Type 2 diabetes is now a pandemic and shows no signs of abatement. In this Seminar we review the pathophysiology of this disorder, with particular attention to epidemiology, genetics, epigenetics, and molecular cell biology. Evidence is emerging that a substantial part of diabetes susceptibility is acquired early in life, probably owing to fetal or neonatal programming via epigenetic phenomena. Maternal and early childhood health might, therefore, be crucial to the development of effective prevention strategies. Diabetes develops because of inadequate islet β-cell and adipose-tissue responses to chronic fuel excess, which results in so-called nutrient spillover, insulin resistance, and metabolic stress. The latter damages multiple organs. Insulin resistance, while forcing β cells to work harder, might also have an important defensive role against nutrient-related toxic effects in tissues such as the heart. Reversal of overnutrition, healing of the β cells, and lessening of adipose tissue defects should be treatment priorities.

Introduction

Type 2 diabetes mellitus is a metabolic disorder of fuel homoeostasis characterised by hyperglycaemia and altered lipid metabolism caused by islet β cells being unable to secrete adequate insulin in response to varying degrees of overnutrition, inactivity, consequential overweight or obesity, and insulin resistance. The burden of this disorder is enormous, owing to its rapidly increasing global prevalence, the devastating damage it can do to many organs of the body, and the direct and indirect costs. In this Seminar we discuss developments in the understanding of the pathogenesis of type 2 diabetes from epidemiology, genetics, epigenetics, and molecular cell biology, with emphasis on the emerging role of fetal and neonatal programming, and we underscore the need for a whole-of-life approach to prevention and management.

Epidemiology

A growing non-communicable disease epidemic

The estimated worldwide prevalence of diabetes among adults was 285 million (6·4%) in 2010, and this value is predicted to rise to around 439 million (7·7%) by 2030 (table 1). Type 2 diabetes is the predominant form and accounts for at least 90% of cases. The rise in prevalence is predicted to be much greater in developing than in developed countries (69% vs 20%). In developing countries people aged 40–60 years (ie, working age) are affected most, compared with those older than 60 years in developed countries. This increase in type 2 diabetes is inextricably linked to changes towards a western lifestyle (high-energy diets with reduced physical activity) in developing countries and the rise in the prevalence of overweight and obesity.

Type 2 diabetes in youth and pregnancy

Until 1990, type 2 diabetes was seldom seen in young people and in pregnant women, but this is no longer the case. In some countries type 2 diabetes is still rare in children and adolescents, for instance in Germany, where prevalence is 2.3 per 100 000 in people aged 0–20 years. The incidence of type 2 diabetes in young people has, however, become greater than that of type 1 diabetes in some ethnic groups, as seen in the USA (12·1 vs 7.4 per 100 000 in Asians and Pacific Islanders aged ≤20 years, and 19.0 vs 15.7 per 100 000 in African Americans aged 0–19 years). In young people type 2 diabetes associated with obesity frequently remains undiagnosed and is difficult to manage.

The younger ages at which type 2 diabetes is seen also translates into an increasing number of pregnant women being affected, many of whom are not diagnosed before pregnancy. Outcomes of pregnancy related to type 2 diabetes are at least similar to or possibly worse than those related to type 1 diabetes, with rates of congenital malformations and perinatal death being high. Poor awareness among health professionals of the risks prompted the International Association of Diabetes in Pregnancy Study Groups (IADPSG) consensus panel on the classification of hyperglycaemic disorders in pregnancy to advise testing women early in pregnancy for overt diabetes.

The burden of type 2 diabetes: complications and excess mortality

The excess global mortality in 2000 attributable to diabetes overall, most of which was attributable to type 2 diabetes, was 2.9 million (5.2%) deaths. In 2004, heart disease and stroke were reported on 68% and 16%, respectively, of diabetes-related death certificates in the USA.
USA.26 Furthermore, diabetes is the leading cause of blindness among adults aged 20–74 years, and leads to around 44% of end-stage renal failure and 60% of non-traumatic lower-limb amputations in the USA.16 The pattern of complications in Asian populations differs from that in white populations, with more deaths among Asians being attributed to strokes and renal failure.1 Type 2 diabetes is also associated with non-alcoholic fatty liver disease, including non-alcoholic steatohepatitis, polycystic ovarian syndrome, and possibly some malignancies.17–20

### Diagnosis

Recommendations for diagnostic strategies and criteria for hyperglycaemic disorders, including diabetes, in the general population as well as in pregnant women, have been revised and issued by WHO, the American Diabetes Association (ADA), and the IADPSG (table 2; for a more detailed discussion see webappendix p 1).21,22 Of particular note, WHO and ADA have both recommended that a glycated haemoglobin A₁c (HbA₁c) concentration of 6.5% or higher can be used to diagnose diabetes.21,22 The committees assessed data that examined the relation between prevalence of diabetes complications, in particular retinopathy, and HbA₁c concentrations.21,23 WHO also analysed the DETECT-2 collaboration data of gradable retinal photographs and markers of glycaemic control from 44623 participants across nine studies (figure 1).21,24 Various international professional bodies and health authorities are considering and adopting these recommendations.

### Pathophysiology

A brief overview of normal glucose homoeostasis is presented in figure 2.

