

Managing diabetes in people with cancer

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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
 - Case studies

Why is diabetes important?

Retinopathy

Commonest cause of blindness in people of working age

Cirrhosis

Third commonest cause of cirrhosis world wide

Cancer

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



Stroke

3x increased risk

Heart Disease

75% of patients with diabetes die of CVD

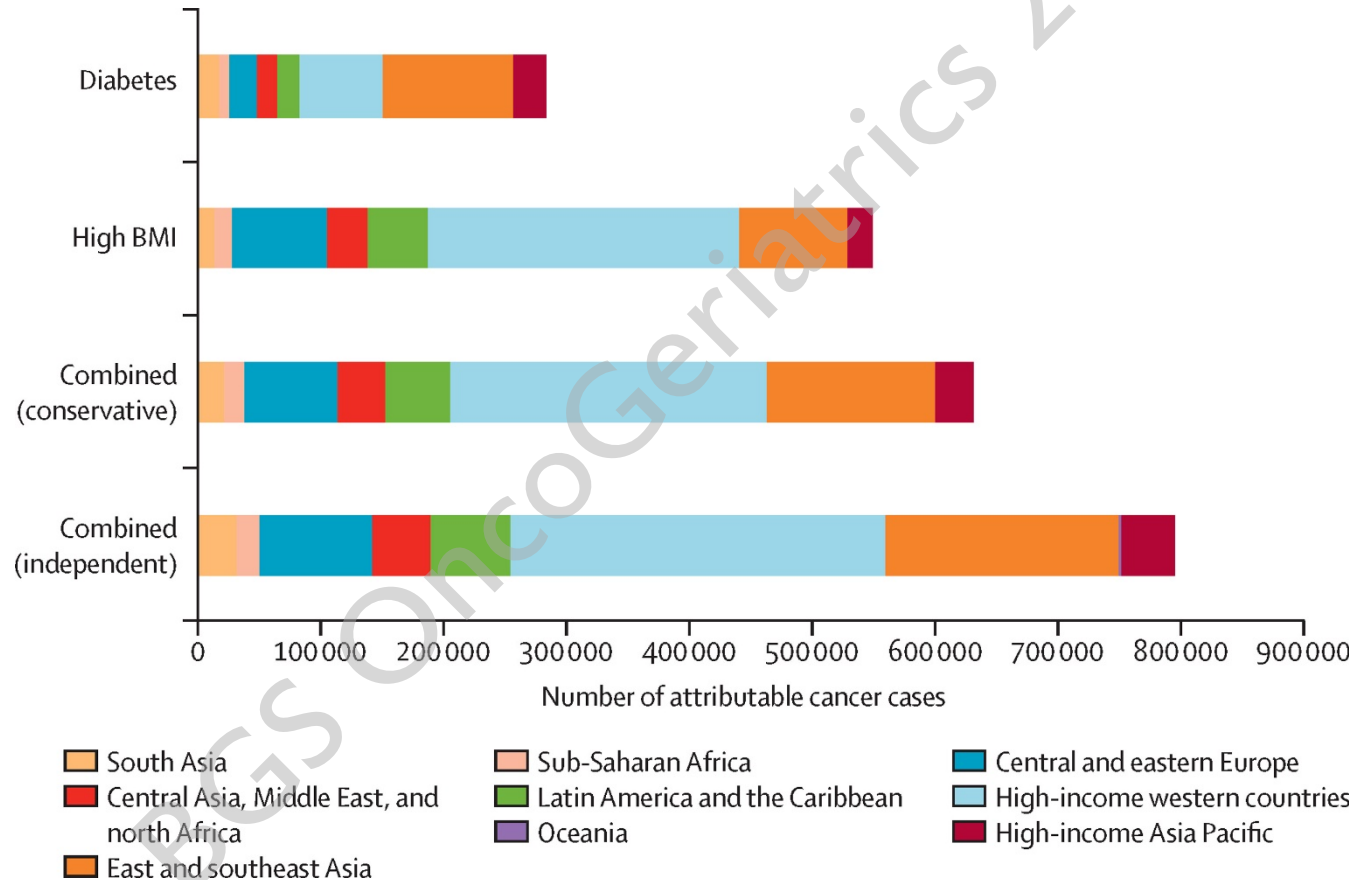
Nephropathy

Commonest cause of ESRF

Foot Problems

Commonest cause of amputation

Global cancer cases in 2012 attributable to diabetes and high BMI



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

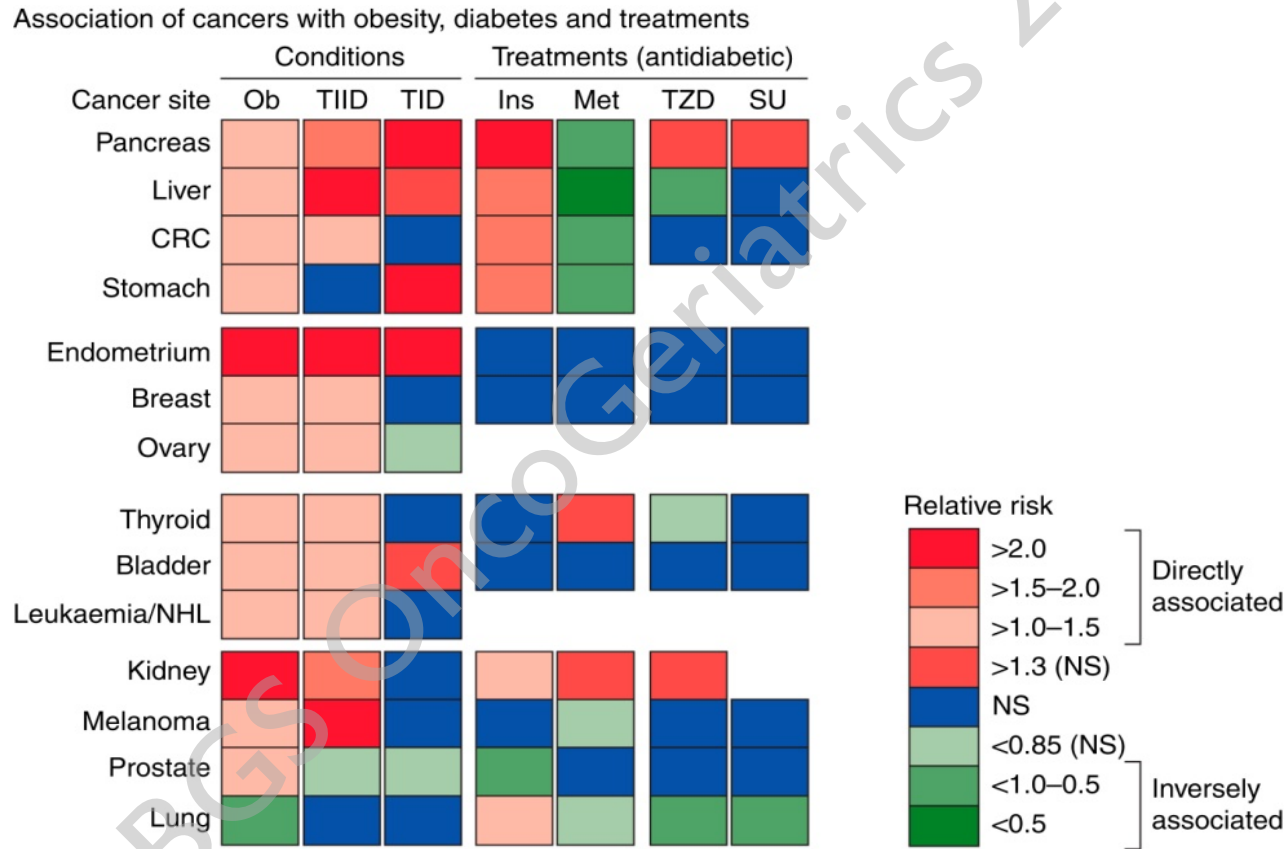
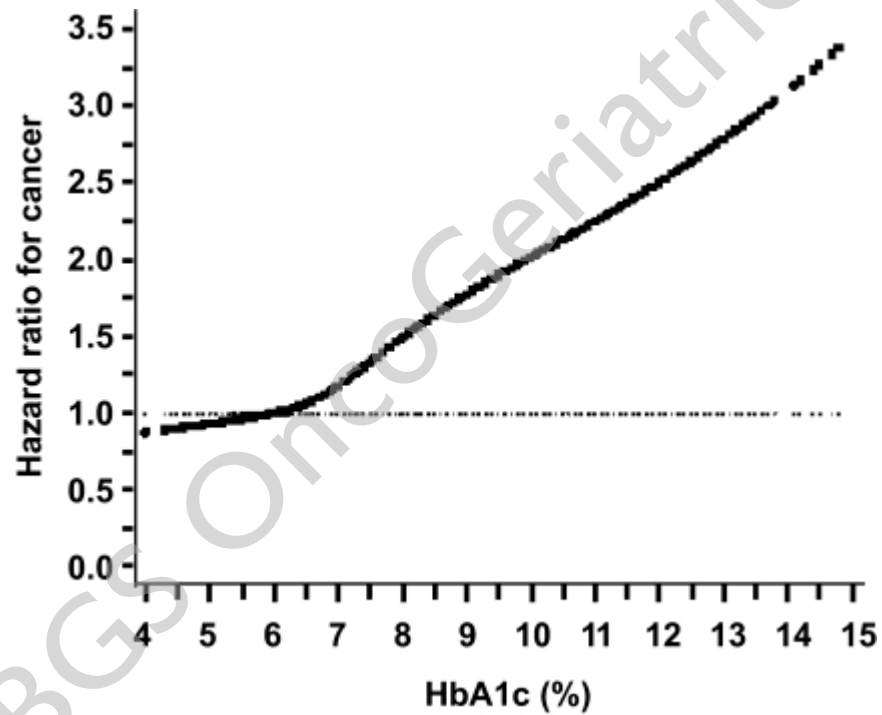


