DIABETES EXAMINED

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The classification, diagnosis and management of diabetes are looked at in this article, along with medication and lifestyle interventions.

Diabetes mellitus is defined as a metabolic disorder characterised by elevated blood glucose levels with disturbances of carbohydrate, protein and fat metabolism due to insufficient insulin production, insulin action or both.[1,6] The chronic hyperglycaemia of diabetes is associated with long-term complications, including neuropathy with risk of ulcers and amputations, retinopathy with potential loss of vision and nephropathy leading to renal failure. Individuals who present with diabetes are also at heightened risk of peripheral, cerebrovascular and cardiovascular disease (CVD). Heart disease and stroke are two to four times higher in individuals with diabetes compared to their non-diabetic counterparts,[2] with hypertension and hypercholesterolemia commonly evident.[2-4]

The classification of diabetes can be attributed to four main types: Type 1 diabetes, Type 2 diabetes, gestational diabetes mellitus (GDM) and maturity-onset diabetes of the young (MODY). The majority of individuals will present with either Type 1 or Type 2.

The presentation of diabetes mellitus varies from asymptomatic Type 2 diabetes to the acute, life-threatening diabetic ketoacidosis (DKA) or a non-ketotic hyperosmolar state, which may develop and lead to coma and, if effective treatment is not provided, death. DKA occurs when blood glucose levels rise >11mmol/L accompanied by a lack of insulin which causes the body to switch to burning fatty acids and producing acidic ketone bodies.[5] Short-term consequences of uncontrolled diabetes include hypoglycaemia (fasting blood glucose levels <4mmol/L), which can lead to loss of consciousness, and hyperglycaemia (blood glucose levels >7mmol/L). Both hypo- and hyperglycaemia can present a substantial clinical impact in terms of mortality, morbidity and quality of life.[4]

Diabetes is complex, in that several pathogenetic processes are involved in its development. These processes occur following exposure to a certain causation factor which destroys the β-cells of the pancreas, resulting in subsequent insulin deficiency, or impaired insulin sensitivity. Known causes include; certain viruses, endocrinopathie, diseases of the exocrine pancreas and the immune system, drug or chemical induced diabetes and gene mutations.[4]

CLINICAL DIAGNOSIS

The clinical diagnosis of diabetes is characterised by the presence of a wide range of presenting symptoms, mainly; polyuria, polydypsia, unexplained weight loss, fatigue and blurred vision and is confirmed by documented hyperglycaemia.[6] Depending on the type of diabetes, the occurrence of symptoms may be rapid (typical of Type 1 diabetes) or slow onset (typical of Type 2 diabetes). In Type 2 diabetes, often symptoms are not severe, or may be absent and, consequently, hyperglycaemia sufficient to cause pathological and functional changes may be present for a long time before a diagnosis is confirmed.[6]

Gestational diabetes mellitus (GDM)

GDM is defined as any degree of glucose intolerance with onset or first recognition during the third trimester of pregnancy.[6] GDM complicates 4% of pregnancies in

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the UK (NHS, 2014).[5] However, the diagnosis of GMD is contentious, in that the NICE diagnostic criteria is higher than that recommended by the International Association of Diabetes and Pregnancy Study Groups (IADPSG) – fasting blood glucose of >5.6mmol/L compared to the lower cut-off of >5.1mmol/L – therefore resulting in fewer diagnoses and lower prevalence rates.[7,8] Risk factors for the development of GDM include: obesity, personal history of GDM, family history of diabetes and glycosuria.

The management of GDM varies between individuals where some women can manage their condition solely via diet and lifestyle interventions, whereas others will require the use of medications or the administration of insulin for successful management. GDM usually resolves following pregnancy, although it has been shown to increase the patient's chance of developing Type 2 diabetes in later life.[5]

Diabetes of the young (MODY)

MODY is a term used to describe several forms of diabetes which are associated with monogenetic defects in β-cell function and which are frequently characterised by the onset of hyperglycaemia in those <25years. MODY is a rare condition, which has a strong genetic link and is known to affect 1-2% of the population.[9] MODY presents as impaired insulin secretion with minimal or no defects in insulin action. Again, the treatment for MODY varies depending on its type, where some individuals can effectively control their condition without the use of medication, whilst others require multiple daily injections of insulin in order to achieve good glucose control.

