Diabetes: Classification, Pathophysiology and the Relationship with Pancreatic Cancer

Anna Burton

Specialist Pancreatic Dietitian

Leeds Teaching Hospitals NHS Trust

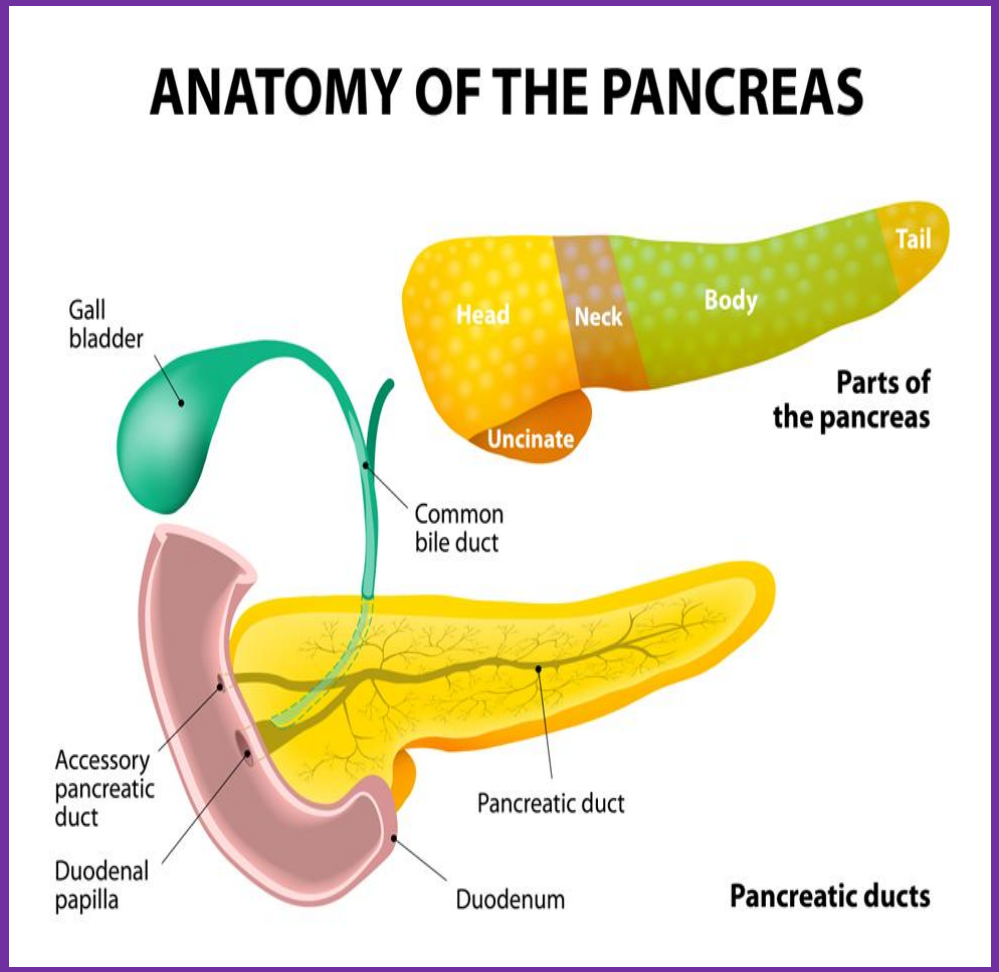
Pancreatic CANCER UK

Pancreatic physiology

- **Exocrine:** production of digestive enzymes (lipase, amylase, proteases) and sodium bicarbonate.
- **Endocrine:** production of hormones

Islets of Langerhans

1-2% of pancreas



Endocrine hormones and glucose homeostasis

- **Alpha cells – glucagon** is secreted in response to **falling** blood glucose levels and stimulates the breakdown of glycogen (glycogenolysis) primarily within the liver to glucose.
- **Beta cells – insulin** (anabolic hormone**)** is secreted in response to **rising** blood glucose levels, enabling glucose uptake within the liver, muscle and adipose cells – converted to glycogen (glycogenesis).
- **Delta – somatostatin** suppresses the production of **insulin** and **glucagon.**
- **Epsilon – Ghrelin** (hunger hormone) is produced by the stomach. Small amounts secreted by the pancreas act on beta cells to inhibit insulin, and act on alpha cells to secrete glucagon.
- **PP cells – (F cells) producing pancreatic polypeptide**. It acts on the liver to increase insulin sensitivity and therefore suppresses the breakdown of glycogen to glucose.