#### Type 2 diabetes: a failure to contain a chronic fuel surfeit

Chronic fuel surfeit is the primary pathogenic event that drives the development of type 2 diabetes in genetically and epigenetically susceptible people.25,26 Many chronically overnourished and overweight or obese individuals, however, do not develop diabetes at all or develop it very late in life. They remain resistant to type 2 diabetes and safely partition excess calories to subcutaneous adipose tissue (SAT) rather than to the heart, skeletal muscle, liver, and islet β cells (figure 3), owing to the following mechanisms: successful islet β-cell compensation; maintenance of near-normal blood nutrient concentrations; development of minimal insulin resistance; increased expansion of SAT relative to visceral adipose tissue (VAT); and limited increase in liver fat.27,28 In this way, key organs of the body avoid nutrient-induced damage.

Susceptible overnourished individuals develop type 2 diabetes owing to the failure of these adaptive responses to safely dispose of the fuel surfeit (figure 3). The following metabolic defects are crucial to the development of type 2 diabetes: inability of islet β cells to compensate for the fuel surfeit; increased glucagon secretion and reduced incretin response; impaired expansion of SAT, hypoadiponectinaemia, and inflammation of adipose

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### Table 1: Estimated numbers of adults aged 20–79 with any type of diabetes mellitus and prevalence, by region, in 2010 and 2030

<table>
<thead>
<tr>
<th>Region</th>
<th>Number of adults with diabetes (million)</th>
<th>Prevalence (%)</th>
<th>Number of adults with diabetes (million)</th>
<th>Prevalence (%)</th>
<th>Percentage increase in number</th>
</tr>
</thead>
<tbody>
<tr>
<td>Africa</td>
<td>12.1</td>
<td>3.8%</td>
<td>23.9</td>
<td>4.7%</td>
<td>98.1%</td>
</tr>
<tr>
<td>EMME</td>
<td>26.6</td>
<td>9.3%</td>
<td>51.7</td>
<td>10.8%</td>
<td>93.9%</td>
</tr>
<tr>
<td>Europe</td>
<td>55.4</td>
<td>6.9%</td>
<td>66.5</td>
<td>8.1%</td>
<td>20.0%</td>
</tr>
<tr>
<td>North America</td>
<td>37.4</td>
<td>10.2%</td>
<td>53.2</td>
<td>12.1%</td>
<td>42.4%</td>
</tr>
<tr>
<td>South and Central America</td>
<td>18.0</td>
<td>6.6%</td>
<td>29.6</td>
<td>7.8%</td>
<td>65.1%</td>
</tr>
<tr>
<td>Southeast Asia</td>
<td>58.7</td>
<td>7.6%</td>
<td>101.0</td>
<td>9.1%</td>
<td>72.1%</td>
</tr>
<tr>
<td>West Pacific</td>
<td>76.7</td>
<td>4.7%</td>
<td>112.8</td>
<td>5.7%</td>
<td>47.0%</td>
</tr>
<tr>
<td>Worldwide</td>
<td>284.8</td>
<td>6.4%</td>
<td>438.7</td>
<td>7.7%</td>
<td>54.1%</td>
</tr>
</tbody>
</table>

Adapted from reference 1 with permission of Shaw and colleagues.1 EMME=Eastern Mediterranean and Middle East.2 For each region values are standardised to world age distribution for that year.

See Online for webappendix

### Table 2: Diagnostic criteria for diabetes, IFG, IGT, prediabetes, and gestational diabetes

<table>
<thead>
<tr>
<th>HbA₁c (%)</th>
<th>Fasting plasma glucose (mmol/L)</th>
<th>75 g OGTT post-load plasma glucose (mmol/L)</th>
<th>Random glucose (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥6.5%</td>
<td>7.0</td>
<td>≥11.11</td>
<td>≥11.1 with classic symptoms</td>
</tr>
<tr>
<td>NA</td>
<td>IFG ≥6.1 and &lt;7.0</td>
<td>IGT 2 h, ≥7.8 and &lt;11.1</td>
<td>NA</td>
</tr>
<tr>
<td>NA</td>
<td>ODP ≥7.0</td>
<td>GDM, 1 h ≥10.1</td>
<td>ODP ≥11.1</td>
</tr>
</tbody>
</table>

ADA=American Diabetes Association. IFG=impaired fasting glucose; IGT=impaired glucose tolerance; GDM=gestational diabetes mellitus; ODP=overt diabetes in pregnancy. IADPSG=International Association of Diabetes in Pregnancy Study Groups. HbA₁c=glycated haemoglobin A₁c; NA=not applicable; OGTT=oral glucose tolerance testing.21 While WHO and ADA diagnostic criteria for diabetes are identical, the approaches to assessment of intermediate hyperglycaemia or prediabetes differ.21–23 Fasting blood sugar of ≥5.1 mmol/L and <7.0 mmol/L at any time of pregnancy is diagnostic of GDM. The usual time of OGTT in pregnancy for GDM is 24–28 weeks’ gestation.21–23 Screening for ODP by measurement of HbA₁c, fasting plasma glucose, or random blood glucose concentration is recommended for the first antenatal visit. Elevated random plasma glucose values need to be confirmed.21 In the absence of unequivocal hyperglycaemia, results should be confirmed by retesting.

