Diabetes mellitus Type 2 – the new face of an old lady

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Summary

Already 600 years before Christ, type 2 diabetes was known as a disease of elevated blood sugar levels associated with obesity. Since then, it appears, our understanding of the disease has not changed much, aside from the replacement of tasting the patients' urine [1] by the measurement of plasma glucose and glycated haemoglobin levels (HbA1c) [2] for its diagnosis and the discovery of some new drugs. Already, in those old days a physician from India named Sushrut described diabetes mellitus as a disease characterised by the passage of large amounts of urine and its "honey-like" taste and, noteworthy, as a disease that is mainly associated with obesity and a sedentary lifestyle, recommending physical activity as the primary treatment option [3]. Although these milestone observations remain valid, major progress in the underlying pathogenesis of type 2 diabetes has been achieved showing a new face of this old disease and opening doors for novel treatment options.

This review will highlight recent pathophysiological aspects of type 2 diabetes, actual diagnostic and treatment guidelines and discuss some possible upcoming new therapeutic strategies.

Key words: diabetes

Pathophysiological aspects

The first event in the pathophysiology of type 2 diabetes is insulin resistance, due to over-nutrition and inactivity in genetically predisposed individuals. To cope with the increased demand of insulin, the pancreatic islet is forced to enhance its secretory activity. At early stages this adaption is successful in most individuals. Over time, in some individuals this adaption cannot be preserved due to a failure of β cell secretory capacity [4]. Importantly, the dynamic of the disease is largely directed by the changes in β cell functional mass while insulin resistance remains largely unchanged as long as body weight is stable. Therefore, the onset of diabetes and the progressive increase in the requirement of anti-diabetic medication is largely dictated by the decline in insulin secretion [5].

Understanding the importance of islet dysfunction in type 2 diabetes has motivated research aiming at understanding the underlying mechanisms of insulin failure and development of treatments targeting the pancreatic islet. The leading hypothesised mechanisms to explain this islet dysfunction and also insulin resistance have been oxidative stress, endoplasmic reticulum stress, amyloid deposition in the pancreas, ectopic lipid deposition in the muscle, liver and pancreas, and lipotoxicity and glucotoxicity. All can be caused by overnutrition [6–10]. Interestingly each of these cellular stresses are thought to either induce an inflammatory response or to be exacerbated by inflammation [11–15]. Inter-individual variability in the response to metabolic stress can be explained by genetic predisposition, and by adverse foetal events which may e.g., lead to limited beta cell mass at birth and increased risk for type 2 diabetes and obesity [16].

Diagnosis

What defines diabetes? – Criteria for the diagnosis of diabetes

Diabetes is classically diagnosed by the measurement of plasma glucose, either in the fasting state, at 2 h of the 75 g-oral glucose tolerance test (OGTT) or randomly in the presence of symptoms consistent with hyperglycaemia [17]. Therefore glucose should be measured in plasma from venous blood and measurements should be confirmed on a subsequent day if values are not unequivocal and come along with classical symptoms of hyperglycaemia [2].

Since 2009 HbA1c has been included as an additional diagnostic tool for the diagnosis of diabetes [18] (see table 1 and [19] for technical pitfalls). The advantage of using HbA1c over plasma glucose is that it can be assessed at any time during the day without the need for a fasting period and that it is less influenced by short-term events like infection or stress. Furthermore, since treatment targets HbA1c levels, it allows immediately assessing the level of intervention required. However, in some cases HbA1c measurement may not be reliable such as in cases of changes in red blood cell life span due to blood loss, transfusion, haemolysis, iron- and vitamin b12 deficiency [20]. In addition, haemoglobinopathies, uraemia, pregnancy, intake of great amounts of alcohol or high dosages of vitamin C and E, can influence HbA1c values, depending on the clinical constellation and the analytical method used to detect HbA1c values [20].

