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Diabetes mellitus: an overview

Abstract

Diabetes is one of the leading causes of mortality in the world with about 422million (8.5% of the global population) are currently diagnosed. The incidence is predicted to continue expanding despite great efforts on the means of treatments are exerted. This article provides an overview on diabetes mellitus, its epidemiology, treatment and the role of different healthcare professionals in its management.

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Mohammed H Abutaleb

Jazan Health Affairs, Ministry of Health, Jazan, Saudi Arabia

Correspondence: Mohammed H Abutaleb, Jazan Health Affairs, Ministry of Health, Jazan, Saudi Arabia; Email abutaleb33@yahoo.com

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Definition

Diabetes is a multi-factorial, chronic and progressive metabolic disorder characterized by chronic hyperglycemia due to defects in the metabolism of carbohydrate, fat and protein. Persistent hyperglycemia is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels.[1]

Classifications

Diabetes is classified into three major types: type 1, type 2, and gestational diabetes mellitus (GDM). Other specific types result from specific causes. Type 1 diabetes usually affects children and people below thirty years of age, but can also affect older adults. Although the pathogenesis is not fully understood, type 1 diabetes is characterized by loss of insulin secretion due to idiopathic attack or autoimmune destruction of insulin-secreting beta cells of the islets of Langerhans in the pancreas.[2] Therefore; it is mainly treated by insulin replacement therapy.

Type 2 diabetes is the most common globally. It predominantly affects adults above thirty years of age although many cases have recently been diagnosed amongst obese children. Type 2 diabetes has also been known as non-insulin-dependent diabetes mellitus (NIDDM) or late onset diabetes; however, that term is no longer used because of confusion it may cause if patients were classified on the basis of treatment rather than pathogenesis. Gestational diabetes mellitus (GDM) occurs when glucose intolerance is first observed during pregnancy. The pathogenesis of GDM still remains largely unknown; nonetheless studies have shown involvement of dysregulation and defects in the insulin signaling pathway, resulting in reduced glucose uptake and transport in skeletal muscles and adipocytes.[3] Other specific types are those in which the underlying defect or disease process can be identified in a relatively specific manner. They include disease of the exocrine pancreas, such as fibrocalculouspancreatopathy or secondary to use of medicines such as corticosteroids.

Diagnosis

All types of diabetes including type 2 are diagnosed when fasting plasma glucose is more than 7mmol/L on at least two occasions. Other diagnostic criteria are shown in Table 1.

Criteria
1- Glycated haemoglobin (HbA1c) of 6.5% (48 mmol/mol) as recently recommended by WHO. The test should be performed with stringent quality measures, standardised to the international reference values, and no conditions present known to preclude its accurate measurement (4).
Or
2- Fasting plasma glucose concentration ≥126 mg/dl (7.0 mmol/L). (Fasting is defined as no caloric intake for at least 8 hours); plus classic symptoms of diabetes, which include polyuria, polydipsia, and unexplained weight loss.
or
3- Casual plasma glucose concentration ≥200 mg/dl (11.1 mmol/l) plus classic symptoms of diabetes. Casual is defined as any time of day irrespective of meal time.
or
4- Two-hours post-load glucose concentration ≥ 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test (OGTT). The test should be performed as described by WHO, using a glucose load containing the equivalent of 75 gm anhydrous glucose dissolved in water.
If no symptoms of hyperglycaemia, criteria 2-4 should be confirmed by a repeat testing on a different day.
Adapted from WHO reports, 2006 (5), and ADA 2015 (6)