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tissue; increased endogenous glucose production; and development of peripheral insulin resistance.\textsuperscript{25,26,29–34} Importantly, the fuel surfeit is not safely deposited into SAT, such that it has to be disposed of elsewhere. The “elsewhere” is less healthy VAT and “ectopic” storage in organs, such as the liver, heart, skeletal muscle, and pancreas, which causes widespread tissue damage.\textsuperscript{30} Worsening islet β-cell function can lead to the need for insulin therapy.

Genetic and environmental factors

Although the main metabolic defects of type 2 diabetes are present to some degree in most patients, this disorder is highly heterogeneous. Many different susceptibility genes have been identified that interact with environmental factors, during gestation, early childhood, and later in life.\textsuperscript{3,25,35–40}

Genes

The heritability of type 2 diabetes is high (estimated to be >50\%), as indicated by the high concordance rates in monozygotic twins and the notably raised risk in individuals with affected first-degree relatives.\textsuperscript{36,41–47} Twin studies need to be considered carefully, however, as the intrauterine environments of dizygotic-twin (separate placentas), monozygotic-twin (60–70\% share one placenta), and singleton pregnancies (one placenta without competition for maternal nutrients) will all be different, and this can be a confounder in the interpretation of effects.\textsuperscript{44} A large study from Sweden on familial risk of type 2 diabetes showed that the relative risks were highest in individuals with at least two affected siblings, irrespective of parental diabetes status.\textsuperscript{42} This finding suggests that a recessive pattern of inheritance from uncommon genetic defects, the sharing of similar intrauterine, postnatal, or both environments by siblings (eg, breastfeeding or bottle feeding or childhood nutrition), or a combination of these factors is important.

Genome-wide association studies have helped to raise the number of confirmed diabetes-associated loci to more than 40.\textsuperscript{36,38,48–50} A greater number of these loci are associated with impaired β-cell function (\textit{KCNJ11}, \textit{TCF7L2}, \textit{WFS1}, \textit{HNF1B}, \textit{SLC30A8}, \textit{CDKAL1}, \textit{IGF2BP2}, \textit{CDKN2A}, \textit{CDKN2B}, \textit{NOTCH2}, \textit{CAMK1D}, \textit{THADA}, \textit{KCQI}, \textit{MTNR1B}, \textit{GCKR}, \textit{GCK}, \textit{PROX1}, \textit{SLC2A2}, \textit{G6PC2}, \textit{GLI3}, \textit{ADRA2A}, and \textit{GIPR}) than impaired insulin sensitivity (\textit{PPARG}, \textit{IRS1}, \textit{IGF1}, \textit{FTO}, and \textit{KLF14}).\textsuperscript{38,48,50} Of these, \textit{TCF7L2} is the strongest susceptibility locus for type 2 diabetes, being associated with β-cell dysfunction.\textsuperscript{48} Most patients with monogenic forms of diabetes also have gene defects that affect islet β-cell function.\textsuperscript{51,52} Nevertheless, only around 10\% of the heritability of type 2 diabetes can be explained by susceptibility loci identified so far, with each locus having a low effect size.\textsuperscript{36} The remaining heritability might be related to a large number of less common variants (allele frequency <5\%) that are difficult to find with current approaches of genome-wide association studies, and/or epigenetic phenomena.

Early-life environment: fetal and neonatal programming and epigenetic effects

Strong epidemiological and experimental evidence indicates a link between intrauterine growth restriction and adult diseases, such as obesity, hypertension, type 2 diabetes, and cardiovascular disease.\textsuperscript{40,53} The evidence that
Overview of normal glucose homeostasis

In the fasting state, blood glucose concentration is determined by the balance between EGP production, mainly through hepatic glycogenolysis and gluconeogenesis, and use by insulin-independent tissues, such as the brain. EGP prevents hypoglycaemia and is supported by a low insulin-to-glucagon ratio in plasma. The brain is dependent on glucose and, therefore, other tissues, such as heart and skeletal muscle, are mainly provided with non-glucose nutrients (eg, non-esterified fatty acids from adipose tissue lipolysis). In the fed state (meal with carbohydrate) glucose concentrations in the blood rise because of absorption in the gut, which stimulates insulin secretion by islet β cells and suppresses glucagon secretion from α cells. EGP is suppressed (which helps to curtail total glucose input into blood) and uptake into insulin-sensitive peripheral tissues, such as the heart, skeletal muscle, and adipose tissue is activated (which increases the rate of glucose disposal). Neurohormonal processes include the release of the incretin hormones, such as GLP-1, which increases glucose-stimulated insulin secretion and glucose suppression of glucagon secretion. Adipose tissue lipolysis is suppressed and anabolic metabolism is promoted. Glucose concentrations become close to the fasting level within 2 h. GLP:1-glucagon-like peptide 1. EGP=endogenous glucose production.