When does diabetes start? – Criteria for the diagnosis of prediabetes and recommendations when to screen asymptomatic adults for diabetes

As discussed above type 2 diabetes is a chronic and progressive disease developing over a prolonged period of time (month to years) until onset. Prediabetes is subsuming conditions like impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) and is diagnosed by measurement of fasting plasma glucose, 75 g OGTT and now as well by detection of HbA1c (the international diagnostic criteria for detecting prediabetes are depicted in table 2). Although individuals at this stage do not suffer from specific symptoms they are at high risk of developing diabetes [22, 23]. However, the term "prediabetes" is somehow misleading since prediabetes is already a risk for developing diabetes complications like retinopathy [24] and cardiovascular diseases [25–28]. Accordingly the international diabetes associations now also recommend screening for diabetes in asymptomatic patients, while detection of plasma glucose values in the fasting state, at 2 h at OGTT or HbA1c is appropriate (see table 3 for American Diabetes Association criteria when to test for diabetes in asymptomatic adults). It has been recommended to re-test individuals at risk with a negative test result after 3 years, although there is no data available concerning the optimal intervals for testing, while individuals identified as having prediabetes should be tested annually for diabetes [29].

Overall, identifying individuals at risk for the development of diabetes as early as possible is crucial in preventing diabetes and to initiate treatment of risk factors for cardiovascular events.

Treatment recommendations

Theoretically, treatment of type 2 diabetes is very simple. Patients need to decrease their body weight, exercise, adhere to a healthy diet and, in some cases, need specific drugs. The challenge is to implement these life-style changes in the patients' day-to-day behaviour. In doing so, motivation is probably the key. We believe that the basis for both successful prevention and treatment of diabetes is to educate the patient about the pathophysiology of the disease, to inform about possible treatment strategies and to highlight the patient's active role in this process. To ensure compliance, the goals should be set in a realistic frame to allow positive, encouraging feedback to the patient. We also recommend following the patients up on a regular basis, similarly to other chronic diseases. While in larger studies, and in individual experiences, life style changes are often seen as disappointing or even not achievable, there is now good evidence that a patient-centred, individual therapeutic approach is effective and successful [30, 31].

Prediabetes

Patients diagnosed with prediabetes (for criteria see table 2) should be counseled on lifestyle changes as discussed above. Metformin will probably be beneficial [32] especially for patients with a BMI >35 kg/m^2, aged <60 years, and for women with prior gestational diabetes mellitus [21] although some prefer not to give medication too early fearing loss of motivation to change the life style.

Table 1: Criteria for the diagnosis of diabetes (adapted from American Diabetes A. Standards of medical care in diabetes – 2012. Diabetes Care. 2012;35(Suppl 1):S11–63).

The diagnosis of diabetes mellitus can be made based on one of the following criteria (repeated measurement is recommended to confirm diagnosis):
– HbA1c ≥6.5% or
– Fasting plasma glucose ≥7.0 mmol/L (fasting = no caloric intake for ≥8h) or
– 2-h Plasma glucose ≥11.1 mmol/L during an 75g-OGTT or
– Symptoms of hyperglycaemia and random plasma glucose ≥11.1 mmol/L

Table 2: Criteria for the diagnosis of prediabetes (adapted from American Diabetes A. Standards of medical care in diabetes – 2012. Diabetes Care. 2012;35(Suppl 1):S11–63).

The diagnosis of prediabetes mellitus can be made based on one of the following criteria (repeated measurement is recommended to confirm diagnosis):
– Fasting plasma glucose 5.6–6.9 mmol/L (impaired fasting glucose) or
– 2-h Plasma glucose 7.8–11.0 mmol/L during an 75 g-OGTT (impaired glucose tolerance) or
– HbA1c 5.7–6.4%

Table 3: Criteria for testing asymptomatic individuals for diabetes (adapted from American Diabetes A. Standards of medical care in diabetes – 2012. Diabetes Care. 2012;35(Suppl 1):S11–63).

