Addressing vascular risk factors in diabetes

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Vascular risk factors should be comprehensively assessed and treated in a person with diabetes because of the slow evolution of vascular damage before it becomes clinically evident. Individual and multiple risk-factor control have been shown to improve clinical outcomes and also to be associated with metabolic memory. The mnemonic GLOBES is proposed in this article as an aid to managing patients with diabetes.

Key points

- **Cardiovascular disease is a common cause of morbidity and premature mortality in people with type 1 or type 2 diabetes.**
- **A cardiovascular risk calculator is available online (www.cvdcheck.org.au).**
- **Multiple risk factors are often present in people with diabetes.**
- **A mnemonic for remembering the vascular risk factors in people with diabetes is GLOBES (or GLOBE^{2}S^2) – Glucose, Lipids, Obesity, Blood pressure, Education and Emotion, Smoking and Screening.**

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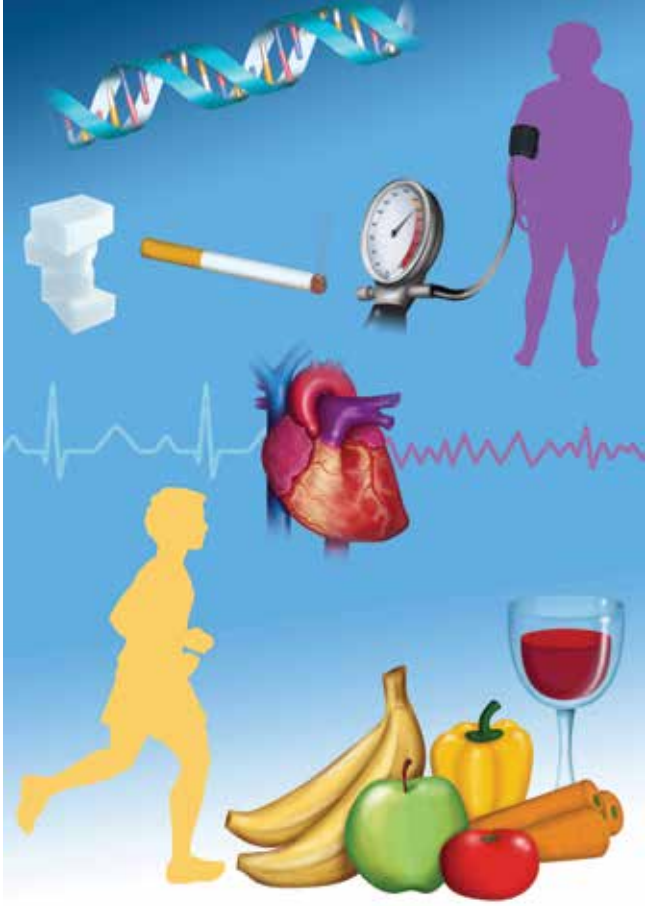

Atherosclerosis in diabetes begins early and progresses rapidly

Atherosclerosis can begin in childhood, although vascular events do not usually become clinically evident until middle age or older. Cardiovascular disease (CVD) is the cause of death in about 44 to 65% of people with diabetes.[1,2] In people with diabetes, atherosclerosis is accelerated, beginning earlier, progressing rapidly and also extending more distally into the arterial tree. In western cultures, children and adolescents with type 1 or type 2 diabetes can have vascular endothelial dysfunction (which can be assessed using research tools) and, as shown by postmortem studies, atheromatous plaques.

Likely related to increased adiposity and physical inactivity, type 2 diabetes, previously regarded as a condition commencing in middle age or later, is now not uncommon in young adults and even in adolescents and children. For young adults with type 2 diabetes, the risk of vascular complications is even greater than that in patients with type 1 diabetes of similar diabetes duration.[3] This is likely to be related to the usually higher rates of adverse vascular risk factors (e.g. obesity, hypertension and dyslipidaemia) in youth with type 2 diabetes. In addition, paralleling increasing obesity rates in general society, more people with type 1 diabetes are overweight or obese and have features of the metabolic syndrome, sometimes called 'double diabetes', which is associated with an increased risk of vascular complications.[4,5]

Multiple risk factors for vascular disease in diabetes

There are multiple pathological processes involved in vascular disease, including lipid accumulation, endothelial dysfunction, inflammation, thrombosis and abnormal angiogenesis. Multiple risk factors promote these pathological processes, such as age, ethnicity, family history (all unmodifiable risk factors), obesity, hyperglycaemia, insulin resistance, hypertension, dyslipidaemia, smoking, renal disease, poor diet

GLOBES: a mnemonic to aid in the management of people with diabetes

Glucose
Better blood glucose control reduces risk of vascular complications.
The body has a metabolic memory for glucose control.

