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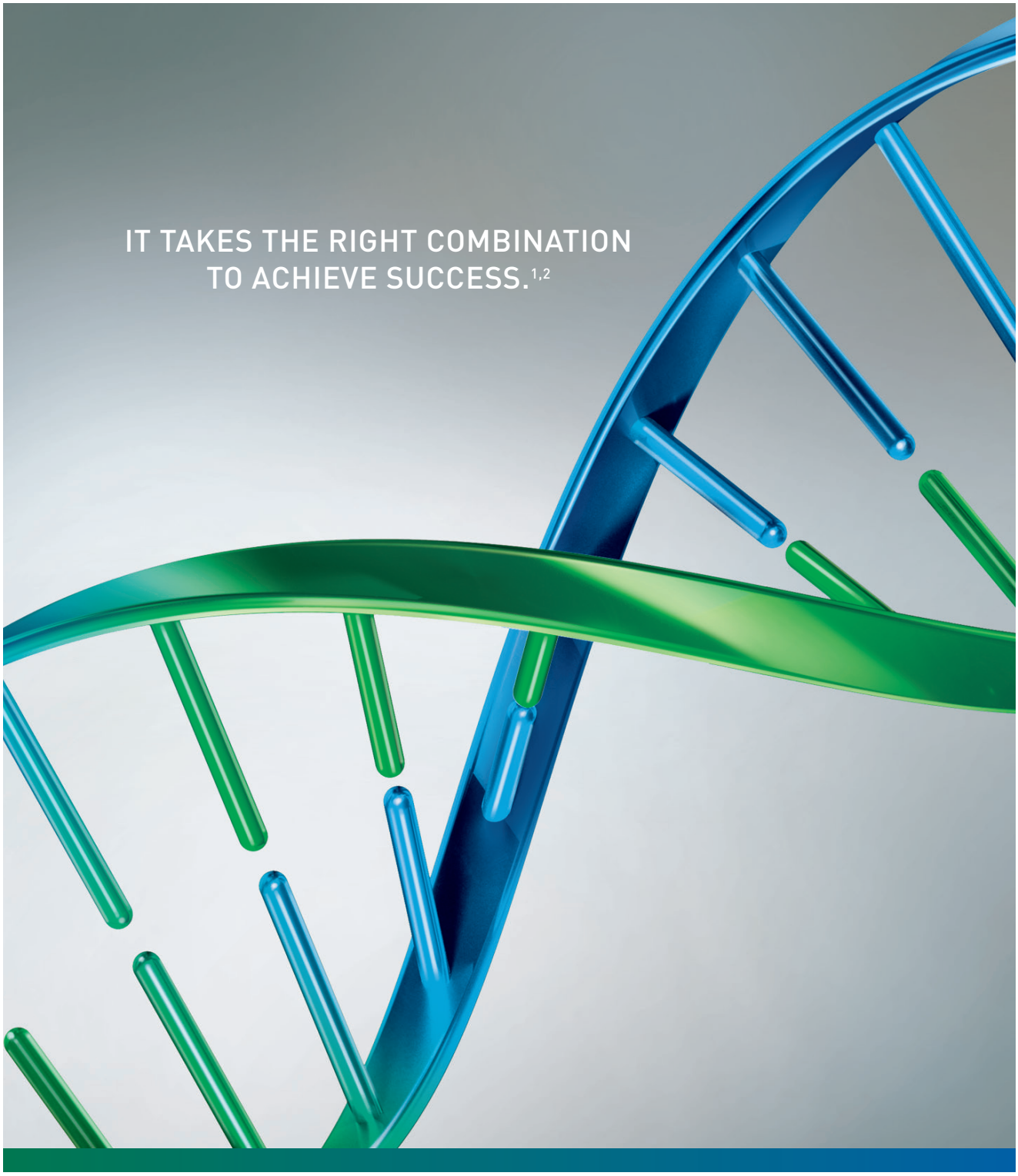

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South African hypertension practice guideline 2014

HYPERTENSION GUIDELINE WORKING GROUP: YK SEEDAT, BL RAYNER, YOSUF VERIAVA

Abstract

Outcomes: **Extensive data from many randomised, controlled trials have shown the benefit of treating hypertension (HTN). The target blood pressure (BP) for antihypertensive management is systolic < 140 mmHg and diastolic < 90 mmHg, with minimal or no drug side effects. Lower targets are no longer recommended. The reduction of BP in the elderly should be achieved gradually over one month. Co-existent cardiovascular (CV) risk factors should also be controlled.**
Benefits: **Reduction in risk of stroke, cardiac failure, chronic kidney disease and coronary artery disease.**
Recommendations: **Correct BP measurement procedure is described. Evaluation of cardiovascular risk factors and recommendations for antihypertensive therapy are stipulated. Lifestyle modification and patient education are cornerstones of management. The major indications, precautions and contra-indications are listed for each antihypertensive drug recommended. Drug therapy for the patient with uncomplicated HTN is either mono- or combination therapy with a low-dose diuretic, calcium channel blocker (CCB) and an ACE inhibitor (ACEI) or angiotensin receptor blocker (ARB). Combination therapy should be considered ab initio if the BP is ≥ 160/100 mmHg. In black patients, either a diuretic and/or a CCB is recommended initially because the response rate is better compared to an ACEI. In resistant hypertension, add an alpha-blocker, spironolactone, vasodilator or β-blocker.**
Validity: **The guideline was developed by the Southern African Hypertension Society 2014©.**

Keywords: South Africa, hypertension, guideline

This is the sixth hypertension guideline published by the Southern African Hypertension Society (SAHS). Currently 30.4% of the adult population have hypertension (HTN),[1] necessitating a simplified approach to assessment and treatment, which reflects realistic objectives that can be implemented by medical practitioners, nurse practitioners and pharmacists to diminish the impact of HTN and related cardiovascular disease (CVD) risk in this country. For full details on management not contained in this document please refer to the more detailed hypertension guideline 2011.[2]

Objective

The objective of this guideline was to promote evidence-based, accessible and comprehensive management of HTN by healthcare professionals in the public and private sectors. Applicable HTN and CVD treatment and prevention guidelines were reviewed as well as HTN trials reporting clinical end-points, including those with individuals with important co-morbidities such as diabetes mellitus and chronic kidney disease.[3-9]

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S Afr J Diabetes Vasc Dis 2014; **11**: 139–144

Table 1. Definitions and classification of office BP (mmHg). Adapted from ref 9

Stage	Systolic BP (mmHg)		Diastolic BP (mmHg)
Normal	< 120	and	< 80
Optimal	120–129	and/or	80–84
High normal	130–139	and/or	85–89
Grade 1	140–159	and/or	90–99
Grade 2	160–179	and/or	100–109
Grade 3	≥ 180	and/or	≥ 110
Isolated systolic	≥ 140	and/or	< 90

BP should be categorised into the highest level of BP whether systolic or diastolic.

Definition and grading of hypertension

HTN is defined as a persistent elevation of office blood pressure (BP) ≥ 140/90 mmHg (Table 1). The optimal BP is a value < 130/85 mmHg. High normal is BP levels from 130–139 mmHg systolic and 85–89 mmHg diastolic. This high-normal group of subjects is at higher CV risk and is also at risk of developing HTN, but does not require drug treatment.[10] HTN is stratified into three grades depending on severity, which is useful in defining the approach to treatment.

Measurement of blood pressure

BP measurement is a vital clinical sign that is poorly performed by all healthcare professional categories. These recommendations apply to both clinic and self-measurement of BP. Failure to follow these

Table 2. Recommendations for blood pressure measurement

Allow patient to sit for 3–5 minutes before commencing measurement
The SBP should be first estimated by palpation to avoid missing the auscultatory gap
Take two readings 1–2 minutes apart. If consecutive readings differ by > 5 mm, take additional readings
At initial consultation measure BP in both arms, and if discrepant use the higher arm for future estimations
The patient should be seated, back supported, arm bared and arm supported at heart level
Patients should not have smoked, ingested caffeine-containing beverages or food in previous 30 min
An appropriate size cuff should be used: a standard cuff (12 cm) for a normal arm and a larger cuff (15 cm) for an arm with a mid-upper circumference > 33 cm (the bladder within the cuff should encircle 80% of the arm)
Measure BP after 1 and 3 minutes of standing at first consultation in the elderly, diabetics and in patients where orthostatic hypotension is common
When adopting the auscultatory measurement use Korotkoff 1 and V (disappearance) to identify SBP and DBP respectively
Take repeated measurements in patients with atrial fibrillation and other arthythmias to improve accuracy

guidelines leads to significant errors in BP measurement. BP should be recorded using an approved and calibrated electronic device or mercury sphygmomanometer (Table 2). Repeat measurements should be performed on at least three separate occasions within four weeks unless BP is ≥ 180/110 mmHg.

Self- and ambulatory measurement of BP

Self BP measurement (SBPM) and ambulatory BP measurement (ABPM) are recommended in selected circumstances and target groups:[11]

- suspected white-coat HTN (higher readings in the office compared with outside) or masked HTN (normal readings in office but higher outside)
- to facilitate diagnosis of HTN
- to guide antihypertensive medication, especially in high-risk groups, e.g. elderly, diabetics
- refractory HTN
- to improve compliance with treatment (SBPM only).

Masked HTN should be suspected if, despite a normal BP in the clinic, there is evidence of target-organ damage.

All devices used for SBPM and ABPM should be properly validated in accordance with the following independent websites: www.dableducational.com or http://afssaps.sante.fr.

In general, only upper-arm devices are recommended, but these are unsuitable in patients with sustained arrhythmias. For SBPM the patient should take two early morning and two late afternoon/early evening readings over five to seven days, and after discarding the first day readings, the average of all the remaining readings is calculated.

Wrist devices are recommended only in patients whose arms are too obese to apply an upper arm cuff. The wrist device needs to be held at heart level when readings are taken.

The advantages of SBPM measurement are an improved assessment of drug effects, the detection of causal relationships between adverse events and blood pressure response, and possibly, improved compliance. The disadvantages relate to increased patient anxiety and the risk of self-medication.

ABPM provides the most accurate method to diagnose HTN, assess BP control and predict outcome.[12] Twenty-four-hour ABPM in patients with a raised clinic BP reduces misdiagnosis and saves costs.[13] Additional costs of ABPM were counterbalanced by cost savings from better-targeted treatment. It can also assess nocturnal BP control and BP variability, which are important predictors of adverse outcome. However the assessment is limited by access to ABPM equipment, particularly in the public sector, and impracticalities of regular 24-hour ABPM monitoring.

Table 3. Definitions of hypertension by different methods of BP measurement

	Office	Automated office	Self	Ambulatory
Predicts outcome	+	++	++	+++
Initial diagnosis	Yes	Yes	Yes	Yes
Cut-off BP (mmHg)	140/90	Mean 135/85	135/85	Mean day 135/85 Mean night 120/70
Evaluation of treatment	Yes	Yes	Yes	Limited, but valuable
Assess diurnal variation	No	No	No	Yes

The appropriate cut-off levels for diagnosis of HTN by SBPM and ABPM are listed in Table 3.[11]

Automated office BP measurement

Despite efforts to promote proper techniques in manual BP measurement, it remains poorly performed. Automated office BP measurement offers a practical solution to overcome the effects of poor measurement, bias and white coating.[14] It is more predictive of 24-hour ABPM and target-organ damage than manual office BP measurement. Six readings are taken at two-minute intervals in a quiet room. The initial reading is discarded and the remaining five are averaged. The appropriate cut-off level for HTN is 135/85 mmHg.[14]

CVD risk stratification

The principle of assessing and managing multiple major risk factors for CVD is endorsed. However, because the practical problems in implementing previous recommendations based on the European Society of HTN (ESH) and the European Society of Cardiology (ESC) HTN guidelines, it has been decided to use a modification of this approach.[9]

Once the diagnosis of HTN is established, patients with BP ≥ 160/100 mmHg should commence drug therapy and lifestyle modification. Patients with stage 1 HTN should receive lifestyle modification for three to six months unless they are stratified as high risk by the following criteria: three or more major risk factors, diabetes, target-organ damage or complications of HTN (Table 4).

Routine baseline investigations

Table 5 lists recommended routine basic investigations. The tests are performed at baseline and annually unless abnormal. Abnormal results must be repeated as clinically indicated.

Table 4. Major risk factors, target-organ damage (TOD) and complications. Adapted from the ESH/ESC guidelines[9]

Major risk factors

- Levels of systolic and diastolic BP
- Smoking
- Dyslipidaemia:
  - total cholesterol > 5.1 mmol/l, OR
  - LDL > 3 mmol/l, OR
  - HDL: men < 1 and women < 1.2 mmol/l
- Diabetes mellitus
  - Men > 55 years
  - Women > 65 years
- Family history of early onset of CVD:
  - Men aged < 55 years
  - Women aged < 65 years
- Waist circumference: abdominal obesity:
  - Men ≥ 102 cm
  - Women ≥ 88 cm

  The exceptions are South Asians and Chinese: men: > 90 cm and women: > 80 cm.

TOD

- LVH: based on ECG
  - Sokolow-Lyons > 35 mm
  - R in aVL > 11 mm
  - Cornel > 2 440 (mm/ms)
- Microalbuminuria: albumin creatine ratio 3–30 mg/mmol, preferably spot morning urine and eGFR > 60 ml/min

Complications

- Coronary heart disease
- Heart failure
- Chronic kidney disease:
  - macroalbuminuria > 30 mg/mmol
  - OR eGFR < 60 ml/min
- Stroke or TIA
- Peripheral arterial disease
- Advanced retinopathy:
  - haemorrhages OR
  - exudates
  - papilloedema

Table 5. Routine investigations

Test	Comment
Height, weight, BMI	Ideal BMI < 25 kg/m², overweight 25–30 kg/m², obese > 30 kg/m²
Waist circumference	Men < 102 cm; women < 88 cm. South Asians and Chinese: men < 90 cm and women < 80 cm
Electrolytes	Low potassium may indicate primary aldosteronism, or effects of diuretics
ECG	S in V1 plus R in V5 or V6 > 35 mm or R in aVL > 11 mm or Cornel product (R in aVL + S in V3 + 6 in females) × QRS duration > 2 440 (mm/ms)
Echocardiogram (if indicated and facilities available)	LVH: men > 115 g/m² and women > 95 g/m²
Fasting glucose	Consider HBA_{1c} or GTT if impaired fasting glucose (6.1–7.1 mmol/l)
Cholesterol	If total cholesterol > 5.1 mmol/l – fasting lipogram
Creatinine	Calculate eGFR
Uric acid	High uric acid is relative contra-indication to diuretics
Dipsticks urine	If abnormal, urine microscopy and protein estimation

Goals of treatment

There has been considerable controversy about BP goals and SAHS accepts that to simplify management, a universal goal of antihypertensive treatment is < 140/90 mmHg regardless of CV risk and underlying co-morbidities.[5] The only exception is that in patients over 80 years of age, therapy should be initiated if SBP is > 160 mmHg and the goal is between 140 and 150 mmHg, based on the HYVET study in which the majority of patients received indapamide and the ACEI perindopril.[15]

SAHS does not support the JNC-8 committee recommendations of a goal BP < 150/90 mmHg for persons over 60 years without diabetes and CKD, as (1) increasing the target will probably reduce the intensity of antihypertensive treatment in a large population at high risk for cardiovascular disease, (2) the evidence supporting increasing the SBP target from 140 to 150 mmHg in persons aged 60 years or older was insufficient, (3) the higher SBP goal in individuals aged 60 years or older may reverse the decades-long decline in CVD, especially stroke mortality.[8,16]

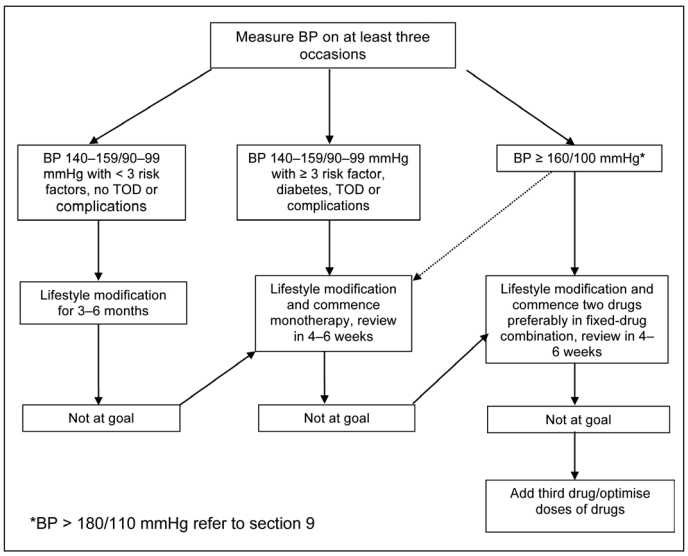

Fig. 1. Overview of approach to treatment.

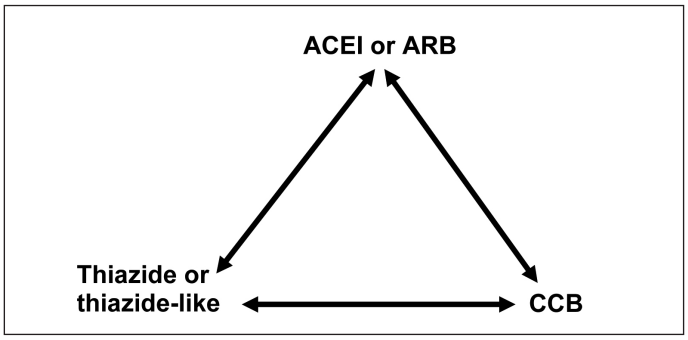

Fig. 2. Initial choices of antihypertensive treatment or combinations.

It is also essential to control hyperlipidaemia and diabetes through lifestyle and drug therapy, according to the Society for Endocrine Metabolism Diabetes of South Africa and South African Heart Association/Lipid and Atherosclerosis Society of Southern Africa guidelines, respectively.[17,18] Aspirin should not be routinely prescribed to hypertensives (especially if BP is not controlled),[19] and should mainly be used for secondary prevention of CVD (transient ischaemic attack, stroke, myocardial infarction).

Management of hypertension

All patients with HTN should receive lifestyle counselling as outlined in Table 6, and this is the cornerstone of management. The approach to drug treatment is outlined in Fig. 1. If the SBP is ≥ 180 mmHg or the DBP is ≥ 110 mmHg then refer to section 8 on severe (grade 3) HTN, as this section does not apply.

Before choosing an antihypertensive agent, allow for considerations based on the cost of the various drug classes, patient-related factors, conditions favouring use and contra-indications, complications and target-organ damage (TOD) (Tables 4, 7).

In otherwise uncomplicated primary HTN, the initial first choice of antihypertensive drug is a diuretic (thiazide-like or thiazide), ACEI or ARB, and/or CCB used as mono- or combination therapy (Fig. 2). Combination therapy should be considered if clinically appropriate ab initio if BP is ≥ 160/100 mmHg (Fig. 1) as this is associated with better clinical outcomes and earlier achievement of goal BP.[20,21]

Table 6. Recommended lifestyle changes

Modification	Recommendation	Approx ↓ SBP (mmHg)
Weight reduction	BMI 18.5–24.9 kg/m²	5–20 per 10 kg
Dash diet	↓ saturated fat and total fat, ↑ fruit and vegetables	8–14
Dietary Na^+	< 100 mmol or 6 g NaCl/day	2–8
Physical activity	Brisk walking for 30 minutes per day most days	4–9
Moderation of alcohol	No more than two drinks per day	2–4
Tobacco	Complete cessation	–

Fixed-drug combinations are preferred because of better patient adherence and control of BP.[22] A treatment algorithm is outlined in Fig. 1 if the goal is not reached after initial treatment.

In black hypertensive patients a diuretic and/or a CCB is recommended.[23] Beta-blockers should generally be avoided in combination with diuretics as first-line therapy because of predisposition to diabetes,[9] but this may not apply to highly selective beta-blockers. Beta-blockers may also be considered if there is intolerance to one of the first-line drugs. Loop diuretics such as furosemide should not be used because of their short duration of hypotensive activity of about six hours, unless there is evidence of chronic kidney disease (CKD) with estimated glomerular filtration rate (GFR) < 45 ml/min.