Causes

Despite the volume of research that has been invested in diabetes research over past decades, the pathogenesis of type 1 diabetes is not fully understood but is thought to stem from multiple factors involving genetic abnormalities and/or environmental factors, leading to either a loss of insulin secretion or a decrease in insulin action. The pathophysiology of type 2 diabetes is simply characterized by insulin resistance, impairment of hepatic glucose production regulation and reduced β cells function subsequently leading failure of β cells.[7] The primary outcome thus is believed to be an initial reduction in insulin secretion secondary to genetic abnormalities and other risk factors involved in most type 2 diabetes patients. These result in beta-cells responding less effectively to hyperglycemia or to a decrease in the insulin biological response at the target tissues.[8] The decreased insulin biological response (insulin resistance) occurs because insulin is unable to bind to its receptor due to defects in the insulin receptor binding sites or disturbances in the insulin signal transduction pathway. Overcoming insulin resistance requires the pancreatic β cells to increase the amount of insulin secreted, a state called hyperinsulinemia. Because accelerated endogenous glucose output occurs simultaneously with hyperinsulinemia, at least in early and mid-disease stages, insulin resistance in hepatic cells becomes the major driver of hyperglycemia in type 2 diabetes.[7] The release of pro-inflammatory adipose tissue-derived cytokines and elevated level of free fatty acids have also been shown to play a role in the development of insulin resistance in the liver and skeletal muscle and fat cells.[8]

Risk factors

Several risk factors have been associated with the development of type 2 diabetes. Genetic factors in some ethnic groups, family history of diabetes, and increasing population age are examples of unmodifiable risk factors. However, lifestyle factors associated with unhealthy diet, physical inactivity and smoking usually leading to overweight, dyslipidemia, high blood pressure and impaired glucose tolerance (IGT) are the most common risk factors for escalating diabetes epidemiology.[9] Environmental factors such as exposure to arsenic and mercury, physical living conditions, stress levels, job strains and low socioeconomic status are also believed to contribute to diabetes development.[9] The fact that people with type 2 diabetes can remain undiagnosed for manyyears or to be unaware of the long-term damage being caused by the disease warrants health system screening measures.

Epidemiology

Rising combinations of the aforementioned risk factors have contributed to the global epidemiology of both type 1 and type 2 diabetes. Type 2 diabetes is now one of the most common diseases in the world. The number of people with type 2 diabetes is increasing in every nation. The global prevalence of diabetes among adults is currently estimated to be about 382million; with 175million undiagnosed and the greatest incident is between 40 and 59years of age.[10] By 2035, this number is expected to increase to over 592million.[10,11] In 2014, it is estimated that diabetes affects 422million (8.5%) of the population in the world.[12] These numbers are far greater than previous estimates.[13–16] Diabetes is considered one of the major problems and greatest challenges facing the health systems.[17–19] The incidence of diabetes in the world is increasing, particularly among children.[20,21] In a WHO report, it was estimated that the global diabetes occurrence would increase to about 4.4%, affecting more than 366,212million in 2030 with a change of around 114% since 2000.[16] It is estimated that 23% of Saudis are in diabetes or pre-diabetes phase.

Clinical manifestation and complications

Clinical manifestation in diabetes patients is similar in both type 1 and type 2 diabetes but the intensity of the clinical features differs. Major symptoms include polydipsia (excessive and prolonged thirst), polyphagia (excessive hunger) and polyuria (excessive urination), weight loss, cramps in muscles of the limbs, blurred vision, constipation and fatigue. The progressive nature of diabetes over time is associated with two types of long-term diabetes complications: macrovascular and microvascular. The latter usually occur earlier and may involve retinopathy, nephropathy and peripheral neuropathy. The former may lead to coronary heart disease, stroke, peripheral vascular disease and damage or loss of vision, extremities and kidney.[1]

Diabetes management

Management of patients with diabetes consumes more than 10% of the annual NHS budget, more than half of which supports patients with serious complications of diabetes.[22,23] The expanding diabetes population in the UK will have a massive impact on NHS spending unless the cost of treatment is significantly reduced, which could have an impact on patient care.[24] A significant increase in diabetes rates will also burden the workload of those managing and preventing the disease and its complications, and this will also have significant cost implications care.[24] Implementing national guideline into routine clinical practice has been associated with uptake of technologies and drug prescribing[25] better use of anti-hyperglycemic medications and improve glycaemic control to the recommended level of HbA1c.[26] Appendix 1.0 lists and summarizes available pharmacological agents for glycaemia control. The major aim of diabetic care is to improve the quality of life of people with diabetes as well as to increase their life expectancy. Achievement of such an outcome is dependent on the provision of comprehensive, complementary and integrated health and social care across both primary and secondary settings through diabetes specialist professionals.