As already stated, the patient majority will present with either Type 1 diabetes or Type 2 diabetes. The aetiology and causation of these two conditions differs greatly.

Type 1 diabetes

This comprises 5-10% of those with diabetes and was previously encompassed by the terms of insulin-dependent diabetes or juvenile-onset diabetes. These terms are now less commonly used given the increased number of young individuals being diagnosed with Type 2 diabetes and the heightened use of insulin therapy in the management of Type 2 diabetes (which will be discussed in this article). It is believed that Type 1 diabetes is an autoimmune condition that occurs as a result of cellular-mediated destruction of the β-cells of the pancreas. This leads to the body being unable to produce insulin, causing hyperglycaemia. The destruction of the β-cells is linked with multiple genetic predispositions and is also related to environmental factors that are poorly understood. Various triggers have been identified, including; certain viruses, vaccines and some medications.[10]

Type 2 diabetes

This is the most common form of diabetes and accounts for 90-95% of those with diabetes. It was previously referred to as non-insulin-dependent diabetes, or adult onset diabetes. Type 2 diabetes is a preventable, but progressive metabolic disorder, which also involves a complex relationship between both genetics and environmental factors. Individuals diagnosed with Type 2 diabetes present with impaired insulin sensitivity and usually have relative (rather than absolute) insulin deficiency, either of which may be the predominant feature.[4,11]

Symptom occurrence in Type 2 diabetes is generally a slow process that develops over a prolonged period of time, unlike the rapid onset of presenting symptoms usually evident in those with Type 1 diabetes. Due to the slow presentation of symptoms, many individuals with Type 2 diabetes simply associate their symptoms with increased age and, therefore, fail to act upon them. As a result, the condition can often go undiagnosed for many years. It is estimated that there are approximately one million individuals living in the UK with undiagnosed Type 2 diabetes.[12] However, such undiagnosed diabetes carries the risk of insidious tissue damage.

As previously stated, it is well documented that patients with Type 2 diabetes often have pathological degrees of hyperglycaemia for several years before a diagnosis is made.[2,4]

Although the specific aetiologies of Type 2 diabetes are currently unknown, disease development is associated with several risk factors. These are both modifiable and non-modifiable, including increasing age, Asian ethnicity, genetics, lack of physical activity and obesity.[13,14,15]

Obesity is the most potent risk factor for Type 2 diabetes

An abundance of high quality research has shown that there is a strong inheritable genetic connection with the development of Type 2 diabetes, where individuals who have a first degree relative with the condition are at a substantial increased risk of disease development.[4,16,17] The genetics are complex and not fully understood, but it is hypothesised that the condition is associated with several genes. It is speculated that the development of Type 2 diabetes occurs when a diabetogenic lifestyle (excessive caloric intake, insufficient caloric expenditure, obesity) is superimposed upon a susceptible genotype.[1]

OBESITY AND TYPE 2 DIABETES

Obesity is the most potent risk factor for Type 2 diabetes, with research showing that it accounts for 80-85% of the overall risk of disease development.[15] It is suggested that abdominal obesity promotes adipose tissue to release pro-inflammatory cytokines, which in turn decreases the body's sensitivity to insulin. This is known as insulin resistance.[18] Furthermore, adipose cells possess the ability to secrete hormones that contribute to insulin insensitivity.[19] Consequently, it is now well documented that there is an inverse relationship between BMI and insulin sensitivity, where an increase in BMI reflects a corresponding reduction in insulin sensitivity.[20] This information is worrying given the spiralling levels of overweight and obesity currently evident in the UK population.[21] As already stated, historically, Type 2 diabetes mainly presented in adults, however, this is no longer the case.[1,4] The increased prevalence of Type 2 diabetes in young individuals coincides with the increased occurrence of obesity in the same population group, which has more than tripled in the past 25 years.[21]

Research has shown that there is a convincing link between ethnicity, obesity and the risk of developing Type 2 diabetes.[3] Individuals from South Asian descent are six times more likely to develop the condition compared to their Caucasian counterparts.[3] Similarly, those from African and Afro-Caribbean background have three times the increased risk of developing Type 2 diabetes when compared to those from a non-African background.[3] Generally, these individuals present with a smaller body frame which increases their likelihood of central obesity and, therefore, the development of Type 2 diabetes. These findings have led to NICE recommending that individuals from these backgrounds maintain a BMI <23kg/m^2 to reduce their risk of disease development.[22]