Management of severe hypertension

Patients with severe HTN (grade 3; BP ≥ 180/110 mmHg) may fall into one of three categories, which determine the urgency of their treatment. Patients should be managed or referred to the appropriate level of care and caregiver in accordance with local resources. Sustained, severe HTN requires immediate drug therapy and lifestyle modification, and close follow up.

Asymptomatic severe hypertension

These patients are asymptomatic but have severe HTN without evidence of progressive TOD or complications. The patient must be kept in the care setting and BP measurement repeated after resting for one hour. If still elevated at the same level, commence oral therapy using two first-line drugs. Follow up within a week or earlier, with escalation of treatment as needed. Early referral is advised if BP is not controlled within two to four weeks.

Hypertensive urgencies and emergencies[24]

While not common, hypertensive emergencies and urgencies are likely to be encountered by all clinicians because of the high prevalence of chronic HTN. It is essential that all professionals are familiar with treatment. There is a paucity of information from well-conducted studies on the outcomes of various antihypertensive drugs and BP-lowering strategies.

• *Hypertensive urgency*[25]

This level of HTN is symptomatic, usually with severe headache, shortness of breath and oedema. There are no immediate life-threatening neurological, renal, eye or cardiac complications, such

Table 7. Indications and contra-indications for the major classes of antihypertensive drugs. Adapted from the ESC/ESH guidelines[9]

Class	Conditions favouring the use	Contra-indications	
		Compelling	**Possible**
Diuretics (thiazide; thiazide-like)	• Heart failure (HF) • Elderly hypertensives • Isolated systolic HTN (ISH) • Hypertensives of African origin	• Gout	• Pregnancy • β-blockers (especially atenolol)
Diuretics (loop)	• Renal insufficiency • HF		• Pregnancy
Diuretics (anti-aldosterone)	• HF • Post-myocardial infarction • Resistant hypertension	• Renal failure • Hyperkalaemia	
CCB (dihydropyridine)	• Elderly patients • ISH • Angina pectoris • Peripheral vascular disease • Carotid atherosclerosis • Pregnancy		• Tachyarrhythmias • HF especially with reduced ejection fraction
CCB non-dihydropyridine (verapamil, diltiazem)	• Angina pectoris • Carotid atherosclerosis • Supraventricular tachycardia	• AV block (grade 2 or 3) • HF	• Constipation (verapamil)
ACEI	• HF • LV dysfunction • Post-myocardial infarction • Non-diabetic nephropathy • Type 1 diabetic nephropathy • Prevention of diabetic microalbuminuria • Proteinuria	• Pregnancy • Hyperkalaemia • Bilateral renal artery stenosis • Angioneurotic oedema (more common in blacks than in Caucasians)	
ARB	• Type 2 diabetic nephropathy • Type 2 diabetic microalbuminuria • Proteinuria • LVH • ACEI cough or intolerance	• Pregnancy • Hyperkalaemia • Bilateral renal artery stenosis	
β-blockers	• Angina pectoris • Post-myocardial infarction • HF (carvedilol, metoprololol, bisoprolol, nebivolol only) • Tachyarrhythmias	• Asthma • Chronic obstructive pulmonary disease • AV block (grade 2 or 3) • Pregnancy (atenolol)	• Peripheral vascular disease • Bradycardia • Glucose intolerance • Metabolic syndrome • Athletes and physically active patients • Non dihydropyridine CCBs (verapamil, diltiazem)

as are seen in hypertensive emergencies. Ideally, all patients with hypertensive urgency should be treated in hospital.

Commence treatment with two oral agents and aim to lower the diastolic BP to 100 mmHg slowly over 48 to 72 hours. This BP lowering can be achieved with the use of: (1) long-acting CCBs; (2) ACEI, initially used in very low doses, but avoid if there is severe hyponatraemia (serum Na < 130 mmol/l indicates hyper-reninaemia and BP may fall dramatically with ACEI); (3) β- blockers; and (4) diuretics.

• *Hypertensive emergency*

A hypertensive emergency is severe, often acute elevation of BP associated with acute and ongoing organ damage to the kidneys, brain, heart, eyes (grade 3 or 4 retinopathy) or vascular system. These patients need rapid (within minutes to a few hours) lowering of BP to safe levels. Hospitalisation is ideally in an intensive care unit (ICU) with experienced staff and modern facilities for monitoring. If an ICU is unavailable, the patient may be closely monitored and treated in the ward.

Intravenous antihypertensive therapy, tailored to the specific type of emergency, has become the standard of care. Labetalol, nitroprusside or nitroglycerin are the preferred intravenous agents. Overzealous lowering of BP may result in stroke. A 25% reduction in BP is recommended in the first 24 hours. Oral therapy is instituted once the BP is more stable. Although most adult patients with a hypertensive emergency will have BP > 220/130 mmHg, it may also be seen at modest BP elevations; for example, in a previously normotensive woman during pregnancy (eclampsia) or in the setting of acute glomerulonephritis, especially in children.

Severe HTN associated with ischaemic stroke and intracerebral haemorrhage should be managed according to the recommendations of the Neurological Association of South Africa.[26] Great caution should be exercised in lowering BP after an ischaemic stroke due to the risk of extending the ischaemic penumbra.

Resistant hypertension

HTN that remains > 140/90 mmHg despite the use of three antihypertensive drugs in a rational combination at full doses and including a diuretic (hydrochlorothiazide 25 mg or indapamide 2.5 mg) is known as resistant HTN. Common causes of resistant HTN are listed in Table 8.

The therapeutic plan must include measures to ensure adherence to therapy and lifestyle changes. Unsuspected causes of secondary HTN are less common, but need to be considered based on history, examination and special investigations. It is essential to exclude pseudo-resistance by performing SBPM or 24-hour ABPM. Referral to a specialist is often indicated for a patient with resistant HTN.

Once the issues relating to lifestyle, adherence to therapy, white coating, etc. outlined in Table 7 have been satisfactorily managed, then consideration should be given to the addition of the fourth- and fifth-line drug. Currently spironolactone (25–50 mg only) with careful monitoring of serum potassium, beta-blockers and/or long-acting doxazasin is recommended.[27,28] Other choices include direct-acting vasodilators (hydralazine, minoxidil), or centrally acting drugs (methyldopa, moxonidine, reserpine).

Initial studies of renal denervation in patients with resistant HTN showed very promising results.[29,30] The recent publication of the Simplicity 3 study showing no significant effect on BP compared to sham procedure, the place of renal denervation in the treatment of resistant HTN remains to be established and is not supported by this guideline.[31]

Table 8. Causes of resistant hypertension in South Africa

Non-adherence to therapy	• Instructions not understood • Side effects • Cost of medication and/or cost of attending at healthcare centre • Lack of consistent and continuous primary care • Inconvenient and chaotic dosing schedules • Organic brain syndrome (e.g. memory deficit)
Volume overload	• Excess salt intake • Inadequate diuretic therapy • Progressive renal damage (nephrosclerosis)
Associated conditions	• Smoking • Increasing obesity • Sleep apnoea • Insulin resistance/hyperinsulinaemia • Ethanol intake of more than 30 g (three standard drinks) daily • Anxiety-induced hyperventilation or panic attacks • Chronic pain • Intense vasoconstriction (Raynaud's phenomenon), arteritis
Identifiable causes of hypertension	• Chronic kidney disease • Renovascular disease • Primary aldosteronism • Coarctation • Cushing's syndrome • Phaeochromocytoma
Pseudoresistance	• 'White coat hypertension' or office elevations • Pseudohypertension in older patients • Use of regular cuff in obese patients
Drug-related causes	• Doses too low • Wrong type of diuretic • Inappropriate combinations • Rapid inactivation (e.g. hydralazine)
Drug actions and interactions	• Non-steroidal anti-inflammatory drugs (NSAIDs) • Sympathomimetics: nasal decongestants, appetite suppressants • Cocaine, Tik and other recreational drugs • Oral contraceptives • Adrenal steroids • Liquorice (as may be found in chewing tobacco) • Cyclosporine, tacrolimus, erythropoietin • Antidepressants (monoamine oxidase inhibitors, tricyclics)

Special considerations for hypertension in certain populations

Blacks and Asians

Blacks are more prone to complications of stroke, heart failure and renal failure, while the incidence of coronary heart disease, although increasing in frequency, is less common compared with that in whites and Asians.[32] The prevalence of diabetes mellitus and the metabolic syndrome is higher in Asians compared to other racial groups.[33]

Compared to whites, blacks respond poorly to ACEI and β-blockers as monotherapy, but this difference disappears once these drugs are combined with diuretics. Overall, CCBs show the most consistent response in blacks compared to other classes of drugs used as monotherapy.[23,34] However there is a higher incidence of angioedema in blacks treated with an ACEI.[35]

Hypertension in children and adolescents[36,37]

HTN in children is an important issue beyond the scope of this guideline. In adolescents, the HTN is increasingly linked to obesity and affects up to 10% of people between the ages of 15 and

25 years.[38] The international trend of poor diet and lack of exercise in children is leading to an epidemic of obesity, with the early onset of HTN and even type 2 diabetes. The early recognition of HTN in these adolescents will be an important motivation for both children and parents to institute important lifestyle changes.

HIV/AIDS

There are an estimated 5.8 million people living with HIV in South Africa. The co-existence of HIV with HTN and diabetes is increasing, and patients should be screened for associated glomerulonephritis.[39] Prolonged highly active antiretroviral therapy (HAART) is associated with a higher prevalence of systolic HPT,[40] and it is essential that BP is monitored in patients receiving HAART.

Two of the three major classes of antiretroviral drug, the protease inhibitors and the non-nucleoside reverse transcriptase inhibitors, are involved in many drug interactions by inhibiting or inducing the key hepatic enzyme system, cytochrome P450. CCBs are the major class of antihypertensives affected by such drug interactions, leading to inhibition or induction of their metabolism.[41,42] This results in either an enhanced or loss of antihypertensive efficacy.

Disclaimer

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Sodium-glucose co-transporter (SGLT) inhibitors: a novel class of oral anti-diabetic drugs

P NAIDOO, K HO, V RAMBIRITCH, N BUTKOW

Abstract

The prevalence of type 2 diabetes mellitus has reached pandemic proportions. The armamentarium of anti-diabetic agents is vast, but there remain unmet medical needs. The latest addition is the sodium glucose co-transporter inhibitors. Members of the class include dapagliflozin, canagliflozin, empagliflozin, ipragliflozin and tofoglilozin. This class of agents reduce blood glucose concentrations by inhibiting renal re-absorption of glucose. This mechanism of action is independent of beta-cell function and insulin resistance. This article explores potential effects of this class of agents, extrapolated from the mechanism of action, and compares these potential effects to effects demonstrated in clinical studies.

Type 2 diabetes mellitus (T2DM) is a progressive disorder of protein, fat and carbohydrate metabolism characterised by hyperglycaemia and changes in the secretion of both insulin (and/or resistance to the effects of insulin) and glucagon.[1-4]

The prevalence of T2DM has reached pandemic proportions.[5] Currently, over 366 million people are living with T2DM. By 2030 this figure will have risen to approximately 552 million.[6] The global prevalence of T2DM is 4.3%, with 81.2% undiagnosed.[6] Sedentary lifestyle and high caloric intake is strongly associated with obesity, which contributes to the T2DM pandemic.[4]

Ten per cent of adults in the USA, Switzerland and Austria are affected by T2DM. It is predicted that in the Middle East, sub-Saharan Africa and Latin America, the prevalence will increase 2.5 times by 2030. In the economically advanced countries the increase will be about 50% in 2030.[5]

The prevalence of T2DM is increasing rapidly in sub-Saharan Africa[7] and population prevalence rates vary from a low of 1% in rural Uganda to 12% in urban Kenya.[8] In South Africa, the prevalence is 7%, accounting for approximately two million cases, with another 1.5 million remaining undiagnosed.[6]

Type 2 diabetes therapy

Lifestyle modification encompassing both a carbohydrate- and fat-restricted diet and an exercise programme remains the cornerstone of management.[9] However, successful lifestyle modification is challenging for the majority of patients. Furthermore, T2DM is associated with a gradual decline in pancreatic beta-cell function and consequently these patients eventually require medication, in addition to lifestyle modification.

Lowering blood glucose concentrations unequivocally reduces the risk of microvascular complications such as nephropathy, neuropathy and retinopathy.[10] There is inadequate evidence to show that glycaemic control reduces macrovascular complications. However, macrovascular complications account for a large proportion of the morbidity and mortality in patients with T2DM and has led to many guidelines accepting the diagnosis of T2DM as a 'cardiovascular risk equivalent'. Therapy for T2DM patients must therefore not only

Table 1. Pharmacological agents for type 2 diabetes mellitus[1,13]

Class	Example	Abbreviated mode of action
Biguanides	Metformin	Decreases insulin resistance, decreases hepatic gluconeogenesis
Sulphonylurea	Glibenclamide, gliclazide, glipizide, glimepiride	Increases insulin release from pancreas
Meglitinides	Repaglinide, nateglinide	Increases insulin release from pancreas
Thiazolidinediones	Pioglitazone	Increases insulin sensitivity
Glucagon-like peptide-1 (GLP) analogues	Exenatide, liraglutide	Incretin mimetic
Dipeptidyl peptidase IV (DPPIV) inhibitors	Sitagliptin, vildagliptin, saxagliptin	Reduces incretin breakdown, thereby increasing incretin effect
α-Glucosidase inhibitors	Acarbose	Reduces glucose absorption from the gastrointestinal tract
Insulin	Ultra short-acting insulin analogues Aspart Lispro Glulisine	Facilitates glucose transit from blood to tissues. Inhibits glycogenolysis and hepatic gluconeogenesis
	Short-acting insulin analogues 'Regular' human insulin	
	Intermediate-acting insulin Neutral protamine Hagedorn (NPH)	
	Long-acting insulin analogues Glargine Detemir	

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Table 2. SGLT location and function[14,15]

	Location	Function
SGLT1	Small intestine, trachea, kidney, heart and colon	Main uptake mechanism for glucose and galactose in the intestine; 10% of the renal glucose re-absorption
SGLT2	Predominantly kidney. Small amounts in cerebellum and low levels in heart, salivary gland, liver and thyroid	90% of the total renal glucose re-absorption
SGLT3	Neurons of the small intestine and in neuromuscular junctions of skeletal muscle	Transports sodium upon glucose binding
SGLT4	Intestine, kidney, liver, brain, lung, trachea, uterus and pancreas	Renal monosaccharide and/or sodium re-absorption
SGLT5	Kidney	Possibly similar to SGLT2, but role in monosaccharide transport not established
SGLT6	Brain, spinal cord, kidney, intestine	Monosaccharide transport

focus on achieving glycaemic targets but modifiable cardiovascular risk factors such as hypertension, dyslipidaemia, kidney disease and obesity must also be targeted.[10]

There is currently a vast array of anti-diabetic drugs. Biguanides, specifically metformin, is advocated as initial therapy, if not contra-indicated and if tolerated.[11,12] Sulphonylureas remain popular, despite weight gain, increased risk of hypoglycaemia and limited long-term durability, because they are efficacious, affordable and clinicians are familiar with them. Other classes include dipeptidyl peptidase IV (DPPIV) inhibitors, glucagon-like peptide-1 analogues, alpha-glucosidase inhibitors, meglitinides, thiazolidinediones, and insulin. The pharmacological action and examples of the main groups are shown in Table 1.

The newest addition to the armamentarium is the sodium glucose co-transporter (SGLT) inhibitors and includes dapagliflozin, canagliflozin, empagliflozin, ipragliflozin and tofoglilozin. None of these drugs are currently registered in South Africa.

Sodium glucose co-transporters (SGLT) in healthy individuals

There are various types of SGLTs, and these are listed in Table 2. This section will focus on SGLT1 and SGLT2.

The kidney filters approximately 180 litres of plasma per day and produces only one to two litres of urine. Therefore re-absorption of sodium, water and other substances in the healthy non-diseased kidney is substantial. This filtered fluid contains approximately 162 g of glucose.[16] In non-diabetic individuals, 95% of the filtered glucose is reabsorbed in the proximal convoluted tubules (PCT) of the nephron. This is mediated by sodium glucose co-transporters (SGLT).

There are two subtypes of SGLT in the PCT of the nephron, SGLT 1 and SGLT 2. SGLT 2 is found in segment 1 and 2 of the PCT.[16,17] and is a high-capacity, low-affinity transporter responsible for 90% of the re-absorption of glucose.[16,17] SGLT 1 is found in segment 3 of the PCT and is a high-affinity, low-capacity transporter responsible for re-absorption of 10% of filtered glucose.[16] SGLT 1 is also present in the intestine and is responsible for absorption of glucose and galactose.[16]

SGLT in type 2 diabetes mellitus

The number and activity of SGLT receptors are increased in type 2 diabetes.[16,18] Therefore, although there is hyperglycaemia, the kidney actually increases the re-absorption of glucose from the glomerular ultra-filtrate, thus worsening the existing hyperglycaemia. The reaction of the body to increase renal re-absorption seems counter-

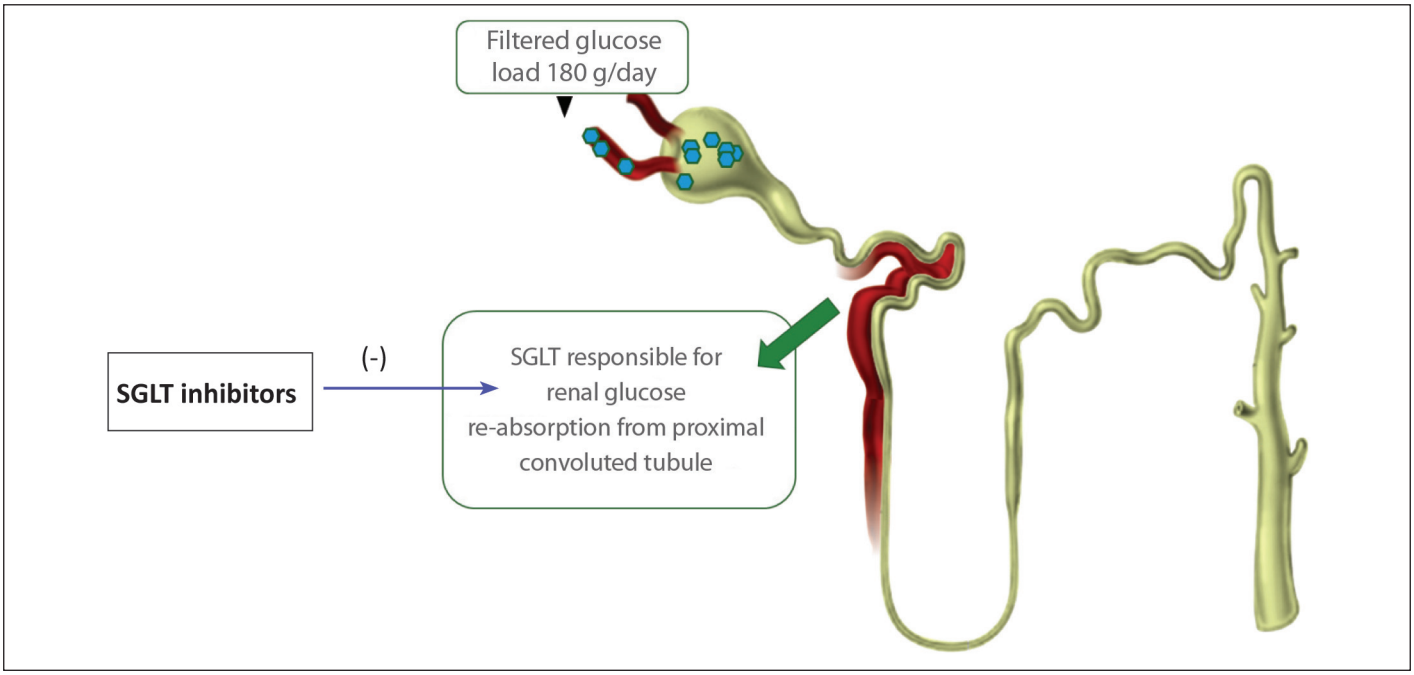

Fig. 1. Sodium glucose co-transporter (SGLT) inhibitors reduce glucose re-absorption in the proximal tubule, leading to urinary glucose excretion and osmotic diuresis. Modified from Ferrannini and Solini.[4]

intuitive, however, it must be noted that the kidney may be reacting to perceived inadequate intracellular glucose levels.

