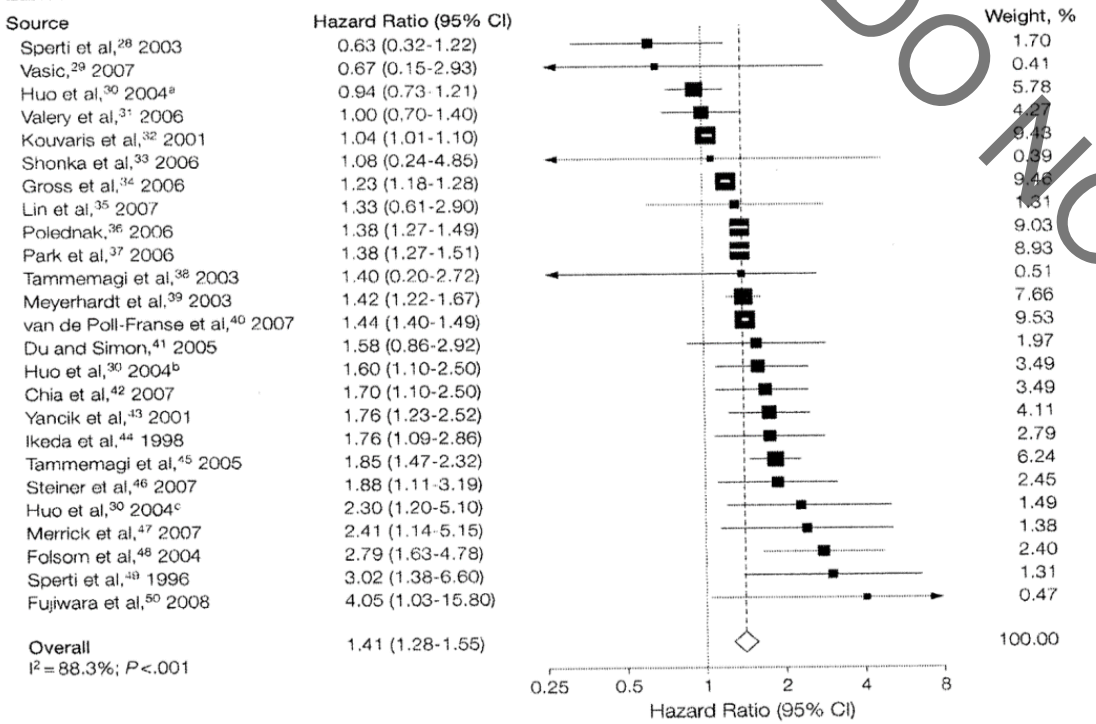
- Diabetes begets cancer



- Cancer begets diabetes

Diabetes and Cancer – does glucose matter?

Figure 2. Meta-analysis and Pooled Hazard Ratio of Long-term, All-Cause Mortality in 23 Studies Comparing Cancer Patients With and Without Preexisting Diabetes Mellitus



The 23 studies provided 25 estimates. Weights are from random-effects analysis. Data markers are proportional to study sample sizes. CI indicates confidence interval.
[a]Patients who had no resection, Childs Pugh B.
[b]Patients who had no resection, Childs Pugh A.
[c]Patients undergoing surgical resection.

- No RCT evidence that tight glucose control improves outcomes in cancer
- The diagnosis of diabetes in a person with cancer increases their risk of:
  - Overall mortality by about ~30-50%
  - ~ 50% increased surgical mortality and morbidity
  - Failure to respond to chemo / radio therapy

Clinical Message

- The diagnosis of diabetes increases the risk of poorer outcomes in patients with cancer
- There is, however, no clear evidence that improved glycaemia reduces this risk
- Therefore pragmatic management of glycaemia is required –
  - avoiding extremes of hypo- and hyperglycaemia

What are the challenges in managing diabetes patients with cancer?