Lipids and lipid-lowering drugs
Lipids (including high LDL-C and triglyceride levels and low HDL-C levels) are a risk factor for vascular complications.
Use of statins and fibrates can reduce vascular complications.
The body has a metabolic memory for lipid levels and use of lipid-lowering drugs.

Obesity
Obesity, common in both type 1 and type 2 diabetes, increases risk of vascular complications and can worsen other risk factors such as glucose control, dyslipidaemia and blood pressure.

Blood pressure and blood pressure-lowering drugs
Hypertension is more common in people with diabetes and is a risk factor for vascular complications. Use of blood pressure-lowering drugs may lower risk of tissue damage, even in the absence of hypertension. The body has a metabolic memory for blood pressure and use of blood pressure-lowering drugs.

Education and Emotion
Education, and re-education, about diabetes and a patient's personalised diabetes care plan is helpful to support adherence.
Diabetes can be associated with reduced mental wellbeing, which can reduce treatment adherence and can worsen outcomes.

Smoking and Screening
Smoking is a major risk factor for vascular complications.
Supporting a nonsmoking status is important.
Regular screening is key for early detection and treatment of vascular risk factors. Early treatment may even reverse some vascular damage.

and physical inactivity. Many individuals with diabetes have more than one risk factor. In the 2011-12 Australian Health Survey, 94% of Australian adults with diabetes had three or more vascular risk factors concurrently, of whom 25% had three risk factors, 41% had four risk factors and 28% had five or six risk factors.[6]

Many people who develop vascular disease do not have extreme adverse values for risk factors; rather they have mild to moderate perturbations in multiple risk factors. The presence of several risk factors at a low level (e.g. mildly elevated blood pressure, weight or LDL-cholesterol levels), which can often be disregarded by the patient or their clinician, can place a person at moderate or high vascular risk. The importance of this is recognised by recent Australian guidelines to assess and treat absolute cardiovascular risk.[7]

Cardiovascular risk calculators

Absolute risk is an estimate of the chance that an individual will experience a cardiovascular event, usually reported as within the next five to 10 years. The Australian absolute cardiovascular risk calculator, released in May 2012, was developed by the National Vascular Disease Prevention Alliance, including the National Heart Foundation, Diabetes Australia, Kidney Health Australia and the National Stroke Foundation. This online calculator (see: www.cvdcheck.org.au) estimates an individual's risk of a vascular event in the next five years based on age, sex, systolic blood pressure, smoking status, total and HDL-cholesterol level, diabetes and left ventricular hypertrophy.[7] Age is a powerful driver of CVD risk in many of these calculators, and some calculators may underestimate risk for young people with diabetes. These tools can be helpful for assessment and education. However, we recommend considering additional factors in patients with diabetes for the prevention and management of macrovascular and microvascular complications.

GLOBES – a mnemonic for major vascular risk factors

As a mnemonic is a learning technique that can help with information retention, we propose the mnemonic GLOBES as an aid to care for the patient with diabetes: Glucose, Lipids, Obesity, Blood pressure, Education and Emotions, and Smoking and Screening, or perhaps GLOBE^{2}S^2 to reflect the two E's and two S's (Box). The major reasons for including each of the elements of the GLOBES mnemonic are briefly outlined below.