Mechanism of action of SGLT inhibitors

Inhibition of SGLT limits re-absorption of glucose from the glomerular ultra-filtrate in the proximal convoluted tube. This increases urinary glucose excretion.

Increased urinary glucose excretion directly ameleriorates hyperglycaemia. In addition, reduction in blood glucose levels results in the reduction of glucotoxicity and consequently improves beta-cell function and insulin resistance.[16] This mode of action targets (directly and indirectly) three pathological hallmarks of type 2 diabetes mellitus, hyperglycaemia (directly), beta-cell dysfunction (indirectly), and insulin resistance (indirectly). Fig. 1 shows the site of action of SGLT inhibitors.

Effects extrapolated from the mechanism of action

This section extrapolates possible effects from mode of action; it is based on intuition and not clinical data. The section that follows this attempts to link potential effects to data from clinical studies.

Given that the kidney is removing increased amounts of glucose, one may expect the class to ameliorate hyperglycaemia and have a potential to increase hypoglycaemic episodes. Increased urinary glucose excretion may reduce available calories and consequently could result in weight loss.

Osmotic diuresis may lower blood pressure. However, osmotic diuresis has the potential to result in volume depletion. Osmotic diuresis may also increase the frequency of urinary voiding.

Due to the inhibition of renal SGLT, increased urinary glucose excretion may serve as a substrate for micro-organisms and thus potentially increase the risk of urinary tract and genital infections. In addition, high urinary glucose concentrations may adversely impact on the cells lining the urinary tract and thus impair the innate immunity of the urinary tract and predispose to urinary tract infections.

Table 3. Potential advantages and disadvantages extrapolated from mode of action

Potential advantages	Potential disadvantages
Efficacy not limited by degree of beta-cell impairment or insulin resistance	Increased urinary frequency
Weight loss	Volume depletion
Blood pressure reduction	Hypoglycaemia
Reduces glucose toxicity and indirectly improves insulin resistance and beta-cell dysfunction	Increased urinary tract and genital infections

Lowering blood glucose levels, the glucotoxic effect of glucose is diminished irrespective of the degree of beta-cell function. This potentially protective mechanism of action on the beta-cells could result in more residual beta-cells and hence insulin production being maintained. This beta-cell-independent mode of action will mean that the class is potentially efficacious despite the severity of beta-cell depletion/dysfunction.

The ability of this class to work independently of beta-cell dysfunction and insulin resistance allows a potentially synergistic action with other anti-diabetic drugs. It may also allow lower doses of anti-diabetic agents to be used, which may reduce the risk of adverse effects.

Table 3 lists potential theoretical advantages and disadvantages of the effects extrapolated from the mode of action.

Clinical experience with SGLT inhibitors

This section attempts to compare theoretical effects expected from the mode of action of the SGLT inhibitors with actual clinical findings.

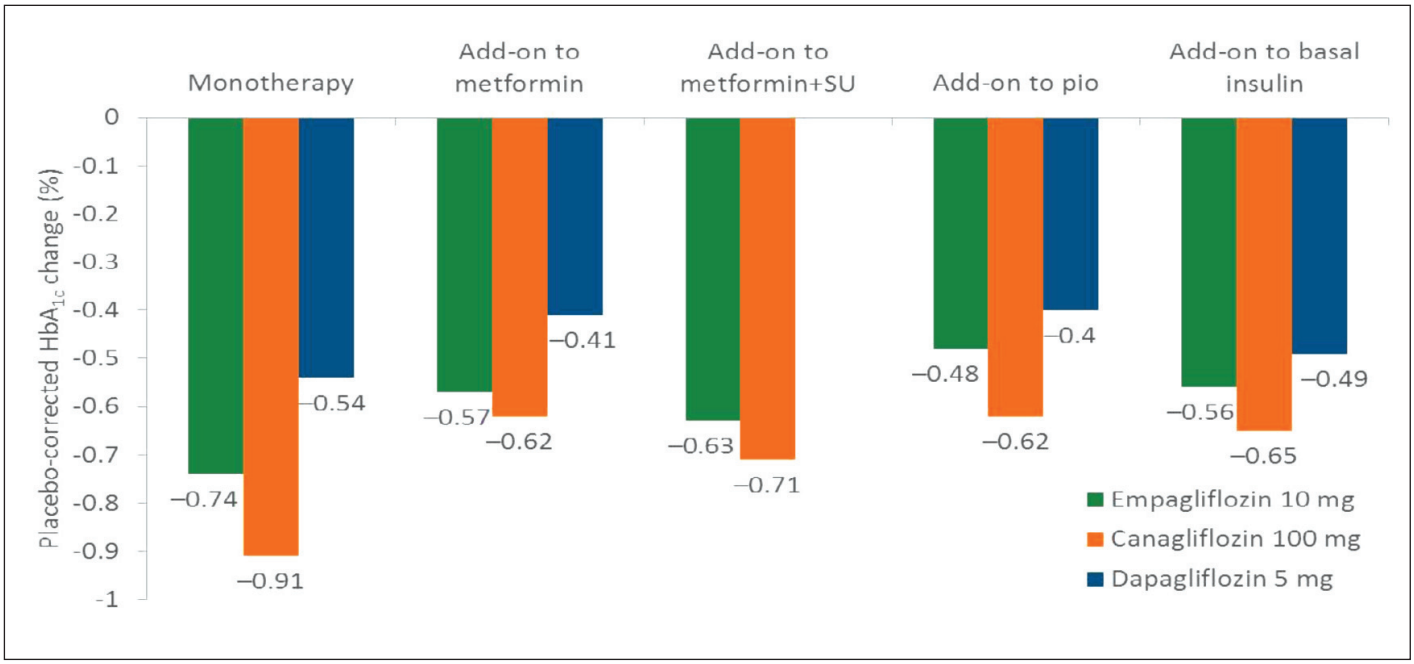

Fig. 2. Placebo corrected HbA_{1c} for SGLT2 inhibitors in different subgroups of patients.[19-25]

Table 4. Linking extrapolated effects to actual effects demonstrated in clinical studies

Effect extrapolated from mode of action	Data from clinical studies	Reference
Weight reduction	Mean reduction 2–3 kg	13
Blood pressure reduction	Reduces systolic/diastolic blood pressure by 4–5/2–3 mmHg	33
Urinary tract infections	Lower urinary tract infections increased. Responds to standard therapy. Mild to moderate severity.	29
Genital tract infections	Mycotic infections increased. Responds to standard therapy. Mild to moderate severity.	29
Increased urinary volume with volume depletion	Equates to one increased void per day. Does not cause volume depletion	31
Hypoglycaemia	Monotherapy as safe as placebo; hypoglycaemia only increased when concomitant drugs causing hypoglycaemia added, e.g. sulphonyureas and insulin	21, 27
Bladder cancer*	Not significantly increased when compared to placebo	20, 30
Breast cancer*	Not significantly increased when compared to placebo	20, 30

*Not extrapolated from mode of action but relevant to discussion of SGLT inhibitor class

SGLT inhibitors increase urinary glucose elimination and reduce HbA_{1c} levels by approximately 0.7–0.8% in type 2 diabetes patients with an initial baseline HbA_{1c} level of 8%.[16] Fig. 2 shows placebo-corrected change in HbA_{1c} levels for members of the SGLT2 inhibitor class. Importantly, data is not directly comparable because these were not head-to-head studies and patient characteristics were variable.

The incidence of hypoglycaemia is comparable to placebo[26,27] The mechanism for low incidence of hypoglycaemia is unknown but postulations include activation of counter-regulatory mechanisms and reduced renal perfusion and associated reduced renal glucose clearance. However, there is an increase in hypoglycaemic episodes when combined with agents that commonly cause hypoglycaemia, specifically insulin and sulphonylureas.[23,28]

Mycotic genital infections are increased in patients exposed to SGLT inhibitors. Causative organisms include *Candida albicans* and *Candida glabrata.* Reported incidence for one member of the class ranged from 3 to 13% versus 0 to 5% in the placebo group.[29] Genital infections rarely resulted in discontinuation of therapy and responded to standard topical therapy.[29]

In general, urinary tract infections (UTIs) are higher in patients receiving the SGLT inhibitors.[29] Urinary tract infections with one SGLT inhibitor ranged between one and 12.9% versus 6.2% in controls and 9% on metformin monotherapy. Most urinary tract infections were mild to moderate in intensity, non-recurrent, and responded to standard management.[29] Risk factors for developing urinary tract infections in patients treated with SGLT2 inhibitors included female gender and history of urinary tract infections. It is advised to avoid this class of drugs in patients with recurrent urinary and genital infections.

Bladder cancer was diagnosed in nine out of 5 478 (0.16%) patients treated with a SGLT inhibitor versus one in 3 156 patients on placebo (0.03%, $p = 0.15$).[20] Of these nine cases of bladder cancer, five patients initially had haematuria, suggesting that bladder cancer may have been present at the start of the study. [20]

Nine of 2 223 women developed breast cancer in the SGLT inhibitor-treated group (0.4%) versus one of 1 053 patients on placebo (0.09%, $p = 0.27$).[20] It was suggested that because of aggressive screening for UTIs, the identification of haematuria was higher and subsequent investigations for bladder cancer were entertained when no microbial cause for the haematuria was identified.[20,30] Furthermore, breast cancer may have been easy to diagnose because of the weight loss.[20,30] This explanation is limited since it is highly debatable that a mean weight loss of 2 to 3 kg would increase the ability of the patient or clinician to notice a breast mass. The short duration of the studies suggests that a causal relationship between dapagliflozin and breast cancer is unlikely. The difference between these cancers and the placebo was not statistically significant. However, careful monitoring and long-term studies are required.

There was no clinically significant increase in mean urine volume when compared to placebo.[31] The increase in mean urine volume translated to one extra void per day and did not result in volume depletion.[27]

Clinical studies have shown a mean reduction in weight of approximately 2 to 3 kg.[13] Bolinder *et al*.[32] studied the effects of dapagliflozin on body weight, total fat mass and regional adipose tissue distribution, and concluded that the weight loss is largely due to loss of body fat. One would have expected a greater weight loss but this did not occur. Study subjects probably compensated by eating more. Nevertheless, weight loss of 2 to 3 kg in an overweight/obese patient is significant and at least weight gain is not a problem, unlike other anti-diabetic drugs.

SGLT inhibitors reduce systolic/diastolic blood pressure by 4–5 /2–3 mmHg.[33] The exact mechanism remains to be determined, but may be related to the mild diuretic effect, weight loss or effects on the renin–aldosterone–angiotensin system. Further studies are required to elucidate the mechanism of blood pressure reduction. Table 4 provides a summary of this discussion.

Conclusion

SGLT inhibitors are a novel class of oral anti-diabetic drugs with a mode of action that is independent of beta-cell function and insulin resistance. Beneficial effects of this class of drugs on measures of glycaemia, blood pressure and weight will be gauged by its ability to mitigate long-term complications of type 2 diabetes mellitus, including adverse cardiovascular events, e.g. myocardial infarction and cerebrovascular accidents.

Declaration: Dr P Naidoo and Dr K Ho are employees of Boehringer-Ingelheim, South Africa

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Excess cardiovascular risk in patients with type 2 diabetes: do we need to look beyond LDL cholesterol?

ALAN REES

Abstract

Despite impressive advances in treatment, cardiovascular disease (CVD) remains a significant healthcare burden in the UK and worldwide. The clustering of CVD risk factors in patients with type 2 diabetes underlines the need for a multifactorial treatment approach, yet even when receiving optimal therapy according to best standards of care, there remains a substantial risk of CVD and microvascular disease. Risk-prediction tools traditionally provide an estimate of risk over 10 years, however this approach is dominated by chronological age and gender and has a number of recognised limitations. A move from 10-year to lifetime risk calculation has been proposed, and should encourage intervention at a much earlier stage. This move, alongside aggressive and broad control of modifiable risk factors, aims to ease the burden of atherosclerosis prior to the manifestations of CVD. This will be of particular benefit to those with type 2 diabetes, who have been exposed to hyperglycaemia and other risk factors for extended periods of time. The atherogenic dyslipidaemia common in this group also ensures they will benefit most from treatment strategies under investigation to further reduce macro- and microvascular risk.

Keywords: residual risk, cardiovascular disease, type 2 diabetes, lifetime risk, atherogenic dyslipidaemia, macrovascular

Introduction

Annual mortality from cardiovascular disease (CVD) has almost halved in the UK in the last 50 years, to about 180 000 people in 2009 – representing a fall from 51 to 32% of all-cause mortality.[1] Nevertheless, CVD remains the leading cause of death both in the UK1 and world wide.[2] However, this progressive decrease in CVD mortality is being attenuated by the counterbalancing increase in obesity, the metabolic syndrome and type 2 diabetes.

The prevalence of obesity has been increasing exponentially over the past two decades,[3] and is the most prevalent metabolic disease worldwide.[4] This increase in obesity is fuelling a rise in the numbers of people with metabolic syndrome or type 2 diabetes,[5,6] with prevalence estimates for the metabolic syndrome varying between 20 and 30% of adults[7] and diabetes affecting 8.3% of the global population.[5,8] Until recently type 2 diabetes was considered to be a disease of adulthood, however over the past two decades an increase in children and adolescents has been reported – from < 3% of all cases of new-onset diabetes in adolescents in 1990 to 45% in 2005.[9] Young people with this disorder have an increased risk of morbidity and mortality during the most productive years of life.[10,11] As coronary disease is the major cause of death associated with diabetes,[12,13] it may be expected that the observed mortality decline would also be reflected in patients with diabetes. However, a large cohort study based in the USA showed that cardiovascular mortality rates in men with diabetes have not decreased to the same extent as those seen in the general population, and have even increased among women.[14]

The combined increase in prevalence of obesity, the metabolic syndrome and diabetes is having tangible effects on coronary heart disease (CHD) mortality. Recent epidemiological data from 1984 to 2004 in the UK show a significant overall reduction in CHD mortality among adults, but in younger men, mortality rates increased in 2002 for the first time in over two decades. This was reflected in data for both men and women aged 45 to 54 where a slowing of the decline in mortality rates was observed, with trends reflected in data from the USA.[15] Unfavourable trends in risk factors for CHD were considered a likely explanation for the observed mortality rates.[15,16]

The increasing prevalence of diabetes and its attendant CVD risk makes management of this disease and its complications of paramount importance. Type 2 diabetes is a complex disease defined by hyperglycaemia due to insulin resistance and progressive beta-cell failure. Among the first studies to confirm independent associations between glycated haemoglobin (HbA_{1c}) and vascular complications, including cardiovascular complications, were the landmark UKPDS (UK Prospective Diabetes Study)[17] and its long-term follow-up analysis.[18] This association has also been highlighted in a number of large population-based observational studies,[19-21] and was subsequently quantified in a large meta-analysis including data from almost 700 000 patients. The meta-analysis found that serum glucose is independently associated with an increased risk of CHD (HR: 2.00, 95% CI: 1.83–2.19), ischaemic stroke (HR: 2.27, 95% CI: 1.95–2.65) and an aggregate of other vascular deaths (HR: 1.73, 95% C:I 1.51–1.98).[22]

The financial burden of excess CVD in type 2 diabetes

The cost burden of diabetes mellitus to the National Health Service (NHS) is estimated to be up to 10% of the total resource expenditure, with a recent study estimating the annual cost in 2010/2011 to be around £9.8 billion.[23] Type 2 diabetes was responsible for around 90% of this cost, with less than a quarter relating to the treatment and ongoing management of diabetes and the remainder accounted for by treating its complications.[23] The large hospital-care burden is a result of the treatment of retinal, renal, neuropathic, cerebrovascular and cardiac complications, which occur with increasing frequency and severity as the disease progresses.[24]

For example, a study conducted into secondary care treatment for patients with diabetes in Wales found that those with diabetes represented over a quarter of nephrology admissions and almost

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one-fifth for cardiology, contributing to around 20% of their total costs. Extrapolating these data to the UK as a whole, they estimated that £1.00 in every £8.00 spent on hospital care in the UK was spent on a patient with diabetes.[25] Hospital costs incurred in the final years of life have also been shown to be greater in patients with diabetes than those without diabetes at a ratio of 1.39 ($p < 0.001$) after standardisation for age and gender, and accounted for 15.6% of revenue.[26]

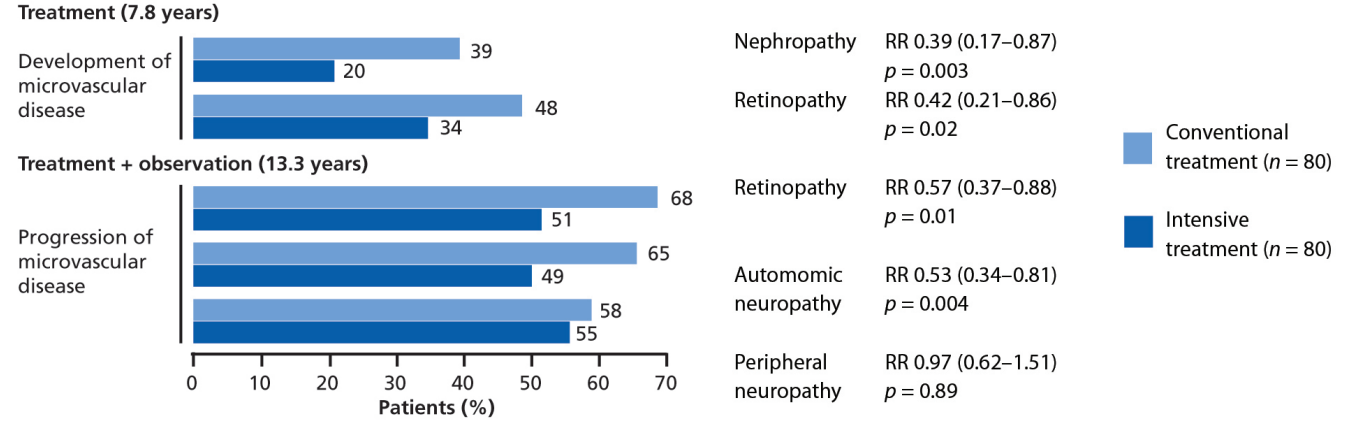
It is not just the direct cost to healthcare services that is important, the non-health-service costs (including the social and productivity costs of diabetes) are considerably higher and are largely borne by the individual or their carers. Diabetes was estimated to cost approximately £23.7 billion in the UK in 2010/2011, with non-health-service costs accounting for £13.9 billion of this figure. If no changes are made to the way diabetes is treated by 2035/2036 then costs are expected to increase further, with direct healthcare costs representing around 17% of NHS expenditure at £16.9 billion and non-health-service costs increasing to £22.9 billion.[23] Additional studies investigating the incidence and prevalence of diabetes from 2000 to 2060 estimate that a 3% annual increase in the UK resident population is likely to disguise a much greater increase among the elderly, resulting in a 20% increase in the number of people with type 2 diabetes from 2000 to 2030 and inflicting an increasingly large burden on the UK health service.[27]

Cardiovascular risk factors in patients with diabetes

The INTERHEART study arguably provides the most comprehensive global picture of the relative contribution of major modifiable risk factors to CVD.[28] INTERHEART is a case–control study of acute myocardial infarction (MI) which enrolled almost 30 000 individuals from 52 countries, representing every inhabited continent. The study investigated the relationship of CVD risk factors such as smoking, hypertension, diabetes, blood lipids, diet and exercise to MI. It was found that smoking, a raised apolipoprotein B: apolipoprotein A1 (ApoB:ApoA1) ratio, history of hypertension, diabetes, abdominal obesity, and psychosocial factors were all associated with a significant increase in the risk of acute MI. Daily consumption of fruit and vegetables, regular alcohol consumption and regular physical activity were all associated with a significant decrease in the risk of acute MI ($p < 0.0001$ for each risk factor other than $p = 0.03$ for alcohol). These associations were noted in men and women, across all age ranges and in all regions of the world. Collectively, these nine risk factors accounted for 90% of the population-attributable risk (PAR) for MI in men, and 94% in women.[28]

