Diana's diabetes

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Increasing age is the main driver of diabetes prevalence and many older women have undiagnosed type 2 diabetes.

MedicineToday 2011; 12(3): 57-64

Type 2 diabetes, like several other endocrinological conditions, is common and often goes unrecognised in older women. This article reviews type 2 diabetes, including its prevalence and risk factors, the metabolic syndrome and medications associated with weight gain (hypoglycaemics and others).

CASE SCENARIO

Diana is 68 years old and is concerned that she might have diabetes after one of her friends told her that one in two Australians have early or established diabetes.

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What is the prevalence of diabetes?

The AusDiab study showed that one in four adult Australians have prediabetes (impaired fasting glucose [IFG] or impaired glucose intolerance [IGT]), undiagnosed diabetes or diagnosed diabetes (type 1 or type 2).[1] Other Australian studies have not found such a high prevalence of prediabetes or undiagnosed diabetes but it is generally agreed that diabetes prevalence in adult Australians is approximately 8% and that prediabetes is at least as prevalent.[1,2]

Regarding diabetes prevalence, 30% is a useful percentage to remember: nearly 30% of adult Australians have diabetes or prediabetes (about 4% undiagnosed diabetes, 4% diagnosed diabetes and 16% prediabetes) and 30% of those with IGT can be expected to develop diabetes within three years.[1,3]

In Australia, the prevalence of diabetes in people in the 20 to 79 years age group is expected to increase by about 17%

TABLE. TOP FIVE: NUMBERS OF PEOPLE WITH DIABETES MELLITUS[4]

Country	Estimated numbers of people aged 20 to 79 with diabetes (millions) 2010	2030	Increase
Top five countries in 2010			
India	50.8	87.0	71%
China	43.2	62.6	45%
USA	26.8	36.0	34%
Russian Federation*	9.6	10.3	7%
Brazil	7.6	12.7	67%
For comparison			
Australia	1.1	1.5	36%

* Pakistan is expected to replace the Russian Federation in fourth place by 2030, with a 94% increase from 7.1 million people with diabetes in 2010 (seventh place) to an estimated 13.8 million people in 2030.

(from 7.2 to 8.4%) between 2010 and 2030.[3]

The top five countries in terms of number of people with diabetes in 2010 and 2030 are expected to remain the same except for the replacement of the Russian Federation with Pakistan in the number four spot (Table).[3] Most of the diabetes will remain in India and China. The rate of increase in the top five or so countries is much higher than the global average, suggesting that these countries will remain at the top of the table for some time to come.

Why is diabetes increasing in Australia?

The 'diabetes drivers' include overweight, inactivity, longevity, ethnicity and disadvantage (Figure 1).[4] The three major drivers are conveniently the 'F' words – Forty, Family, Fat.

Diabetes drivers work before and after birth. Parental genes are important in determining lifetime outcomes and an adverse intrauterine environment can reset metabolism for life. For example, a woman with gestational diabetes passes on her genes but pregnancy hyperglycaemia adds a second 'whammy' to her baby's diabetes predisposition. Indigenous Australians and some immigrant groups have especially high genetic predispositions and their children are also more likely to be exposed to a diabetogenic intrauterine environment.

Adverse postnatal environments, including high energy foods and low activity levels, and increasing duration of life are further drivers of diabetes prevalence in Australia. Social and economic disadvantage is associated with adverse pre- and postnatal environments, and chronic diseases including diabetes are disproportionately represented in disadvantaged people.

The diabetes drivers are all moving in the wrong direction (Figure 1).[4] Fatness is increasing and fitness is decreasing; people are living longer and increasingly in a multicultural society (both good) but longer life and high-risk ethnicity (such as immigrants from Asia and the western Pacific) both increase diabetes risk. Finally, societies are becoming more divided, with an increasing prevalence of disadvantage.

