

Pre-diabetes: Who is at risk and what can primary care do about it?

Vineet Thapar

Pre-diabetes refers to a cardiometabolic state that predisposes to the development of true diabetes using current diagnostic criteria (*Box 1*) and appears to be an emerging phenomenon. Primary care is ideally placed to target people who fall into this group, as increasing volumes of data collected in primary care allow for sophisticated personal risk stratification. Intervention strategies for a 'pre-disease' such as pre-diabetes will require a strong evidence base to influence change in healthcare professional behaviour, as well as new policies. In future, incentives may drive identification of individuals with pre-diabetes in the primary care setting, particularly with regards to obesity. This article describes the groups known to have a high risk of developing type 2 diabetes, reviews the intervention strategies available and suggests approaches primary care can make to address the needs of people at risk.

A shift towards a greater focus on preventive activities, rather than the management of existing chronic diseases, is increasingly being acknowledged in the primary care setting. The effect of an ever-increasing affluent society and rising rates of obesity on diabetes prevalence is a prime example. Furthermore, the primary care workforce can very efficiently respond to changes in contracting arrangements. The advent of the Quality and Outcomes Framework (QOF) alongside advances in computer data collection for the new GMS contract have allowed for a wealth of data to be collected that can be locally and nationally analysed to guide future prevention strategies. There is also recognition of the importance of

preventing chronic diseases at the level of the European Parliament by the Vienna Declaration (European Parliament, 2006) and the IMAGE (Development and Implementation of a European Guideline and Training Standards for Diabetes Prevention) project (2007).

Primary care is ideally placed to target high-risk groups for the early development of type 2 diabetes, particularly with regards to identifying risk factors that predispose to microvascular and macrovascular disease. A recent executive summary by the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) attempts to give a higher profile to the pre-diabetic state (Rydén et al, 2007).

With increasingly accurate data generated

Article points

1. Primary care is ideally placed to target high-risk groups for the early development of type 2 diabetes.
2. With so much data now available from people using primary care, it is possible to create a register of individuals at risk of developing type 2 diabetes.
3. In the case of type 2 diabetes and the pre-diabetic state, focusing our energy on high-risk groups remains the approach of choice with the most appropriate intervention being aimed at promoting lifestyle changes to eat healthily and take more exercise to avoid obesity.

Key words

- Pre-diabetes
- Preventative medicine
- Risk modification

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1. It would be a missed opportunity not to produce a register of individuals at risk of developing type 2 diabetes when such a rich pool of data is on our computers.
2. The WHO recommends an oral glucose tolerance test (OGTT) if one or two fasting plasma glucose levels are in the IFG range.
3. The new GMS contract has allowed active case finding with the formation of disease registers for people with hypertension and a history of IHD and stroke.
4. Close attention to BMI, blood pressure, cholesterol and the development of chronic kidney disease allows a good degree of secondary prevention of type 2 diabetes.

from the new GMS contract, the recorded prevalence of chronic conditions such as diabetes is on the increase (Hippisley-Cox, 2007; Hippesley-Cox and Ryan, 2007). It is estimated that with incentives in place for case finding, prevalence rates will continue to rise over the next few years. This rapid access to large volumes of personalised data enables cardio-metabolic risk stratification (*Box 2*).

At-risk groups for type 2 diabetes

Several factors have increased the surveillance of individuals registered with a practice – see *Box 3*. It would be a missed opportunity not to produce a register of individuals at risk of developing type 2 diabetes when such a rich pool of data is on our computers. Such an automated register would allow targeting of risk factors that could be monitored at least annually. We are aware of large groups of individuals that fall into a high-risk category and these are discussed below.

Impaired fasting glycaemia (IFG) and impaired glucose tolerance (IGT)

Both IFG and IGT are risk factors for cardiovascular disease (Jarrett, 1996; Tuomilehto et al, 2001). The WHO recommends an oral glucose tolerance test (OGTT) if one or two fasting plasma glucose levels are in the IFG range.

Hypertension, ischaemic heart disease (IHD) and stroke

The new GMS contract has allowed active case finding with the formation of disease registers for people with hypertension and a history of IHD and stroke. Almost all of these people will be under some form of recall system assisted by software that allows easy audit of monitoring cardio-metabolic factors that may predispose to the development of type 2 diabetes. Close attention to BMI, blood pressure, cholesterol levels and the development of chronic kidney disease allows a good degree of secondary prevention.

The proactive use of specific antihypertensive drugs – angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) – may be preferred as they are

Box 1. Diagnostic criteria.