Some of the increased cardiovascular risk in patients with diabetes can be explained by a clustering of traditional risk factors within this population, and it has long been established that people with diabetes are more likely to have additional cardiovascular risk factors than those without diabetes.[29,30] Data from the UKPDS show that in patients with type 2 diabetes, increased concentrations of low-density lipoprotein (LDL), decreased concentrations of high-density lipoprotein (HDL), hyperglycaemia, hypertension and smoking are risk factors for coronary artery disease,[31] with all factors other than increased LDL also risk factors for peripheral vascular disease.[32] The MRFIT study also found that, compared with men without diabetes, 12-year CVD mortality rates were much higher at every level of serum cholesterol, systolic blood pressure and smoking among diabetic men.[30] In addition, a number of randomised trials that investigated the effect of intensified intervention on a single risk factor in patients with type 2 diabetes demonstrated microvascular benefits in the eyes and nerves and both micro and macrovascular benefits in the kidneys.[17,33,34,35]

For this reason, both national and international guidelines for the management of type 2 diabetes advocate a multifactorial approach including the treatment of risk factors such as hypertension, dyslipidaemia and encouraging smoking cessation in addition to glycaemic control.[36,37,38] The effect of implementing a multifactorial treatment approach for cardiovascular risk in patients with diabetes was evaluated in the STENO-2 study. This relatively small study of 160 patients compared an intensive, targeted, multifactorial intervention (including both behavioural and pharmacological therapy) to conventional treatment, and found that patients



RR, relative risk (95% CI)

Diabetic nephropathy was defined as urinary albumin excretion > 300 mg per 24 hours in two of three sterile urine specimens. Diabetic retinopathy was graded according to the six-level grading scale of the European Community-funded Concerted Action Programme into the Epidemiology and Prevention of Diabetes by two independent ophthalmologists who were unaware of treatment assignment. Peripheral neuropathy was measured with a biothesiometer. Autonomic neuropathy was diagnosed based on measurement of the RR interval on an ECG during paced breathing and an orthostatic hypotension test conducted by a laboratory technician who was unaware of patients' treatment assignment

Figure 1. Intensive multifactorial intervention in the STENO-2 study significantly reduced the development or progression of diabetes-related microvascular disease, but failed to prevent this in many patients.[39,40,67]

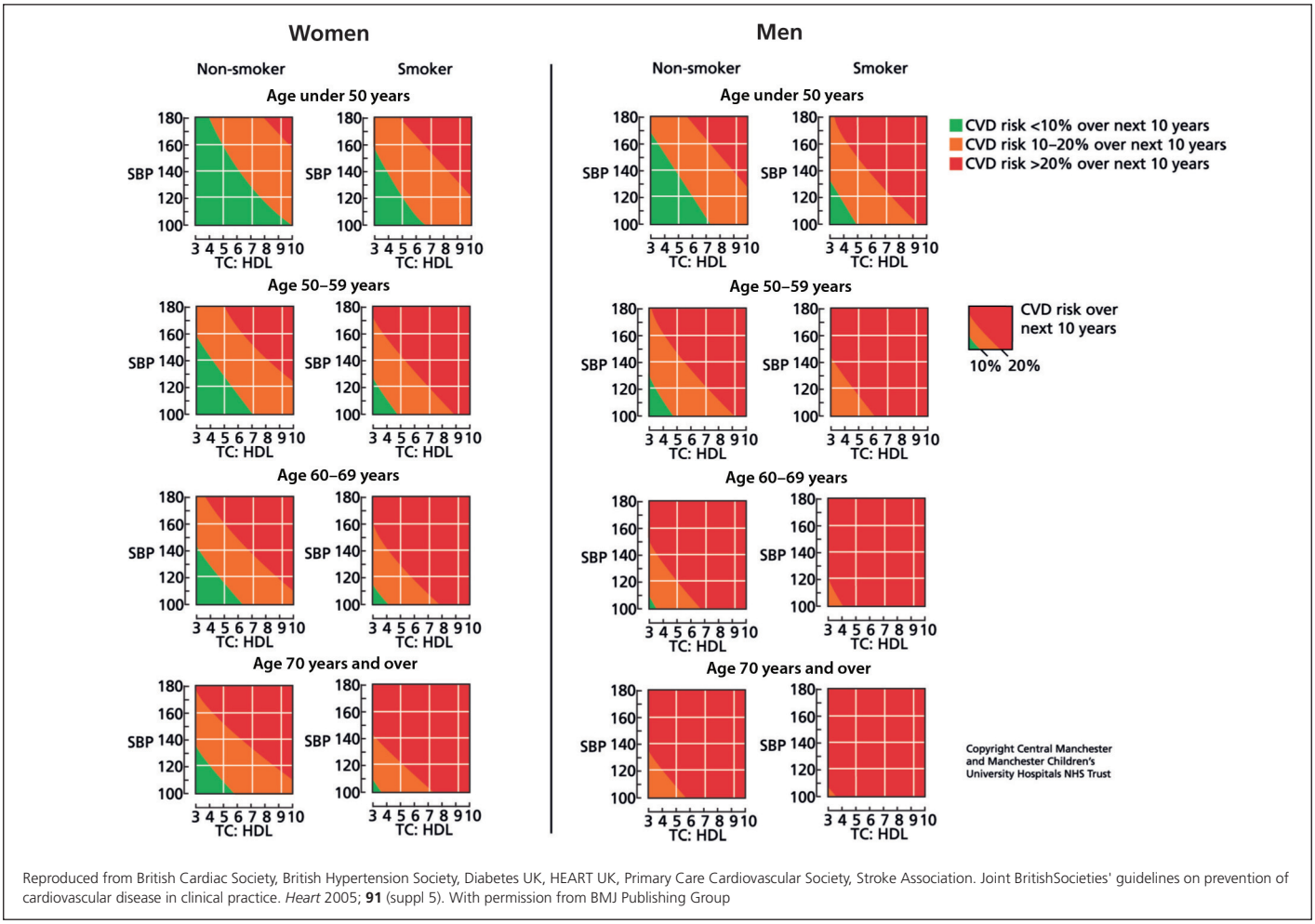


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Figure 2. JBS2 CVD risk prediction charts for men and women.[41]

receiving intensive therapy had a significantly lower risk of CVD (HR 0.47, 95% CI 0.24–0.73), nephropathy (HR 0.39, 95% CI 0.17–0.87), retinopathy (HR 0.42, 95% CI 0.21–0.86) and autonomic neuropathy (HR 0.37, 95% CI 0.18–0.79).[39] The mortality benefits of such an intervention were also investigated in an extension of the STENO-2 study (mean 13.3 years follow-up), where the multifactorial intervention was shown to have a sustained benefit on both vascular complications and cardiovascular mortality.[40] Y*et al*though a comprehensive risk factor approach is essential when treating patients with type 2 diabetes, data from the STENO-2 study show that despite reductions versus conventional treatment, multifactorial interventionis insufficient to prevent the development or progression of microvascular disease in up to 50% of patients (Fig. 1). It is, therefore, clear that there is a need for renewed focus on eff ective interventions that are capable of reducing the residual risk of cardiovascular events and microvascular complications in patients with type 2 diabetes receiving optimal therapy according to current standards of care.

Quantifying cardiovascular risk

Patients with type 2 diabetes benefit from sustained and early intervention for risk factor control; however, treatment interventions are often initiated too late for maximum CVD benefit. Ensuring that we are quantifying risk correctly is crucial to achieving early risk factor control and addressing the residual cardiovascular risk seen in type 2 diabetes patients.

The concept of medical intervention based on estimated total CVD risk in asymptomatic patients is well established both in the UK[41] and internationally.[42,43] Underpinning this are studies such as the Framingham Heart Study, which to date has enrolled three generations of participants to identify the common factors or characteristics that contribute to CVD.[44] These data have enabled researchers to construct multivariate risk prediction algorithms intended to provide an estimate of CHD or CVD risk over a specified time period, generally 10 years.

The second edition of the Joint British Societies' guidelines on cardiovascular disease in clinical practice (JBS-2) uses a risk estimate tool adapted from the equations published from the Framingham study in 1991.[45] The tool estimates total CVD risk (a combined endpoint of CHD, stroke and transient cerebral ischaemia) for an asymptomatic individual from several, wellestablished risk factors such as age, sex, smoking habit, systolic blood pressure and ratio of total cholesterol to HDL cholesterol.

This is then expressed as a probability of developing CVD over 10 years, based on the number of cardiovascular events expected over 10 years in 100 men or women with the same risk factors as the individual being assessed. Charts have subsequently been created to easily assess risk based on these factors (Fig. 2), and are split into

CVD risk categories of ≥ 10%, ≥ 20% and ≥ 30% over 10 years. Asymptomatic individuals with a CVD risk of ≥ 20% are classified as high risk, with this level being a threshold for treatment with antihypertensive and lipid-lowering therapies. It should be noted that charts have not been created for patients with diabetes, and several studies have suggested that these types of equations considerably underestimate the risk of both cardiovascular disease and mortality in this group.[46-48] Guidelines instead recommend all patients with diabetes should be considered high risk and managed to the same lifestyle and defined risk-factor targets as individuals with established CVD and others at high 10-year risk of developing CVD.[41]

However, there are well recognised limitations to a 10-year risk metric for the calculation of cardiovascular risk. The 10-year risk metric is dominated by two particular risk factors – chronological age and gender. This fact effectively disenfranchises the middle-aged and females, resulting in a delay in initiating treatment until a particular chronological age is reached. Lloyd-Jones and colleagues evaluated data from the Framingham Study to examine the lifetime burden of CVD by traditional risk factor burden at 50 years of age. Participants were stratified into five mutually exclusive categories, as shown in Fig. 3, and they found that an absence of risk factors at 50 years of age is associated with a very low lifetime risk for CVD (5.2% for men and 8.2% for women). Conversely, those with two or more major risk factors for CVD at 50 years of age had a markedly higher lifetime risk (68.9% for men and 50.2% for women), and for both men and women the adjusted cumulative incidence curves across risk strata separated early from those without risk factors and continued to diverge throughout the lifespan.[49]

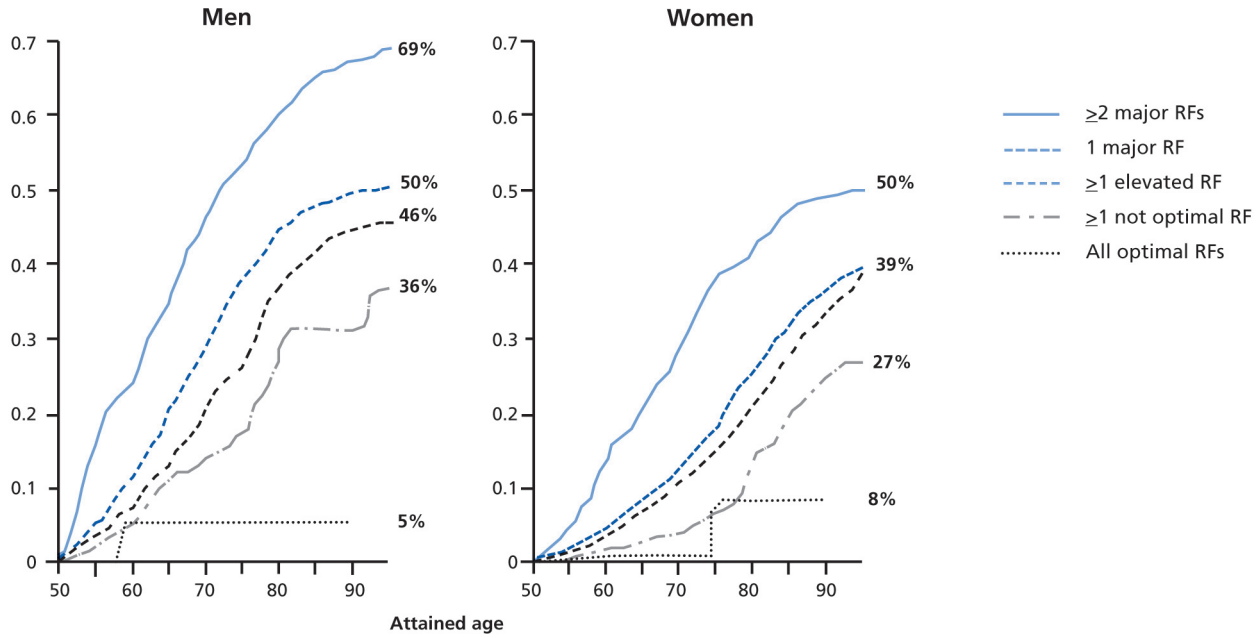
The importance of early risk-factor intervention is reinforced by observational data from patients with a nonsense mutation in the gene PCSK9 (proprotein convertase subtilisin/kexin type 9), resulting in lifelong reductions in LDL cholesterol. It was found that in those with the mutation, a 28% lifetime reduction in mean LDL cholesterol translated into an 88% reduction in the risk of CHD (p = 0.08 for the reduction; HR: 0.11, 95% CI: 0.02–0.81).[50] Moreover, a recent meta-analysis of published data has estimated the effect of long-term exposure to lower LDL cholesterol on the risk of CHD mediated by nine poly-morphisms in six different genes. Mendelian randomisation studies were combined in this meta-analysis and showed that all nine polymorphisms were associated with a highly consistent reduction in the risk of CHD per unit lower LDL cholesterol with no evidence of heterogeneity of effect. A meta-analysis combining non-overlapping data from 312 321 participants revealed that naturally random allocation to long-term exposure to lower LDL cholesterol was associated with a 54.5% reduction in the risk of CHD for each mmol lower LDL cholesterol. This represents a three-fold greater reduction in the risk of CHD per unit lower LDL cholesterol than that observed during treatment with a statin started later in life.[51]

It is clear, therefore, that the use of a 10-year risk metric disenfranchises clinicians to control risk factors in younger patients and treatment interventions are often initiated too late for maximum CVD benefit. For this reason, the third edition of the Joint British Societies guidelines (JBS3) is expected to advocate a move from the current 10-year risk score to a lifetime CVD risk calculator. The lifetime risk calculator will tell patients how likely they are to suffer a cardiovascular event at various points in their lives.

It is likely that this move to assessing lifetime risk will result in intervention to reduce cardiovascular risk at an earlier stage.

When should we intervene to reduce cardiovascular risk?

In recent years, it has become increasingly clear that despite the impressive gains made through the use of 10-year risk calculators,



Optimal risk factors are defined as total cholesterol < 4.65 mmol/l (< 180 mg/dl), blood pressure < 120/< 80 mmHg, non-smoker, and non-diabetic. Not optimal risk factors are defined as total cholesterol of 4.65 to 5.15 mmol/l (180 to 199 mg/dl), systolic blood pressure of 120 to 139 mmHg, diastolic blood pressure of 80 to 89 mmHg, non-smoker, and non-diabetic. Elevated risk factors are defined as total cholesterol of 5.16 to 6.19 mmol/l (200 to 239 mg/dl), systolic blood pressure of 140 to 159 mmHg, diastolic blood pressure of 90 to 99 mmHg, non-smoker, and non-diabetic. Major risk factors are defined as total cholesterol ≥ 6.20 mmol/l (≥ 240 mg/dl), systolic blood pressure > 160 mmHg, diastolic blood pressure > 100 mmHg, smoker, and diabetic.

Figure 3. Remaining lifetime risk for cardiovascular disease in men and women at 50 years of age[49]

this approach may give individuals a false sense of security that they are at low risk for CHD when in fact their lifetime risk is high.[52] Indeed, studies from the USA have shown that around 50% of the population are classified as having a low 10-year risk but a high lifetime risk of CVD.[53,54] Those with a low 10-year but high lifetime risk have greater subclinical disease burden and greater incidence of atherosclerotic plaque progression (measured by techniques such as carotid intima–media thickness) compared with individuals with a low 10-year and low lifetime risk, even at younger ages.[53]

However, despite these advantages there are limitations associated with moving to a lifetime risk metric. In contrast to data from Lloyd-Jones and colleagues (Fig. 3), a pooled analysis of over 900 000 person years showed high (> 30%) lifetime risk estimates for total CVD for all individuals, even those who are middle-aged with optimal risk factors and without diabetes.[55] In addition, a comparison of lifetime risk for individuals with diabetes and stratified by obesity status from the Framingham Heart Study also showed a lifetime risk of CVD among normal-weight men and women with diabetes of 78.6 and 54.8%, respectively, increasing to 86.9 and 78.8% among those who were obese.[56] These data must be considered when attempting to define the level at which a patient is considered to be at a high lifetime risk of CVD, particularly in those with type 2 diabetes, given its increasing prevalence in young adults. There will also be a significant cost impact associated with developing CVD management strategies based on lifetime risk due to both earlier intervention and the potential for a large increase in the number of patients considered at risk.

In patients with type 2 diabetes, chronic hyperglycaemia often precedes diagnosis by several years, causing extensive vascular damage and leading to the early development of clinical complications. Up to 50% of patients have diabetic complications at diagnosis,[57,58] for example nephropathy and retinopathy are present in approximately 20% of patients.[58,59] These facts provide an imperative to intervene at an earlier stage in type 2 diabetes. This is not limited to improving glycaemic control but to address all modifiable cardiovascular risk factors. Data from patients in the Systolic Hypertension in Europe Trial showed that immediate antihypertensive treatment reduced the occurrence of stroke by 28% ($p = 0.01$) and major cardiovascular events by 15% ($p = 0.03$) compared with delayed treatment.[60] The principle here is that it is not simply the degree of elevation of a risk factor that is important but also the duration of time to which the vascular endothelium is exposed to this insult.

Glycaemic control

There is good evidence that tight glycaemic control improves the risk of microvascular complications in the patients with diabetes, but there is no such consensus in relation to macrovascular disease. Three trials, ACCORD (Action to Control Cardiovascular Risk in Diabetes),[61] ADVANCE (Action in Diabetes and Vascular Disease: Preterax® and Diamicron® Modified-Release Controlled Evaluation)[62] and VADT (Veterans Affairs Diabetes Trial)[63] investigated the effects of pursuing a more intensive treatment strategy to an HbA_{1c} level of either < 6.5% (ADVANCE) or < 6% (ACCORD and VADT). None of these trials demonstrated a statistically significant reduction in the primary combined cardiovascular end points. In the ACCORD study, there was a 22% increase in total mortality in the intensive therapy group largely driven by increases in cardiovascular mortality. While there remains the possibility that this increase in mortality may be related to hypoglycaemic events, it has been noted that most of the deaths were among patients with poor glycaemic control who were not reaching target, there has been no consensus reached as to the precise cause.

However, a meta-analysis of five studies and over 30 000 patients included data from all three of these studies and found that a more intensive treatment strategy was associated with a significant reduction of incident cardiovascular events and MI [OR 0.89 (0.83–0.95) and 0.86 (0.78–0.93) respectively]. Similar reductions were not, however, found for either stroke or cardiovascular mortality [OR 0.93 (0.81–1.07) and 0.98 (0.77–1.23) respectively].[64] Longer term macrovascular benefits also became evident in the 10-year follow up of the UKPDS as more events occurred, with reductions in the risk of MI and death from any cause in both the sulfonylurea-insulin [RR 0.85 (0.74–0.97) and 0.87 (0.79–0.96) respectively] and metformin groups [RR 0.67 (0.51–0.89) and 0.73 (0.59–0.89) respectively].[65]

Nevertheless, it is clear that not all patients will benefit from pursuing an aggressive strategy for glycaemic control.[36] Consequently, the European Association for the Study of Diabetes (EASD) and American Diabetes Association (ADA) have recently released a joint position statement emphasising the importance of individualising glycaemic targets in managing patients with diabetes.[36]

Diabetic dyslipidaemia and cardiovascular risk

Managing dyslipidaemia is an important part of a multifactorial treatment approach in patients with diabetes, as it is a significant independent predictor of CHD and mortality.[66] Patients with type 2 diabetes may have a relatively normal total cholesterol level. However these patients may have an atherogenic dyslipidaemia characterised by elevated triglycerides (TG), low HDL cholesterol concentrations and small dense LDL particles.[43,41,67] The formation of small dense LDL is of particular significance in this population as these particles have been shown to be the major determinant of the serum concentration of glycated ApoB.[68] Both small-dense LDL and glycation of LDL are associated with an increase in susceptibility to oxidative modification,[69-71] promoting its rapid uptake by macrophages to create foam cells central to the atherosclerotic process. In addition, patients often show elevated ApoB (reference range 55–140 mg/dl in men and 55–125 mg/dl in women) and non-HDL cholesterol concentrations. The risk associated with atherogenic dyslipidaemia is uncorrelated with, and additive to, that of the LDL cholesterol concentration alone.[67]

Extensive evidence shows that in diabetic patients, elevated TG, low HDL cholesterol and ApoB are predictors for macrovascular complications such as CVD; and this relationship is independent of LDL cholesterol.[67,72-75] Non-fasting TG levels, measured two to four hours post-prandially, may be of even greater relevance to CVD risk since atherogenic lipoprotein remains, secreted by the liver and intestine after food, circulates in higher concentrations than when fasting.[76,77] Although LDL cholesterol levels in persons with diabetes tend not to be higher than those of persons matched for age, gender and body weight, the LDL particles are more numerous as they are smaller and more dense (depleted of cholesterol) than in the general population.[43] As each atherogenic particle such as LDL carries one molecule of ApoB, the ApoB concentration is often increased and has been shown as a better predictor for CHD risk than LDL cholesterol.[67] Non-HDL cholesterol reflects the combined

cardiovascular risk of all changes in ApoB-containing lipoproteins in diabetes, and as such has also been found to be a strong predictor for cardiovascular risk,[78] particularly in patients with diabetes.[79] The measurement and use of non-HDL as a therapeutic goal may therefore be of particular clinical utility in this population.