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gestational or overt diabetes in pregnancy can affect diabetes risk in offspring is limited but highly suggestive.4

In longitudinal studies of Pima Indians, among whom the prevalence of obesity-associated type 2 diabetes is very high, offspring of mothers with established disease during pregnancy develop type 2 diabetes earlier than those born to mothers without diabetes.5,13,14 Furthermore, obesity and type 2 diabetes were more frequent among siblings born to the same mother after she developed diabetes.9 In the multiethnic SEARCH for Diabetes in Youth Study, a diagnosis of type 2 diabetes was made at a younger age in children of mothers who had diabetes during pregnancy than of those without diabetes.25 Lastly, in a Danish study, compared with the offspring of mothers without diabetes, adjusted odds ratios were raised for prediabetes or type 2 diabetes in the offspring of women who had gestational diabetes treated by diet (7·8, 95% CI 2·6–23·4) or who had type 1 diabetes during pregnancy (4·0, 1·31–12·3) at age 22 years.39 The effect of maternal type 1 diabetes was greatest if hyperglycaemia was present in the third trimester (odds ratio per mmol/L glucose 1·41, 95% CI 1·04–1·91) and, therefore, the hyperglycaemic intrauterine environment is strongly implicated in the pathogenesis of type 2 diabetes.34

Of potential importance is the finding that vitamin B12 deficiency during pregnancy, particularly in women replete for folic acid, has been associated with the development of childhood adiposity and insulin resistance in India.39 Evidence also suggests that breastfeeding is protective against the development of type 2 diabetes before age 21 years.60

Fetal and neonatal programming has been a major area of research activity, with particular interest being paid to the role of epigenetics and fetal origins of adult disease.55,61 Strong evidence from animal studies indicates that early life programming can affect neurohormonal weight control networks and development of pancreatic islets.55 A glossary of terms relating to this new important field of epigenetics is provided in panel 1.

Ongoing environmental factors

A westernised lifestyle, which involves a high-energy diet and reduced physical activity, is indisputably linked to the pandemics of obesity and type 2 diabetes. Rates of overweight, obesity, and diabetes rise sharply in populations that move from traditional rural to urban environments.3,39,40,65 Dietary changes are typically from unprocessed, low-energy, high-fibre foods to processed, energy-dense foods characterised by high sugar and fat contents.43,44 Mismatch of epigenetic regulation for a life of low-energy intake when born into a traditional setting with a subsequent high-energy intake associated with the transition to an urban setting may place the transitioning generation at particularly high risk of type 2 diabetes.3,55

Micronutrient imbalances, including deficiency in concentrations of vitamin D, vitamin B12 in individuals replete with folic acid, and increased body iron stores have been implicated in the pathogenesis of type 2 diabetes.54,60 Evidence also suggests that exposure to synthetic organic pollutants (eg, pesticides and plasticisers) affects endocrine cells and increases the risk of developing type 2 diabetes.79

The gut microbiota, which can be influenced by events in early life, such as methods of delivery and feeding, and by later life by factors such as use of antibiotics and diet composition, might also contribute to increased risk of type 2 diabetes.27 A potential role for probiotics to alter the gut microbiota in beneficial ways is being intensively investigated.77 Increased use of technologies to reduce energy expenditure, including cars, and raised television viewing
times contribute to sedentary lifestyles, which are strongly associated with overweight, obesity, and type 2 diabetes. Low socioeconomic status and depression also affect risk. Sleep deprivation and obstructive sleep apnoea are strongly associated with obesity and type 2 diabetes and might have pathogenic roles.

Molecular mechanisms: a brief overview

Neurohormonal weight control networks

Dysfunction of the mechanisms that control the body’s energy balance and weight and cause overweight and obesity is of major importance in type 2 diabetes pathogenesis. This dysfunction occurs within the complex neurohormonal weight control network of the body in which central signals (from the brainstem and higher cortical centres, eg, cognitive, visual, and other reward cues) and peripheral signals of energy stores (from adipose tissue eg, leptin) or related to hunger (from the gut, eg, ghrelin) and to satiety (from gut and pancreas, eg, vagal afferent neural signals, cholecystokinin, glucagon-like peptide 1 [GLP-1], insulin, and nutrient levels) feed into the hypothalamus and other key areas in the CNS to control appetite, physical activity, and body-weight. This network is also highly regulated by the circadian clock, which supports a pathophysiological link between sleep disorders, obesity, and type 2 diabetes.

Obesity is associated with resistance to the central actions of leptin and insulin. Monogenic forms of obesity with severe phenotypes do exist (eg, owing to mutations in LEP, LEPR, MC4R, and POMC), but are uncommon (<5% of all obesity). The heritability of obesity is, however, very high, and genome-wide association studies so far have identified 32 common variant loci, yet these only explain an estimated 1-45% of the variance in body-mass index. The identification of rare genetic variants or epigenetic causes is, therefore, necessary to further understand the strong heritability. Hypothalamic weight-control neurons do seem to be notably affected by the environment in early life. For instance, epigenetic alteration of the regulatory set point for expression of the POMC gene by hypermethylation has been reported in rats overfed early in life.