- Diabetes: fasting glucose >7 mmol/l on two occasions.
- IFG: >6.1 mmol/l but <7 mmol/l.
- OGTT: oral load of 75 g.

Classification	Fasting	2 hours
Normal	<6.1	<7.8
IGT	6.1–6.9+	≥7.8–11.0
Diabetes	≥7.0	>11.1

Box 2. Cardiometabolic parameters assisting risk stratification for type 2 diabetes.

- Age, sex, ethnic group.
- Height, weight and BMI.
- Waist circumference.
- Blood glucose levels.
- Blood pressure.
- Family history.
- Renal function – creatinine and estimated glomerular filtration rate.
- Past medical history of ischaemic heart disease, myocardial infarct and stroke.

Box 3. Factors increasing surveillance of individuals at risk of type 2 diabetes.

- The *National Service Framework (NSF) for Diabetes: Standards* ensures people with diabetes are identified as early as possible (DoH, 2001).
- Incentives in the new GMS contract in medical services for domains of diabetes, stroke, hypertension, ischaemic heart disease, obesity and depression.
- Increased pathology testing, including fasting glucose, as a part of an annual screen for at-risk groups such as patients with hypertension, stroke and ischaemic heart disease (other tests include fasting lipid profile, urea and electrolytes, estimated glomerular filtration rate, creatine kinase levels and liver function tests).
- Better recall systems using computers.
- Improved personalised data collection.

associated with a lower incidence of developing diabetes, whereas β -blockers and diuretics both increase the risk (Yusuf et al, 2000; Lindholm et al, 2002; Julius et al, 2004; Abuissa et al, 2005).

Table 1. Prevalence of diabetes in England by ethnic group and sex (DoH, 1999).

	Standardised risk ratios	
	Men	Women
General population	1	1
Irish	1.4	1
Indian	3	2.9
Pakistani	5.4	5.6
Bangladeshi	5.8	5.8
Black Caribbean	2.5	4.2
Chinese	1.4	2.1

Polycystic ovarian syndrome (PCOS) and metabolic syndrome

Insulin resistance and its association with the endocrine properties of visceral fat appears to be the common factor in people with PCOS and type 2 diabetes. PCOS is the most common endocrine disturbance in women characterised by oligo- and/or anovulation, hyperandrogenism (commonly presenting as hirsutism) and polycystic ovaries on ultrasound (Balen, 2006).

The metabolic syndrome consists of several metabolic abnormalities including glucose intolerance, dyslipidaemia, obesity and hypertension (Alberti et al, 2006). Hence, this is another example of a syndrome that allows the easy identification of risk factors that allow the potential of monitoring within the primary care setting.

The insulin sensitiser metformin has been the subject of a Cochrane review supporting its use for anovulation in PCOS to treat sub-fertility, and with some evidence of benefit on parameters of the metabolic syndrome (Lord et al, 2003).

Ethnic groups

Numerous ethnic groups that have an increased susceptibility to developing type 2 diabetes now inhabit the UK, including South Asian individuals and those from an Afro-Caribbean background. Data from the NHS national survey show that the South Asian population is particularly at risk (Table 1; DoH, 1999). Not only do these groups bring with them a possible

increased genetic predisposition, but the host nation's affluent lifestyle is also acquired and this may compound the problem. On a global level, the largest increase in prevalence of diabetes is likely to be in India with an increasing affluent middle class arising from a booming economy.

At the cellular level, there may be a range of factors that influence this group to develop diabetes, in addition to genetic predisposition including lower adiponectin levels, higher CRP levels, higher plasminogen activator inhibitor and probable higher homocysteine levels. A higher susceptibility to the metabolic syndrome, a tendency towards central visceral obesity, and cultural and sedentary lifestyle factors all make multi-factorial contributions to the increased prevalence of diabetes (Bhopal and Fischbacher, 2002; Barnett et al, 2006). Challenges lie not only in making individuals responsive to personal lifestyle interventions that promote a healthy diet and more activity, but those that attempt to address some of the cultural barriers that resist change (Greenhalgh et al, 2005; Brown et al, 2007). The three main groups of South Asians – those from India, Pakistan and Bangladesh – have in themselves subsets with differing lifestyles not always apparent.

It may be prudent to have lower thresholds for starting statins for dyslipidaemia, anti-hypertensive drugs for hypertension and aggressive early use of oral hypoglycaemic drugs to delay the early development of cardiovascular disease in people at risk due to ethnicity.