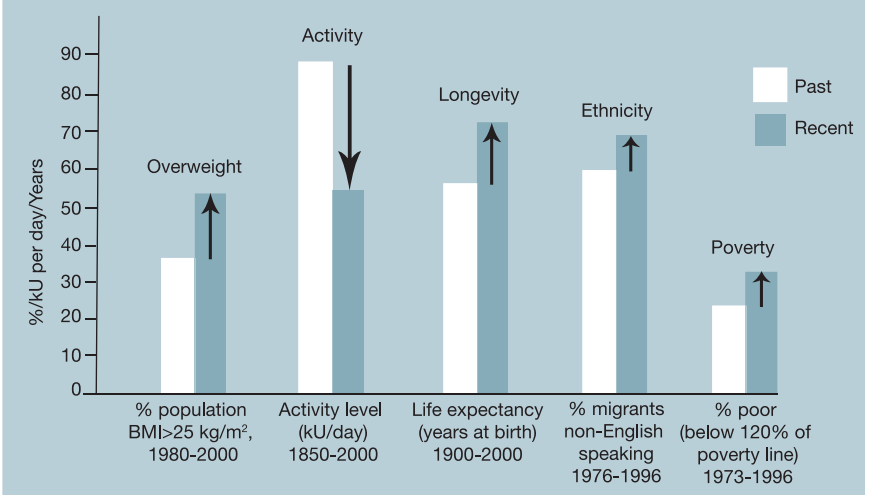

Figure 1. Diabetes drivers – going the wrong way.[4]

If Diana were to have impaired glucose tolerance, what would be the likelihood of her developing diabetes?

Were Diana to have IGT and no intervention, there would be a 30% chance that she would develop diabetes within three years.

Several studies in different countries, including China, India, Scandinavia and the USA, have shown a high rate of progression from prediabetes to diabetes. In the US study (the Diabetes Prevention Program), a group of people with IGT who were aged at least 25 years and had a body mass index (BMI) of 24 kg/m^2 or higher was split into the three groups control, metformin (850 mg twice daily) and intensive lifestyle modification, and followed by an annual oral glucose tolerance test (OGTT) to diagnose type 2 diabetes.[5]

The trial was stopped after three years because it was clear that metformin and lifestyle had significantly reduced the progression of IGT to type 2 diabetes (by 31% and 58%, respectively, as compared with placebo).[5] In the placebo, metformin and intensive lifestyle modification groups, 11, 7.8 and 4.8 people, respectively, progressed to diabetes per 100 years (Figure 2).[5]