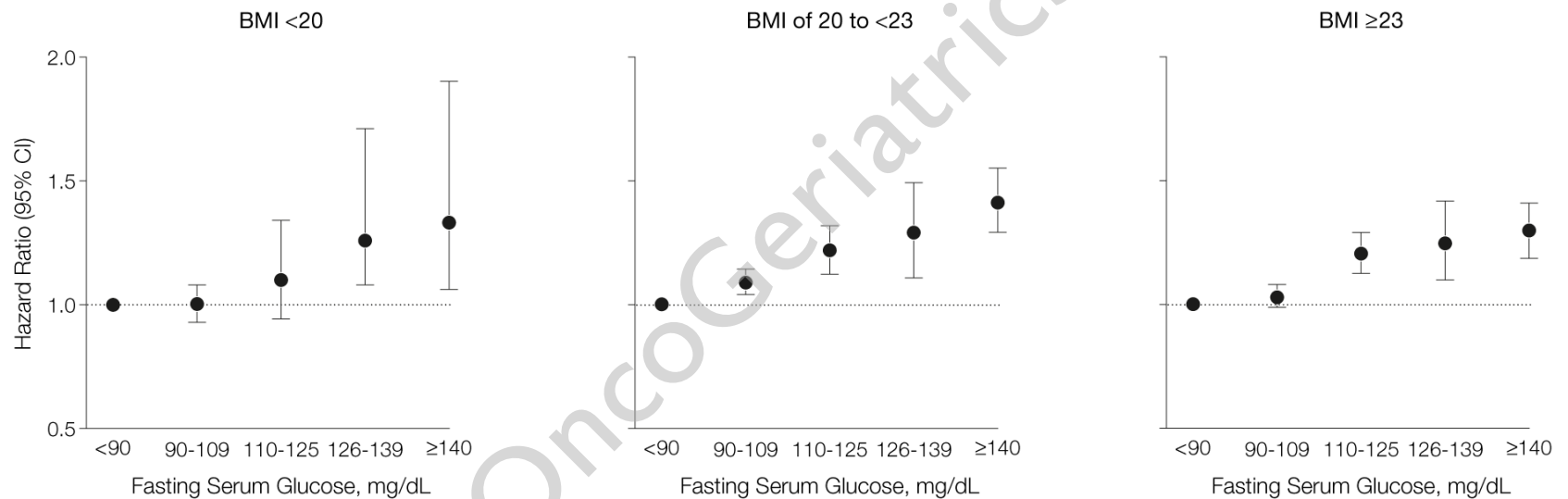
Figure 1 from Garcia-Jimenez *et al.*
British Journal of Cancer doi: 10.1038/bjc.2016.37