Islet β cells

In human beings islet β cells are vulnerable to nutrient-induced damage and, therefore, contribute notably to the development of type 2 diabetes. β cells have to: maintain synthesis of proinsulin with correct post-translational modification; ensure secretory granules are ready for secretion; sense nutrient concentrations in blood, mostly via intracellular metabolism with the production of nutrient-secretion coupling factors (figure 4); sense other neurohormonal signals; and appropriately execute insulin granule release via activation of a complex exocytosis machinery. The mechanisms underlying β-cell failure, therefore, can be many, varied, and complex. Islet β-cell dysfunction generally occurs when compensation is required for fuel excess, which can mean that minor deficiencies become important. We have proposed that it is the mix of β-cell susceptibility factors that determines the initial mechanism of damage, but that once substantial hyperglycaemia has developed, glucotoxic and glucolipotoxic mechanisms ensue in most patients, resulting in acceleration of the rate of failure. One factor peculiar to islet β cells in human type 2 diabetes is their propensity to develop islet amyloid polypeptide deposits, but these probably play a part in disease progression rather than initiation. Studies of β-cell failure in rodent models suggest a range of mechanisms, from poor function only, for instance in the Zucker fatty rat 60% pancreatectomy
model,\textsuperscript{41} to substantial loss of β-cell mass in the Sprague Dawley intrauterine growth restriction model.\textsuperscript{41} The latter model is of particular interest because Sprague Dawley rats are normally very resistant to the development of diabetes. The loss of islet β-cell mass in this intrauterine growth restriction model has been linked to epigenetic downregulation of Pdx1, a pancreatic homeobox transcription factor essential for normal β-cell differentiation.\textsuperscript{42} Loss of 40–60% of β-cell mass has been seen in pancreas samples from people with impaired fasting glucose and type 2 diabetes, but less than 24% at 5 years after disease onset has also been reported.\textsuperscript{43,44} Whether a subset of people with type 2 diabetes have predominant functional deficiencies in β cells without loss of mass is unknown, but this may have implications for treatment.

**Glucagon secretion and incretin effect**

Glucagon secretion and the incretin effect, which involves GLP-1 and gastric inhibitory polypeptide, are disturbed in type 2 diabetes.\textsuperscript{45–47} Glucagon secretion is increased during fasting and fails to suppress after meals.\textsuperscript{48} The incretin effect, which is the added increase in insulin secretion from an oral glucose compared to a glycaemia-matching intravenous glucose load, is severely impaired.\textsuperscript{48} The latter feature could be caused by impaired GLP-1 production (although the overall evidence for this is not strong) and reduced sensitivity of β cells to gastric inhibitory polypeptide.\textsuperscript{49,50} Dysfunction in the secretion of glucagon caused by altered incretin action is also possible.\textsuperscript{51} All these disturbances aggravate hyperglycaemia, but are unlikely to be primary defects in the pathogenesis of type 2 diabetes.\textsuperscript{52} Gut hormones, including GLP-1, also have roles in CNS regulation of energy balance and appetite.\textsuperscript{53}

**Adipose tissue and inflammation**

The need to have fat that can expand for metabolic health is exemplified by two extremes in white adipose tissue: rare disorders in which this type of fat is absent, such as congenital and acquired lipodystrophies, can lead to severe metabolic syndrome, whereas some very obese individuals do not develop metabolic syndrome at all.\textsuperscript{54–56} Thus, healthy white adipose tissue prevents nutrient spillover to other tissues and protects against metabolic disease.\textsuperscript{57–59}

White adipose tissue in metabolic syndrome or type 2 diabetes is abnormal in multiple ways: distribution favours VAT; reduced adipocyte differentiation and adiponectin expression and secretion; suppression of lipolysis by insulin is impaired; increased expression and secretion of inflammatory cytokines (eg tumour necrosis factor α, interleukin-1β, and monocyte-chemoattractant protein-1); and increased tissue inflammation (eg, macrophage infiltrates).\textsuperscript{55,56} Decline in secretion of adiponectin and raised concentrations of inflammatory cytokines and non-esterified fatty acids aggravate insulin resistance in muscle and are pathogenic in non-alcoholic steatohepatitis.\textsuperscript{56–58}

The discovery of functional brown adipose tissue in adult human beings raises the possibility for an overlooked role of this tissue in human energy homeostasis and a preventive role in type 2 diabetes.\textsuperscript{69} The detectability of this tissue in humans lessens with increasing age and is decreased in individuals with high body-mass index and fasting plasma glucose values.\textsuperscript{70–72} Genome-wide association studies have shown that only 0·1% of variation in fat distribution (waist circumference and waist-to-hip ratio) can be explained genetically, and, therefore, genetic differences affecting this aspect of adipose tissue seem unlikely between obese people who do and do not develop type 2 diabetes.\textsuperscript{73} Regional differences in gene expression of preadipocytes, however, persist in cells in culture after several passages, which suggests that these cells have epigenetic memory.\textsuperscript{74} Furthermore, preadipocytes from people with type 2 diabetes have an intrinsic gene expression profile that also persists after two passages.\textsuperscript{75} Thus, the early-life environment could affect adipose tissue phenotype. Additionally, abnormalities in adipose tissue might be induced by hyperglycaemia and, therefore, could occur downstream from β-cell impairment.\textsuperscript{76,77}

**The liver**

Increases in endogenous glucose production, predominantly of hepatic origin, are a major determinant of fasting

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**Panel 1: Glossary of terms relating to epigenetics**

- **Genome**: the entire genetic information (genes) for an organism, which is maintained in the nucleotide sequence of DNA; each organism has only one genome.
- **Genetic disease**: disease caused by common variations (polymorphisms) and mutations (variants whose frequency in the population is <1%) in the nucleotide sequence of the genome.
- **Epigenetics**: the study of heritable (from cell to daughter cell, parents to offspring, or both) changes in genome function by chemical modifications of DNA and DNA-associated proteins that occur without a change in the DNA nucleotide sequence.
- **Epigenome**: the pattern of genes that can be expressed in a cell type and passed on to daughter cells; multicellular organisms have different epigenomes for each cell type.
- **Epigenetic imprinting**: the epigenetic suppression of certain genes—ie, the activation or silencing of specific alleles—after fertilisation, dependent on from which parent they were received.
- **Epigenetic mechanisms**: the organisation of chromatin by enzymes into accessible (open for expression) and inaccessible (closed for expression) configurations through methylation or demethylation of DNA and acetylation or deacetylation of DNA-related histone proteins.