Digestion and metabolism of carbohydrates

- Glucose is the body's main energy source (brain).
- Glucose comes from food (**carbohydrates**) or the body's glucose storage (**glycogen).**
- Digestion of carbohydrates in food, enters the bloodstream as glucose (the simplest form of sugar).
- **Insulin** - moves glucose from the blood into cells for energy and storage.
- Interruption to this process due to **insulin resistance** or **deficiency of insulin** leads to glucose remaining in the blood.

Hyperglycaemia

Symptoms

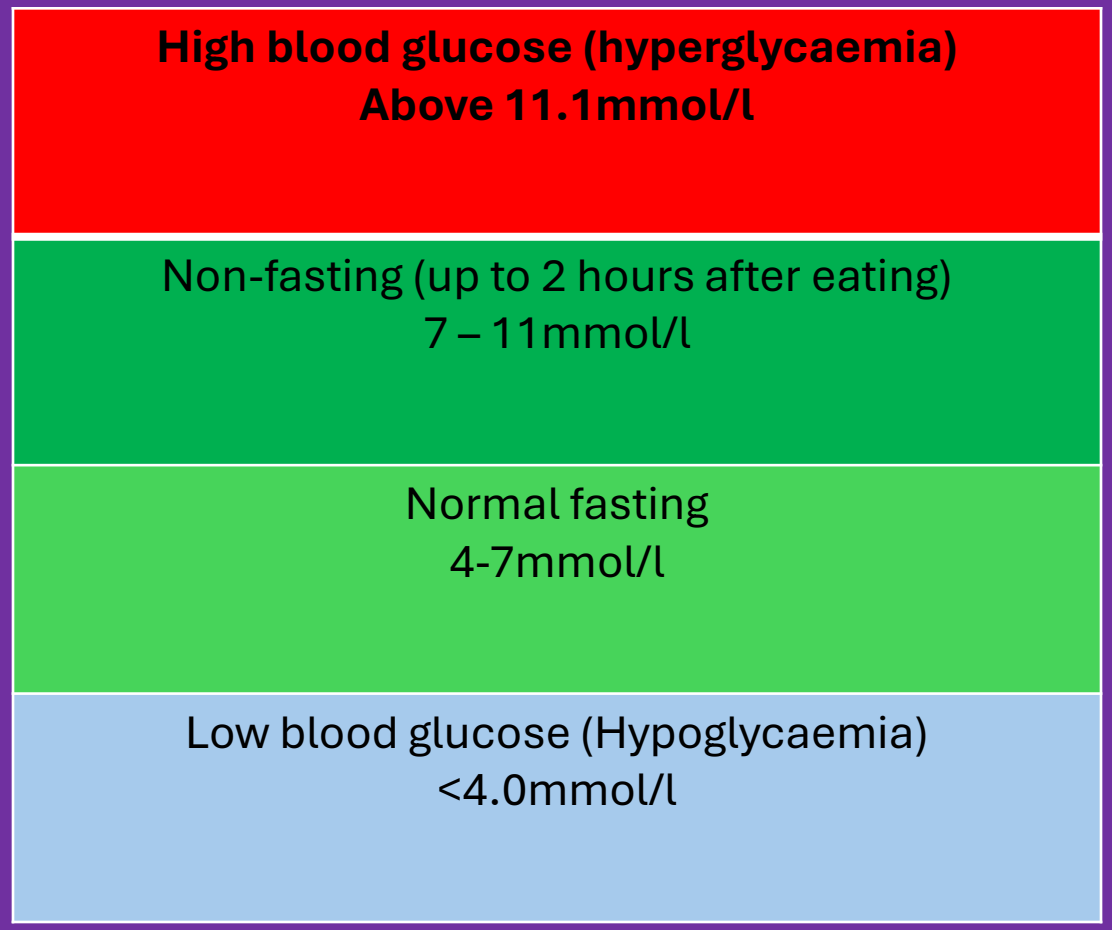
- Thirst
- Tiredness
- Weight loss
- Nocturia/polyurea
- Craving sugary drinks and foods
- Blurred vision
- Delayed wound healing
- Infections

Chronic complications

- Retinopathy
- Peripheral neuropathy
- Cardiovascular
- Nephropathy
- Gum disease
- Foot problems

Diabetes is associated with shorter survival in pancreatic cancer patients (Mao et al, 2015).

Blood glucose levels



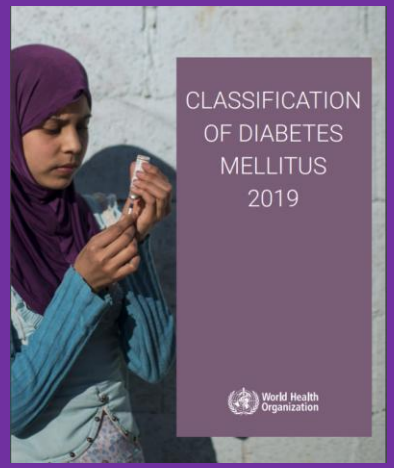
HbA1c test for diabetes:

- Normal: Below 42mmol/mol
- Prediabetes: 42 – 47mmol/mol
- Diabetes: 48mmol/mol or over.