Risk of Cancer and HbA_{1c}



Yang et al, Diabetes 2010

Effect appears to be independent of BMI



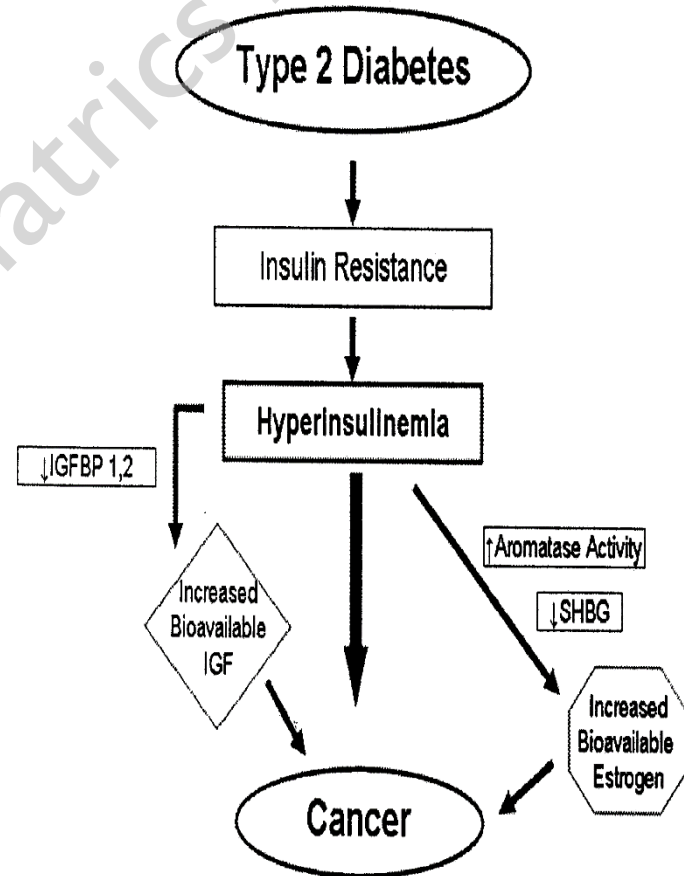
Clinical Message

- 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)

How are diabetes and cancer linked?