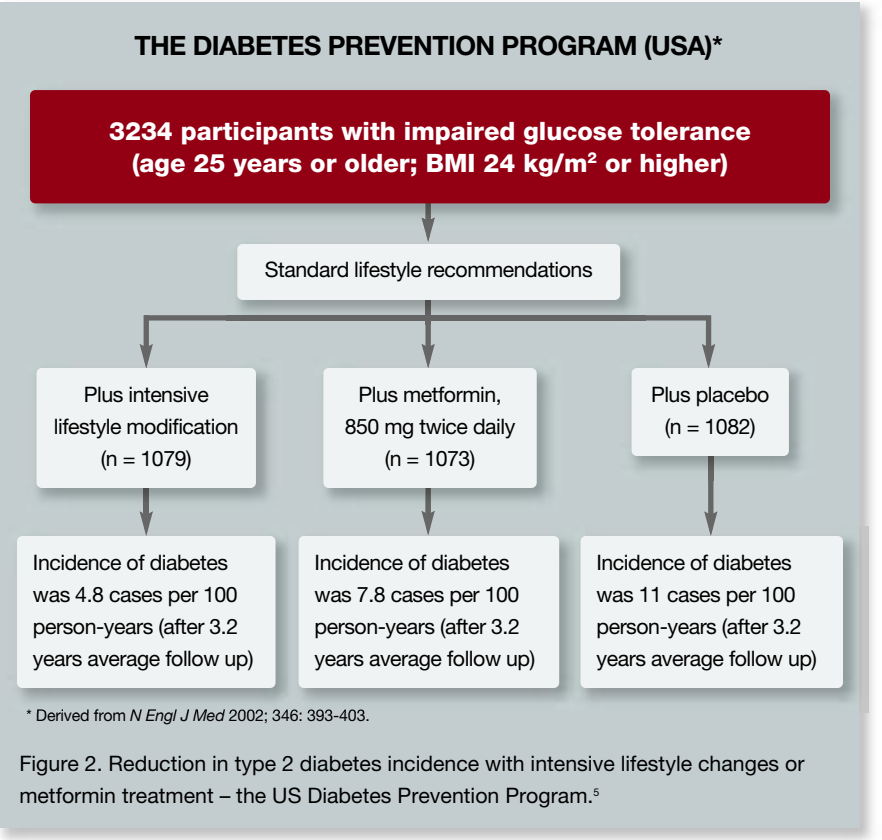

Figure 2. Reduction in type 2 diabetes incidence with intensive lifestyle changes or metformin treatment – the US Diabetes Prevention Program.[5]

CASE SCENARIO CONTINUED

Diana's fasting blood glucose level is checked, and the result is 5.4 mmol/L. Diana is pleased that it is unlikely she has diabetes (i.e. her fasting blood glucose level is below 5.5 mmol/L)[6] but asks whether she and her family may develop diabetes in the future. Her mother had 'old age' diabetes but, as far as she knows, no other family members have had diabetes. She is 170 cm tall and weighs 69.4 kg (BMI, 24 kg/m²).

What is Diana's risk of developing type 2 diabetes in the future?

Diana's risk of developing type 2 diabetes is considerably greater than that of the general population by virtue of her age (Figure 3a).[7] Age dominates the F words and is the major driver of diabetes prevalence overall. In young people (under 40 years), the other F words (Family and Fat) are important, but they become progressively less so with increasing age (Figures 3b and c).

Age has increased Diana's risk of developing diabetes to more than 20 times that of a woman aged about 25 years. Her positive family history and her healthy weight are less important factors.

What are her siblings' and her family's risks of developing type 2 diabetes in the future?

Diana's siblings have an increased risk of developing type 2 diabetes in the future compared to the general population. They will be of similar age to Diana and also have a positive family history: Diana herself.

Diana's children also have an increased risk of developing type 2 diabetes in the future compared to the general population. Their being some 20 to 40 years younger, family history will be a more important contributor to the risk of developing diabetes than it would be for Diana or her siblings (Figure 3b).[7] In people aged less than 40 years, family history and fatness are important risk factors for diabetes. Those developing diabetes at this relatively young age are likely to have both of these F words, with or without one in a large 'dose' (i.e. strong family history and/or very fat), or a large 'dose' of one of them.

If the father of Diana's children were genetically predisposed to diabetes, their children would have an 80% lifetime risk of developing diabetes. Adding overweight or obesity would further contribute to a high risk of developing diabetes at a young age.

Is Diana's family history (maternal) her most predictive risk factor for future diabetes?

Family history is a minor contributor to risk for future diabetes at Diana's age, increasing her risk by only twofold. However, family history could be very important for her children, especially if their father were predisposed to diabetes.

For example, the relative risk of future diabetes is increased nearly fivefold for a man, and about threefold for a woman, aged 25 years with a positive family history compared with someone of the same age who has no family history (Figure 3b).

How much would Diana's risk be increased if she were overweight or obese?

Similarly to family history at Diana's age, fatness increases her risk for future diabetes relatively little (by twofold and

