CASE 1

- 39 year Asian woman referred for hyperglycemia.

- History of present illness:
  - Diagnosed with diabetes around 30 years of age
  - Insulin started soon after diagnosis.
  - Currently, lantus 12 units daily, aspart 1:10 with meals
  - FSBS ranging from the 160-200s.
CASE 1

- Past Medical History:
  - Thalassemia major
  - Central hypothyroidism
  - Central hypogonadism
  - Hepatitis C, now cured

CASE 1

- Medications:
  - Levothyroxine
  - Oral contraceptive
  - Transfusion every 3 weeks
  - Iron chelation with jadenu
  - Insulin as above
CASE 1

- Labs:
  - Hb 10.3
  - Ferritin 824 (12-240)
  - Cr 0.83
  - A1c 9.2, fructosamine 308 (190-270)
  - Total cholesterol 114, TG 188, HDL 40, LDL 36

CASE 1 QUESTIONS

1) Why could her hemoglobin A1c be misleading?
   A. Central hypothyroidism
   B. Transfusion
   C. Iron chelation therapy
   D. Hypogonadism
1) Why could her hemoglobin A1c be misleading?
   A. Central hypothyroidism
   B. Transfusion
   C. Iron chelation therapy
   D. Hypogonadism

WHAT IS FRUCTOSAMINE?

- A measure of total glycated protein in the serum.
- The predominant protein in serum is albumin.
- Indicates average BS over 2 weeks.
- Sources of error:
  - Disorders of albumin metabolism
  - Nephrotic syndrome
  - Severe defects in liver synthetic function
  - Elevated serum IgA
  - Elevated uric acid
HbA1c and FA measured on the same sample in 153 patients.

Robert M. Cohen et al. Dia Care 2003;26:163-167

©2003 by American Diabetes Association

**WHY FRUCTOSAMINE?**

- Often used in place of A1c in renal failure given changed red cell life in these patients.

- However, fructosamine’s utility in renal failure is controversial with some studies suggesting poor correlation to FSBS. FSBS may be the best alternative in these cases.

- Glycated albumin is an alternative and may be more specific.
2) What is etiology of her diabetes mellitus?
   A. Type 1 diabetes
   B. Type 2 diabetes
   C. Neither type 1 nor type 2 diabetes
THALASSEMIA MAJOR AND DIABETES

- Thalassemia major – two mutant copies of β-hemoglobin (HBB)
  - Anemia starting at 3-6 months old, persistent fetal hemoglobin expression
  - Requires frequent transfusion causing Fe overload.

- Prevalence of diabetes in cross sectional studies of treated patients
  - Adolescents 0-10%
  - Young adults 17-24%

CASE 1 QUESTIONS

3) Why do thalassemia major patients get diabetes?
   A. Beta cell failure
   B. Hepatic insulin resistance
   C. Muscle insulin resistance
   D. All of the above
3) Why do thalassemia major patients get diabetes?
   A. Beta cell failure
   B. Hepatic insulin resistance
   C. Muscle insulin resistance
   D. All of the above

**PATHOPHYSIOLOGY**

- Iron is required for proper glucose stimulated insulin secretion

- Iron overload causes beta cell dysfunction without causing complete insulin deficiency.

- Iron overload causes increased hepatic insulin resistance and in mouse models, macrophage and muscle insulin resistance.
TREATMENT

- Chelation therapy improves glycemic control
  - Probably the most data driven
- Insulin
- Metformin to improve insulin resistance
- Sulfonylurea
- DPP IV inhibitors

CASE 2 – NEW DIABETES IN AN INPATIENT

- Asked to consult for hyperglycemia on a 62 y/o Asian man with no history of diabetes.
- History of present illness:
  - 2015 – diagnosed with metastatic cholangiocarcinoma to liver
  - 3 months prior to admission, lab blood sugars are 80-90
  - 1 month PTA, lab blood sugars are 110
CASE 2 – NEW DIABETES IN AN INPATIENT

- 1 week PTA, random BS 129, 4th cycle of pembroluzimab for metastatic cholangiocarcinoma with extensive liver mets
- 5 days PTA, woke in the middle of the night and was hungry, had snacks
- 2 days PTA, polydipsia, polyuria, weak, blurry vision, nausea and vomiting, mouth very dry. Asks to get added on into Heme/Onc clinic.
- Admitted from clinic.