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hyperglycaemia in type 2 diabetes. Lack of suppression of production after eating contributes to fed-state hyperglycaemia.26 The mechanisms underlying this dysregulation are complex, involving peripheral supply of gluconeogenic substrate from peripheral tissues, an effect of raised concentrations of non-esterified fatty acids to activate hepatic gluconeogenesis, and the hepatic response to raised concentrations of glucagon.26,98 Type 2 diabetes is strongly associated with non-alcoholic fatty liver disease—each is highly predictive of the other13,26—and is a determinant of its severity and that of non-alcoholic steatohepatitis, and of liver-related mortality.10 Nevertheless, the liver does not seem to be a primary cause of type 2 diabetes.

**Skeletal and cardiac muscle**

The traditional view emphasises a pathogenic role for skeletal-muscle insulin resistance in type 2 diabetes, but we believe that this idea needs careful reconsideration. Type 2 diabetes is a disease of relative inactivity and overnutrition with failure of the body to safely contain fuel excess. As discussed above, this failure can be explained by islet β-cell and adipose tissue deficiencies, with secondary contributions from the liver. So does muscle insulin resistance per se play a causal role in type 2 diabetes pathogenesis? Skeletal muscle inactivity (lack of exercise) certainly contributes to fuel surfeit, but this is not a consequence of insulin resistance. Rather, insulin resistance is downstream from failure to contain the fuel surfeit. Skeletal muscle in individuals with type 2 diabetes is nutrient replete, or even nutrient overloaded, such that it responds with insulin resistance as protection against steatosis or metabolic stress of the tissue.30,31,99 Even with short-term overfeeding, attuned to having a “feast”, skeletal and cardiac muscles develop insulin resistance to divert excess nutrients to safe storage in adipose tissue.110,112 Thus, if skeletal and cardiac muscle insulin resistance is protective against nutrient toxicity, attempts to directly reverse it without concomitant nutrient detoxification, or to override it by forcing nutrients into muscle (eg, by aggressive insulin therapy) could be harmful.

An important issue that should be considered separately from insulin resistance, however, is that the number and function of muscle mitochondria are deficient in individuals with type 2 diabetes and their first-degree relatives.113 This feature could have genetic causes, be acquired early in life, or could merely be a consequence of chronic inactivity.110,113 Treatments that promote mitochondrial biogenesis, function, or both, in muscle, rather than those that increase insulin sensitivity directly, could be beneficial in people with type 2 diabetes. The effects would mimic those of exercise, which lessens insulin requirements and β-cell exhaustion. The indirect effect is improvements in insulin sensitivity of skeletal muscle as the cells revert from needing to keep energy out to taking it in.

**Figure 4:** Role of islet β-cell metabolic activation by fuels and neurohormonal agonists in insulin secretion

Glucose is metabolised via glycolysis to pyruvate and in the mitochondrion to acetyl-CoA, which is then oxidised in the TCA cycle. These actions lead to an increased cytosolic ratio of ATP to ADP, which closes the K⁺,ATP channel, depolarises the plasma membrane potential, and opens voltage-gated Ca²⁺ channels, causing influx of Ca²⁺ and the triggering of insulin-granule exocytosis. Pyruvate from glucose can also be metabolised via PC into the anaplerotic cycle when raised concentrations of Mal-CoA, via the anaplerotic pathway, inhibits partitioning of LC-CoA into FA oxidation, which increases the availability of the LC-CoA for esterification. Glucose also provides glycerol-3-phosphate, which is necessary for FA esterification. Glycerolipids are rapidly hydrolysed by lipases back to NEFA and glycerol to create the GL/FA cycle process. This cycle produces lipid signalling molecules, such as diacylglycerols, that enhance glucose-stimulated insulin secretion. Aminoacids, such as glutamine and leucine, also interact with the glucose metabolism pathways to increase the coupling signals produced by glucose alone. The β cell responds to other neurohormonal and metabolic extracellular signals via various plasma membrane receptors. PC—pyruvate carboxylase. PDH—pyruvate dehydrogenase. ACh-R—acetylcholine receptor. GP-B—gastric inhibitory polypeptide receptor. GLP-1-R—glucagon-like peptide-1 receptor. FFAR1—free-fatty-acid receptor 1. α-ADR-R—α2-adrenergic receptor. SSN-R—somatostatin receptor. OAA, oxaloacetate; CoA=coenzyme A; MAG, monoacylglycerol; DAG, diacylglycerol; TG, triacylglycerol; Δψm, change in plasma membrane potential; Mal-CoA=malonyl-CoA. LC-CoA=long-chain acyl-CoA. GL=glycerolipid. FA=fatty acid. NEFA=non-esterified fatty acids.