Dyslipidaemia is also implicated in the pathogenesis of diabetic microvascular disease.[80] Elevated levels of total and LDL cholesterol,[81,82,83] and high TG levels[83] may have causative roles in the development of retinal hard exudates and diabetic maculopathy. High TG levels have also been linked with an increased risk for proliferative diabetic retinopathy.[84] The DCCT/EDIC (Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications) study found the severity of retinopathy was positively associated with TG and negatively associated with HDL cholesterol levels in all patients, and with ApoB and LDL levels in men.[85] Data from the UKPDS showed that elevated TG levels are independently associated with incident microalbuminaemia (HR: 1.13, 95% CI: 1.07–1.19) and macroalbuminaemia (HR: 1.19, 95% CI: 1.11–1.27), both markers of nephropathy.[86] In addition, atherogenic lipid abnormalities have been implicated in the development of diabetic nephropathy.[87,88]

Despite the presence of other lipid abnormalities in atherogenic dyslipidaemia, there is evidence that reductions in LDL cholesterol levels with statins are of benefit in patients with type 2 diabetes. The HPS study investigated the effect on vascular mortality of a substantial LDL reduction among 5 963 patients with diabetes, and found that use of simvastatin was associated with a 22% reduction in the relative risk of vascular events.[89] These results were reflected in the CARDS (Collaborative Atorvastatin Diabetes Study) study, which found a rate reduction of 37% for major cardiovascular events in the atorvastatin group.[90] A meta-analysis of 18 686 patients across 14 statin trials (21.7% of all participants) subsequently confirmed the benefits of statin treatment, with each 1 mmol/l reduction in LDL levels associated with a 9% reduction in all-cause mortality, 13% reduction in vascular mortality, 21% reduction in major vascular events, 22% reduction in MI or coronary death, 25% reduction in coronary revascularisation and 21% reduction in stroke.[91]

It is clear from extensive large-scale clinical trials that statin therapy is of benefit for people with diabetes, and should be considered for all diabetic individuals who are at sufficiently high risk of cardiovascular events[91] yet, despite reductions in event rates, a large residual macrovascular risk remains.[89-91] The reasons behind this excessive residual risk are unknown; however, it is postulated to be either the result of an underestimate of the benefits of long-term LDL-lowering strategy as survival and event curves continue to diverge, or that it is not possible to further reduce risk through LDL lowering and the excess risk is instead a result of other factors such as the high TG and low HDL cholesterol levels seen in the atherogenic dyslipidaemia common in patients with diabetes.

Pharmacological interventions to reduce cardiovascular risk

The investigation of agents as add-on therapies to statin treatment to reduce cardiovascular risk may help to determine the cause of this excess risk, and several clinical trials have investigated, or are investigating, the use of existing agents such as nicotinic acid, as well as ongoing trials of novel molecules to treat dyslipidaemia in high-risk patients.

One of the more significant developments in recent times has been the undermining of the role of HDL as a suitable therapeutic target for cardiovascular risk reduction. While the plasma HDL concentration remains a significant risk predictor and an essential component of patient diagnosis and risk evaluation, the central role HDL plays as a causal mediator in atherogenesis has been called into question.

Large-scale Mendelian randomisation studies of both common and rare genetic variants that alter HDL concentration[92-95] show no relationship with clinical events, in marked contrast to the strong and consistent relationship seen with similar genetic variants affecting LDL concentrations.[54] The strengths and weaknesses of using studies of this type to determine causal mechanisms have been debated,[96] however it is argued that, if genetic variants determining HDL concentrations are not themselves independently associated with clinical outcomes, then HDL concentration in isolation is unlikely to be a direct cause of clinical events. Instead, HDL may be a surrogate marker of other, more fundamentally causal particles.

Recent clinical trials into therapeutic interventions to alter HDL concentration reinforce these findings. The use of nicotinic acid as an add-on to statin therapy was investigated in two large-scale trials, the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial97 and the recently published HPS2-THRIVE (Heart Protection Study 2 – Treatment of High-Density Lipoprotein to Reduce the Incidence of Vascular Events).[89,98] Both of these studies showed that adding nicotinic acid to raise HDL levels had no impact on clinical outcomes. While the AIM-HIGH trial could be criticised for being insufficiently powered to detect clinical events, the results of HPS2-THRIVE are considered more definitive and are likely to bring to an end the use of niacin as a therapeutic agent to reduce cardiovascular risk. On a cautionary note, however, it should be noted that, while AIM-HIGH used an extended-release nicotinic acid preparation (Niaspan), HPS2-THRIVE used a combination of extended-release nicotinic acid with laropiprant, an anti-flushing agent and prostaglandin D-inhibitor. It is assumed that both of these agents are equivalent, yet there remains the possibility that off-target effects of laropiprant confounded the results.

Inhibition of cholesterol ester transfer protein (CETP) has been shown to have the potential to impact on the lipid content and concentration of all lipoprotein factions, notably with significant increases in HDL concentration. However the development of two CETP inhibitors, torcetrapib and dalcetrapib, was terminated following phase III trials showing, respectively, an increase in total mortality rate and a lack of clinical efficacy.99,100 The problem with interpreting these clinical data is that the HDL particle is considered to have several independent functional characteristics such as reverse cholesterol transport and an anti-oxidant effect, and therefore merely measuring the HDL concentration may not be sufficient without more sophisticated functional assays.[101]

Novel molecules in development may provide additional options for this patient group. Two further CETP inhibitors, anacetrapib and evacetrapib, are currently in clinical development, and in addition to their activity to raise HDL levels, also reduce LDL levels over and above statin therapy.[102,103] The ongoing phase III REVEAL (Randomized EValuation of the Effects of Anacetrapib Through Lipid-modification) and ACCELERATE studies will determine whether this class of agents is able to reduce the risk of major coronary events in patients with established vascular disease,[104,105] and in light of recent evidence, it appears unlikely that any additional risk reduction observed will be able to be attributed to their effect on HDL levels.

The insulin-sensitising properties of peroxisome proliferator-activated receptor γ (PPAR-γ) agonists in patients with diabetes are

well established following the development of the thiazolidinediones pioglitazone and rosiglitazone, and the PPAR-α agonists such as fibrates have been shown to decrease TG levels, increase HDL levels and reduce LDL levels.[43,106] Efforts have been made to combine these effects in a dual PPAR-α/γ agonist to effectively manage both glycaemic control and dyslipidaemia. However, several attempts to develop a dual PPAR agonist for diabetes have as yet been unsuccessful due to various safety concerns, including renal dysfunction,[107] bladder cancer,[108] and an increase in mortality and cardiovascular events.[109] The latest dual PPAR-α/γ agonist in development was aleglitazar, which had been shown to decrease TG and LDL levels, and raise HDL levels alongside insulin-sensitising properties.[110] However following an interim routine safety review the phase III ALECARDIO study was terminated due to safety concerns and a lack of efficacy.[111] It is expected that this will spell the end of development of this class of molecules, however a selective PPAR-α modulator (SPPARM-α) known as K-877 remains under development and has been shown to have a more potent effect on triglycerides and HDL cholesterol levels than fibrates with a reduced risk of adverse events. K-877 is currently in the early stage of clinical development, but if successful has the potential to supersede fibrates in the treatment of atherogenic dyslipidaemia.[112]

Conclusions

Despite impressive advances in its treatment, CVD remains a significant healthcare burden in the UK and worldwide. The clustering of cardiovascular risk factors often seen in patients with type 2 diabetes underlines the necessity of our current multifactorial treatment approach, yet even when receiving optimal therapy according to best standards of care, there remains a substantial residual risk of CVD and microvascular disease in this population. The move from 10-year to lifetime cardiovascular risk calculators should encourage intervention to reduce cardiovascular risk at a much earlier stage, and its proposal alongside aggressive and broad control of modifiable risk factors aims to ease the burden of atherosclerosis prior to the manifestations of CVD. This approach will be of particular benefit to patients with type 2 diabetes, who have been exposed to hyperglycaemia and other risk factors for several years prior to diagnosis and consequently have developed complications pre diagnosis. The atherogenic dyslipidaemia common in this patient group also ensures they will benefit most from existing or novel treatment strategies currently under investigation to potentially further reduce residual cardiovascular and microvascular risk.

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The foot attack: where are the defense mechanisms?

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Abstract

There is a need to raise awareness of foot complications and to decrease amputations in people with diabetes. The cost of care for these patients is high once they develop foot complications. With the correct management, up to 80% of amputations are preventable, and decision makers are acknowledging that they can play an important role in the prevention and treatment of foot complications and thereby reduce the amputation rate. Commissioning high-quality foot-care and auditing standards of foot management pathways will be beneficial, as will prompt patient referral to a multidisciplinary foot-care team. Signposting of these services to patients and carers may be the most important factor in preventing a minor foot problem escalating to an amputation.

Keywords: amputation, ulcers, foot, diabetes

Introduction

In 2001 the Diabetes National Service Framework announced 12 standards for the achievement of high-quality diabetes care, consequent to which several documents have been published to assist in the attainment of these standards. The National Diabetes Support Team guide for the care of the diabetic foot considered screening, prevention, care pathways and multidisciplinary care provision to assist in strategic development and implementation to achieve high-quality care.[1] However the challenge remains.

In addition to healthcare systems improving, patient awareness (e.g. regular self/carer inspection of feet) can prevent and reduce the progression of several conditions. Indeed, lack of sensation in the foot can result in unrecognised injury.[2] Neuropathy is a precipitator of foot deformity as well as being the underlying cause of about 60% of foot ulcers. Peripheral vascular disease is a major contributor to 50% of foot ulcers and is associated with reduced healing and increased susceptibility to infection leading to gangrene and amputation.[3] The commissioning of high-quality foot-care and auditing standards of foot management pathways offer significant benefits, as does prompt patient referral to a multidisciplinary foot-care team.[4]

In 2010–11, the NHS in England spent around £650 million on diabetic foot ulcers and amputation; this estimate equates to 0.6–0.7% of its budget.[5] In England > 6 000 major amputations are carried out each year in patients with diabetes and, if the current rate continues, the number of amputations will rise to > 7 000 in 2015/16.[6] People with diabetes are more likely to be admitted to hospital with a foot ulcer than with any other complication of diabetes. If infection and ischaemia are not addressed promptly, this may result in a minor or major amputation. Between 2006 and 2011 there has been a 46% increase in amputations.[7] Amputations and foot ulcers have a huge impact on quality of life and the mortality rate remains high with up to 80% of people dying within five years of having an amputation. This is a higher mortality rate than colon, breast or prostate cancer, compared with which there is relatively little investment in public awareness and screening.

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Foot screening

Feet are examined as part of the diabetes annual review and a foot risk status assigned.[1] The examination should include a check for corns, calluses or changes in the shape of the feet as well as assessment of peripheral nerve function and pulses in the feet plus advice about foot care, including protection with correctly fitted footwear. Unfortunately, 15% of people with diabetes are not getting their annual foot check and there is variation between regions, ranging from 47–87% and 73–90% of people with type 1 and type 2 diabetes respectively[7] (Fig. 1). Diabetes UK has heard from patients who have supposedly received their foot check without being asked to remove their shoes! However the foot check alone is not enough as there is poor correlation between screening and amputation rates.

Raising patient awareness

Diabetes increases the risk of amputation 20–30 fold and amputation rates vary widely from one area to another – in the worst performing area a person with diabetes is 10 times more likely to have a major amputation than in the best.[7,8]

The foot-care pathway appears to be key to facilitating best practice. About 15% of patients with diabetes experience serious foot problems, and foot ulcers lead to about 85% of amputations. The ideal treatment pathway includes a 'foot protection team' and access to a multidisciplinary team within 24 hours of acute presentation with a foot complication. Surprisingly, more than half

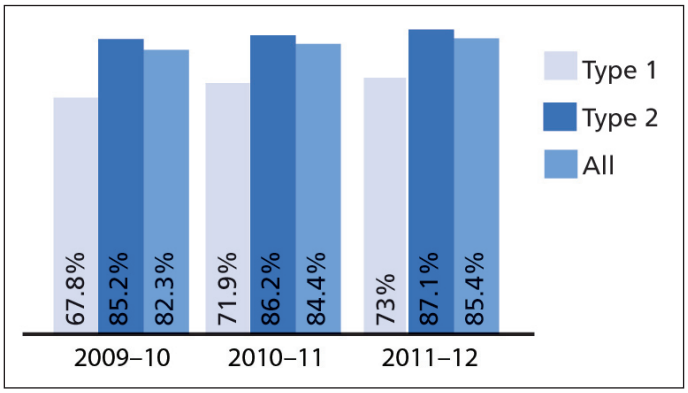

Figure 1. Patients receiving annual foot checks.[7]

of people with diabetes surveyed in 2007 said that they did not realise that diabetes increased the risk of having an amputation.[9] It is hoped that awareness has improved since then, but the key to improved awareness is placing patients with diabetes at the centre of their own care, as set out in the 'Year of Care' programme.[10]

In common with other diabetes-related complications, foot problems are associated with chronic sub-optimal control of modifiable risk factors – blood pressure, cholesterol and glucose levels, and smoking. Good diabetes management and support for self-management, including smoking cessation, is important for the prevention of complications.

Patients should be empowered to look after their feet, told of their risk of developing a complication, understand the implications of their risk status and be aware of the healthcare they should receive. It is crucial that patients realise the importance of urgently seeking medical attention in the event of any problems. A 'Touch the Toes' test guide is available on the Diabetes UK website and there is information about foot care, the leaflet '10 Steps to Healthy Feet' is also available in several languages.

Quality training for staff

There is a need for improved education and training for staff in primary and secondary care to facilitate provision of quality foot checks, risk status assessment, explanation of implications for the patient and appropriate referral pathways. Standards of care should be monitored nationally, and the impact on amputation rates measured. All staff should be encouraged to participate in diabetes audits. In the community there should be trained staff in foot-protection services with speedy (< 24 hours) access to multidisciplinary foot-care teams (MDfTs).

The competency frameworks of these teams are documented in Diabetes UK's 'Putting Feet First' campaign located in the professional resources section of the Diabetes UK website.[11]

Giving patients the tools

The term 'foot attack' is used to describe a foot injury to a foot, or feet, of someone with diabetes who has neuropathy or peripheral vascular disease. Patients need to be aware that there may be no pain, even with a visible wound and that even a small injury or blister may lead to a major complication unless arrested early.

Diabetes UK has produced a booklet called 'How to Spot a Foot Attack' for people who have been identified as being at risk. This booklet, which was sent to every GP surgery in England and Northern Ireland at the beginning of May, informs patients that they should have been referred to a foot protection team or specialist podiatrist, describes how to spot a 'foot attack' and what to do if they are experiencing one. The booklet also includes a card, where the person can write the emergency contact numbers of their GP, MDfT team and podiatry/foot-care services.

The strength of a pathway and a multidisciplinary team is that the patients are triaged rapidly to the right sub-speciality within the right timeframe. All patients with diabetes should know how to access these services if they develop a 'foot attack' and be encouraged to be insistent if their referral or treatment is delayed as a 'foot attack' can progress rapidly.[12]

Equality in access

In England and Wales the National Diabetes Audit measures the effectiveness of diabetes healthcare against the National Institute for Health and Care Excellence (NICE) clinical guidelines and NICE quality standards. This summer the National Foot-Care Audit will commence an audit of specialist foot-care services in England and Wales, aiming to highlight areas of good practice as well as areas which have not developed all elements of a high quality foot-care pathway. This will provide benchmarking data to assist clinical commissioning groups (CCGs) to commission excellent diabetic foot-care services.

The Vascular Society of Great Britain and Ireland published a Quality Improvement Framework for Major Amputation Surgery recommending that patients should be managed pre-, peri- and post-operatively by a multidisciplinary vascular team with current amputation experience.[13] The National Confidential Enquiry into Patient Outcomes and Deaths is due to publish its lower limb amputation study in Autumn 2014. This should inform on pre-, peri- and post-operative care as well as organisational factors.[14] The Circulation Foundation has also raised awareness of the 'foot attack' with the 'Save Lives and Limbs' campaign as well as lobbying the All-Party Parliamentary Vascular Group (APPVG). The APPVG has recently published recommendations which should improve patient outcomes (Table1).[15] Additionally, Strategic Clinical Networks have been tasked with raising awareness of and reducing major amputations by 2015.

Table 1. The-All Party Parliamentary Vascular Group recommendations to improve patient outcomes

1. Services should be commissioned on outcomes: an amputation should be considered a failure; a functioning foot with minimal surgery, a success.
2. Telemedicine should link services so that appropriate care can be delivered locally with established pathway co-ordinators in hub centres and integrated clear pathways for the diabetic foot. There should be a named contact person in a hospital/community 24 hours a day who is a member of the MDfT in case of emergencies.
3. All commissioners should have a sub-24-hour policy to refer patients with suspected critical limb ischaemia (CLI) to a MDfT. Time is of the essence with this condition, and every hour treatment is delayed increases the risk of amputation.
4. All commissioners and providers should have a clear pathway for suspected peripheral arterial disease and the diabetic foot. This pathway must be made standard practice, and the route that patients with CLI are referred to a hospital should be rapid, clear, and properly understood by all healthcare workers, from primary to specialist care. There should be a policy for referral to a multidisciplinary team with clear links to secondary care.
5. The Quality Outcomes Framework needs to be improved so that all 'high-risk' patients are referred for preventative podiatry and structured education.
6. A patient pathway must be established as standard practice for all providers and commissioners.
7. Commissioning structures need to balance centralisation of care for complex high-risk vascular procedures with the need to maintain equity of patient access for peripheral arterial disease. This recognises that many diabetic foot complications occur in well-perfused feet and do not need vascular intervention. Diabetic foot services therefore need to be aligned to the centralisation of vascular services but may not correlate completely.
8. Education for patients at risk should be made more widespread in the community. Guidance and support on smoking cessation and exercise, in particular for patients with diabetes, is one of the key areas that need attention.

Key messages

Diabetes patients should be:

- made aware of their foot risk and signposted to the foot-protection team.
- empowered to optimise self-care of the feet
- referred rapidly to a MDfT in the event of a 'foot attack'

Early intervention reduces complications and amputations.

Conclusion

An integrated structured foot-care service between primary and specialist care is essential in reducing the risk of both minor and major amputations. Commissioners should be aware of the commissioned service within their area and aspects to be improved to reduce the cost of care for these high-risk patients.

The current rate of major amputation is too high. It is vital that healthcare professionals understand the importance of performing good-quality annual foot checks, providing patients with the tools they need to understand their risk of a 'foot attack' and, if necessary, enable patients to access specialist help as quickly as possible.

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Bariatric surgery has better outcomes after 15 years

Bariatric surgery comes out ahead with greater weight loss, more incidents of diabetes remission and fewer cardiovascular disease (CVD) complications than standard medical care. Fifteen years after undergoing bariatric surgery, 30% of patients no longer had diabetes, but only 7% of patients who received usual care were in diabetes remission.

These long-term findings from the Swedish Obese Subjects (SOS) prospective, matched-cohort study by Dr Lars Sjöström from Sahlgrenska University Hospital in Gothenburg, Sweden, and colleagues (*J Am Med Assoc* 2014; **311**: 2297–2304, 2277–2278) were published to coincide with the American Diabetes Association conference in San Francisco.