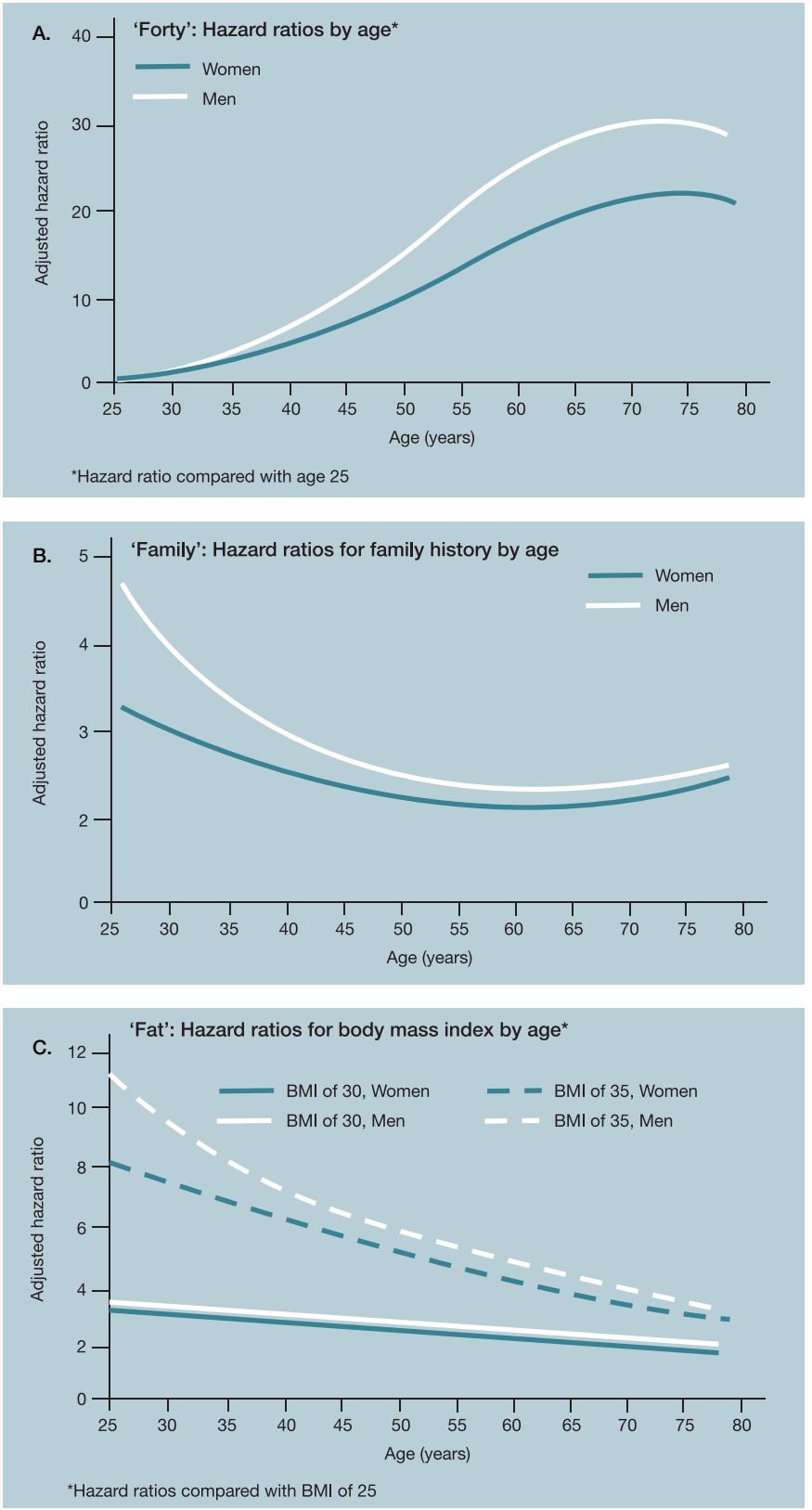

Figure 3. Diabetes 'F' words: Forty, Family and Fat. Age interactions for men and women at risk of type 2 diabetes.[7]

Reproduced from: Hippisley-Cox J, Coupland C, Robson J, Sheikh A, Brindle P. Predicting risk of type 2 diabetes in England and Wales: prospective derivation and validation of QDScore. BMJ 2009; 338: b880. (Open access.)

fourfold for overweight and obesity respectively; Figure 3c).[7] However, as noted above, in those aged less than 40 years both family history and fatness are important risk factors for diabetes.