Diabetes is a complex disease and its management requires addressing the prevention, early detection and management of complications as well as optimal control of hyperglycemia, hypertension, dyslipidemia, obesity and other CVD risk factors. Management of diabetes and associated complications and their risk factors involves prescribing different pharmacological and non-pharmacological modalities in addition to regular screening to prevent long-term complications.[27,28] For implementing such measures, the key priority is patients' education and empowerment,[29] in addition to care system provided by multidisciplinary specialist team.[30]

Within the modern health systems, diabetes care is usually provided in primary care through specialized clinics for diabetes, but complex cases are treated in specialized diabetic centers in secondary care where multidisciplinary diabetes-specialist members are available following a national guideline or local protocols adapted from a national guidance or known evidence-based algorithm. The diabetes team is usually led by a medical diabetologist and in most cases includes diabetes specialist nurses, dieticians, podiatrists, and other collaborators such as ophthalmologists, nephrologists and pharmacists, in addition to services of care provided by the family medics. This has improved clinical efficiency, communication and patient-centeredness care.[31] In the last decade, new evidence on lifestyle monitoring, education on self-management and monitoring, and various new treatments have been introduced for different management aspects. The main aspects of the national guideline for type 2 diabetes in the UK are summarized below.

Patient-centered care

Structured education should be offered to people with type 2 diabetes and their carriers at the time of diagnosis. This structured education programme is an evidence-based approach carried out by a trained educator and tailored to individual requirements to enhance self-management. Advice on nutritional needs should be given by nutrition experts and must suit cultural needs, and dietary advice should be based on healthy eating habits. Newly diagnosed patients should have plasma glucose level monitored daily as part of self-education, with help in interpreting results. Support on setting targets for HbA1c levels, lipid levels and blood pressure should be given and HbA1c levels should be checked at least once every six months.

Treatment aimed at lowering blood glucose

The main pharmacological treatments used to control hyperglycemia in type 2 diabetes are insulin and/or oral antidiabetic agents, as illustrated in Appendix 1. Metformin should be offered as the first line of treatment if HbA1c is not reduced to target levels unless the patient has contraindications due to renal impairment or hypotension. Sulphonylurea should be used as a second line of treatment, and these treatments should be assessed by measuring HbA1c levels. If the level is not controlled, then the dosage should be increased. People using sulphonylureas should be educated on the danger of hypoglycemia. Rapid acting insulin analogues (eg, insulin aspart, lispro and glulisine) should only be administered to people with uncontrolled hyperglycemia and unstable lifestyles such as those who cannot regularly eat a similar amount of food at a similar time due to, for example, shift work. People with HbA1c levels above 7.5% are required to take human insulin or thiazolidines if insulin is inappropriate. In obese individuals with > 7.5% HbA1c, exenatide, an insulin secretion stimulator and glucagon secretion inhibitor, should be given when HbA1c does not improve at this point and exenatide should be discontinued after twelve months if body weight is not lost and blood glucose is not reduced. A pen injector of insulin should thus be suggested, starting with human insulin, followed by a mixture of insulin analogues or insulin glargine. A structured programme should be employed when starting insulin by titrating blood glucose level with insulin concentration administered to establish the best dose for avoiding hypoglycemia.

Treatments aimed at lowering blood pressure

Blood pressure should be monitored at least every year or more frequently in patients at risk of high blood pressure. In case of patients already taking anti-hypertensive at diagnosis, blood pressure control and treatment should be reviewed. Advice on healthy lifestyle should be offered to people with blood pressure above 140/80 mmHg or 130/80 mmHg in people with kidney disease; Cerebrovascular or eye damage surveillance should be offered. Angiotensin-converting enzyme (ACE) inhibitors or angiotensin 2 receptor blockers (ARB) should be administered when possible and based on individual requirements for the drug. If blood pressure is not controlled, calcium channel blocker should be administered as the second or third line of treatment if target blood pressure is not achieved.

Blood lipid control and cardiovascular risk management

Formal assessment of CVD risk is not required, as type 2 diabetes patients are already at premature risk of CVD. The UKPDS risk engine should be used instead for management. CVD risk should be evaluated annually, checking full lipid profile. People aged above 50years should be offered low dose (typically 75-100mg/day) aspirin. Clopidogrel should be used only for aspirin intolerant people. In patients where serum triglyceride is abnormal, fasting serum lipid profile should be assessed. Simvastatin should be administered to people above 40years or people below 40years who have poor prognosis of developing CVD. Increasing cholesterol-lowering treatment should be considered if the target cholesterol level is not achieved.