For individuals diagnosed with diabetes, the aim of successful management is to maintain quality of life and reduce diabetes related complications, predominantly by achieving glycosylated haemoglobin (HbA1c) levels that are within the target range of 48mmol/mol to 53mmol/mol (6.5%-7%), as recommended by NICE and Scottish Intercollegiate Guidelines Network (SIGN).[23,24] HbA1c is a well-recognised marker of glycaemic control in those with established diabetes as it reflects average glucose levels over the past two-to-three-month period.[24]

MANAGEMENT AND CONTROL

The management of Type 1 and Type 2 diabetes differs mainly due to the fact that there is a complete lack of insulin production in those with Type 1 diabetes. Therefore, to effectively manage the condition, subcutaneous insulin is always necessary for those diagnosed with Type 1 diabetes. This may be administered via daily injections or through the use of an insulin pump. There are many different types of insulin including rapid acting, short acting and intermediate and long acting insulin. Traditionally, many people with Type 1 diabetes were managed with a twice-daily insulin regimen; however, this allowed

no flexibility in terms of diet or exercise and, therefore, we have moved towards multiple daily insulin injections to improve overall diabetes control and quality of life. This has involved taking basal insulin once or twice daily along with bolus insulin whenever carbohydrates (CHOs) are consumed. It is also necessary that people on this regimen are accurately identifying and counting their CHO to adjust their insulin accordingly.

For those on insulin pumps, only one type of insulin is used – rapid acting. A small device is worn on the outside of your body. A tube connects a reservoir of insulin to a catheter that's inserted under the skin of the abdomen. There is also a wireless pump option. Pumps are programmed to dispense specific amounts of rapid-acting insulin automatically. This steady dose of insulin is known as your basal rat, and it replaces whatever long-acting insulin the patient was previously using.

When CHOs are consumed, the pump is programmed with the amount of CHOs and current blood glucose levels and it will give you what's called a bolus dose of insulin to cover meals and to correct blood sugar if it's elevated. When using the pump, insulin to CHO ratios will have also been programmed into the device. Different basal rates can also be set for when additional insulin is required, such as dawn phenomenon and less insulin, eg, exercise. An insulin pump combined with a continuous glucose monitoring (CGM) device may provide even tighter blood sugar control.

With regard to the management of Type 2 diabetes, dietary advice for weight loss is the first line of treatment and may or may not be combined with one or more of a wide range of therapeutic options.[24] For some individuals with Type 2 diabetes, the condition can be managed solely via diet and lifestyle interventions; however, this is seldom sufficient. Thus, pharmacological adjuncts are required in early management for the majority of patients.

Metaformin

Insulin production occurs in the β-cells of the pancreas. However, the gradual destruction of these cells and the decline in pancreatic function is a progressive phenomenon in those with Type 2 diabetes, therefore, the intensification of medication is a common practice.[1] Metformin is an oral hyperglycaemic agent (OHA) commonly used as first-line treatment for those with Type 2 diabetes and who are overweight (BMI >25kg/m^2; Asians >23kg/m^2).[24] Metformin works by reducing glucose output via suppression of gluconeogenesis. It also improves insulin action and reduces post-prandial glucose levels by increasing glucose uptake into the muscles where it is stored.[25] The main side effects include nausea, diarrhoea and abdominal discomfort.

Sulphonylureas

If metformin fails to achieve adequate glucose control (4mmol/L to 7mmol/L pre-meals), then another type of OHA, sulphonylureas, can be added for use as a dual therapy. Sulphonylureas increase endogenous release of insulin from the pancreatic β-cells. However, patients who take sulphonylureas have an increased risk of hypoglycaemia, compared to those on diet alone.[26] Recent research has shown that 1% of individuals on sulphonylureas experienced hypoglycaemia compared to 0.2% for those treated with metformin.[26] Furthermore, a greater degree of weight gain is noted in those on sulphonylureas with studies showing an approximate weight gain of 5kg within the first six months of commencement, compared to those on a placebo.[27]

Other inhibitors

Thiazolidinediones and Dipeptidyl preptidase-4 (DPP-4) inhibitors are other forms of OHAs, which can be used when sulphonylureas are not well tolerated, or if additional drugs are required to achieve good glucose control. Thiazolidinediones increase whole body insulin sensitivity and reduce glucose levels through two main mechanisms: increased tissue uptake of glucose and decreased hepatic glucose production.[28] Thiazolidinediones require a sufficient amount of insulin production to be able to exert a therapeutic effect, therefore, their use is blunted in some individuals. It should be noted that thiazolidinediones also promote weight gain.[28] DPP-4 inhibitors work by inhibiting the activity of the enzymes DPP-4 and, therefore, prolong the activity of the incretin hormone glucagon-like peptide-1 (GLP-1).