■ Hyperinsulinaemia

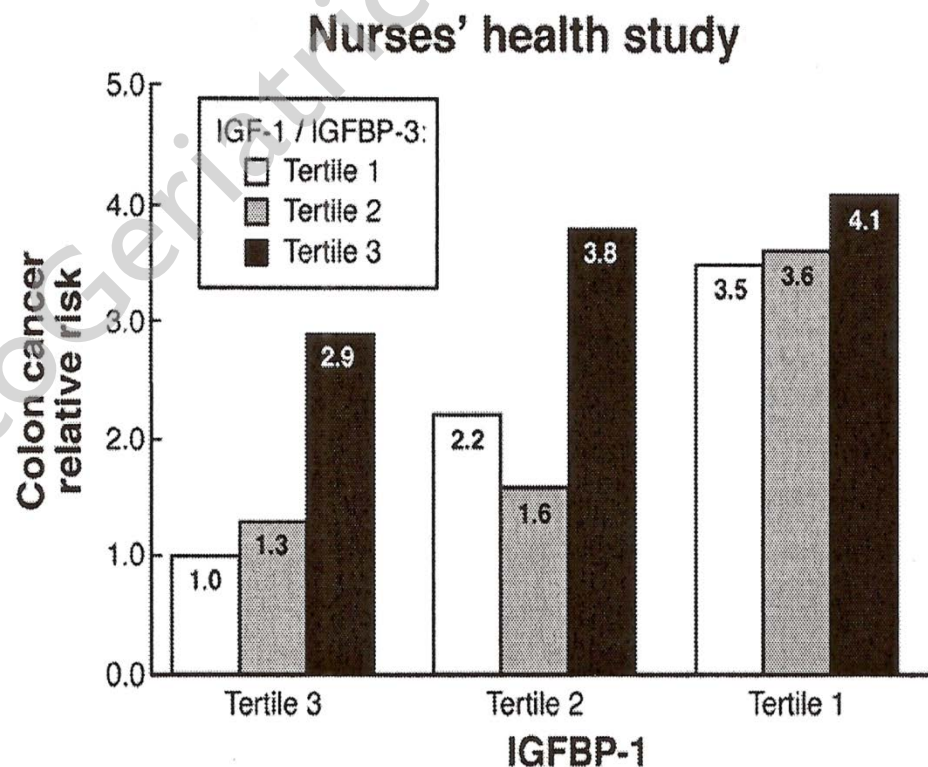
- In vitro, insulin is mitogenic
- Breast cancer
 - Insulin induces aromatase and reduced SHBG, hence increasing free oestrogen
 - Breast cancer cells have insulin receptors
- Patients with cancer have higher levels of C-peptide and insulin compared to patients without



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

- Therapies that cause hyperglycaemia include:
 - Glucocorticoids
 - Androgen Deprivation Therapy
 - LHRH analogues (Goserelin) – 44% increased risk of diabetes
 - Cisplatin
 - 5-fluorouracil
 - mTOR kinase inhibitors (everolimus)
 - ABL kinase inhibitors (nilotinib)