CASE 2 – NEW DIABETES IN AN INPATIENT

- Past Medical History:
  - Hypothyroidism – developed while on pembrolizumab

- Meds:
  - Pembrolizumab
  - Levothyroxine 50 mcg
  - MVI
  - zolpidem
CASE 2 — NEW DIABETES IN AN INPATIENT

- VS: BP 97/58  HR 96, Temp 36.6 °C (97.8 °F) (Oral) Resp 22  Ht 169 cm (5' 6'')  Wt 47.7 kg
- Exam: Dry skin, RRR, lungs clear
- Labs:
  - Glucose 875
  - Bicarb 13
  - pH 7.16 (VBG)
  - \( \beta \)-hydroxybutyrate 8.52 (nl <0.27)
  - Lactate 4.7
  - BUN 48, Cr 2 (last ~1)

CASE 2 — NEW DIABETES IN AN INPATIENT

- Labs:
  - Insulin C-peptide <0.1, concurrent glucose 695
  - GAD65, islet cell antibody, Zn transport 8 auto antibodies negative
62 year old man, metastatic cholangiocarcinoma, new diabetes and DKA. What is the etiology of his diabetes?

A) Type 1 diabetes
B) Type 2 diabetes
C) Paraneoplastic
D) Iatrogenic
CASE 2 — NEW DIABETES IN AN INPATIENT

- Anti-PD-1 antibodies:
  - Nivolumab
  - Pembrolizumab

- Anti-PD-1 ligand antibodies:
  - Atezolimumab (FDA approved for urothelial cancer, 2016)

PD-1 / PD-1L PUTS THE BRAKES ON THE IMMUNE RESPONSE

(Hickmont et al. Targeted Oncology, 2017)
ALL THREE PD-1 INHIBITORS CAN CAUSE AUTOIMMUNITY:

- **Endocrine:**
  - Hypophysitis
  - Thyroiditis
  - Adrenalitis
  - Type 1 diabetes

- **Non-endocrine:**
  - Dermatitis
  - Colitis
  - Hepatitis
  - Myocarditis
  - Pneumonitis

- Weeks to months after PD-1 directed treatment.
- Some, but not all patients have autoantibodies.
- Some but not all patients have high risk HLA haplotypes.
- Discontinuation of anti-PD1 agent not usually indicated.
CASE 2 FOLLOW UP

- Diabetes controlled with lantus 7 units daily, aspart 1:10 for carbs. Fears lows and uses a CGM.

- Pembrolizumab continued.

- Liver lesions initially responded, but now progressing.

REFERENCES

- Case 1

- Case 2
CASE 3 – NEW OUTPATIENT DM

- 90 year old woman referred for hyperglycemia.
  - Long-standing (over 10-yr) history of diabetes.
    - Treated with combination of metformin and glyburide
    - Well controlled for several years.
  - Autoimmune hepatitis requiring steroid Rx led to hyperglycemia for which insulin was started.
  - Diabetes worsened despite insulin and weaning of steroids; PCP consulted us for help.

CASE 3

- Insulin Management
  - Basal bolus for 1-2 yrs; Lantus ~7 units and Aspart 2-4 units with meals.
  - Over time, insulin requirements began to decrease from these doses.
  - Eventually, managed only with basal insulin
  - A1c <7
  - Azathioprine maintained for hepatitis.