GLP-1 analogues

GLP-1 analogues are a relatively new injectable therapy that work by mimicking endogenous

GLP-1 activity. GLP-1 is an incretin hormone produced in the intestinal l-cells of the pancreas and secreted in the gut following nutrient ingestion. GLP-1 works by increasing the production of insulin when needed and reducing the manufacturing of glucose when not needed.[29] The physiological effects that GLP-1 provides are of much interest as they can provide huge clinical benefit for diabetes management.[24] These benefits include; delayed gastric emptying, the inhibiting of glucagon secretion from the β-cells of the pancreas along with decreasing post-prandial glucose levels. In the pancreas, GLP-1 increases β-cell mass, therefore promoting insulin secretion and improving insulin sensitivity.[30] Furthermore, GLP-1 facilitates insulin gene transcription and neogenesis, both showing significant clinical relevance in the treatment of diabetes. GLP-1 is known to play a role in the central nervous system where is induces satiety and suppresses the appetite.[30] Unfortunately GLP-1 is rapidly metabolised by the body and, therefore, the benefits are short lived. However, the administration of GLP-1 analogues can result in prolonged action of GLP-1 hormones, which could have profound benefits for the successful management of Type 2 diabetes.

In most guidelines, GLP-1 analogues are currently prescribed as a triple therapy, alongside metformin and sulphonylurea.[23,24] GLP-1 analogues have consistently been shown to significantly improve glucose control in those with suboptimal blood glucose levels.[31,32] Not only do they improve glycaemic control, but they also facilitate weight loss and reduce both blood pressure and lipid levels, therefore reducing overall CVD risk.[33,34] These benefits can be witnessed within the first three months of treatment commencement.[35]

Insulin

If medication and lifestyle interventions fail to achieve good glucose control in Type 2 diabetes, insulin therapy is generally the next option.[24] The benefits that insulin provides in terms of assisting in achieving good glycaemic control are well known.[24] However, it should be noted that not only does the commencement of insulin administration promote an average weight gain of 5kg-7kg, which is usually greatest at the beginning of insulin use,[19,35] it also increases an individual's risk of hypoglycaemia. This is of a huge concern as, not only is hypoglycaemia dangerous, but it may impact upon compliance, limiting the attainment of lower glycaemic targets.[1,37] Given that weight loss is a fundamental aspect for the successful management of Type 2 diabetes, the introduction of insulin can, therefore, be contraindicated. Interestingly, from 1991-2010 there was a seven-fold increase in the number of individuals with Type 2 diabetes who were commenced on insulin.[38] This heightened use may be as a result of the increased frequency of diabetes mellitus along with the failure to adequately control diabetes via dietary and lifestyle interventions/weight loss and the use of OHAs.

CONCLUSION

Despite this wide range of therapeutic options, many individuals still fail to meet the recommended HbA1c target range (HSCIC, 2014).[21] This is worrying given that an abundance of research has shown that the achieving of HbA1c levels close to the target range can help facilitate a decline in both the short- and long-term complications of diabetes in addition to promoting quality of life and longevity.[1,3,39,40] Lowering HbA1c levels by as little as 1% can result in a reduction of retinopathy by 38%, nephropathy 28%, neuropathy 28% and cardiovascular events by as much as 57%.[41] These statistics are of much importance given the financial burden placed on the NHS budget for the treating of these complications, with diabetes costing the NHS £10 billion per annum, with most of this being spent on diabetes comorbidities, a figure projected to only get worse.[42] Good management of diabetes can lower these complications and subsequently save the NHS substantial money.

A contributing factor to the failing of good glucose control may be the undesirable side effects, as discussed previously, experienced with the utilisation of many of these medications, which can subsequently hinder compliance rates.[43] Thus, therapies that allow the attainment of glycaemic control without promoting weight gain and with minimal side effects, are in high demand, where they can allow evidence-based cost effective care.