Serum blood glucose test:

- Random >11.1mmol/l
- Fasting >7.0mmol/l
- 2-hour Oral glucose Tolerance Test (OGTT) 75g. >11.1mmol/l.

WHO classification of diabetes - 2019



Diseases of the exocrine pancreas

- Any process that diffusely damages the pancreas: pancreatitis, trauma, infection, pancreatectomy.
- Diabetes related to pancreatic adenocarcinoma is caused by other mechanisms then reduction of beta cell mass.

Table 2: Types of diabetes

Type 1 diabetes
Type 2 diabetes
Hybrid forms of diabetes
Slowly evolving immune-mediated diabetes of adults
Ketosis prone type 2 diabetes
Other specific types (see Tables)
Monogenic diabetes
- Monogenic defects of β-cell function
- Monogenic defects in insulin action
Diseases of the exocrine pancreas
Endocrine disorders
Drug- or chemical-induced
Infections
Uncommon specific forms of immune-mediated diab
Other genetic syndromes sometimes associated with
Unclassified diabetes
This category should be used temporarily when there … he time of diagnosis of diabetes
Hyperglyacemia first detected during pregnancy
Diabetes mellitus in pregnancy
Gestational diabetes mellitus

Diseases of the exocrine pancreas

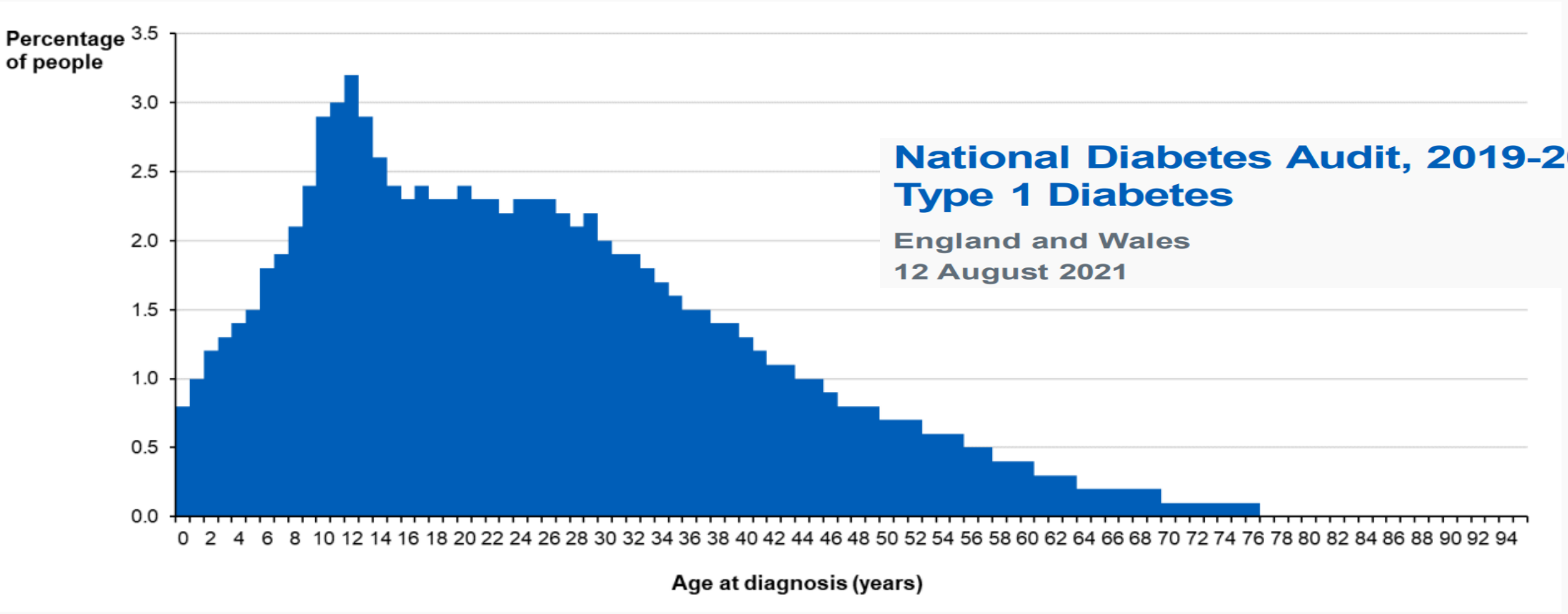
- Fibrocalculous pancreatopathy
- Pancreatitis
- Trauma/pancreatectomy
- Neoplasia
- Cystic fibrosis
- Haemochromatosis
- Others