- Diabetes patients often have multiple co-morbidities
  - Renal / CVD / Neuropathy – all exacerbated by chemotherapy
- Chemo / steroids exacerbate pre-existing diabetes or induce new onset hyperglycaemia
  - Especially difficult in intermittent regimes
- Cancer patients needs nutrition
  - High calorie feeds / enteral feeds can be tricky to manage
- Better control of diabetes MAY improve outcomes
  - But an evidence free area
- De-intensifying therapy in poor prognosis or end of life care

Some principles of management

- Try to avoid intravenous insulin unless unable to eat and drink
- In glucocorticoid induced hyperglycaemia, treat post prandial glucose levels
- *Cyclical* regimes of anti-diabetic therapy may be necessary in patients on cyclical chemo / glucocorticoids
- Doses of tablets / insulin may need to increase 2-3 fold
- Avoid hypoglycaemia
- Encourage metformin therapy if no contra-indications

What about metformin and cancer?

- Retrospective cohort study in UK GPs, 62,809 diabetic patients, followed for 5 years:
  - Metformin associated with a reduced mortality from cancer
- In vitro metformin inhibits cancer cell proliferation and growth
- Metformin selectively kill cancer stem cells in breast cancer
- Metformin may reduce risk of breast / colon cancer
- Emerging data suggesting metformin added to chemo improves outcomes in breast and colon cancer

Drug Class	HR (95% CI)
Metformin	1.0
Metformin + SU	1.08 (0.96-1.21)
SU	1.36 (1.19-1.54)
Insulin	1.42 (1.27-1.60)
Insulin + MF	0.54 (0.43-0.66)

Decensi A, Puntoni M, Goodwin P, Cazzaniga M, Gennari A, Bonanni B, Gandini S. Metformin and cancer risk in diabetic patients: a systematic review and meta-analysis. Cancer Prev Res (Phila). 2010 Nov;3(11):1451-61.

JBDS: The management of glycaemic control in people with cancer

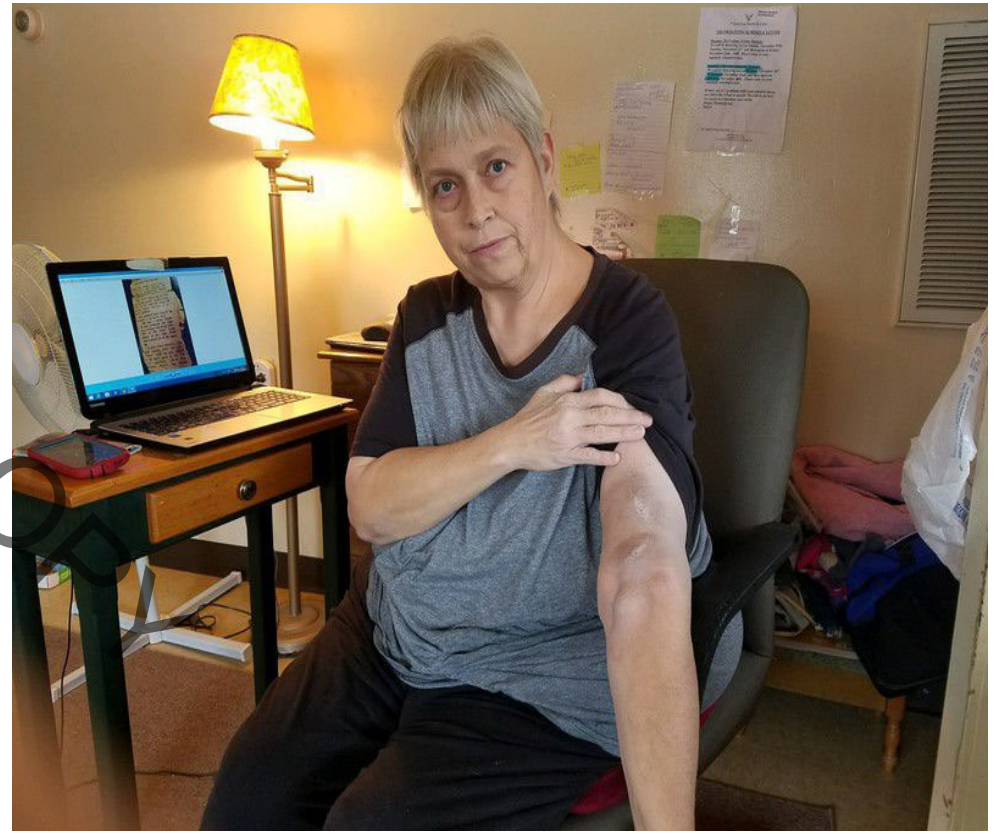
Managing a person with diabetes undergoing SACT

1. All oncology patients should have a baseline HbA1c and random venous plasma glucose before starting SACT
2. Ensure PWD are been supplied with a blood glucose meter, and should be encouraged to undertake regular CBG monitoring upon commencing SACT
3. Monitor HbA1c three monthly whilst receiving SACT
4. Rapid antidiabetic therapy changes may be required when commencing high dose GCs /SACT to maintain CBG between 6-12 mmol/L
5. Modifications to antidiabetic therapy may be necessary if CBG is found to be ≥12mmol/L.