The study also shows that 'obese diabetics whose diabetes was of shorter duration or who had the greatest weight loss between the time of surgery and two years later were the most likely to have a sustained remission at 15 years. These patients likely had bariatric surgery before the failure of the insulin-producing cells of the pancreas was irreversible'.

The SOS study enrolled 4 047 obese patients in Sweden between 1987 and 2001. The current analysis looked at those who had diabetes at baseline, 260 patients, who then received usual medical care, and 343 patients who underwent bariatric surgery – vertical banded gastroplasty (227 patients), non-adjustable or adjustable banding (61 patients) or Roux-en-Y gastric bypass (55 patients).

The patients had a mean age of about 50 years, a mean body mass index (BMI) of about 41 kg/m^2 and about 60% were women. They had had diabetes for approximately three years.

The researchers tracked microvascular complications of the kidney, eyes and peripheral nerves, and macrovascular complications – coronary heart disease, heart failure, stroke and peripheral arterial disease – after a median of about 17 years. Diabetes remission was defined as having a blood glucose level below 110 mg/dl (6.11 mmol/l) and not taking antidiabetic medication.

Bariatric surgery was associated with higher diabetes remission rates and weight loss compared with usual care, although these rates declined over time in both groups. Bariatric surgery was also associated with a significantly decreased risk for microvascular and macrovascular complications (hazard ratios: 0.43 and 0.74, respectively).

Additional follow up of newer studies is required to answer the question of which bariatric procedure is best for inducing long-term remission of diabetes, but those data will not be available for another five to 10 years.

Source

http://www.diabetesincontrol.com/articles/diabetes-news/16456-bariatric-surgery-has-better-outcomes-after-15-years

Anxiety associated with self-monitoring of capillary blood glucose

AMY SHLOMOWITZ, MICHAEL D FEHER

Abstract

Aims: **The aims were to evaluate (1) prevalence and contributing factors of anxiety to the finger-prick method used to self-monitor glucose; (2) whether individuals report avoidance of self-monitoring due to fear of the finger-prick method; and (3) levels of general anxiety.**

Methods: **Individuals attending a specialist diabetes out-patient centre, and who self-monitored their capillary blood glucose concentrations, were invited to complete a standardised questionnaire to assess anxiety associated with the finger-prick method of blood glucose measurement, and general day-to-day anxiety.**

Results: **From 315 (58% male) individuals with diabetes, finger-prick anxiety was observed in 30% and general anxiety in 33%. Positive correlations were found for finger-prick anxiety with avoidance of testing and with general anxiety. Older individuals had less general anxiety and females reported greater anxiety to the finger-prick method and general anxiety. There were ethnic differences in anxiety to the finger-prick method and avoidance of testing, but not to general anxiety.**

Conclusions: **One-third of a general diabetes out-patient cohort had general anxiety and anxiety to the finger-prick method for glucose testing. There are important implications for both patients and healthcare professionals in identifying barriers to achieving improved diabetes control.**

Keywords: finger-prick anxiety, anxiety, diabetes, glucose testing, lancet

Introduction

Self-monitoring of blood glucose is routine practice for many individuals with diabetes. This requires a drop of capillary blood to be obtained by pricking the tip of a finger with a modified lancet.[1] To date there is limited evidence evaluating anxiety to the finger-prick method, in contrast to several studies assessing anxiety and phobia to self-injection with needles used for subcutaneous insulin.[2] This is set in a background for a diabetes group, where simple phobias and general anxiety are twice as common compared to the general population.[3] Anxiety has also been linked to worse glycaemic control.[4]

The aims of the current study were to evaluate in a diabetes cohort (1) the prevalence and contributing factors of anxiety to the finger-prick method used to monitor blood glucose concentrations; (2) whether individuals avoid self-monitoring due to fear of the finger-prick method; and (3) levels of general anxiety.

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Patients and methods

The study design was a cross-sectional questionnaire survey. Recruitment over a four-month period included individuals with either type 1 or type 2 diabetes who attended for routine out-patient follow up at the specialist Beta Cell Diabetes Centre of the Chelsea and Westminster Hospital Foundation Trust, London. Unselected patients who consented completed a written questionnaire , which assessed demographic and treatment details, aspects of anxiety to the finger-prick method to measure glucose levels, and levels of general anxiety.

General anxiety was measured using the well-known Anxiety subscale of the Hospital Anxiety and Depression Scale (HADS).[2] Anxiety to the finger-prick method, defined as finger-prick anxiety (FPA), was assessed using the previously published injection anxiety measure[2] with the questions being tailored to focus on the finger-prick method rather than the needle injection used to administer insulin (Appendix 1 available online at www.bjdvd.com). Components tested were attitudes to self-monitoring of blood glucose and subjective current physical and psychological responses prior to and at the time of testing. Participants were given a score according to responses (score categories: unconcerned = 0, concerned = 1, mild/moderate and fear = 3) when they actually tested their blood glucose. An affirmative answer to the question about physical symptoms prior to monitoring, received one point for each symptom with a maximum possible score of four points. The other four questions scored one point for an affirmative answer. For the whole test, the minimum total score obtainable was 0 with a maximum total score of 14. A total score of ≥ 3 was used to classify those as having at least some anxiety to the finger-prick method.[2] An additional assessment was made to gain further details on reasons why an individual might avoid the finger-prick method of glucose monitoring. The questions asked were: 'do you test less than recommended or not test at all due to dislike/fear of needles or other reasons?' Participants could answer 'yes', 'no', or state other reasons.

To explore general psychological factors further, general anxiety was assessed by the anxiety subscale of the hospital anxiety and depression score (HADS)5 (Appendix 2 available online at www.bjdvd.com). A general anxiety score (GAS) of > 8 (the minimum score being 0 and maximum 21) was used as the threshold to identify anxiety according to previous published studies.[6]

The study evaluated responses of those undertaking the finger-

Figure 1. Examples of lancing devices for finger-prick blood glucose testing.

prick method and did not assess which specific device was used. Most modern glucometers have the manufacturer's own finger-prick device where the lancet is inserted into a delivery barrel where the needle is covered (see Fig. 1). While the authors acknowledge that the pressure of release and the depth of the needle may influence responses, this was not assessed. Additionally, details of glycaemic control and any relationship with anxiety scores were not evaluated in this study.

Statistical methods used were Kendall's tau_b for rank correlations to investigate associations between anxiety to the finger prick, with continuous variables such as general anxiety, age, disease duration, type of treatment, amount of testing, and avoidance of testing. A chi-square test was carried out to evaluate whether FPA and general anxiety differed across categorical variables of gender and ethnic groups.

Ethical approval was obtained from Riverside Research Ethics Committee.

Results

From 350 outpatients invited to participate in the study, 315 completed the questionnaire (response rate of 90%). The study group, with 58% male subjects, had a mean age of 47 (range 19–86) years. Ethnic groups comprised Caucasian (74%), Asian or Asian British (11%), black or black British (7%), mixed (5%), othernot specified (3%). Treatments used were either insulin alone or in combination with oral glucose-lowering agents (54%), oral glucose-lowering agents alone (40%), or with diet alone (6%).

Self-reported glucose monitoring

From the study sample, 93% reported that they performed routine self blood glucose monitoring, with 50% testing at least twice per day, 23% testing once per day, 20% testing at least twice per week, and only 7% testing once per week or less.

Finger-prick anxiety

FPA (Table 1) was observed in 30% of patients; more women (38%) than men (24%) reported FPA (x^2 (1) = 6.352, p < 0.01); the black group had a significantly higher proportion of FPA compared to other ethnic groups (x^2 (4) = 17.680, $p < 0.01$). There was no significant effect of age.

General anxiety

General anxiety (Table 1) was observed in 33% of the group; anxiety was highest in the mixed ethnic group (43%) and women (46%); and in the 31- to 40-year age group. In the older age group (71+) there was less general anxiety (14%).

Significant negative correlations were found between age and general anxiety (Kendall's tau_b –0.119, $n = 292$, $p <$ with younger adults reporting increased general anxiety, and general anxiety was more prevalent in women (x^2 (1) = 13.041, $p < 0.01$). There were no differences between the different ethnic groups.

Avoidance by patients of finger-prick blood glucose testing

Avoidance of testing was significantly correlated with FPA (Kendall's tau_b 0.179, n = 311, p < 0.001) as well as FPA with general anxiety (Kendall's tau_b 0.225, $n = 299$, $p < 0.001$), demonstrating that those who avoided self-monitoring had higher levels of FPA and higher levels of general anxiety.

In response to the additional specific question of avoidance of monitoring due to FPA, 13.7% of the total group and 19% of those who did not routinely monitor their blood glucose answered yes. Avoidance was higher in the non-defined ('other') ethnic group (Table 2) and was statistically significant (x^2 (8) = 27.104, $p <$ 0.001); however, age and gender were not.

Several reasons for avoidance of glucose testing were given (Table 3). While only one in five of this total group had specific anxiety to the finger-prick method, other reasons for reduced

Table 1. Prevalence of anxiety to the finger-prick method of blood glucose testing (finger-prick anxiety) and general anxiety according to gender, ethnicity, and age in individuals with diabetes ($n = 315$).

	Whole group	Gender	Ethnicity	Age groups (years)
Finger-prick anxiety (defined as an FPA score >3)	95 (30%)	Women 51 (38%) Men 44 (24%)	Black 14 (62%) Other 5 (50%) Asian 14 (42%) Mixed 5 (36%) Caucasian 57 (25%)	18–30 9 (26%) 31–40 13 (26%) 41–50 16 (29%) 51–60 23 (36%) 61–70 22 (34%) 71+ 12 (24%)
General anxiety (defined as a GAS score > 8)	104 (33%)	Women 56 (46%) Men 44 (25%)	Mixed 6 (43%) Asian 12 (40%) Caucasian 77 (34%) Black 6 (33%) Other 3 (30%)	18–30 9 (29%) 31–40 22 (43%) 41–50 19 (38%) 51–60 23 (37%) 61–70 24 (39%) 71+ 7 (14%)

Table 2. Prevalence of avoidance of testing and ethnicity (n = 313)

Ethnicity	No avoidance	Avoidance (fear)	Avoidance (other)	Total
Caucasian	63.9% (149)	9.4% (22)	26.6% (62)	(233)
Asian/Asian British	73.5% (25)	17.6% (6)	8.8% (3)	(34)
Mixed	66.6% (10)	26.6% (4)	6.6% (1)	(15)
Black/black British	52.3% (11)	28.5% (6)	19.0% (4)	(21)
Other ethnic group	40.0% (4)	50.0% (5)	10.0% (1)	(10)
Not specified			0.01% (2)	

testing (Table 3), unrelated to anxiety to the finger prick, were reported in 22.5% and included: (Table 3) 'don't like it', 'forgetting', 'time pressure', 'pain', 'no need as readings stable','broken meter', 'laziness', 'fearful of glucose result', 'only test when unwell', 'not necessary to test', 'boring to test', 'self conscious of testing in public', and 'scared of infection'.

Discussion

This is one of the first studies specifically to assess anxiety to the finger-prick method of blood glucose testing. The results show that a third of diabetes out-patients report at least some anxiety to the finger-prick method of glucose testing in addition to increased levels of general anxiety. There is limited evidence about this important aspect of patient self-management. Other studies have shown indirect evidence of levels of anxiety. In a Dutch study, fear of monitoring glucose was characterised by emotional distress and avoidance behaviour in a group of insulin-treated individuals.[7] A small group (less than 10%) who scored highly in the Diabetes Fear of Injecting and Self-testing questionnaire were invited to participate in a behavioural avoidance test and nearly a quarter refused to perform an additional self blood glucose test.[7]

This study is consistent with previous studies on injection-related phobia, which is also more common in women than men.[8]

Differences were also found in general anxiety levels between gender and age groups. Older adults reported less general anxiety, with a possible explanation that they may have developed effective coping strategies over time or have fewer stressors (for example, workplace related) in their retirement. In addition, women reported higher levels of general anxiety, as has been highlighted in previous research.[9] It has been argued that, despite the HADS having a sensitivity of 80–100% for identifying high anxiety levels, it is not diagnostic of general anxiety. It has been suggested that the proportion of cases, for example, on the HADS having a DSM-1V-R diagnosis of general anxiety is poor.[10] One of the purposes of the present study was to identify possible cases of general anxiety rather than diagnose generalised anxiety disorder, and the results concur with previous reports.

The strong association found for FPA with general anxiety corroborates previous findings with subcutaneous injection,[2] and supports the notion that high levels of injection anxiety are associated with high levels of general anxiety and suggests that methods to decrease general anxiety may have a positive effect on reducing injection anxiety and needle phobia.

Despite the high proportion of FPA, the study found a large proportion of participants claiming to monitor their blood glucose. Of those reporting a reduced frequency of testing, a considerable proportion reported pain as the reason and this is consistent with previous research with avoidance of insulin injections.[11] A USA-based study found that 6% (of 1 895 participants), reported fear of needles as a reason for reduced testing, and of the participants not monitoring their blood glucose, 14% reported a fear of needles.[12] In the present study (Table 3), 32% of the total group avoided glucose testing due to either dislike (with no reason stated) or injection pain, while 26% forgot or cited 'laziness'. One in eight subjects considered ' time pressure' as the reason for avoidance, while 5% were scared of the result or infection and a further 5% had technical issues or no testing strips. This highlights two distinct potential management strategies: a practical/educational strategy and psychological intervention strategies, such as cognitive behavioural therapy. In our view psychological intervention would be best to manage the reasons reported including specific 'anxiety'/'dislike'/'scared responses' while 'forgetfulness', 'time pressures', 'broken meters' could potentially be remedied by education and appropriate practice support targeting these issues.

Possible limitations of the study were that the assessment of FPA was undertaken using a self-reported method derived from injection-anxiety assessment and self-reported rather than observed behavioural characteristics. Some psychological symptoms are similar to physical responses to a low glucose level and may be confounders when assessing feelings to undertaking the finger prick. The type of device used may also be a determinant of the response. Despite using questions from established psychological assessments, further work is required to refine and validate the scoring system of injection anxiety with regard to all groups within diabetes.

The present study, by assessing FPA and general anxiety, places in context the recent findings that psychological reasons for not monitoring blood glucose are not always addressed in diabetes clinics.[11]

Conclusions

The high levels of FPA and general anxiety observed in the current study highlight that professionals should be sensitive to the

Table 3. Reasons for avoidance of self glucose testing with the finger-prick method

Finger-prick anxiety specifically to the finger-prick method	**13.7% prevalence in total group (n = 315)**
Reasons other than finger-prick anxiety	**Number in subgroup (n = 71) who had reasons other than anxiety to finger-prick method**
Don't like (or no reason)	17 (23.9%)
Forgetting	15 (21.1%)
Time pressures	9 (12.6%)
Injection pain/soreness	6 (8.4%)
Readings stable	6 (8.4%)
Broken meter or no strips	4 (5.6%)
Laziness	4 (5.6%)
Scared of result	3 (4.2%)
Test only when unwell	2 (2.8%)
Not necessary to test	2 (2.8%)
Boring	1 (1.4%)
Scared of infection	1 (1.4%)
Self-conscious in public testing	1 (1.4%)

Key messages

- A third of diabetes out-patients report some anxiety to the finger-prick method of glucose testing and also general anxiety.
- Females report greater anxiety to the finger-prick method as well as general anxiety and older individuals have less general anxiety.
- This highlights two separate management strategies such as practical/educational and psychological intervention strategies, for example cognitive behavioural therapy.

psychological factors relating to self blood glucose monitoring with the finger-prick method. In those who cited forgetfulness, laziness or time pressure and technical issues, further diabetes education strategies could have a defined focus.

Increased awareness of the problem plus more specific assessment tools should identify those who might benefit from psychological treatments including cognitive behavioural therapy techniques. In extreme cases identification and referral for specialist psychological input may be warranted. These strategies may improve the glycaemic control, and general wellbeing of those individuals.

Conflict of interest None
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Losing weight at any age can improve cardiovascular health

Weight loss at any age in adulthood is worthwhile because it could yield long-term heart and vascular benefits. The results are from a study ongoing from 1946, examining the impact of lifelong patterns of weight change on cardiovascular risk factors in a group of British men and women followed since birth.

They showed that the longer the exposure to excess body fat (adiposity) in adulthood, the greater the cardiovascular-related problems in later life, including increased thickness of the carotid artery walls, raised systolic blood pressure, and increased risk of diabetes. The findings were published online on 21 May 2014 in the *Lancet Diabetes & Endocrinology*.

For the first time, the findings also indicate that adults who drop a body mass index (BMI) category, from obese to overweight, or from overweight to normal at any time during adult life, even if they regain weight, can reduce these cardiovascular manifestations.

The study used data from 1 273 men and women from the UK Medical Research Council National Survey of Health and Development (NSHD). Participants were classified as normal weight, overweight or obese in childhood and at 36, 43, 53 and 60–64 years of age. Cardiovascular phenotyping between the ages of 60 and 64 years with carotid intima–media thickness (cIMT; a surrogate marker for cardiovascular events) was used to assess the effect of lifetime exposure to adiposity on cardiovascular risk factors.

Prof John Deanfield, lead author, from University College London (UCL) said, 'Our study is unique because it followed individuals for such a long time, more than 60 years, and allowed us to assess the effect of modest, real-life changes in adiposity. Our findings suggest that losing weight at any age can result in long-term cardiovascular health benefits, and support public health strategies and lifestyle modifications that help individuals who are overweight or obese to lose weight at all ages.'

Elizabeth Cespedes and Frank Hu from the Harvard School of Public Health, Boston, USA, commented on the study. 'Although it is encouraging that even transitory weight loss during adulthood has cardiovascular benefits, only 2% of participants in the present study had a sustained reduction in BMI category in adulthood, underscoring the importance of weight maintenance and prevention of weight gain as priorities for public health programming and policy. Improvements in diet and increases in physical activity are crucial levers of long-term weight maintenance and prevention of weight gain in middle-age and early adulthood.

Overweight individuals might have even greater health benefit from lifestyle changes such as increased physical activity than do normal-weight individuals. The results of this study affirm a continued emphasis on public health policies that enable lifestyle changes to achieve and, especially, to maintain a healthy BMI.'

They add, 'Ideally, future research will address long-term patterns of intentional versus unintentional weight loss, the means to achieve weight loss and the weight loss maintenance necessary to reduce cardiovascular endpoints.'

Source

http://www.diabetesincontrol.com/articles/53-/16395-losing-weight-at-any-age-can-improve-cardiovascular-health.

The use of liraglutide, a GLP-1 agonist, in obese people with type 1 diabetes

SYED MR GILLANI, BALDEV M SINGH

Abstract

Aim: **Optimisation of glycaemic control in type 1 diabetes often results in unwanted weight gain. Glucagon-like peptide-1 (GLP-1) agonist use is associated with weight reduction in type 2 diabetes but its use in type 1 diabetes is little studied.**
Methods: **We developed a protocol for GLP-1 use in people with type 1 diabetes and obesity in which liraglutide was initiated and up-titrated while insulin doses were simultaneously titrated according to glycaemic parameters.**
Results: **Of 15 patients offered treatment, eight proceeded. Baseline parameters were (*n* = 8, mean ± SD): (age 50 ± 6 years, BMI 40.4 ± 5.5 kg/m², weight 123.0 ± 23.9 kg, HbA_{1c} 8.5 ± 1.7%, total daily insulin dose 131 ± 112 units/day. By intention to treat analysis (*n* = 8, 12 months), at three, six and 12 months compared to baseline, weight loss was 6.8 ± 4.1 kg, 10.0 ± 5.6 kg and 8.9 ± 8.4 kg, respectively (*p* = 0.026). The reductions in insulin dosage were significant over six months (*n* = 8, *p* = 0.045) or when analysing only those who completed 12 months of liraglutide therapy (*n* = 6, *p* = 0.044).**
Conclusions: **GLP-1 agonist use in patients with type 1 diabetes may be advantageous where weight reduction becomes both a constraint and a therapeutic objective.**

Keywords: GLP-1, insulin, liraglutide, obese, type 1 diabetes, weight

Introduction

The management of type 1 diabetes is complex with multiple challenges. Optimisation of glycaemic control plays a key role in the prevention of both macro- and microvascular complications[1] but often results in unwanted weight gain[2] and adverse clinical outcomes.[3] Even small reductions in weight significantly improve outcomes of obesity-related chronic diseases.[4] Currently lifestyle modifications are the mainstay of treatment of obesity in type 1 diabetes. While pharmacotherapy can augment the effect of life style modifications,[5] its role is limited such that bariatric surgery is often the only effective treatment for morbid obesity.[6] One of its subsidiary mechanisms may be increased production of glucagon like peptide-1 (GLP-1)[7] since GLP-1 regulates appetite and satiety. That may be one reason, among many, why GLP-1 agonist use is associated with significant weight reduction in type 2 diabetes[8] and the non-diabetic obese population.[9,10] GLP-1 agonist use in type 1 diabetes is little studied either for the modification of glycaemic control or for weight. Preliminary evidence suggests liraglutide use in type 1 diabetes benefits glycaemic control, glucose variability, reduced dosage of insulin and body weight.[11-13] Based on this, we have developed and audited a local protocol for the use of liraglutide in obese patients with type 1 diabetes.