Type 1 diabetes - 8% of all diabetes (Diabetes uk)

- **Autoimmune disease** – beta cells in the islet of Langerhans are destroyed – insulin deficiency.
- **Cause** – genetic, environmental (virus) – **research ongoing**.
- **Positive for islet autoantibodies:**
    - GAD (Glutamic Acid Decarboxylase).
    - IA-2 (Islet Tyrosine Phosphatase
    - ZnT8 (Zinc transporter 8)
- **Treatment –** insulin

Type 1 Diabetes: Age at diabetes diagnosis

Figure 2: People with type 1 diabetes, by age of diagnosis*, England and Wales, 2019-20



Presentations of type 1 diabetes climb steeply through childhood and peak in adolescence. They continue to present at a steady high rate to around 30 years old where they decline gradually with low rates presenting from the mid-fifties. Approximately two-thirds are diagnosed by aged 30 years old and one third thereafter.

Type 2 Diabetes - 90% of all diabetes (Diabetes uk)

Insulin Resistance (IR)

- Visceral adipose tissue produces **inflammatory** cytokines (TNF and interleukin (IL)-6).
- Cytokines inhibit insulin receptors and the action of insulin.
- Leading to **Insulin resistance**.
- Hyperglycaemia and Insulin resistance leads to hyperinsulinaemia.
- Leading to beta cell exhaustion

- **Risk factors**: Overweight/obese, family history, inactivity, ethnicity, history of gestational diabetes, PCOS, metabolic syndrome.
- Negative for autoantibodies.
- Treatment: lifestyle – diet: healthy eating, exercise, weight loss, oral hypoglycaemic agents – first-line Metformin, may progress to insulin.