Ref: JBDS_17_Oncology_Guideline_with_QR_code_January_2023.pdf

Case study 1 – multiple co-morbidities

- Case Study
  - 65 y/o woman
  - Type 1 diabetes
  - ESRF aged 40
  - Renal transplant aged 46
  - Retinopathy / Neuropathy
  - No significant CVD
  - eGFR ~ 40 mls/min
- Developed multiple skins cancers – frequently removed by dermatology
- Colon cancer – aged 60 – subtotal colectomy + post operative chemo – relatively good post operative course
- Acute Myeloid Leukaemia – aged 63



Case Study 1

- Cyclical chemotherapy + high dose dexamethasone
- Hyperglycaemia reasonably managed on IV insulin (due to severe vomiting)
- Developed acute kidney injury due to chemo
- Required dialysis acutely during in-patient stay
- Post chemo renal function 50% worse (eGFR ~20 mls/min)
- Considering whether to go for further chemo

Clinical Lesson

- Renal / other organ dysfunction is common with chemotherapy
- People with diabetes are at high risk of deterioration

Case study 2 - glucocorticoids

- 72 y/o woman
  - Type 2 diabetes – 6 years, well controlled on orals
    - Mild peripheral neuropathy
  - Diagnosed with multiple myeloma
  - Treated with dexamethasone 16mg (+ others) to induce remission (not discussed with the diabetes team)
  - Admitted with acute HHS – managed on ICU
  - Good recovery – requiring > 130 units of insulin / day whilst on DXM
  - Off all insulin therapy when DXM stopped

Case study 2

- Later treated with Velcade / Thalidomide
- Developed bad neuropathic pain
  - EMG – indistinguishable from diabetic neuropathy
- Persistent difficult to treat neuropathic pain despite good control on sulfonylurea + metformin
- Cyclical insulin with DXM

Clinical lesson

- *Cyclical* glycaemic therapy may be necessary , especially with cyclical glucocorticoids
- Chemotherapy may exacerbate underlying diabetic complications
- Oncologists and diabetes specialists / primary care clinicians should work together to anticipate such problems

Glucocorticoids

- Characteristically causes post prandial hyperglycaemia - glucose high post evening meal:
- In new onset hyperglycaemia, gliclazide often useful
- *Once daily human isophane insulin* may be the most useful initial regime
  - Eg human insulin given with breakfast
- *Prandial* insulin may necessary
  - Rapid acting insulin with meals
  - Can be dosed *after* meals if oral intake is unpredictable

	7.00 am	12.00 pm	18.00 pm	22.00 pm
mmol/L	5.6	8.7	15.6	27.0

- In patients with pre-existing insulin therapy
  - Doses may have to increase 2-3 fold original dose
  - Doses must be reduced as glucocorticoid dose comes down
  - http://www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_Steroids.pdf

Case study 3 – a diabetic emergency

- 52 y/o woman – no history of diabetes
  - Metastatic breast cancer
  - Commenced on pembrolizumab as 3rd line therapy
  - Shortly after 3rd cycle
    - Developed acute nausea, vomiting, abdominal pain
    - Glucose 26 mmol/l, pH 7.02. Bicarb 12, Ketones 4.7 mmol/l
  - Treated for Diabetic Ketoacidosis
  - Good response to basal bolus therapy

Immune checkpoint inhibitors and diabetes

- Immune checkpoint inhibitors (ICP)
  - Major innovation in SACT
  - CTLA-4 or PD-1 inhibitors
- May induce de novo diabetes, although this occurs at a low frequency (<1%)
- Often causes a significant worsening of pre-existing diabetes
- Appears to be an autoimmune form of diabetes – GAD +ve in ~ 50%
- 75% of patients with new onset diabetes present with DKA
- Also causes hypophysitis and thyroiditis