Interestingly, the pathogenesis of type 2 diabetes may be linked to the coexistence of metabolic syndrome and PCOS in people of South Asian origin and may, in part, explain the increased prevalence of type 2 diabetes in this group (Weerakiet et al, 2007). There may even be a further link with male siblings of people with PCOS who are also at increased risk (Kaushal et al, 2004).

Gestational diabetes

The impact of both type 1 and type 2 diabetes in pregnancy on perinatal and maternal morbidity has been well documented (Macintosh et al, 2006; CEMACH, 2005). In gestational diabetes, glycaemic control often

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3. On a global level, the largest increase in prevalence of diabetes is likely to be in India with an increasing affluent middle class arising from a booming economy.
4. A higher susceptibility to the metabolic syndrome, a tendency towards central visceral obesity, and cultural and sedentary lifestyle factors all make multi-factorial contributions to the increased prevalence of diabetes.
5. In gestational diabetes, glycaemic control often reverts to normal shortly after childbirth. However, women have a substantially higher risk of developing type 2 diabetes later in life.

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2. Challenges lie in adopting the best method of reducing obesity to suit each individual.
3. Successful interventions to prevent the onset of diabetes need to be culturally sensitive, individualized and sustained.

reverts to normal shortly after childbirth and women who have experienced gestational diabetes have a substantially higher risk of developing type 2 diabetes later in life (Hunger-Dathe et al, 2006). Interestingly, migration of women from South Asian countries and Africa to Western Europe with consequent negative lifestyle changes (such as a diet of refined carbohydrates, lack of exercise and greater affluence) has compounded the figures (Kousta et al, 2001).

Obesity

The increase in the prevalence of obesity, a risk factor for type 2 diabetes and cardiovascular disease, means that obese people remain the single most challenging group to healthcare professionals. BMI remains the main marker for obesity but waist circumference has also been suggested (Wilding, 2007). What remains controversial and is currently not incentivised in the new GMS contract is the cut-off point at which aggressive case finding could be undertaken to identify high-risk individuals. Identifying and targeting those individuals with a BMI greater than 35 kg/m² is an easier task than one where a cut-off point of 30 kg/m² is used and where a register could rapidly enlarge with an inevitable workload implication. It may be that future revisions to the GMS contract will include assessments and interventions that promote weight loss in obese people.

A number of methods can be employed to reduce obesity, see *Box 5*. Challenges lie in adopting the best method of reducing obesity to suit each individual (Pinkney and Kerrigan, 2007). Behaviour modification is complex in this area, involving assessment of intention to change, repeated messages from respected health professionals and availability of personal and community resources to assist weight loss. Although drugs and surgery are suggested for resistant and extreme cases, there is scepticism about using external methods routinely in a condition that essentially requires close scrutiny to the internal locus of change in individuals, thus favouring a psycho-therapeutic approach

Box 5. Methods to reduce obesity.

- Increased physical activity: 30–60 minutes daily.
- Dietary measures: a lower calorie and higher dietary fibre intake, a low glycaemic load and a high polyunsaturated to saturated fat ratio.
- Pharmacotherapy: orlistat, sibutrimine and rimonabant. Short-term benefits have been observed, but long-term benefits are still to be demonstrated.
- Bariatric surgery: gastric restrictive procedures and malabsorption procedures.

(Ogden, 2002).

Iatrogenic effects of drugs

The effects of both long- and short-term use of steroids on glycaemic control are well established (British Medical Association and Royal Pharmaceutical Society, 2007). Another group of drugs that may also do this are the antipsychotic drugs, particularly olanzapine and clozapine in the treatment of schizophrenia (Leslie and Rosenheck, 2004).

Methods of modifying the risk of developing type 2 diabetes

Successful interventions to prevent the onset of diabetes need to be culturally sensitive, individualised and sustained (Narayan et al, 2002; Davies et al, 2004). The use of drugs in a pre-disease condition is limited by economic considerations and lack of sustainability of use in trials that lack feasibility to confirm long-term benefit. No trials have shown that prevention with pharmacotherapy improves outcomes important to patients (Montori et al, 2007).

Intensive lifestyle changes

NICE has published guidance dietary advice for a healthy lifestyle (see *Box 6*). A recent Cochrane review on the long-term effects of non-pharmacological weight loss for pre-diabetes using dietary, physical activity, or behavioural interventions showed significant improvements in weight among people with pre-diabetes and a significant decrease in diabetes incidence (Norris et al, 2007).

Box 6. Dietary advice for a healthy, balanced diet (NICE, 2006).