Kidney, eye and nerve complications

Prevention of nephropathy can be assessed by testing urine microalbumin and, if present, kidney failure should be assessed by measuring creatinine clearance or glomerular filtration rate (GFR).[28,32] For eye problem assessment, eye screening should be performed at diagnosis and then annually afterwards. Topical mydriasis should be used post-assessment of visual acuity and pre-digital retinal photography. Development of neuropathic symptoms should be assessed annually and findings discussed, including management and prognosis if any neuropathic symptoms are present. Analgesics should be administered to alleviate pain, and if treatment does not provide the desired result, tricyclic antidepressant drugs should be considered and the response obtained should be evaluated. If the result is still not as desired, then duloxetine, pregabalin or gabapentin should be tried, following current drug practice. Erectile dysfunction should be assessed annually and discussed. If there is erectile dysfunction, a phosphodiesterase type-5 inhibitor should be administered, and if it does not produce the desired result, other forms of interventions should be discussed, such as intracavernosal injections.[33]

Clinical outcomes measured in diabetes care

A goal of diabetes management is to achieve better glycaemic, blood pressure and lipid control. Glycaemia is usually measured by HbA1c levels. HbA1c is a representative of the percentage of total glycated Haemoglobin usually over a period of 3 months. It is considered a standard measure of blood sugar and glycaemic control over the stated period. HbA1c is preferred to FBS in testing blood sugar levels in diabetes patients in that it does not involve requiring the patient to fast for 8hours minimum prior to testing as done in the latter and can serve as marker to detect microvascular complications.[34] Intensive glycaemic management resulting in HbA1c levels lower than 7% have been shown to be beneficial for type 2 diabetes mellitus;[35,36] however, extra caution is needed in those in whom established complications can be detected or exaggerated especially with sharp and progressive intensity.[37–39] Clinicians should consider these facts during the management of the diseases. The HbA1c level was the first objective measure used to assess the severity of the hyperglycemia in different age-adjusted ethnic cohorts with diabetes.[40]

Other clinical outcomes measured in diabetes care are systolic and diastolic blood pressures for hypertension control, total cholesterol, triglyceride and LDL and HDL lipoproteins for monitoring hyperlipidaemia, and weight or body mass index (BMI) for obesity.[28] The main targets set by NICE for the management of type 2 diabetes in the UK are in concert with other guidelines in most countries including those of the American Diabetes Association (ADA) standards.[41,42] ADA serve as a regulatory body for diabetes treatment in the US just as NICE act in the UK and according to them, the following sets are the preferred targets for diabetes management of most patients as some patients should have individualized targets according to their special needs:

a. HbA1c <7.5% or <6.5% with patients prone to CVD or microvascular complications

b. BP <140/80mmHg or <130/80mmHg in patients with kidney, cerebrovascular and eye damage.

c. Lipid targets: Total Cholesterol <4mmol/L, HDL >1.4mmol/L and LDL <2mmol/L.

d. BMI is often used to estimate body weight to classify such individual as underweight if BMI <18.5kg/m^2, normal weight if BMI is between 18.5-24.9kg/m^2, overweight if BMI is between 25.0-29.9kg/m^2, or obese if BMI ≥30.0kg/m^2 based on World Health Organisation guidelines.[43]