Just as a large 'dose' of genetic predisposition increases diabetes risk, so does increasing BMI. For example, at age 25 years, the relative risk of future diabetes is increased elevenfold and eightfold for obese men and obese women respectively, compared with those of the same age but who have a healthy BMI (Figure 3c).

The Australian Type 2 Diabetes Risk Assessment Tool (AUSDRISK) estimates an individual's five-year risk of diabetes based on nine risk factors that are either known or easily self-assessed. These are age, sex, ethnicity, parental history of diabetes, history of high blood glucose levels, use of antihypertensive medications, smoking, physical inactivity and waist circumference. The tool has been validated in Australia and is available online (www.ausdrisk.com).[8]

CASE SCENARIO CONTINUED

You explain to Diana that the factors currently affecting her diabetes risk and those of her children and grandchildren are different. You suggest that she visits the Diabetes Australia website for more information (www.diabetesaustralia.com.au).

At a subsequent visit she tells you that she persuaded her son and her two daughters, who are all overweight, to have their diabetes risk checked. Apparently she opened a Pandora's box of problems. Her 48-year-old son, Michael, not only has prediabetes but also has hypertension. He has decided to lose 5 to 10 kg because he is very overweight. One daughter, Polly, who has always had problems relating to her weight (including irregular periods, excess facial hair and difficulty becoming pregnant), found she had diabetes. The other daughter, Sue, 'is in the clear for now'.

How high is Michael's five-year risk of a myocardial infarct?

As a rough guide, men aged 50 years and women aged 60 years have a 1% per year risk of a cardiovascular event (CVE; myocardial infarct or stroke). Additional risk factors increase that risk (see the box on this page).[9]

Diana's son is close to age 50 years, has one clear risk factor (hypertension) and his abnormal glucose tolerance and possibly his overweight further increase that risk. His risk of having a CVE over the next five years is likely to be moderate – that is, about 15%. It will be important for his GP to assess other potential risk factors, actively intervene and consider cardioprotective doses of aspirin if his risk exceeds 15% per five years. The Australian absolute CV disease risk calculator produced by the National Vascular Disease Prevention Alliance is a useful resource (www.cvdcheck.org.au).

What other problems related to being overweight might Michael, Polly and Sue have?

Central overweight or obesity is classically associated with the 'hypers' relating to levels of lipids, insulin, glucose and blood pressure, and often also with five other problems, as listed in the box on this page.[9] Diana's children are likely to have many of these problems.

Michael and Polly have the syndrome currently called the metabolic syndrome. There have been many other names for this syndrome, including syndrome X and the deadly quartet. Different countries and organisations have different detailed definitions but all include the same three basic components: overweight/overwaist, cardiovascular risk factors and abnormal glucose metabolism (see the box on this page).[9]

The genetic basis of the metabolic syndrome is not known but it is clearly a family affair. Families not only share the same genes but also often have similar environments in terms of eating, activity and recreation. The familial nature of the metabolic syndrome is summarised in the verse on page 63 (personal communication, Dr Warren Kidson).

In Diana's family, we know Michael has two of the 'hypers' (hypertension and hyperglycaemia) and Polly has hyperglycaemia. In addition, Polly has probably had polycystic ovary syndrome for some years, which would explain her being overweight and her hirsutism, menstrual irregularities and infertility. Diana's waist measurement and weight are probably in the healthy ranges (her BMI is 24 kg/m^2) but her children's father may also have the metabolic syndrome and the problems associated with it.

Diana's children are probably of an age (over 40 years) at which the cardiodiabetes problems associated with the metabolic syndrome start becoming significant health risks. Diana may be able to persuade them to address the modifiable components of that risk.

Which groups of medication are likely to further increase weight?