Glucose

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study and UK Prospective Diabetes Study, in type 1 and in type 2 diabetes, respectively, were landmark studies demonstrating that better HbA_{1c} levels are associated with substantially reduced risk of vascular complications, in particular microvascular complications.[8,9] In addition, follow up of these studies demonstrated that the body 'remembers' the beneficial or adverse effects of good or poor glycaemic control for at least as many years after the glycaemia has changed.[10] This phenomenon, called 'metabolic memory' or the 'legacy effect', may relate to advanced glycation end-products (AGEs) and/or epigenetic effects. AGEs are a family of potentially harmful products, which form at greater rates in circulating proteins and in long-lived proteins, such as collagen, in people with diabetes.[11] This area of metabolic memory has been previously reviewed elsewhere.[10] In addition, there are also acute benefits of glucose control, including avoidance of marked hyperglycaemia or hypoglycaemia, fluid and electrolyte balance, wound healing, resistance to infection and psychomotor effects.

Lipids and lipid-lowering drugs

There are many epidemiological studies showing that an adverse lipid profile is associated with and predictive of both macrovascular and microvascular complications of diabetes in people with type 1 (in both paediatric and adult age groups) or type 2 diabetes.[11] In the 2011-12 Australian Health Survey, 86% of adults with diabetes had dyslipidaemia with two-thirds having uncontrolled dyslipidaemia,

compared with 67% and 56%, respectively, in those without diabetes.[6]

Lipid-lowering drugs, in particular the HMG CoA reductase inhibitors ('statins'), protect against CVD events in both forms of diabetes.[12] In type 2 diabetes, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid studies investigated the peroxisome proliferator-activated receptor-α agonist fenofibrate, alone in FIELD or on a statin background in the ACCORD study. These studies demonstrated the benefits of fenofibrate use for CVD reduction in people with high triglyceride and low HDL-C levels, for retinopathy and renal function.[13-18] The FIELD study also demonstrated a benefit of fenofibrate use in reducing microvascular amputations and neuropathy.[19] Interestingly, these benefits of fenofibrate, except for renoprotection, were independent of traditional lipid levels. Fenofibrate is now approved for use in Australia for patients with type 2 diabetes with existent diabetic retinopathy, irrespective of lipid levels. Recent follow-up studies also demonstrate vascular metabolic memory for lipid levels and lipid-lowering treatment.[20]

Obesity

Being overweight or obese, particularly with central obesity, is increasingly common in people with type 1 or type 2 diabetes in Australia, reflecting changes in general society. In the Australian Institute of Health and Welfare analysis of the Australian Health Survey, the body mass index distribution of Australians with type 1 or type 2 diabetes peaked at a BMI of 29 kg/m^2 and was skewed towards higher BMI values relative to the general population.[6] Excess weight is an independent risk factor for both CVD and the microvascular complications of diabetes. Some of the adverse effects of obesity on vascular health are likely to be related to adverse effects on lipids, blood pressure and insulin resistance. Increased inflammation and changes in adipokines related to adiposity, such as reduced levels of the vasoprotective insulin sensitiser adiponectin, may also contribute to vascular damage.[21,22]

Blood pressure and blood pressure-lowering drugs

Hypertension is a well-recognised risk factor for both CVD and microvascular complications in people with diabetes, and blood pressure-lowering drugs, particularly those related to the renin–angiotensin–aldosterone system (RAAS), have been shown to have protective effects against vascular complications. Such RAAS drugs are usually recommended for treatment of increased albuminuria, even in the setting of normal blood pressure levels. In the 2011 to 2012 Australian Health Survey, 77% of people with diabetes and 27% of adults without diabetes had high blood pressure, of whom 38% of those with diabetes and 19% of those without diabetes had uncontrolled hypertension.[6] It is not uncommon for people with diabetes to need three or more antihypertensive drugs to control blood pressure levels. As with glucose control and with lipid levels and lipid-lowering drugs, vascular metabolic memory has also been demonstrated for blood pressure-lowering drugs.[20]

Education

People with diabetes require education about many facets of diabetes and risk-factor control, including diet and exercise, mental health, the need for diabetes complication screening, means and benefits of treating risk factors to target, use and side effects of medications, and support groups. In addition, patients may have other health conditions or health needs such as vaccination or age-appropriate screening for cancer, that also need addressing.