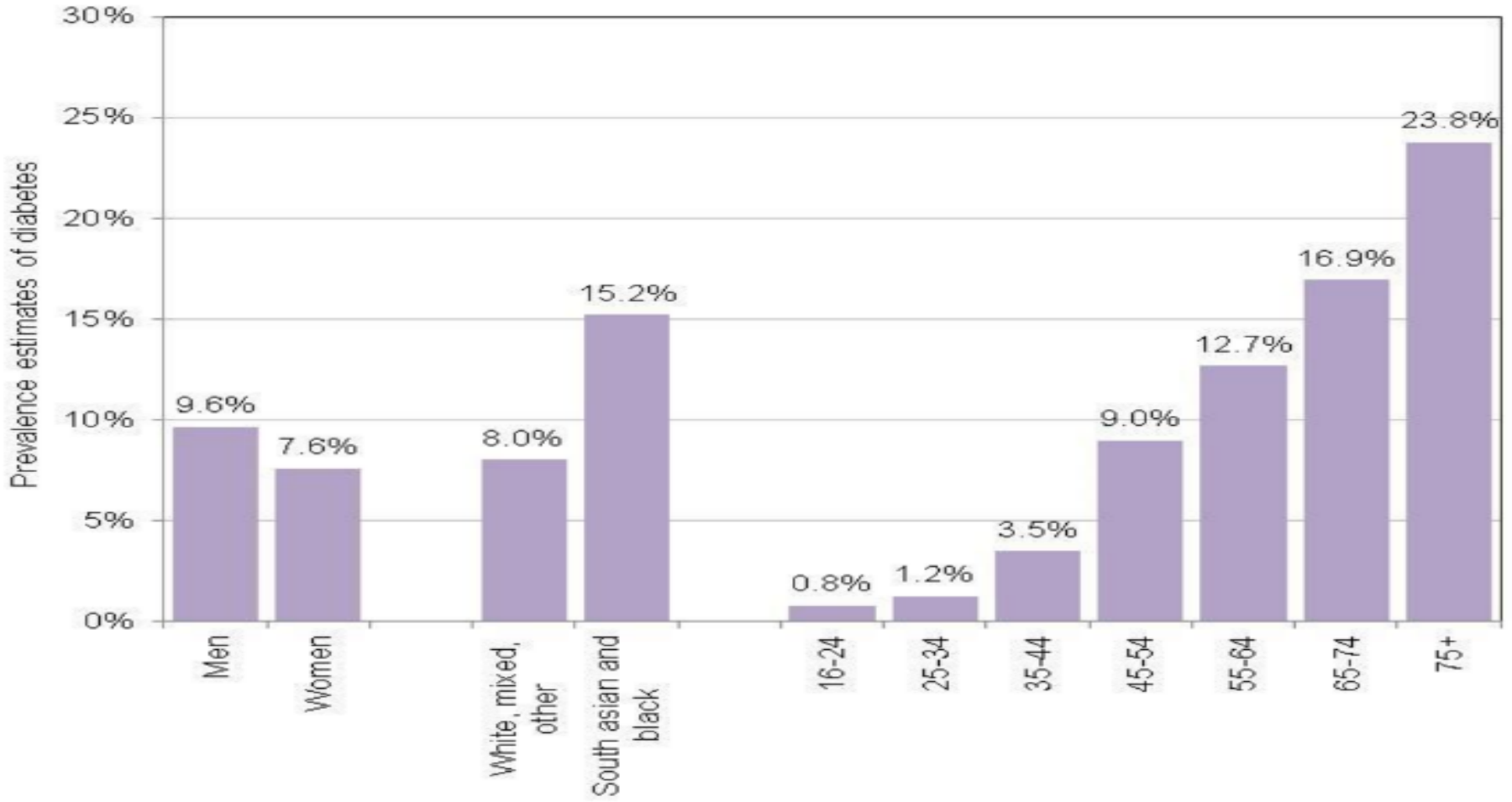
Public Health England

Protecting and improving the nation's health

Diabetes Prevalence Model

It is estimated that 3.8 million people aged 16 years and over in England have diabetes (diagnosed and undiagnosed). This is equal to 8.6% of the population of this age group.

Chart 1. Summary of expected diabetes prevalence (diagnosed and undiagnosed) for England in 2015 by age group, sex and ethnicity



American Diabetes Association (2022)

Diabetes Care Volume 37, Supplement 1, January 2014

Diagnosis and Classification of Diabetes Mellitus

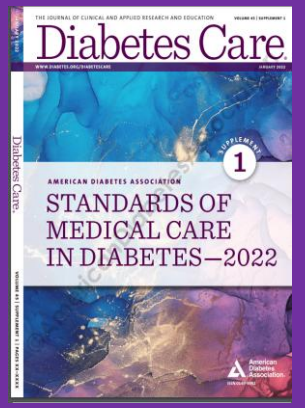
American Diabetes Association

Table 1—Etiologic classification of diab

I. Type 1 diabetes (β-cell destruction, usually le
   A. Immune mediated
   B. Idiopathic

II. Type 2 diabetes (may range from predomina
   insulin deficiency to a predominantly secret

III. Other specific types
   A. Genetic defects of β-cell function
      1. MODY 3 (Chromosome 12, HNF-1α
      2. MODY 1 (Chromosome 20, HNF-4α
      3. MODY 2 (Chromosome 7, glucokina
      4. Other very rare forms of MODY (e.g., M
         MODY 6: Chromosome 2, *NeuroD1*; M
      5. Transient neonatal diabetes (most c
      6. Permanent neonatal diabetes (mos
         subunit of β-cell K_{ATP} channel)
      7. Mitochondrial DNA
      8. Others
   B. Genetic defects in insulin action
      1. Type A insulin resistance
      2. Leprechaunism
      3. Rabson-Mendenhall syndrome
      4. Lipoatrophic diabetes
      5. Others
   C. Diseases of the exocrine pancreas
      1. Pancreatitis
      2. Trauma/pancreatectomy
      3. Neoplasia
      4. Cystic fibrosis
      5. Hemochromatosis
      6. Fibrocalculous pancreatopathy
      7. Others
   D. Endocrinopathies
      1. Acromegaly



- ‘Pancreatic Diabetes is the preferred umbrella term’.
- Diverse set of aetiologies within the classification of diabetes in the context of the exocrine pancreas.
- The distinguishing feature is concurrent pancreatic exocrine insufficiency.

Poll Question: What % of all adult diabetes is caused by pancreatic disease (Type 3c).

0.5 - 1.15%

1 - 2%

2 - 4%

5 - 6%

5 - 10%

Don’t Know

Type 3c diabetes – misdiagnosis

Ewald et al, 2012

- Patients (n 1868) admitted to the hospital within the last 24 months.
- Reclassified according to **ADA classification.**

- **9.2%** of all diabetes classified as **type 3c.**
- Misclassified as type 2 DM.