- Base meals on starchy foods, such as potatoes, bread, rice and pasta, choosing wholegrain where possible.
- Eat fibre-rich foods – oats, beans, peas, lentils, grains, seeds, fruit and vegetables, as well as wholegrain bread, brown rice and pasta.
- Eat at least five portions of fruit and vegetables.
- Eat a low-fat diet.
- Eat as little as possible of: fried foods; drinks and confectionary high in added sugars; and other food and drinks high in fat and sugar, such as some take away and fast foods.
- Eat breakfast.
- Watch portion size of meals and snacks.
- Avoid taking too many calories in the form of alcohol.

In a consensus statement, the American Diabetes Association have recommended that people with IGT undertake 150 minutes per week of moderate-to-vigorous exercise that should be combined with a healthy diet with moderate energy restriction (Sigal et al, 2006). A pragmatic approach to exercise guidance may be at least three episodes a week of exercise lasting 30 minutes to 1 hour where an acceleration of the heart is achieved.

Oral hypoglycaemic agents

When lifestyle alone has not achieved desired glucose tolerance goals then metformin alone could be considered in diabetes prevention strategy. For those who tolerate it, acarbose could also be considered. There are some promising results for glitazones, but recent associations with cardiac problems and lack of sustainable benefits currently limits its use in this context (DREAM 2006, Alberti et al 2007; Montori 2007).

Anti-obesity drugs

Orlistat has some less-weighted evidence (Heymsfield, 2000). Sibutramine has little evidence available for primary prevention of type 2 diabetes, and rimonabant shows some

promise in the short term when combined with exercise (Scheen et al 2006). Results of the RAPSODI (Rimonabant in Pre-diabetic Subjects to Delay Onset of Type 2 Diabetes) trial are awaited with interest.

ACE inhibitors and ARBs

A recent meta-analysis of the use of ACEs and ARBs in primary prevention show some promising results (Abuissa, 2005), but the recent DREAM (2006) study showed little benefit when ramipril was used.

Discussion

There is a view that primary care health professionals have for several years been exposed to the concept of ‘pre-disease’ syndromes. Just in case politicians and the public feel we are not doing enough for our patients with established conditions, the ‘worried well’ may increasingly be the focus of a surveillance culture to identify pre-diseases. To give an example, hypertension is a risk factor for ischaemic heart disease and stroke. Does this mean that hypertension is a disease? Other examples include osteoporosis as a risk factor for future fractures and chronic kidney disease as a risk factor for developing end-stage renal failure.

Although risk identification in the name of prevention, in theory, may reduce mortality figures, there inevitably follows an increase in morbidity in an aging population and its subsequent impact on resources and, in some cases, a poorer quality of life. The medical research community has yet to design trials that not only use reduced mortality figures as outcomes, but also quality of life issues in a consequent aging population. In theory, if diabetes could be detected earlier by detecting pre-diabetes, favourable morbidity and quality-of-life parameters may result.

It is highly likely that it is not a coincidence that quite a few of these high-risk groups have overlapping factors that predispose to type 2 diabetes, for instance, early insulin resistance, metabolic syndrome, ethnic groups (genetics, lifestyle and culture) and PCOS and this relationship may become clearer with further

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research.

In the author's opinion, there is no doubt that primary care has responded well to the many challenges of target setting in the new GMS contract. Future targets may include tackling obesity more aggressively and identifying groups at high risk of developing type 2 diabetes. Primary care could prepare for future changes to the GMS contract that could address identification of groups at risk, require periodic checks on these individuals, guide lifestyle changes and use lower thresholds for South Asians (see *Box 7*).

Striking the balance between what is achievable within given resources for the detection of 'pre-disease' and the psycho-social effects of medicalising the variety of lifestyles and behaviours that may or may not go onto to develop disease remains a challenge. Furthermore, indications to intervene in a 'pre-disease' should only be adopted where weighted evidence exists from high-quality trials. In the case of type 2 diabetes and the pre-diabetic state, focusing our energy on high-risk groups remains the approach of choice with the most appropriate intervention being aimed at promoting lifestyle changes to eat healthily and take more exercise to avoid obesity. ■

Box 7. Practical primary care approaches to identifying pre-diabetes.

- Consider producing an at-risk register of high-risk patients (see *Table 1*).
- High-risk patients are offered an annual 'risk assessment' to include monitoring of blood pressure, fasting glucose, lipids, BMI (and waist circumference).
- Use the annual assessment to advise on lifestyle changes – diet and engagement in exercise through individual target setting, group approaches and workplace based programmes.
- Consider lower thresholds for primary and secondary prevention in South Asian individuals with multiple risk factors.

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