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Methods

We developed a protocol for GLP-1 use in people with type 1 diabetes, obesity [body mass index (BMI) > 35 kg/m²], progressive weight gain with or without constraint to insulin titration for better glycaemic control. The diagnosis of type 1 diabetes was according to standard clinical and biochemical parameters (acute onset, ketosis at presentation, insulin therapy from diagnosis and mandatory ongoing insulin need, C-peptide levels). Acceptance of patients onto the protocol required dual consultant–specialist approval. After providing them with relevant information at consultation and in writing using a standardised information sheet, informed written agreement was obtained from all patients about the dual unlicensed use of liraglutide in type 1 diabetes and for the management of obesity. Liraglutide was initiated and up-titrated from 0.6 to 1.8 mg over a four- to six-week period, while insulin doses were titrated according to glycaemic parameters. Patients had open access to support and follow up, and were minimally reviewed monthly. The key objectives were safe glycaemic control, weight loss of > 5% at six months and GLP-1 agonist tolerability.

Patients were reviewed for withdrawal at three months and withdrawn at six months if these were not attained. This protocol was agreed with local clinical governance committees, but since this was a service development and the presented data are an audit of the protocol, formal ethical committee approval was deemed not to be required. Statistical analysis was in SPSS version 21.

The non-parametric Freidman test for repeated, related measures was applied to test differences in parameters over time with $p < 0.05$ taken as significant. Data are presented as the mean ± SD with the range.

Results

Over one year, of 15 patients offered treatment, seven declined and eight proceeded (age 50 ± 6 years, four females). One patient with BMI 30 kg/m² was included due to rapid weight rise during insulin intensification, such that the patient did not want to proceed without co-management of weight gain.

Summary results are presented in Table 1 and individual outcomes are shown in Fig. 1.

The baseline parameters were: BMI 40.4 ± 5.5 kg/m², (range 30–47.7 kg/m²), weight 123.1 ± 23.9 kg (70.9–153.2 kg), glycated haemoglobin (HbA_{1c}) 8.5 ± 1.7% (7.1–12.5%), total daily insulin dose 131 ± 112 units/day (30–352 units/day), creatinine 76 ± 21 µmol/l

Table 1. Mean ± SD (range) of outcomes of HbA_{1c}, weight and insulin dosage over time in patients with type 1 diabetes treated with GLP-1 agonist therapy; p-values are for the Friedman test for repeated measures over time. Significance is set at 0.05.

					p-value		
					6 months	12 months	
	Baseline	3 months	6 months	12 months	*n* = 8	*n* = 8	*n* = 6
HbA_{1c} (%)	8.5 ± 1.7 (7.1–12.5)	8.4 ± 1.3 (7.0–11.2)	8.0 ± 0.9 (6.7–8.7)	8.3 ± 1.6 (6.5–12.0)	0.497	0.771	0.409
Weight (kg)	123.0 ± 23.9 (70.9–153.2)	116.2 ± 24.5 (66.2–154.8)	113.0 ± 25.9 (62.0–155.0)	114.1 ± 26.4 (63.8–160.0)	0.021	0.026	0.003
Insulin dose (units/day)	131 ± 112 (30–352)	79 ± 49 (30–166)	81 ± 49 (38–168)	89 ± 78 (28–270)	0.045	0.107	0.044
Insulin dose (units/kg/day)	1.0 ± 0.9 (0.4–2.9)	0.7 ± 0.4 (0.4–1.5)	0.7 ± 0.4 (0.4–1.6)	0.8 ± 0.6 (0.4–2.3)	0.044	0.136	0.158

(53–110), albumin:creatinine ratio (ACR) 1.5 ± 2.4 mg/mmol (0.3–7.5), cholesterol 4.4 ± 0.8 mmol/l (3.2–5.5), C-peptide was negative {< 94 pmol/l [analysed by the Mercodia C-peptide enzyme-linked immunosorbent assay (ELISA) assay]} in six patients and low in two (281, 131 pmol/l), retinopathy status (none = 1, background = 2, pre-proliferative and above = 5), foot risk (low risk = 5, intermediate risk = 3) and only one patient had macrovascular complications.

On an intention-to-treat basis at three, six and 12 months, weight loss was 6.8 ± 4.1 kg, 10.0 ± 5.6 kg and 9.0 ± 8.5 kg (range –21 to +6.8 kg) (p = 0.026). Percentage weight loss at year end was 8 ± 6% (range +4 to –16%). Daily insulin dose fell by 52 ± 69 units, 50 ± 69 units and 43 ± 60 units (median 16, range –168 to +6 units) (p = 0.107, ns). Insulin dosage in units/kg was 1.0 ± 0.9, 0.7 ± 0.4, 0.7 ± 0.4 and 0.7 ± 0.6 (p = 0.136, ns). HbA_{1c} changes were not significant (p = 0.962, ns).

Two patients were unable to tolerate liraglutide and withdrew at six months. They are indicated in Fig. 1. In one there was no response in any parameter (HbA_{1c}, weight or insulin dose), also mandating withdrawal. In the other, weight and insulin dosage rose following cessation of GLP-1 therapy. Excluding these two cases (n = 6), insulin dose reduction over one year was significant (p = 0.044) at 12 months (–44 ± 66 units per day) but with no significant difference when assessed by units/kg (p = 0.158, ns). Percentage weight loss at year end was 11 ± 3% (range –7 to –16%, p = 0.003).

Alternatively, analysis to the six-month time point (n = 8) showed significant falls in weight (p = 0.021) and a significant reduction in insulin either by total daily dose (p = 0.045) or in daily units/kg (p = 0.044) while HbA_{1c} remained static.

There were no significant hypoglycaemic events nor any episodes of acute metabolic destabilisation.

Discussion

Under this tightly observed protocol, in motivated patients with type 1 diabetes, under close clinical supervision (and by whatever mechanisms of action[14-17]), significant weight reduction occurred without metabolic destabilisation. Clinically and statistically significant reductions in insulin dosages were achieved, which appeared to be a consequence of the weight loss possibly indicative of an improvement in insulin resistance as determined by the crude

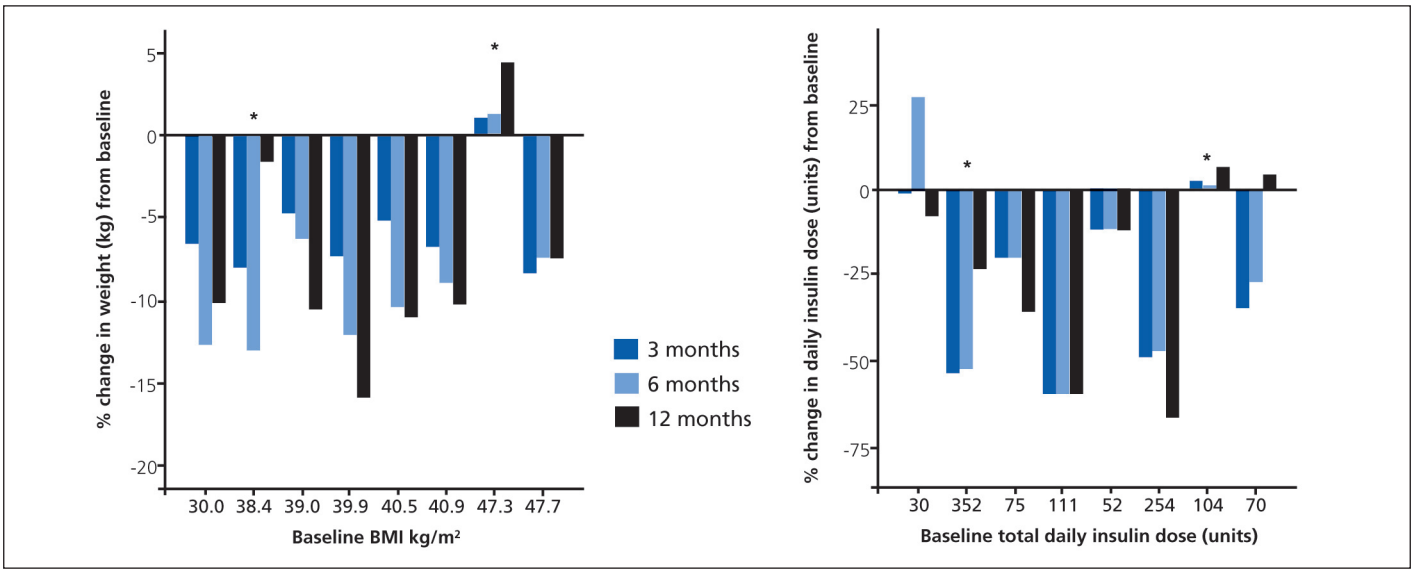

Figure 1. Percentage changes in weight (left panel) and total daily insulin dosage (right panel) over three, six and 12 months compared to baseline in individual cases. Relevant individual baseline parameters are shown on the abscissa and are in ascending BMI order. Cases that withdrew at six months are denoted by an asterisk.

Key messages

In patients with type 1 diabetes and co-existent obesity, GLP-1 agonists

- are currently unlicensed
- can potentially reduce body weight and reduce insulin requirements
- treatment requires close monitoring

measure of the changes in units/kg. Perhaps disappointingly, attainment of glycaemia, did not improve. This at least allowed the true potential for weight loss to emerge independent of changes that might have resulted from sharp improvements or deteriorations in glycaemic control. The magnitude of weight loss in this group appeared to exceed that expected in type 2 diabetes,[18] possibly because of the interplay of GLP-1 effects together with the reduced pro-obesity effect of falling insulin dosage. It is possible that weight loss might not have been so good if we had simultaneously achieved a significant HbA_{1c} reduction, and it is known that intensification of insulin therapy to attain good control is associated with weight gain.[2] Interestingly, we observed a similar amplification effect when adding GLP-1 agonist therapy to those already on insulin therapy in type 2 diabetes.[19]

The individual variation of responses was of clinical importance. One patient had poor tolerability. Otherwise it can be seen that an effective response was clearly evident very early in the use of GLP-1 agonist therapy and, equally, non-responsiveness in a single patient was similarly obvious by three months.

Ethical issues around unlicensed uses of liraglutide in type 1 diabetes must focus on safety. Our preliminary experience is reassuring, but it is small scale and provides no more than a cautious 'proof of concept' among the few other small-scale trials that have been published.[11-13, 20,21] There are no currently available data to suggest harm over and above the standard cautions and side effects understood and observed in mainstream clinical practice. Large, prospectively randomised studies have started to explore the role of liraglutide as additional treatment in type 1 diabetes.[22,23] Until they report, we would urge colleagues not to embark on this therapy without due regard to all local clinical governance processes, tight systems of clinical supervision, clear mechanism for independent peer review and a fully informed and consented patients, who have appropriate (and assessed and documented) levels of self-care proficiency.

We conclude that, under the appropriate conditions, and with appropriate patient selection, GLP-1 agonist therapy in type 1 diabetes may be advantageous where weight reduction becomes both a constraint and a therapeutic objective.

Conflict of interest None
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Obstructive sleep apnoea in diabetes: assessment and awareness

IAN W SEETHO, SARAH V O'BRIEN, KEVIN J HARDY, JOHN PH WILDING

Abstract

In 2008, the International Diabetes Federation (IDF) task force on epidemiology and prevention released a consensus statement recommending targeted screening for obstructive sleep apnoea (OSA) in people with obesity and type 2 diabetes with classic OSA symptoms, and screening for diabetes, hypertension and dyslipidaemia in those with OSA. We conducted a survey to gain a greater understanding of current practice in relation to the IDF recommendations for the assessment of patients in diabetes clinics in the UK. An online survey that was made accessible to diabetes healthcare professionals with the support of the websites of several diabetes organisations was performed. Most (approximately two-thirds) of diabetes healthcare professionals who responded to this survey were not aware of the IDF recommendations either for diabetes screening in OSA patients or for OSA assessment in type 2 diabetes and obesity. Participants indicated that their local diabetes guidelines did not incorporate assessment for OSA in those deemed to be at risk. Furthermore, most participants perceived OSA investigations to be primarily the domain of the respiratory team rather than the diabetes team. The observations from this survey provide a better understanding of the application and impact of the IDF guidance in diabetes clinics.

Keywords: diabetes, sleep disordered breathing, obesity, obstructive sleep apnoea, sleep apnoea

Introduction

Changes in sleep breathing patterns termed SDB are associated with obesity and/or type 2 diabetes. SDB is characterised by a spectrum of altered sleep homeostasis that ranges from simple snoring to obstructive sleep apnoea (OSA) with excessive daytime sleepiness. In OSA, repeated apnoeas or hypopnoeas occur during sleep. An apnoea is defined as the complete cessation of airflow for at least 10 seconds. A hypopnoea is defined as a reduction in air-flow that is followed by an arousal from sleep or a decrease in oxyhaemoglobin saturation.[1] Formal polysomnography counts the number of apnoeas and hypopnoeas per hour during sleep and the AHI (frequency of apnoea and/or hypopnoea) is used to diagnose and classify the severity of OSA[2] (Table 1). The frequency of oxygen desaturation episodes and severity of somnolence symptoms are also used.[4]

Table 1. AHI for diagnosis and classification of OSA[3]

Diagnosis	Events per hour
Normal	< 5
Mild OSA	5–15
Moderate OSA	15–30
Severe OSA	> 30

AHI = apnoea–hypopnoea index; OSA = obstructive sleep apnoea

The estimated prevalence of moderate to severe OSA is 13% in men and 6% in women between 30 and 70 years.[5] The major risk factors for OSA are obesity, gender and increasing age,[6] and OSA is associated with a clustering of clinical cardiometabolic manifestations including hypertension and type 2 diabetes. In OSA, recurrent episodes of upper airway obstruction and changes in intra-thoracic pressure result in recurrent periodic oxygen desaturations, with frequent sleep arousals and fragmented sleep.[7,8]

It has been estimated that up to 40% of OSA patients will have diabetes,[9] and in patients with diabetes, the prevalence of OSA may be up to 23%.[10] Prevalence estimates of OSA in severe obesity have been reported to be 40–90%.[11] Patients may be unaware of the association between OSA and type 2 diabetes. The symptoms and signs of OSA may not be perceived relevant to their diabetes care, therefore their OSA may remain unreported and undiagnosed.

The relationship of OSA with type 2 diabetes has important implications for improving health outcomes, given the worldwide prevalence of diabetes mellitus, predicted to increase from 8.3% in 2013 to 10.1% in 2035 when patient numbers are expected to reach 592 million.[12] Despite the absence of randomised controlled trials (RCT) data supporting cardiovascular risk reduction with continuous positive airway pressure (CPAP) treatment, we know that cardiovascular disease risk is increased in OSA.[13] There is also evidence that OSA may be associated with microvascular complications such as diabetic retinopathy,[14] nephropathy[15] and neuropathy.[16]

In 2008, the International Diabetes Federation (IDF) Taskforce on Epidemiology and Prevention released a consensus statement that recommended a targeted approach to screen individuals with type 2 diabetes and obesity for sleep-disordered breathing (SDB).[17,18] Briefly, the IDF recommended that healthcare professionals should consider the possibility of OSA in patients with type 2 diabetes and work in tandem with the local sleep service to provide a clinically appropriate process of assessment, referral and intervention.[18]

The purpose of this survey was to gain a greater understanding of current practice in relation to the IDF recommendations for assessment of OSA in patients attending diabetes clinics.

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Table 2. Questionnaire on OSA assessment

Please tick the relevant boxes.

Location: Teaching/University Hospital ❑ District General Hospital ❑ GP Practice ❑
Role: Consultant ❑ Registrar ❑ Diabetes Specialist Nurse ❑ Other ❑

	Yes	No	Don't Know
1. I know IDF guidance to screen for diabetes in OSA?	❑	❑	❑
2. I know IDF guidance to screen for OSA in high risk patients with diabetes & obesity?	❑	❑	❑
3. Our local diabetes guidelines recommend OSA screening in diabetes patients at risk of OSA?	❑	❑	❑
4. Local people with diabetes suspected of OSA are investigated by diabetes team?	❑	❑	❑
5. Local people with diabetes suspected of OSA are investigated by respiratory team?	❑	❑	❑

Methods

An online survey open to all health professionals caring for patients with diabetes in the UK was conducted for four months (December 2013 to March 2014). Data were collected using a questionnaire consisting of seven questions designed in light of the IDF statement (Table 2). The survey was publicly announced on the Association of British Clinical Diabetologists (ABCD) and Diabetes UK websites and in the Diabetes UK professional newsletter (Update, December 2013), and on the Young Diabetologist's and Endocrinologist's forum (YDEF) website which provided the links to access the online survey. In order to maintain confidentiality all responses were anonymous.

The first two sections of the questionnaire sought to determine demographic data (location of provision of diabetes care and role of the respondent). Questions 1 and 2 aimed to gauge current awareness of the IDF guidance; question 3 to investigate adoption of the IDF recommendations by local diabetes pathways; And questions 4 and 5 ascertained the perceived roles for investigating OSA in diabetes patients.

Results

A total of 62 responses were received, mainly from hospital-based physicians (Fig. 1), and showed that a minority of respondents were aware of the IDF guidelines and their implications for practice, but 78% of respondents noted that diabetes patients with suspected OSA are investigated by the respiratory team (Table 3). Appendix 1 (available online at www.bjdvd.com) documents questionnaire responses according to role and location. It is noteworthy that all respondents did not answer all questions.

Discussion

The majority (approximately two-thirds) of diabetes healthcare professionals who responded to this survey were not aware of the IDF recommendations either for diabetes screening in OSA patients or for OSA assessment in type 2 diabetes and obesity. Secondly,

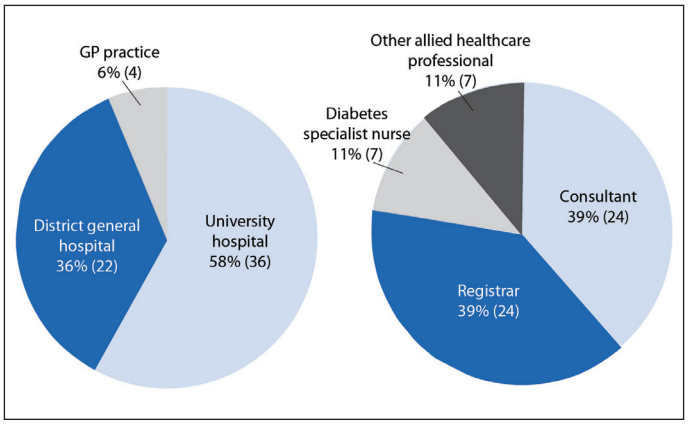

Figure 1. Questionnaire results showing location of work and role of respondents (*n*= 62).

most participants indicated that their local diabetes guidelines did not incorporate assessment for OSA in those deemed to be at risk. Thirdly, for the vast majority of participants, assessments were deemed to be primarily the domain of the respiratory team and not the diabetes team.