Woodmansey et al, 2017

- Adult-onset DM – Primary care records in the UK (n 31780 NOD in adults).
    - **Diabetes in pancreatic disease -1.8%**
- Type 3c misdiagnosed in 87.5% (n559) as type 2 diabetes
- Poorer glycaemic control
- Progressed to insulin use in 5 years:
    - Type 2 - 4.1%
    - Acute pancreatitis - 20.9%
    - Chronic pancreatitis disease - 45.8%

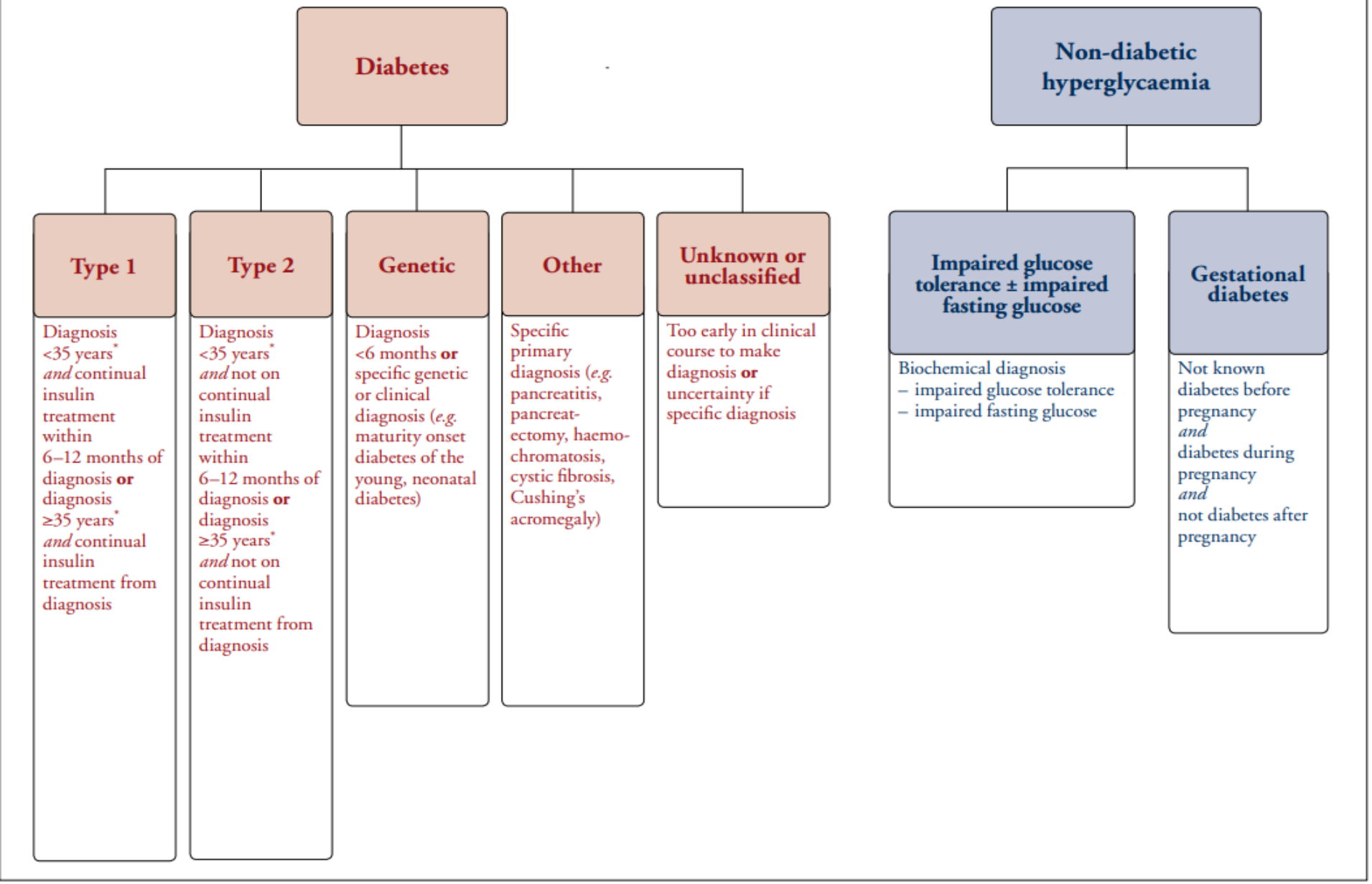


*Figure 1. Practical classification guideline for the diagnosis of diabetes. *=In high-risk racial groups, a cut-off of 30 years should be used.*

Classification of diabetes for primary care: A practical approach

Khaled Sadek, Kamlesh Khunti, Simon de Lusignan

A report was commissioned by NHS Diabetes and the Royal College of General Practitioners in conjunction with the Department of Health to review the coding, classification and diagnosis of diabetes in primary care in England (NHS Diabetes, 2011). It identified errors in misdiagnosis, misclassification and miscoding, which would result in inappropriate management and poor outcomes. A classification algorithm and audit tool were developed to assist with the practical classification of diabetes to enable practitioners to follow clinical-based advice when coding diabetes in the future.