Asymptomatic adult individuals should be tested for diabetes if:
1. They are overweight (BMI ≥25 kg/m^2) and have additional risk factors:
• Physical inactivity;
• First-degree relative with diabetes;
• High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander);
• Women who delivered a baby weighing >3360 g or were diagnosed with gestational diabetes mellitus;
• Hypertension (≥140/90 mm Hg or on therapy for hypertension);
• HDL cholesterol level <0.90 mmol/l and/or a triglyceride level >2.8 mmol/l;
• Women with polycystic ovary syndrome (PCOS);
• HbA1c ≥5.7%, IGT, or IFG on previous testing;
• Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans);
• History of cardiovascular disease.
2. They reach the age of 45 in the absence of risk factors as depicted above
3. The last testing is 3-years ago and results were normal that time, with consideration of more frequent testing depending on initial results and individual risk status.

Diabetes

Therapeutic strategies are guided by HbA1c, since it reflects blood glucose values over a longer period of time and since the appearance of diabetes micro- and macrovascular complications are known to be linked to certain HbA1c threshold values [33]. HbA1c should therefore be measured initially before starting treatment and then every 6 months in patients meeting treatment goals and every 3 months in patients not reaching treatment goals or with a change in therapy.

For most patients the goal is to achieve and maintain HbA1c levels <7% in the absence of hypoglycaemic events. Although for most patients a HbA1c level ≤7% is the therapeutic goal, glucose lowering therapy should be strongly guided by patients resources. Accordingly the ADA and EASD now recommend individualised treatment targets. Thus, in younger and healthier patients tighter targets (6.0–6.5%) should be aimed for, while less stringent therapeutic aims with a HbA1c of 7.5–8% or even slightly higher should be addressed in patients with a history of severe hypoglycaemia, shortened life expectancy, important co-morbidities, severe vascular complications, long-standing disease duration, limited resources and support systems and in less-motivated, non-adherent patients with poor self-care capacities [21, 34]. Initial therapy should be lifestyle intervention, including dietary counseling with reduced intake of saturated fat and increased intake of food rich in fibre e.g. the Mediterranean diet [35] as well as encouragement to reduce body weight [36, 37]. A particular focus should be given to increase physical activity. It is well known that exercise improves glucose disposal via calorie consumption and enhances insulin sensitivity. Recent data point also to a myokine release leading to improved beta cell function [38]. Finally, metformin therapy should be initiated in the absence of specific contraindications as first line medical treatment. Its acceptance may be enhanced by informing the patient about potential gastrointestinal side effects and by a slow increase of the dose by 500 mg until a maintenance dose of 2x1,000 mg a day is reached. Regarding the effect of metformin on cardiovascular mortality beyond its glucose-lowering effects the clinical trial data available is still controversial and lager trials are strongly needed to specifically address this endpoint [39, 40]. If lifestyle modifications and maximal daily metformin doses are not sufficient to control blood sugar levels within 3–6 months, therapy should be extended with either a "basal" (long acting) insulin or an oral antidiabetic drug such as a sulfonylurea or a dipeptidyl peptidase (DPP)-IV inhibitor taking into account advantages and disadvantages of the drugs for each patient: sulfonylurea being of lower costs but associated with body weight increase and risk of hypoglycaemia [34]. In obese individuals glucagon-like peptide (GLP)-1 analogues should be considered. If this regimen is still not effective to achieve blood glucose control different treatments may be combined [34]. Finally, basal insulin therapy may be intensified with the addition of prandial insulins [41].

Beyond controlling glucose levels aggressive management of cardiovascular risk factors like antihypertensive and lipid lowering therapy as well as antiplatelet treatment and smoking cessation are highly important features of an integrated therapy for patients with type 2 diabetes [34].