JBDS: The management of glycaemic control in patients with cancer

- Commencing immune checkpoint inhibitors:
  1. Educate patients to be aware of symptoms of hyperglycaemia
  2. Rule out DKA or HHS which often occurs precipitously
  3. Withhold ICP if evidence of ICP-induced diabetes emergency.
  4. Once patient has been regulated with insulin substitution, consider restarting ICP
  5. Almost all patients require insulin therapy – refer urgently to diabetes team

https://abcd.care/sites/abcd.care/files/site_uploads/JBDS_Guidelines_Current/JBDS_17_Oncology_Guideline_Final_Revised_September_2021.pdf

Case study 4 – de-intensifying therapy

- 88 y/o South Asian man - T2D – 22 years
  - Diagnosed with CLL for 3 years, cognitive impairment
  - Lived with family - treated with maximum doses of sulfonylurea, metformin and once daily NPH insulin, 16 units administered by family.
  - Glycated haemoglobin was 56 mmol/mol (7.3%).
  - Family stated ate erratically, and that if he missed a meal, he was prone to developing hypoglycaemia in the morning.
  - Furthermore, there were times when he became agitated and refused insulin.
  - Body mass index 25.6 kg/m^2

Case study 4 – de-intensifying therapy

- Following discussion with his family, it was felt that as he was at high risk of hypoglycaemia – consider cessation of insulin

- Over two months:
  - insulin reduced by 2 units per week
  - careful monitoring of capillary blood glucose levels and liaison with the community diabetes nurse specialist.
  - insulin stopped with capillary glucoses ranging from 5 – 14 mmol/L fasting.
  - SU reduced to 40 mg bd
  - Repeat glycated haemoglobin at three months was 68 mmol/mol (8.5%).

Clinical Lesson

- Individualise glycaemic targets in frail / co-morbid patients
- Avoid hypoglycaemia
- No evidence of benefit of tight glycaemic control in older people
- Consider deprescribing hypoglycaemic agents (esp insulin / SU), but do it slowly

Case study 5 - End of life care

- 48 y/o South Asian man - known to me for >5 years
- Obese, moderately controlled T2D
- Admitted acutely with fevers – worked up and found to have large brain tumour – inoperable glioblastoma multiforme
  - Given oral dexamethasone for palliation
  - Called to neurosurgical ward to review – glucoses >20 mmol/L
  - Condition deteriorating – GCS 7
  - Family required a lot of support to convince to stop testing glucose levels / give insulin etc.
  - Palliative care and diabetes team heavily involved
  - Put onto compassionate care pathway – insulin low dose subcut od given – testing decreased to a minimum

Clinical Lesson

- The aim of end-of-life care in patients with diabetes is to facilitate a painless, symptom free death, avoiding hypo- and hyperglycaemia

End of life care

- Diabetes UK guideline:
  - Prognosis < 1 year:
    - Withdraw drugs to reduce vascular complications
    - Simplify diabetes regime
    - Relax glycaemic target
  - End of life:
    - Diet / metformin therapy – stop tablets, stop glucose monitoring
    - Other drugs – consider stopping completely, and test intermittently if conscious, giving intermittent soluble insulin if glucose > 20 mmol/L (360 mg/dl)
    - Continue long-acting insulin in Type 1 diabetes

- https://diabetes-resources-production.s3-eu-west-1.amazonaws.com/diabetes-storage/migration/pdf/End-of-life-care-Clinical-recs111113.pdf

Some points to take away

- The co-diagnosis of diabetes and cancer is common
- Diabetes increases the risk of poorer outcomes in patients with cancer
- There is no good data to suggest that tight control is beneficial
- Co-morbidities - renal / cardiovascular / neuropathic – may all be exacerbated by chemotherapy

Some points to take away

- Screen all patients undergoing SACT for diabetes with HbA1c and RPG
- Avoid extremes of hypo- and hyperglycaemia
- Multi-disciplinary management with diabetes and cancer specialists is required
- Careful discussion about pros and cons of treatment in multi-morbid patients
- Metformin is useful and may improve outcomes

And finally…

- Monitor and treat post prandial glucose levels in patients on glucocorticoid therapy
- Consider flexible / cyclical regimes for cyclical chemotherapy
- Monitor for DKA in patients on ICP
- Consider de-intensifying treatment in people with limited life expectancy or on palliative care

THANK YOU FOR YOUR ATTENTION