**Prevention and management**

The pandemic of type 2 diabetes, along with its high human and economic costs, is showing no signs of abatement and, therefore, new approaches are urgently needed to prevent, slow the progression, and limit the consequences of this disease. Changes need to be based on knowledge of the pathophysiology and to take into account new insights from genetic and epigenetic studies. A whole-of-life approach is indicated, particularly for prevention.

**Early life**

Events and lifestyle in early life might substantially affect susceptibility to type 2 diabetes. Fetal and neonatal programming might contribute substantially to susceptibility to obesity, β-cell and adipose tissue.
Major transitions in life

Populations rapidly transitioning from traditional to westernised lifestyles deserve particular attention to prevent disastrous increases in diabetes prevalence (the match-mismatch paradigm of metabolic disease), as has been seen in regions such as Asia. Improvements in maternal public health programmes in pretransition and post-transition populations and provision of education to relevant groups about the risks of rapidly adopting western lifestyles could be considered.

Gestational diabetes

A pandemic of gestational diabetes accompanies that of obesity and type 2 diabetes. The new IADPSG recommendations for diagnosis of hyperglycaemia in pregnancy include early screening for overt diabetes, but most cases of gestational diabetes are still diagnosed between 24 and 28 weeks’ gestation (figure 5). Most women, therefore, do not receive dietary and lifestyle advice or receive insulin therapy, if required, until late in the pregnancy. Two clinical trials have shown that late diagnosis and management are associated with better obstetric outcomes, but whether the child’s risk of developing metabolic diseases later in life is reduced by this approach is unknown. The Australian Carbohydrate Intolerance Study in Pregnant Women showed that, although the standard intervention for gestational diabetes greatly lowered macrosomia rates, it had no effect on body-mass index in children aged 4–5 years.

The window of opportunity to alter adverse fetal programming might arise earlier than 28 weeks’ gestation, or the neonatal or early childhood periods could be crucial in the determination of later metabolic health, such that a broader approach might be needed to prevent disastrous increases in diabetes prevalence (the match-mismatch paradigm of metabolic disease), as has been seen in regions such as Asia. Improvements in maternal public health programmes in pretransition and post-transition populations and provision of education to relevant groups about the risks of rapidly adopting western lifestyles could be considered.

Prediabetes

Prediabetes, in which glucose tolerance, fasting glucose, or both are impaired, is associated with increased probability of incident diabetes (~34% increase in risk in 7–5 years) and cardiovascular disease (~11% in 10 years). Effective management of prediabetes can prevent or delay the onset of both these disorders. Lifestyle interventions (improved diet, increased exercise, or both) can lower the risk of incident diabetes by 28–59% but adherence outside clinical trials is a challenge. Pharmacotherapy with α-glucosidase inhibitors, metformin, and
thiazolidinediones can also effectively lower the risk of incident diabetes, but whether these drugs are truly preventive or treat early symptoms is unclear. Owing to high prevalence rates, public health approaches are clearly required.

Established diabetes

The clinical management of established type 2 diabetes involves optimum control of factors that cause complications, such as blood glucose and lipid concentrations, blood pressure, bodyweight, and smoking, as well as regular screening for and appropriate management of microvascular (eye, renal, and neural) and macrovascular (coronary, cerebral, and peripheral) complications. Local practice guidelines, such as the ADA Clinical Practice Recommendations 2011, should be used.

Glycaemic control of type 2 diabetes becomes more difficult over time as islet β-cell failure is progressive (figure 6). All current guidelines for treatment of hyperglycaemia are largely structured around this expected decline with the main aim of maintaining optimum HbA1c levels. Extension of the therapeutic goals to include the reversal of pathophysiology might now be possible, as suggested by Defronzo. The key problems to focus on are chronic fuel surfeit, including the brain control of energy homoeostasis, islet β-cell dysfunction, the health of adipose tissues and fat partitioning, and regulation of endogenous glucose production (panel 2).

Reduction of the chronic fuel surfeit is extremely challenging because it is linked to the CNS and reward mechanisms. Improvements in diet and exercise should be pursued in all patients and can achieve good results in moderately to severely obese patients.122 The only agents available with a healing effect that act on adipose tissue are the thiazolidinediones (pioglitazone and rosiglitazone). They activate peroxisome proliferator-activated receptor γ, which improves differentiation of fat cells.125 Thiazolidinediones promote SAT expansion, reduce lipolysis and expression and secretion of cytokines as well as adipose tissue inflammation, and increase re-esterification of fatty acids and expression and secretion of adiponectin.126–128 These drugs also lead to sustained good glycaemic control in patients with type 2 diabetes.128–130 The use of thiazolidinediones, however, can lead to weight gain (albeit with more healthy SAT than unhealthy

Panel 2: Desired characteristics of glycaemic control therapies in type 2 diabetes

The therapy, in addition to achieving target HbA1c, should:

- Be disease modifying (ie, reverse one or more of the underlying pathophysiological processes)
  - Reduce chronic fuel surfeit
  - Protect islet β-cells from progressive failure
  - Prevent adipose tissue dysfunction, including abnormal fat distribution and inflammation
  - Restore normal islet α-cell function and incretin physiology
  - Restore normal regulation of hepatic glucose production
  - Enhance skeletal muscle mitochondrial function/oxidative metabolism
  - Enhance energy expenditure and thermogenesis
- Sustain good metabolic control with low therapy-associated unwanted effects
- Enhance quality of life of patients
- Reduce diabetes microvascular and macrovascular complications
- Reduce diabetes-related mortality (includes cardiovascular disease-related), and all-cause mortality