A beneficial effect of OSA treatment with CPAP in terms of blood pressure reduction was found in patients with type 2 diabetes,[19] although the research on the influence of CPAP therapy on glucose homeostasis has yielded mixed findings.[20] Nevertheless, it has been proposed that there may be a role for a multifaceted approach for these individuals in order to manage their cardiometabolic risks.[21] A recent observational study of OSA patients with type 2 diabetes assessed clinical outcomes and cost-effectiveness of CPAP treatment compared with non-treatment. It was found that CPAP use was associated with significantly lower blood pressure, improved glycaemic control, and was more cost-effective than no treatment with CPAP,[22] and a strategy has been proposed to identify, screen and diagnose patients with type 2 diabetes and OSA.[23]

Table 3. Responses to questions 1–5. Total number of respondents = 62*

Question	Responses		
	Yes	No	Don't know
1. I know IDF guidance to screen for diabetes in OSA?	32% (*n* = 19)	38% (*n* = 23)	30% (*n* = 18)
2. I know IDF guidance to screen for OSA in high risk patients with diabetes & obesity?	34% (*n* = 21)	38% (*n* = 23)	28% (*n* = 17)
3. Our local diabetes guidelines recommend OSA screening in diabetes patients at risk of OSA?	19% (*n* = 12)	45% (*n* = 28)	36% (*n* = 22)
4. Local people with diabetes suspected of OSA are investigated by diabetes team?	12% (*n* = 7)	67% (*n* = 40)	21% (*n* = 13)
5. Local people with diabetes suspected of OSA are investigated by respiratory team?	78% (*n* = 48)	3% (*n* = 2)	19% (*n* = 12)

*Some respondents did not answer all questions: two skipped question 1; one skipped question 2; two skipped question 4.

Key messages

- OSA is a common co-morbidity in diabetes and obesity
- A history of snoring, excessive daytime somnolence and witnessed apnoeic events may be suggestive of OSA
- A pro-active approach is encouraged to identify patients at risk of OSA

The Epworth Sleepiness scale is a validated questionnaire to assess the severity of sleepiness symptoms and is a simple screening tool that could be used for patients suspected of SDB. However, it should be borne in mind that although hypersomnolence symptoms may relate to micro-arousals and to changes in sleep architecture, it is non-specific and not always associated with OSA. Therefore it is not sufficiently discriminating to diagnose OSA.[24] Depending on services available, a referral for sleep studies or to the relevant sleep team for further assessment may be necessary. Lifestyle recommendations such as weight reduction for overweight or obese patients, smoking cessation, avoidance of sedatives, decreasing alcohol consumption and proper sleep hygiene may be recommended.

The treatment of OSA aims to reduce daytime sleepiness. CPAP is recommended as a treatment option for individuals with moderate or severe symptomatic OSA given the effects on bloodpressure, implications for quality of life and driving safety.[25] There is evidence that non-sleepy OSA patients treated with CPAP have not shown effective decreases in blood pressure and it is possible that non-sleepy asymptomatic OSA patients may face a different level of risk from those who are sleepy.[26]

This study has several limitations. Despite public announcements of the survey and engaging the help of organisations including the ABCD, the YDEF and Diabetes UK, which has an estimated 6 000 professional members (Richard Elliot, personal communication, 17 June 2014), there were only 62 respondents, so there is likely to be a significant non-response bias given the limited sample size. A higher response rate using a validated questionnaire would increase confidence in the generalisability of the findings.

Nevertheless awareness of OSA and taking it into consideration as part of our holistic patient assessment are very important.

Conflict of interest None

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Can pre-operative carbohydrate loading be used in diabetic patients undergoing colorectal surgery?

AFFIFA FARRUKH, KATH HIGGINS, BALJIT SINGH, ROBERT GREGORY

Abstract

The introduction of enhanced recovery after surgery (ERAS) has been associated with shortening post-operative recovery. It achieves such outcomes by minimising the physical and physiological trauma of surgery. Benefits include superior pain control, reduced duration of ileus, improved pulmonary function and a reduction in thrombo-embolic and cardiac events. Within the ERAS approach, the role of oral carbohydrate supplements is based on dealing with insulin resistance which characterises periods of stress. Aggressive control of blood glucose levels has been shown to benefit both diabetic and non-diabetic patients admitted to intensive care units, however original studies in this area have not been consistently reproducible. The development of low-osmolality carbohydrate drinks during the mid-1990s opened up the possibility of extending these benefits to surgical patients by providing them with a carbohydrate load two to three hours prior to anaesthesia. The benefits of the ERAS approach to colorectal surgery has been confirmed in several reports. However, its role in diabetic patients has, as yet, received limited attention. This review examines this limited number of publications and considers the potential benefit of pre-operative carbohydrate loading in all diabetic patients.

Keywords: diabetes, surgery, carbohydrate loading, pre-operative

Introduction

The introduction of ERAS has been associated with shortening post-operative recovery. It achieves such outcomes by minimising the physical and physiological trauma of surgery. It is claimed that such an approach will benefit all patients.[1] The overall strategy requires that patients are given partnership and responsibility for their care, health is optimised prior to surgery and care and rehabilitation are evidence based. Such an approach has called into question the traditional pre-operative overnight fast and the use of bowel preparation for colonic surgery among other aspects of care. The benefit of such an approach for patients undergoing colorectal surgery is recognised throughout the world.[1,2] Benefits include superior pain control, reduced duration of ileus, improved pulmonary function and a reduction in thromboembolic and cardiac events. Within the ERAS approach the role of oral carbohydrate supplements is based on dealing with insulin resistance which characterises periods of stress. It improves post-operative glycaemic control through endogenous insulin release, not only by reducing the risk of hyperglycaemia during post-operative nutrition but also by improving nitrogen economy and therefore maintaining muscle strength.[3]

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Historic background

In 1877 Bernard demonstrated that stress disturbed glucose homeostasis when he reported hyperglycaemia in association with haemorrhage.[4] This was the first recognition of the existence of insulin resistance. Although this physiological response in which glucose reserves are directed to non-insulin-dependent tissues, such as the brain, may be beneficial after trauma, Ljungqvist *et al.* questioned whether this was true following surgery.[5] These doubts arose following work on insulin resistance as a marker of surgical stress.[6] Elevated blood glucose level is associated with an increased incidence of infections following surgery.[7] Improved glycaemic control was associated with fewer deep sternal infections in diabetic patients who underwent cardiac surgery.[8] Aggressive control of blood glucose levels has been shown to be of benefit to both diabetic and non-diabetic patients admitted to an intensive care unit, with significant reductions in death rates from multiple organ dysfunction.[9] However, since this study was published in 2001, these results have been difficult to reproduce and the NICE-SUGAR study[10] and a meta-analysis[11] have informed consensus opinion that 'aggressive' blood glucose control is potentially harmful. The main issue is that an 'aggressive' approach to glycaemic control increases the likelihood of hypoglycaemic episodes. For this reason moderate control is associated with lower mortality amongst diabetic patients, although this is probably not true for people without diabetes.[12] Indeed a recent study of non-diabetic patients undergoing hepatobiliary surgery again demonstrated the benefits of aggressive control of blood sugar levels leading to reduced incidence of infections and shorter hospital stays, and none of the patients in the study had any episodes of hypoglycaemia.[13] Clearly the need to ensure that blood glucose is kept within an acceptable range is crucial to the success of any intensive insulin regime.[14] Against this background, Ljungqvist *et al.*[5] interpreted their own and other work as showing the need to shorten the catabolic phase related to surgical stress and to achieve this by minimising insulin resistance in the post-operative period.

Current approaches

The novel approach adopted has been to challenge the conventional wisdom of fasting prior to surgical procedures. The traditional basis for fasting had been to prevent aspiration, but this view

was first challenged in the 1980s and, as a result, many patients were allowed clear fluids up until two hours prior to surgery. The development of low osmolality carbohydrate drinks during the mid-1990s opened up the opportunity of providing surgical patients with a carbohydrate load two to three hours prior to anaesthesia. In a comparative study of 14 patients undergoing colorectal surgery Nygren *et al*. halved post-operative insulin resistance by the use of such oral therapy.[15] In a meta-analysis of three small prospective studies, Ljungqvist's team showed that such an approach can lead to a reduction in hospital stay by about 20%.[16] However, a randomised study in Toronto of 26 patients undergoing coronary artery bypass grafting and 12 patients having spinal surgery who received oral carbohydrate supplements in the evening and two hours before surgery showed no improvement in post-operative insulin sensitivity. The patients who received the carbohydrate supplements did, however, have lower blood glucose and higher insulin levels than the traditionally fasted patients, although these differences were not significant.[17] In contrast, in a randomised study from Brazil of gastrointestinal surgery, the addition of whey protein to the carbohydrate drink appeared to have some added value in terms of reduced inflammatory response and lesser insulin resistance.[18]

The benefits of the ERAS approach to colorectal surgery have been confirmed in several reports.[19-21] It can extend for a significant period after surgery.[22] The role of pre-operative carbohydrate supplementation has been assessed in a number of trials. The mechanism by which it acts includes a reduction in catabolism of fat and protein. This was shown in a study of 40 patients who underwent an elective laparoscopic colectomy.[23] However, most studies on the role of pre-operative carbohydrate supplementation have excluded diabetic patients. Clearly the concept of giving a patient with inherent insulin resistance a carbohydrate load prior to surgery is seen by many as 'a step too far'. Indeed, in 2011 the Joint British Diabetes Societies guideline on the management of adults with diabetes undergoing surgery stated: *'The Enhanced Recovery Partnership Programme recommends the administration of high-carbohydrate drinks prior to surgery. This may compromise blood glucose control and is not recommended for people with insulin-treated diabetes.'*[24]

However, such a blanket recommendation against the use of high-carbohydrate drinks prior to surgery requires re-evaluation. Concerns about potential delays in gastric emptying among patients with diabetes and, therefore, the re-introduction of the risk of aspiration, appear unfounded. In a study of 25 patients with type 2 diabetes Gustaffson *et al.* found no delay in gastric emptying compared to healthy volunteers among patients given a carbohydrate drink.[25] In 2011, in a study from Poland, Jodlowski *et al.* investigated the benefit of such drinks in 48 patients who were to undergo elective colorectal surgery. Seven had type 2 diabetes. Their conclusion was that a pre-operative oral carbohydrate load was safe and well tolerated by them, although realistically this is much too small a sample from which to make an inference. Overall for both diabetic and non-diabetic patients it improved peri-operative well-being, reduced hunger and reduced insulin blood levels and insulin resistance on day two after surgery.[26] This study is of particular importance against the background of a report from Michigan which investigated risk factors for anastamotic leak following a colectomy amongst 5 123 patients.[27] The occurrence of a leak was not directly associated with the presence of diabetes but, when it did happen, patients with diabetes had a four-fold mortality of 26.3% compared with 6% for patients without diabetes. Other evidence would suggest that the use of pre-operative carbohydrate loading might reduce this difference in mortality subsequent to an anastamotic leak.[20,21] Unfortunately none of these studies included any reference to whether these patients' diabetes was well controlled or whether they had complications of their diabetes.

The importance of insulin resistance as an independent factor associated with prolonged hospital stay cannot be over emphasised. The potential benefits of carbohydrate loading for patients with diabetes have been shown in the field of cardiac surgery. A randomised, double-blind, placebo-controlled trial in Germany among 160 patients undergoing elective cardiac surgery, including 31 with non-insulin-treated type 2 diabetes, reported that blood glucose levels, gastric fluid volume and insulin requirement did not differ between groups. However, patients receiving a carbohydrate load required less intra-operative inotropic support after initiation of cardiopulmonary bypass weaning ($p < 0.05$).[28] This study provided no details on how well controlled the patients were or the presence of complications, but did specifically exclude patients with type 1 diabetes after initial recruitment.

Conclusions

Although patients with diabetes have been excluded from most trials looking at the role of carbohydrate loading as part of an ERAS programme, there is certainly a need to stimulate a call for a properly conducted large-scale, randomised, controlled trial of its efficacy in this group of patients. There is some evidence, albeit from small studies, to suggest that carbohydrate loading pre-operatively can be safe in patients with diabetes. Naturally there will be a need to carefully monitor and support such patients – but this is integral to the ERAS approach. Clearly, its potential to shorten hospital stay, give a more rapid return to normal activities and reduce the frequency of serious complications would be of particular benefit.

Conflict of interest None.
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Diabetes News

Diabetes and obesity: South Africa's healthcare crisis

November 14 marked World Diabetes Day and this year, the condition has been under the microscope even more than usual, thanks to leading sport scientist and author of *The Real Meal Revolution*, Prof Tim Noakes.

Addressing parliament recently, Noakes stated that South Africa is sitting on a 'time bomb'[1] if diabetes and obesity are not addressed. 'I want us to all save South Africa; that's what we are here to do. Because if we don't reverse (the) obesity and diabetes epidemic, our nation disappears', said Noakes. 'And this is because we will go financially bankrupt because we don't have the money to provide medical services in the near future.'[2]

Dr Larry Distiller, a world-renowned endocrinologist who specialises in diabetes, and the founder of the Centre for Diabetes and Endocrinology, also recently commented that 'the diabetes tsunami is here.'[3] Type 1 diabetes is an autoimmune condition that affects approximately 5–10% of people with diabetes.[4] The other 90–95% of diabetics suffer from type 2 diabetes, a condition caused by a combination of bad eating habits, weight gain, and a lack of exercise that leads firstly to insulin resistance and later to diabetes.[5] Three-and-a-half million South Africans currently suffer from diabetes, with many more still undiagnosed.[6]

Alison Vienings, executive director of the Self-Medication Manufacturers Association of South Africa (SMASA), points out, 'People with a body mass index (BMI) of 30 kg/m^2 or more are up to 80 times more likely to develop type 2 diabetes than people with a BMI of less than 22 kg/m^2.[7] South Africa is currently on track to becoming one of the most obese nations in the world. Regrettably, it already holds the title of the fattest country in sub-Saharan Africa.'[8]

World Health Organisation predictions are that the incidence of obesity-driven diabetes in sub-Saharan Africa will double in the next 20 years.[9] Clearly, action is necessary, but what? According to Noakes, the way to address the current situation is through a high-fat, high-protein diet and by consuming less sugar and processed food, and fewer carbohydrates – an approach that has been met with a range of responses.

Government, on the other hand, is considering introducing a sugar tax on sugar-sweetened beverages (SSBs)[10] that will hopefully make South Africans think twice before consuming them. A research article by academics from the University of the Witwatersrand predicts that such a move may lead to a decrease of more than 220 000 obese adults in South Africa.[11]

According to Vienings, responsible self-care can help stem the tide of both diabetes and obesity in South Africa. 'Detecting diabetes early, getting the right medical care, eating healthily and exercising regularly can reduce the risk of developing complications associated with the disease',[12] she explains. 'Similarly, watching what you eat and committing to a regular exercise programme can prevent obesity, which so often leads to type 2 diabetes.'

In conclusion, she strongly recommends a visit to your local healthcare professional or doctor immediately if you display any or all of the symptoms associated with diabetes, or are concerned that your BMI may be higher than it should be.

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Novo Nordisk 'Changing Diabetes' annual cycle relay takes to the road

The third annual Novo Nordisk 'Changing Diabetes' cycle relay took to the road again on 6 November. The gruelling two-day, non-stop marathon, which featured both cycling professionals and enthusiastic amateurs, is a unique advocacy event aimed at raising much-needed awareness of the growing diabetes pandemic. It is not a competition as such, however, and there are no winners – all participants are given equal recognition for their support of diabetes awareness.

The 1 600-km relay began with a big send-off in Rivonia, Johannesburg, and ended in Cape Town two days later. This is the first time the event has ended in the Mother City rather than in the Garden Route town of George, making it 400 km longer than before.

Teams that had participated before welcomed the BestMed team, which cycled in the event for the first time. Also new to the event were the father of a child living with diabetes, and a team of four female cyclists. Marco Moolman and Kyle Hoods, both 13 years old, also participated. They are among the 500 000 children under the age of 15 living with diabetes worldwide. Moolman said that he took part because he wanted to give hope to desperate parents who may feel that the world is coming to an end because their child has been diagnosed with diabetes.

From the outset, the event has had the dedicated support of rugby legend, Joel Stransky, who also took on the new, longer route this year. 'An event like this gives a sport that I'm passionate about even more meaning', says Stransky. By taking part in the cycle relay, I can use the sport that I love, to raise money for a group of very deserving children. It isn't easy, but it's the outcome that makes it all worthwhile.'

The relay featured free-to-the-public diabetes testing and screening at testing stations in Soweto, Kimberley, Paarl and Cape Town, an initiative that had the support of the municipalities in all of these towns. In Johannesburg, local government support went even one step further. Mayor Parks Tau and Novo Nordisk South Africa's general manager, Dr Timmy Kedijang, joined the teams on the first leg from the company's headquarters in Rivonia to Maponya Mall in Soweto, a distance of 45 km.

Dr Jacques Van Staden founder of Team C4D screening communities for diabetes in Maponya Mall Soweto.

'The cycle relay has become a popular fixture on the sporting calendar', says Dr Kedijang, 'and participants are welcomed at every stop along the way. All of the cyclists feel it's a means to improve awareness on the prevention, diagnosis and management of diabetes.'

This is a key message as diabetes has reached almost epidemic proportions in South Africa and is considered one of the country's most significant healthcare challenges. As a global healthcare company, Novo Nordisk has made a long-term commitment to address this challenge through a programme that includes education on the risk factors, symptoms and treatment of the condition. Its core message is that diabetes is a manageable condition and that, with appropriate treatment and lifestyle interventions, those living with it can have long and active lives.

One of the cyclists who took part in the relay has diabetes himself and is living proof of how effective contemporary treatment protocols can be. Early diagnosis makes an important difference to long-term outcomes, though, and the best results are achieved if treatment is adhered to and monitored regularly. An enjoyable exercise routine and a healthy diet can also make a real difference.

The cycle relay, which was conceptualised and initiated by a healthcare practitioner based in George, Dr Jacques van Staden, raises sufficient funds to provide disadvantaged children living in the George area with the insulin they require to manage their condition for a whole year. Novo Nordisk donated R200 000 to Team 4CD, which was led by Dr van Staden. (Dr van Staden was profiled in a recent issue of this journal, when he discussed his two passions, diabetes care and cycling, and how he had the brainwave of combining them to raise funds to support his work in his community.)

At the conclusion of this year's event, Dr van Staden expressed his gratitude by giving special mention to Novo Nordisk and its partners for their enormous contribution to the event. He thanked all the cyclists who took the time to participate, and honoured them with medals.

Overall, the cycle relay was a great success and Novo Nordisk feels that its aim of raising greater awareness of diabetes was achieved. More than 800 people were tested at the four testing stations that were set up along the route.

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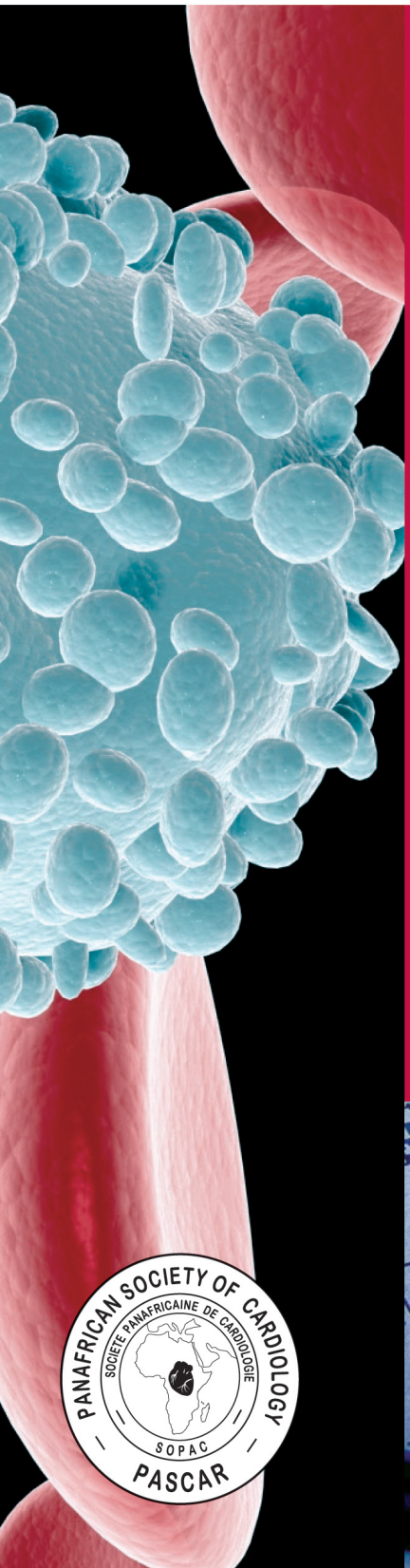

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