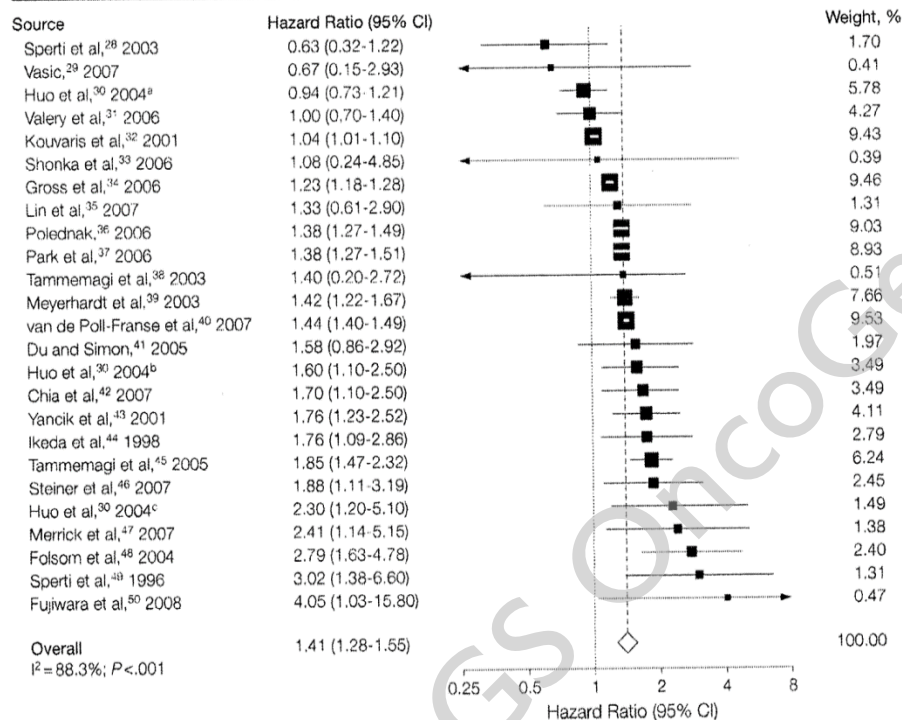
Clinical Message

- Diabetes begets cancer
- Cancer begets diabetes

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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.

^aPatients who had no resection, Childs Pugh B.

^bPatients who had no resection, Childs Pugh A.

^cPatients 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

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
- Withdrawing therapy in terminal 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

Metformin and cancer

- Retrospective cohort study in UK GPs, 62,809 diabetic patients, followed for 5 years:

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)

- 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

Case study 1 – multiple co-morbidities

■ Case Study

- 74 y/o lady
 - 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
- 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 should work together to anticipate such problems

Glucocorticoids

- Characteristically causes post prandial hyperglycaemia - glucose high post evening meal:

	7.00 am	12.00 pm	18.00 pm	22.00 pm
mmol/L	5.6	8.7	15.6	27.0
mg/dl	100	156	281	486

- In new onset hyperglycaemia, meglitinides (prandial glucose regulators) often useful
 - Useful if oral intake is unpredictable due to N&V
- *Once daily human 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

Glucocorticoids

- 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
- Splitting dose of glucocorticoids over the day may help
- Reference:
 - Management of hyperglycaemia and steroid (glucocorticoid) therapy
 - http://www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_Steroids.pdf

Case study 3 - enteral feeding

- 78 y/o South Asian man
 - Type 2 diabetes – 7 years – 30 units bd Humulin M3, HbA1c 67 mmol/mol (8.3%)
 - Mild renal impairment, proteinuria, ischaemic heart disease
- Oral cancer, needing surgery + post op chemo/radiotherapy
- Nasogastric feeding
 - Developed marked hyperglycaemia on feeds overnight 16 hour feeds
 - Hypoglycaemia prior to start of feed
- On ivi insulin – requiring 150 units / day



Case study 3

- Converted to twice daily biphasic 30/70 insulin at start and 8 hours into feed
- Moderate control – glucoses 4-20 mmol/L (72 – 360 mg/dl)
- Metformin powder added at beginning and mid feed
- Insulin adjustment daily
 - Glucoses 6-12 mmol/L (108 – 216 mg/dl)
 - HbA1c 65 mmol/mol (8.1%)

Clinical lesson

- Enteral feeding is challenging in patients with diabetes
- Biphasic mixed insulins are often useful at start and mid way into feed
- Hypoglycaemia off feed is a risk

Enteral feeding

- JBDS guidelines (enteral feeding post stroke):
 - Realistic target is 6-12 mmol/L (108 – 216 mg/dl)
 - Premixed human insulin at start and mid point of feed
 - Metformin powder recommended
- Reference:
 - Glycaemic management during the inpatient enteral feeding of stroke patients with diabetes.
 - http://www.diabetologists-abcd.org.uk/JBDS/JBDS_IP_Enteral_Feeding_Stroke.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/m²

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.
 - 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

- 68 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 palliative 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

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

Summary

- 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

Summary

- Pragmatic management is essential:
 - 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 (including enteral feeding)
 - Monitor and treat post prandial glucose levels in patients on glucocorticoid therapy
 - Consider flexible / cyclical regimes for cyclical chemotherapy
 - Carefully discuss end of life withdrawal of treatment in patients with limited life expectancy

THANK YOU FOR YOUR ATTENTION

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