HbA1c = glycated haemoglobin A1c

Efforts to find new treatments for obesity must continue. The disorder is difficult to treat because agents that affect the CNS carry the risk of severe adverse effects, such as depression.131 For the islet β cell, the GLP-1 mimetics are again the most promising for reversing pathophysiology. For less-obese patients, however, increasing endogenous GLP-1 by treatment with the orally available dipeptidyl-peptidase IV inhibitors early after onset of type 2 diabetes might be beneficial, but these drugs become less effective with increasing duration of disease. Sulphonylureas have no known disease-modifying effects and, although not conclusively proven, might hasten β-cell decline. They also cause weight gain and hypoglycaemia and, therefore, use should be curtailed. Metformin and the thiazolidinediones could also have some direct and indirect protective effects on β cells.

The only agents available with a healing effect that act on adipose tissue are the thiazolidinediones (pioglitazone and rosiglitazone). They activate peroxisome proliferator-activated receptor γ, which improves differentiation of fat cells. Thiazolidinediones promote SAT expansion, reduce lipolysis and expression and secretion of cytokines as well as adipose tissue inflammation, and increase re-esterification of fatty acids and expression and secretion of adiponectin. These drugs also lead to sustained good glycaemic control in patients with type 2 diabetes. The use of thiazolidinediones, however, can lead to weight gain (albeit with more healthy SAT than unhealthy

VAT), oedema, cardiac failure, and osteopenia with distal fractures, and rosiglitazone is possibly associated with cardiac adverse effects. Low doses, however, might have a much better safety profile while maintaining some efficacy. In a diabetes prevention study of 2 mg rosiglitazone combined with 500 mg metformin twice daily for 3 years, and a 12-week study of 7.5 mg pioglitazone daily in patients with type 2 diabetes and poor glycaemic control, both drugs showed significantly beneficial effects.

Metformin that lowers glucose concentrations mainly through effects on endogenous glucose production is beneficial in patients with type 2 diabetes. This drug should continue to be used in combination with other drugs.

Insulin therapy clearly has a place in the treatment of patients who have become insulin deficient and have poorly controlled type 2 diabetes, and possibly to stabilise patients who have become insulin deficient and have drug should continue to be used in combination with aggressive glycaemic control group of the The Action to could have caused the unexpected mortality in the Insulin-mediated tissue injury, particularly of the heart, who are lean and do not have monogenic diabetes or effects by promoting excess glucose uptake in the face of the potential to cause insulin-mediated nutrient toxic therapy overrides insulin resistance in muscle, it also has gain weight\(^{28}\) and are at risk of hypoglycaemia. If insulin therapy overrides insulin resistance in muscle, it also has the potential to cause insulin-mediated nutrient toxic effects by promoting excess glucose uptake in the face of high lipid concentrations (glucolipotoxic effects).\(^{30,31}\) Insulin-mediated tissue injury, particularly of the heart, could have caused the unexpected mortality in the aggressive glycaemic control group of the The Action to Control Cardiovascular Risk in Diabetes study.\(^{119}\)

Changes in treatment strategies must be supported by strong evidence. Carefully designed clinical trials are needed to test new approaches, especially early use of GLP-1 mimetic agents or dipeptidyl-peptidase IV inhibitors in combination with thiazolidinediones at substantially reduced doses. Long-term safety is also a major consideration (panel 2).

With further progress in unravelling the pathogenic roles of genes and epigenetic phenomena in type 2 diabetes, pharmacogenomic and pharmacoepigenomic studies might eventually yield treatment choices that can be personalised for individual patients.

Lean and elderly patients

Although Asian patients with type 2 diabetes are frequently leaner than patients of other ethnic origins, fuel surfeit is still likely to be seen and will cause relative visceral adiposity (webappendix p 1). Some patients, however, have type 2 diabetes without fuel surfeit. These patients are often elderly and probably have some susceptibility to islet \(\beta\)-cell dysfunction, but the disease may well be caused by age-related decline in function. Latent autoimmune diabetes in adults might have increased susceptibility to \(\beta\)-cell dysfunction. Early use of insulin might be appropriate and, indeed, necessary in many of these patient groups, excluding those with some forms of monogenic diabetes.

Conclusions

To turn around the pandemic of type 2 diabetes and its effect on lives and economies worldwide is necessary, but is a major challenge for modern society. An improved understanding of the pathogenesis and natural history is crucial to focus efforts appropriately. Substantial evidence of safety and efficacy of candidate prevention and treatment strategies must be provided before they can be widely implemented. We propose that the whole of patients’ lives need to be considered for effective disease management, and particularly in prevention for reversal of the pandemic. A continued broad but coordinated multidisciplinary approach is needed that involves scientists, public health practitioners, educators, clinicians, and the people at risk, with support from government authorities and non-governmental organisations.

Contributors

All authors contributed to the literature search and the content of this Seminar. CJN wrote the first draft of the paper and all authors contributed to the writing of the final version.

Conflicts of interest

CJN has received speaker’s fees from Eli Lilly, GlaxoSmithKline, Merck Sharp Dhome, Novartis, and Servier, and PD and CJN from Novo Nordisk. MP declares that he has no conflicts of interest.

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