The commonly used 'orexics' (in contrast to 'anorexics' used in weight loss) include medications used in mental health (tricyclic antidepressants and second-generation antipsychotics) and contraception (the oral contraceptive pill). Cyproheptadine (used to reduce itch) and pizotifen

CARDIOVASCULAR RISK FACTORS FOR DIABETES

Fixed

- Age
- Family history
- Gender
- Menopause
- Past history
- Abnormal glucose tolerance
- Renal impairment

Modifiable

Lifestyle

- Smoking
- Healthy lifestyle

Medical

- Hypertension
- Dyslipidaemia
- Prothrombosis

PROBLEMS ASSOCIATED WITH CENTRAL/VISCERAL OVERWEIGHT*[9]

- The hypers
  - hyperlipidaemia
  - hyperinsulinaemia
  - hyperglycaemia
  - hypertension
- Prothrombosis
- Hyperuricaemia
- Polycystic ovary syndrome
- Nonalcoholic fatty liver disease (NAFLD) or nonalcoholic steatohepatitis (NASH)
- Sleep apnoea

* Overweight/obese: for men, waist 94 to 101 cm/over 102 cm; for women, waist 80 to 87 cm/over 88 cm. Waist measurements taken midway between the upper iliac crest and the lowest rib in the mid axillary line.

BASIC COMPONENTS OF THE METABOLIC SYNDROME[9]

- Overweight/overwaist
  - increased body mass index
  - increased waist circumference
  - increased waist:hip ratio
- Cardiovascular risk factors
  - increased blood pressure
  - abnormal triglycerides, HDL cholesterol
  - prothrombosis
  - microalbuminuria
- Glycaemia
  - impaired fasting glucose/impaired glucose tolerance/diabetes
  - insulin resistance

ODE TO THE METABOLIC SYNDROME

'There was a young woman with acne
and hair
Whose menstrual periods were
exceedingly rare
Despite 'exercise and no food on her plate'
Her fatness continued to escalate.

Her father had sugar, her mother a stroke
Her brother was a fat hypertensive
old bloke
They all regularly went to see
Their endo or gynae or local GP.

She met a new partner and pregnancy set
But miscarriage made her very upset
Her gynae said she would need IVF
To the endo's advice he seemed
rather deaf.

This story has a happy conclusion
Since metformin provided a lasting solution
She pregnant did fall and baby was born
Fair-haired, blue-eyed and perfect in
form.'

Adapted from W. Kidson (personal communication)

COMMONLY USED MEDICATIONS ASSOCIATED WITH WEIGHT GAIN*

Hypoglycaemic agents

- Glitazones
- Glitinides
- Insulins (particularly bolus insulins)
- Sulfonylureas

Other medications

- Oral contraceptive pills
- Second-generation antipsychotics
- Tricyclic antidepressants

* Less commonly used medications associated with weight gain include cyproheptadine and pizotifen.

EATING LESS AND/OR WALKING MORE

- Losing 1 g of body fat requires an energy deficit of 8 cal (approx 34 kJ)
- Not gaining 4 kg in one year requires energy deficit of 32,000 cal = 90 cal per day (approx 380 kJ)
- One slice of bread = 15 g of carbohydrate = 60 cal (approx 250 kJ)
- 1½ slices = 90 cal (approx 380 kJ)
- Walking briskly over a distance of 1 km uses (0.7 x body weight) calories or kilojoules
- For a person weighing 65 kg, walking 1.5 km uses (0.7 x 65 x 1.5) = 90 cal (approx 380 kJ)

(used to prevent migraine) are not often used. Patient who have problems controlling their weight and are taking a medication from one of these groups may be able to stop the medication or use an alternative that is less associated with weight gain, for example:

- tricyclic antidepressants (e.g. amitriptyline) – use instead certain of the SSRIs (e.g. fluoxetine)
- second-generation antipsychotics (e.g. olanzapine) – use instead one of the first-generation antipsychotics
- oral contraceptive pill – use instead an intrauterine or intravaginal contraceptive device.

The second-generation antipsychotics and the oral contraceptive pill are independently associated with some of the metabolic syndrome problems (e.g. glucose intolerance, prothrombosis, hypertension and dyslipidaemia). These medications are best avoided in patients such as Michael and Polly.

Commonly used medications associated with weight gain are listed in the box on this page.

Which hypoglycaemics are not associated with weight gain?