- Interval history:
  - Stopped coming to clinic regularly because, at age 90, she "did not see the point"!
CASE 3

- Physical Exam:
  - BP 142/85; HR 75
  - Height 5’2”; Weight 45 kg; BMI 18.1
  - General: NAD, pleasant
  - HEENT: EOMI, no exophthalmos
  - Neck: Normal thyroid, no lymphadenopathy
  - Lungs: clear
  - Heart: RRR normal S1/S2
  - Abd: soft NT, ND
  - Ext: No edema
  - Neuro: alert, oriented, no tremor

WHAT IS THE DIAGNOSIS?

A) Type 1 diabetes
B) Type 2 diabetes
C) Maturity onset diabetes of the young
D) Other
WHAT IS THE DIAGNOSIS?

A) Type 1 diabetes
B) Type 2 diabetes
C) Maturity onset diabetes of the young
D) Other

CASE 3 - RESOLUTION

Autoantibody panel sent:
- GAD65: >250 (nl <5)
- Insulin: <0.4 (nl <0.4)
- Islet cell antibody: negative
- ICA-512: <0.8 (nl <0.8)
- Zinc transporter 8: <10 (nl <10)
CASE 3 = TYPE 1 DIABETES

- Is this latent autoimmune diabetes (LADA)? (Immunology of Diabetes Society)
  - Age 30-70
  - Diabetes associated autoantibodies
  - Did not require insulin for at least 6 months post-diagnosis of diabetes

- Definition is somewhat problematic and more useful for research studies vs clinical practice.

- LADA is probably a form of type 1 diabetes.

- A metabolomic study shows that LADA patients do not have a unique profile and instead look like type 1 or 2 depending on how much C peptide they have. (Al-Majdoub et al., Diabetes, 2016).

AUTOANTIBODIES ARE COMMON IN “TYPE 2 DIABETICS”

- About 5-10% of type 2 patients have GAD65 antibodies.
  - These patients are most likely to have higher risk HLA.
  - These patients tend to be women, lower BMI, worse beta cell function.
  - Tend to progress to insulin dependence slower than our pediatric populations. (Buzzetti, Diabetes Care, 2007).

- Why does it matter?
  - If orals are failing, these patients might do better on insulin.
CASE 3 (CONTINUED)

- Tip-offs that this might not be type 2 DM.
  - Poor response to metformin.
    - However, response to metformin does not exclude this diagnosis during the honeymoon phase.
  - Low BMI.
  - High HDL, low Tg.

- MODY a little less likely given lack of clear family history.
  - Pre-diabetes can be seen with even focal pancreatic cancer.
  - Concomitant autoimmune diagnosis is a tip-off in this case.
  - Worsening of glucose control in context of hepatitis flare.

- This patient did very well with insulin.

- Not all cases of adult onset diabetes are type 2.

CASE 4 — DIABETES IN A 9 YEAR-OLD

- 14 year-old boy from Pakistan referred for hyperglycemia.
  - Body weight:
    - Per mother, obese since age 2.5 y, and has fluctuated near 99%ile since age 4.
    - 7/2015 BMI 31.3, 99%ile; 8/2016 BMI 31.1, 98%ile
  - Glucose control:
  - Medications:
    - Metformin 500 mg daily started 2/2015
    - 1000 once daily by 6/2015
    - Lantus 10 units daily by 8/2016; titrated up to 20 u a few months later
    - Glipizide 10 mg and up-titration of metformin to 750 mg twice daily added to no real effect.
CASE 4

- Ancillary History:
  - Vitamin D Deficiency: 25OHD2 <1.5 and 25OHD3 13.5 on 7/2016
    - Cognitive history normal, development normal
    - Complains of mildly excessive thirst
    - Nocturia x 1 nightly started within last year
    - No recent weight loss

- Family history:
  - No family history of diabetes
  - No stated consanguinity

CASE 4

- Physical Exam:
  - Vital signs all normal
  - BMI 31.1; Height at 98%ile as well
  - General: NAD, pleasant
  - HEENT: EOMI, no exophthalmos
  - Neck: Normal thyroid, no lymphadenopathy
  - Lungs: clear
  - Heart: RRR normal S1/S2
  - Abd: soft NT, ND
  - Ext: No edema
  - Neuro: alert, oriented, no tremor
  - Skin: acanthosis nicricans- groin and axillae
WHAT IS THE DIAGNOSIS?