Outlook – new therapeutic strategies

SGLT-2 inhibitors

Polyuria and "honey-like" tasting urine have been the two features first known to characterise diabetes by ancient physicians of Egypt and India [42]. These well-known features, used as tools for the diagnosis of diabetes for a long time, are now appearing in an altogether different light, providing possible new options for the treatment of type 2 diabetes.

The kidneys are contributing to whole body glucose metabolism by glucose expenditure and gluconeogenesis as well as reabsorption of glucose from the glomerular filtrate [43]. At average glucose levels of 5.5 mmol/l almost all filtered glucose is reabsorbed by the kidney through tubular sodium-dependent glucose co-transporters (SGLTs) [44]. If the glucose concentration in the glomerular filtrate is exceeding a certain threshold, normally around 11 mM, the capacity of the renal tubular glucose transporters is exhausted and glucose levels rise in the filtrate, leading to osmotic polyuria and glycosuria.

Inhibition of SGLT2 transporters decreases the renal glucose threshold, promoting excretion of glucose by the urine and thereby reducing hyperglycaemia. Additionally, this forced glycosuria promote reduction in bodyweight and decrease blood pressure due to loss and the osmotic effect of glucose water.

Among the SGLT2 inhibitors in development, dapagliflozin is the most advanced one and has been shown to be effective either when given alone [45] or as add-on therapy with metformin [46, 47] and insulin [48]. Dapagliflozin has effectively lowered fasting and postprandial plasma glucose levels, leading to reduced Hba1c levels as well as decreasing in body weight. While the risk of hypoglycaemic events seems to be low, treatment with dapagliflozin is associated with an increased number of genital infections, mostly of mild or moderate intensity [45–48]. In addition, numerical imbalances were noted in occurrences of breast and bladder cancer in patients who received dapagliflozin [49]. Long-term observational studies are required to elucidate possible carcinogenic effects.

Bariatric/metabolic surgery

Entering the field in 1995 [50], bariatric or metabolic surgery has put all the other diabetic treatment approaches in the shadow and has brought up one big question: might surgeons be the better diabetologists? Well, from the raw data presented so far it seems like they are: remission of type 2 diabetes after bariatric surgery has been demonstrated to occur in 78% with sustained remission rates in studies with follow up of more than two years [51], however, data on long-term effects are still missing. Interestingly, the improvement in glucose homoeostasis is occurring shortly after surgery and in most cases before a substantial weight loss has taken place [50, 52, 53]. A study comparing conventional weight loss with weight loss due to bariatric surgery procedures showed that despite the same amount

of weight loss was achieved, the improvement in glucose metabolism was much greater in operated than non-operated individuals [54]. Therefore, it has been proposed that mechanisms other than weight loss, most probably of multifactorial nature including changes in incretin secretion and microbiota, may be responsible for the tremendous efficacy in diabetes resolution after bariatric surgery.

However, individuals that underwent such a surgical treatment need lifelong medical monitoring and optimal supplementation of minerals and vitamins as well as life style counseling. Therefore, these procedures should only be undertaken if optimal pre- and post-surgical support can be provided by a specialised team of health care providers, consisting of dieticians, psychologists, endocrinologists and surgeons. Furthermore, although the risk has been diminished over the recent years, there is still some direct surgery-related morbidity and mortality left [55] that need to be discussed with the patient. If the same morbidity and mortality rates were caused by drugs, there is little doubt that they would be considered as unacceptable by the responsible agencies.

Anti-inflammatory treatment

Increasing evidence points to a pathological activation of the immune system in obesity, type 2 diabetes and cardiovascular disease [56]. This can be observed in adipose tissue [57, 58], liver [59], pancreatic islets [14] and the vasculature [60] and suggests that inflammation participates in the pathogenesis of type 2 diabetes and its complications. Preliminary results from clinical trials with interleukin-1 antagonists and salicylates support this notion and have opened the door for immunomodulatory strategies that simultaneously lower blood glucose and potentially reduce the severity and prevalence of its complications [61–63]. Ongoing clinical trials are in phase 3.

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