Use of metformin, acarbose or a GLP-1 agent (the 'enhancers' sitagliptin and vildagliptin and the 'mimetic' exenatide; these are insulin secretagogues) – is not associated with weight gain. Orlistat could possibly also be included here as it is associated with both weight loss and improved glycaemia.[10]

The other insulin secretagogues (the sulfonylureas and the glitinides) and sensitisers (the glitazones) and insulin itself (particularly bolus insulin) are commonly associated with weight gain.[6] None of these medications actively cause weight gain; rather, they make it more difficult to maintain or lose weight. Patients can counter these effects by 'eating less and walking more' (see the box on this page).[11]

There is, however, one factor that often means that people need to modify their lifestyle and induce a negative energy balance to avoid weight gain: significant improvement in glycaemia. A patient who has the 'polys' associated with hyperglycaemia (i.e. polyuria, polydipsia and polyphagia) has glycosuria and is losing a source of energy through the urine. As glycaemia decreases so does glycosuria, and if the person doesn't 'eat less and walk more' they will gain weight. The larger the glycaemic change, the larger the change in glycosuria and in energy balance. This is clearest when starting insulin because insulin therapy is often delayed until there is very significant hyperglycaemia and/or hyperglycaemic symptoms (e.g. glycosylated haemoglobin [A_{1c}] above 10%, implying a blood glucose level in the teens) and insulin is the most effective hypoglycaemic medication.[12]

As a rough rule, for each 1% decrease of A_{1c} body weight increases by 2 kg in the next year.[13] Reducing A_{1c} from 10% to 8% can be expected to increase body weight by 4 kg. The person must induce a negative energy balance of at least 90 calories (approximately 380 kJ) per day to

avoid this weight gain (see the box on page 63).

Australians tend to gain about 0.5 to 1 kg per year as they get older.[9] People with diabetes tend to gain more weight and find it harder to lose weight. Potential weight gain or loss is an important factor in choosing hypoglycaemic medications, and regular review of weight, weight change and lifestyle is an important part of both professional and self diabetes care.

SUMMARY

- The current adult prevalence of diabetes in Australia is about 8%, and prediabetes is at least as common. Both are expected to increase by about 10 to 15% by 2030.
- Lifestyle and metformin reduce the progression of prediabetes to type 2 diabetes by 58% and 31%, respectively.[5]
- The diabetes drivers of overweight, inactivity, longevity, ethnicity and disadvantage are all worsening in Australia, as are also the 'F words' predicting prediabetes and diabetes (in order of importance: Forty, Family and Fat). Age over 40 years is the dominant risk factor, with family history and overweight being important at younger ages.
- Central overweight is associated with the 'hypers' (hyperinsulinaemia, hyperglycaemia, hyperlipidaemia and hypertension) as well as increased risk of cardiodiabetes, hyperuricaemia, polycystic ovary syndrome, liver disease and sleep apnoea. These problems are often familial, reflecting shared genes and intrauterine and postnatal toxic environments.
- Medications associated with weight gain include the sulfonylureas, glitazones and insulin in people with diabetes. Others, including anti-depressants, second-generation antipsychotics and the oral contraceptive pill, should be avoided in those with or without diabetes if possible. If they are necessary, patients should 'eat less and walk more' to counteract their effects. This lifestyle advice applies particularly in patients starting insulin who are markedly hyperglycaemic as this is associated with glycosuria; such patients will otherwise gain approximately 2 kg in the next year for each 1% decrease in A_{1c}.
- The AUSDRISK score is useful to predict an individual's risk of having or developing prediabetes or type 2 diabetes. MT

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COMPETING INTERESTS: Dr Phillips has received research and travel grants, acted on advisory boards and been involved with clinical trials and seminars sponsored by a range of pharmaceutical companies. He does not think these associations have influenced the content of this article.

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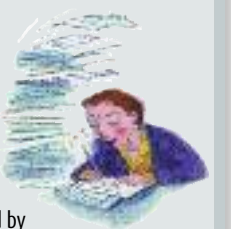

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