Education and re-education are important because there is much for the person with diabetes to know, medical knowledge and therapeutic options change and patient interest may vary as their circumstances change. GPs, specialists, credentialled diabetes educators, practice nurses, allied healthcare professionals, psychologists, exercise physiologists and healthcare workers can all play an important role in education. Patients and their families as well as friends often also turn to the internet and social media for medical information, which can be helpful but can also sometimes provide confusing, misleading or incorrect information. It can be useful to recommend to patient a range of websites, such as those by national diabetes, cardiovascular (heart and stroke) and kidney organisations. It is also important for healthcare professionals to keep up to date with proven diabetes treatment options.

Emotions

Diabetes can be associated with diabetes distress, anxiety, depression and disturbed eating, which merit recognition and treatment in their own right. In addition, negative emotions can affect patient's attention to a healthy diet, exercise and the diabetes treatment regimen and may also contribute to adverse vascular status by neurohumoral effects.[23]

Smoking

People with diabetes who smoke cigarettes increase their risk of both CVD, including amputation, and microvascular complications. Of Australian adults with diabetes, 12% smoke daily, compared with 16% of adults without diabetes.[6] Smoking can impair glycaemic control, induce insulin resistance and increase inflammation, which are recognised risk factors for vascular damage.

Screening

Regular screening for vascular risk factors and complications is recommended with measurement of HbA_{1c} (covered by Medicare up to four times a year), as well as measurement of lipid levels and assessment of renal function and ocular health at least once a year. More frequent checks are recommended for people with vascular damage or with out-of-target risk factors. Regular checks for blood pressure, weight and foot care are also recommended. Podiatrists, optometrists, ophthalmologists and other specialists can be of great assistance. A recommended schedule of vascular health (and other diabetes-related) screening is included in the Royal Australian College of General Practitioners (RACGP) *General Practice Management of Type 2 Diabetes*.[24]

Recommended treatment targets

An excellent guide to the general treatment targets and triggers for action in patients with diabetes is provided in the regularly updated RACGP *General Practice Management of Type 2 Diabetes*.[24] The approach and targets for people with type 1 diabetes are similar.

Although individualisation of targets is appropriate, taking into account factors such as age and comorbidities, the general vascular health-related targets or triggers for action are:

- a healthy diet (perhaps a Mediterranean diet)
- at least 5 to 10% weight loss for people who are overweight or obese
- no smoking status
- at least 30 minutes of moderate physical activity on most if not all days of the week
- HbA_{1c} of 7.0% or less (≤53 mmol/mol), with a range of 6.5 to 7% (48 to 58 mmol/mol) due to test accuracy variation
- blood pressure reading of less than 130/80 mmHg
- urine albumin:creatinine ratio (screening test) less than 3.5 mg/mmol for women and less than 2.5 mg/mmol for men.

General lipid goals are as follows:

- total cholesterol level less than 4.0 mmol/L
- LDL-cholesterol level less than 2.0 mmol/L
- HDL-cholesterol level 1.0 mmol/L or above
- fasting triglyceride level less than 2.0 mmol/L.

Initiation of lipid pharmacotherapy is usually based on the Australian absolute CVD risk calculator discussed above, which considers the often coexistent multiple risk factors. This may result in an evidence-based recommendation to start lipid-lowering drugs even in the setting of seemingly good lipid levels.

Many women of reproductive age have diabetes, and care must be taken to avoid medications that are contraindicated during pregnancy and breastfeeding.

Conclusion

People with diabetes are common in clinical practice. Even if vascular disease is not clinically evident in a person with diabetes, their vascular risk factors should be comprehensively assessed and treated because of the slow evolution of vascular damage (primary prevention) and for the proven benefits of secondary prevention. Individual and multiple risk-factor control has been shown to improve clinical outcomes in people with diabetes and to be associated with metabolic memory.[20]

We hope that the mnemonic GLOBES (or GLOBE^{2}S^2) will help clinicians to achieve better risk-factor control and to improve vascular health in their patients with diabetes. We must also do all that we can to ensure accessibility and affordability of the required healthcare services and medications for all Australians with diabetes. **ET**

References

A list of references is included in the website version (www.medicinetoday.com.au) of this article.

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