▪ A. Monogenic obesity.
▪ B. Bardet-Biedl Syndrome
▪ C. Type 2 diabetes
▪ D. Prader-Willi syndrome
▪ E. Type 1 Diabetes
CASE 4

- Labs:
  - Insulin level at age 5: 37 mIU/L
  - At age 9: 100.3 mIU/L
  - Imaging: Fatty liver, but no NASH
  - Total Chol 215
  - HDL 43

Many genes that cause monogenic obesity in humans are in the leptin-melanocortin regulatory pathway

- Obesity caused by mutations of genes that are involved in physiological regulation of body weight: Lep, Lepr, Pmc, Pcsk1, Mc4r

- Obesity caused by mutations of genes that are involved in the development of the hypothalamus: Sim1, BDNF and NTRK2
Leptin-deficient patients are severely obese but obesity can be reversed by leptin replacement

GWAS Meta-Analysis: Heritable Component of BMI is Dominated by “Brain Genes”
OBESITY IS NOT A HIGHLY PENETRANT DIABETES RISK FACTOR

Two Individuals with POMC Mutations

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patient 1</th>
<th>Patient 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Glucose (mg/dl)</td>
<td>65</td>
<td>76</td>
</tr>
<tr>
<td>Insulin (mU/L)</td>
<td>26.7</td>
<td>9.8</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>99</td>
<td>63</td>
</tr>
<tr>
<td>HbA1C</td>
<td>5%</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

Among people diagnosed with Type 2 diabetes, 55% are BMI ≥ 30 (obese), 30% are BMI ≥ 25 or ≤30 (overweight), and 15% have a BMI ≤ 25 (classified as normal weight). ~70% of Overweight and Obese People do not develop T2DM.

Adapted from: [http://www.obesityinamerica.org/trends.html](http://www.obesityinamerica.org/trends.html)
DEPICT: Heritable Component of Insulin Resistance is Dominated by White Adipose Tissue and its Peripheral Storage Capacity

Lotta, et al. Nature Genetics 49, 17–26 (2017); Involved Two Large Cohorts and a PFLD1 Cohort

WHAT IS THE PREVALENCE OF TYPE 2 DIABETES IN KIDS?

- A. 10% of all diabetes in ages 5-18
- B. 5% of all diabetes in ages 5-18
- C. It is ethnicity dependent
- D. It can be greater than the prevalence of type 1 diabetes
WHAT IS THE PREVALENCE OF TYPE 2 DIABETES IN KIDS?

- A. 10% of all diabetes in ages 5-18
- B. 5% of all diabetes in ages 5-18
- C. It is ethnicity dependent
- D. It can be greater than the prevalence of type 1 diabetes

DISTRIBUTION OF DIABETES TYPES BY AGE AT DIAGNOSIS AND RACE/ETHNICITY
RELATIVE PRICE CHANGES FOR FRESH FRUITS AND VEGETABLES, SUGARS AND SWEETS, AND CARBONATED DRINKS, 1978–2009
SODA EXPENDITURES
Percent of Total Expenditures, National Rank by Tract (2011)

Diabetes Hospitalization Rate*, per 10,000, 2007-2009

Age-adjusted rate per 10,000
- No Data Available
- 3.8 - 4.9
- 6.2 - 10.9
- 12.8 - 18.9
- 22.7 - 26.7
- 40.9 - 68.5

*Age adjusted, adults only

Source: Health Matters in San Francisco
www.healthmatterssf.org
City and County of San Francisco
Department of Public Health
Environmental Health Section
Available at www.thedot.org