It is worth keeping in mind that clinical outcomes of diabetes management can potentially be confounded with the effects of other covariates. These may include patients' specific socio-demographic characteristics or disease-specific biological and clinical characteristics. Socio-demographic characteristics can be reflected by age, sex, marital status, educational level and ethnicity, while diabetes-related biological confounders can be recognised by evaluating the severity of the disease as a "proxy". For example, HbA1c level was the first objective measure used to assess the severity of the hyperglycemia in different age-adjusted ethnic cohorts with diabetes.[40] This followed by a Diabetes Symptom Checklist, which was developed to serve as a subjective tool to assess the severity of diabetes for clinical and epidemiological studies.[44] However, the use of a score incorporating multiple clinical and demographic variables derived from a disease registry allowed for the development of an easier stratification system according to patients' complications.[45] Patients with varying degrees of severity of complications could be better stratified so as to customize care interventions in either inpatients or ambulatory care based on their expected risk.[46] This has important implications for risk stratification, risk adjustment and health resources and policy evaluations.[45–49] Nonetheless, patient demographics and diabetes clinical characteristics should routinely are usually used in routine clinical practice for evaluating diabetes severity and management programme. This include variables such as the duration of the disease, whether patients on insulin, quantity and frequency of prescribed insulin, types and number of anti-diabetic agents, frequency of clinics visits for diabetes and diabetes-related complications.[50]

Diabetes severity indices

There are published indices specific for diabetes severity, which has been used for diabetes research.[45–49] Most of these indices used variables related to diabetes complications. Risk models and equations have been developed to consider or predict the adverse outcome of CVD or identify high risk patients who could be targeted for intervention.[51,52] Although these risk models have been useful in identifying high-risk patients for intervention, they only consider cardiovascular risk factors, which account for just a fraction of diabetes complications.

Diabetes complications can better be assessed by using information corresponding to the severity of disease progression, which can be identified from the amount and intensity of clinical symptoms, biomedical markers, organ complications and/or mortality. For example, Rosenzweig et al.[45] developed a Diabetes Mellitus Severity Index (DMSI) which summarizes the burden of numerous complications associated with diabetes into a single value and is used as a risk stratification tool to evaluate the management of comorbidities and estimate costs.[45] The DMSI was developed a priori based on the consensus of a panel of experts, including endocrinologists, nephrologists, a cardiologist, a podiatrist, a vascular surgeon, a mental health provider, nurse educators and nutritionists. The severity was divided into four levels based on the intensity of care required: low, moderate, high and very high. Patients were stratified according to the severity of their illness in six clinical areas: glycaemic control, CVD, peripheral vascular disease/peripheral neuropathy, eye disease, renal disease, and autonomic neuropathy. This index was initially designed for use in cost analysis although it lacks standardization to indexed diagnostic measures such as ICD-9 codes. It was also constructed using large population of type 1 diabetes in primary care, which would be unsuitable for general use in clinical judgement.

Joish et al.[46] developed a diabetes-specific risk assessment tool, called the Diabetes Severity Index (DSI), using 10 clinical and demographic measures in addition to the comorbid conditions.[46] The laboratory data included were HbA1c, total cholesterol level, LDL, serum creatinine, systolic and diastolic blood pressure and BMI. Among demographics were age, gender, ethnicity and social status. This index was successful to assess the effects of the health status of patients with diabetes on overall healthcare resource use and costs. Young et al.[47] developed the Diabetes Complications Severity Index (DCSI) to measure the severity of diabetes complications.[47] This index comprises seven categories of complications scored in thirteen points based on their severity levels. The complications included are retinopathy, nephropathy, neuropathy, Cerebrovascular, cardiovascular, peripheral vascular disease and metabolic markers. Each complication is to be scored as 1 if abnormality present, or 2 if it is severe or 0 if no abnormality. The DCSI has been validated in American population, and it has been shown to perform better than using only the number of complications. It has also been validated in other areas such Singapore.[49] A recent study has shown that the DCSI as a diabetes complication severity score in type 2 diabetes patients is strongly associated with healthcare costs.[49] It can be used to triage high-risk patients for earlier and more focused clinical interventions, in either primary or secondary care for intensive management in order to prevent or delay the onset of a new complication. However, it is only validated when ICD-9-CM codes are used. In short, such diabetes severity indices can be used in randomised trails or for disease state management programme to prove their costs benefits.

Summary

Diabetes is a disease of multiple organs, which is being spread rapidly. It can be a good example of multi-disciplinary healthcare provision. There are diabetes specialists within many healthcare professions such as medicine, nursing, pharmacy, and paramedics such as podiatrists and dieticians. Implementing NMP would have great impact on the outcomes of diabetes care in terms of the disease control or complication prevention.

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Conflict of interest

Author declares that there is no conflict of interest.

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