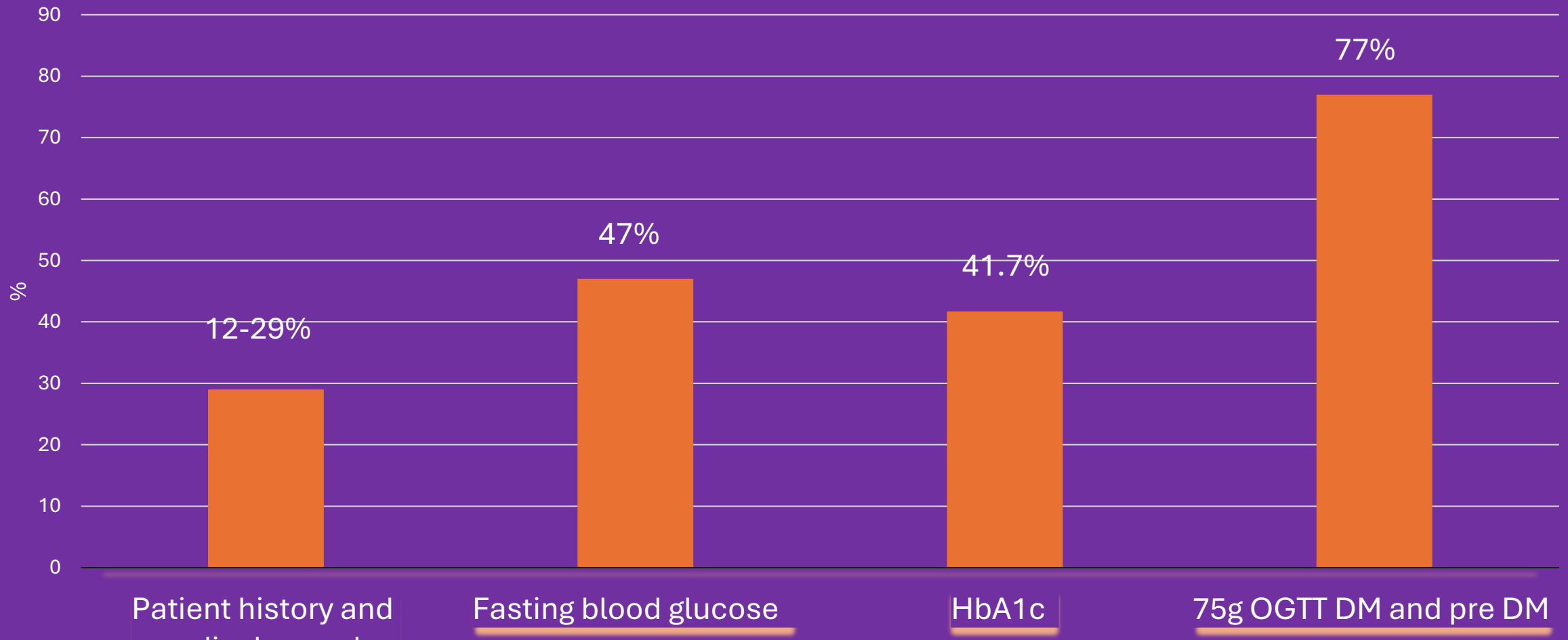
Diabetes and Primary Care Vol 14, No 5 (2012)

Type 3c diabetes and pancreatic cancer

- **Tumour metabolites:** Paraneoplastic mechanism due to tumour metabolites causing **insulin resistance and beta cell dysfunction.**
- **Pancreatic resection** for the treatment of pancreatic cancer: **loss of pancreatic tissue.**
- **Treatments:** Chemo/radiotherapy/steroids

- Treatment – oral hypoglycaemic agents, insulin.
- Nutritional support
    - Weight gain if appropriate
    - **Pancreatic enzyme replacement therapy (PERT)**

The incidence of diabetes in patients diagnosed with pancreatic cancer – the implications of methods and tests used.



Pathophysiology

- **Absence of islets** – total pancreatectomy (absolute deficiency of insulin, glucagon and pancreatic polypeptide)
- **Partial absence of functional islets** – chronic pancreatitis, partial pancreatectomy, severe acute pancreatitis
- **Paraneoplastic** – pancreatic ductal adenocarcinoma

<u>Mechanisms observed within type 3c diabetes</u>

Insulin deficiency

Insulin resistance

Hypoglycaemic risk due to lack of **glucagon** in response to falling blood glucose levels **'brittle diabetes'**

Hepatic insulin resistance caused by a reduction in **pancreatic polypeptide** and unsuppressed hepatic glucose production

Relationship between endocrine and exocrine function:

Reduced incretin effect

Food in the small intestine initiates an incretin hormone response:

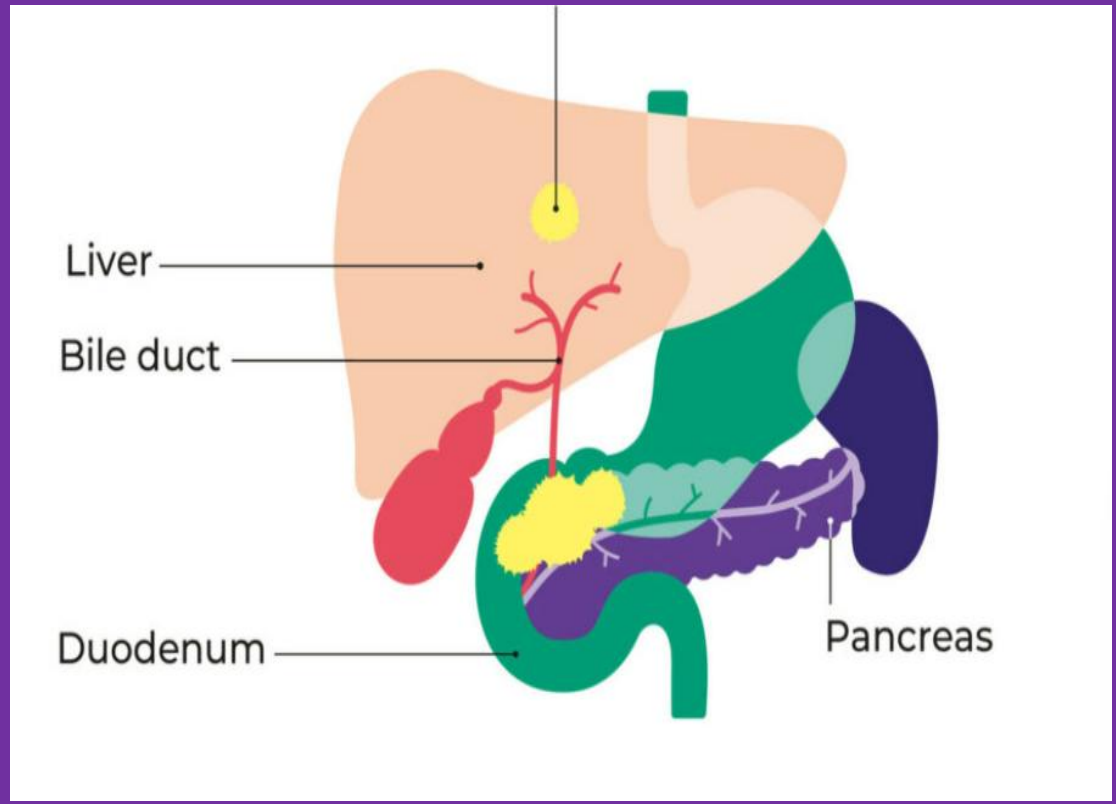
- GIP (glucose-dependent insulinotropic polypeptide)
- GLP-1 (glucagon-like peptide-1)

Incretin hormones signal to the beta cells to release insulin.

In the setting of maldigestion due to PEI a dampened incretin response occurs – leading to hyperglycaemia.

Pancreatic adenocarcinoma in the head of the pancreas impacting the **endocrine** and **exocrine** function

- Tumour metabolites causing beta cell dysfunction and insulin resistance.
- Tumour blocking the pancreatic duct and bile duct causing pancreatic enzyme insufficiency and jaundice.



Pancreatic Cancer UK

Pancreatic cancer and weight loss

72% of people with pancreatic cancer had unintentional weight loss within a year of diagnosis (Hue et al, 2020).

- **Maldigestion** caused by blocked pancreatic ducts.
- **New onset diabetes** relating to pancreatic cancer.
- **Poor appetite** is driven by pancreatic cancer metabolites and symptoms.
- **Increased nutritional requirements** – 10% rise in energy expenditure due to tumour metabolism.

NICE (2015) guidance recommends:

Anyone over the age of 60 presenting with **new-onset diabetes** should be assessed for pancreatic cancer in the presence of any of the following:

- Weight loss
- Diarrhoea
- Back pain
- Abdominal pain
- Nausea,
- Vomiting,
- Constipation

Urgent 2-week wait CT.

Points to consider

- Type 3c – frequently mis and underdiagnosed.
- Classification complicated by terminology and, the impact this can have on people.
- 3c differs in pathophysiology from type 1 and type 2 diabetes.
- Think diabetes – test for and monitor
- Right diagnosis, right treatment for better outcomes.