

Pre-diabetes essential action: a European perspective

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Introduction

Type 2 diabetes is a modern world-wide epidemic. Its complications are now a significant cause of morbidity and mortality in every European country and the consequences of its explosive growth are an intolerable burden both to the individual and to healthcare systems.

The management of diabetes has become increasingly sophisticated over the past decade. Self management has been recognised and developed, there are now over a dozen pharmacological agents available to lower blood glucose (as well as blood pressure and dyslipidaemia), a multitude of ancillary supplies and equipment available, and there is a clear recognition by health care professionals and patients that diabetes is a serious disease. The normalization of blood glucose for any appreciable period of time, however, is seldom achieved. Even in well-controlled so-called “intensively” treated patients, serious complications still occur, and the economic and personal sequelae of diabetes remain [1-3].

Given these facts, it is not surprising that efforts have been initiated to determine the feasibility and benefit of various strategies to prevent or delay the onset of type 2 diabetes. Much of that effort has focused on what is now called “Pre-diabetes”.

Already, a more accurate definition and intense study of pre-diabetes has led to some important insights:

- Pre-diabetes is extremely common (as many as 40% of 40-74 year olds) [4] and needs to be addressed in clinical practice.
- People with pre-diabetes are at high risk of developing diabetes and cardiovascular disease (CVD) and are the ideal target population for prevention programs.
- There are safe, potentially effective interventions, which can affect modifiable risk factors.
- Intensive lifestyle interventions are efficacious and should be encouraged but they may be difficult to broadly apply and sustain.
- Effective pharmacological therapies have been identified to use in combination with these lifestyle interventions.

The enormous impact of diabetes on public health, and the impressive progress made recently in understanding and treating pre-diabetes have encouraged the production of this paper. Managing pre-diabetes is the most cost effective way to avoid the many sequelae of diabetes and importantly the cardiovascular disease that comes with it. If left untreated most of these individuals will go on to develop type 2 diabetes within 10 years and a high proportion of them will suffer from micro- or macrovascular disease [5-7].

A group of European physicians, a diabetes specialist nurse, and patient representatives has reviewed key issues about the nature, identification and management of pre-diabetes in the Europe. They have agreed the available evidence for each question (reviewed here) and where no data is available a consensus of opinion has been provided.

Key-words: Prediabetes · Impaired glucose tolerance · Impaired fasting glucose · Obesity · Metformin · Acarbose · Lifestyle.

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L'importance d'agir dans le pré-diabète : une perspective européenne

Mots-clés : Pré-diabète · Intolérance au glucose · Hyperglycémie modérée à jeun · Obésité · Metformine · Acarbose · Mode de vie.

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A call for urgent action

The authors consider that the following need urgent attention in order to curb the growing epidemic of pre-diabetes and support the prevention of type 2 diabetes and its associated cardiovascular morbidities:

- 1) According to data collected by the International Diabetes Federation, there are currently over 60 million Europeans with impaired glucose tolerance while the number of people with IFG is unknown. Estimates for the number of Europeans with pre-diabetes are not available but based on the above, it can be expected conservatively that one in every ten people already have pre-diabetes.
- 2) While there is clear evidence for an increase in pre-diabetes in adults, the same is happening in younger people.
- 3) The costs, both personal and societal, due to this epidemic are increasing.
- 4) Over 30 per cent of people with pre-diabetes will progress to type 2 diabetes.
- 5) A significant proportion of people with pre-diabetes will develop macrovascular cardiovascular disease e.g. ischaemic heart disease, myocardial infarction or stroke.
- 6) The detection and active management of pre-diabetes is now an urgent public health issue.
- 7) Governments and clinicians must devise both population based and high risk based prevention and management strategies.
- 8) Governments and health insurance companies must ensure that such public health programmes are adequately funded and monies are specifically allocated for prevention.
- 9) Any prevention strategy must be high quality, measurable and flexible.
- 10) Diet and Lifestyle modification must be the mainstay of treatment.
- 11) Should these not achieve an adequate response, metformin, acarbose and orlistat should be considered providing they have a license to treat.
- 12) Every effort must be made to prevent an individual with pre-diabetes being stigmatised as a result.

Question 1: Can we agree on a definition of pre-diabetes? How does it relate to impaired fasting glycaemia (IFG) and impaired glucose tolerance (IGT)? And should we view it as a true disease or just a risk marker?

Answer

– *Definition: Pre-diabetes is a metabolic condition characterised by insulin resistance and primary or secondary beta*

* Note: The group understand the strong link to metabolic syndrome, but our purpose here is to focus only on pre-diabetes.

cell dysfunction which increases the risk of developing type 2 diabetes.

– *IFG and IGT are not diabetes, but generally the presence of either or both is interpreted as indicating the existence of pre-diabetes.*

A working definition of pre-diabetes has been formulated as follows: “Pre-diabetes is a metabolic condition characterised by insulin resistance and primary or secondary beta cell dysfunction which increases the risk of developing type 2 diabetes” [8,9].

In practice, pre-diabetes should be viewed as an umbrella term used to describe individuals with impaired fasting glycaemia and/or an impaired glucose tolerance.

To be clear on our definitions in Europe: IGT is defined as a plasma glucose level of 7.8-11.0 mmol/l (1.40-1.99 g/l) 2 hours after ingestion of 75 g glucose in the setting of non-diabetic fasting plasma glucose levels. There is more debate as to the exact cut off point for IFG, but generally it is understood to exist at plasma glucose levels between 6.1 and 7.0 mmol/l (1.10-1.25 g/l) in a fasting sample [9] (Table I).

The term pre-diabetes brings both IFG and IGT usefully together and creates a clear predictor of risk. Individually both IFG and IGT have different implications of risk and different causes.

Pre-diabetes is an easy to understand term indicating that glucose is not being processed efficiently in the body but frank diabetes has not yet taken hold. It can thus be utilized effectively as a tool to convince people who have IGT or IFG that actions have to be taken to prevent serious long-term morbidity and mortality.

Both IFG and IGT are associated with a substantially increased risk; with the combination of both establishing the highest risk of developing type 2 diabetes [11].

Table I
Comparison of diagnostic criteria for the diagnosis of diabetes, IGT and IFG.

	Diabetes	Impaired glucose tolerance	Impaired fasting glucose
Current ADA criteria (2003) (10)			
Fasting plasma glucose (mmol/l)	≥7.0	< 7.0	5.6 — 6.9 mmol/l
Two hour plasma glucose (mmol/l)	≥11.1	7.8 — 11.1 mmol/l	< 7.8
Current WHO criteria			
Fasting plasma glucose (mmol/l)	≥7.0	< 7.0	≥6.1 but < 7.0
Two hour plasma glucose (mmol/l)	≥11.1	≥7.8 but < 11.1	< 7.8 (if measured)

It is inaccurate to describe pre-diabetes as a true disease, rather people who have pre-diabetes are best viewed as an “at-risk population” for the future development of what are undoubtedly two significant and serious diseases: type 2 diabetes and CVD.

Question 2: What do we know about the pathophysiology of pre-diabetes?

Answer

– *Pre-diabetes is related to obesity, a sedentary lifestyle and high fat and saturated fatty acid diets which in turn can slowly trigger the development of peripheral and hepatic insulin resistance. But the failure of the β cell to compensate for insulin resistance is also an early disorder which may occur by the prediabetic stages.*

Three key pathophysiological defects characterise type 2 diabetes

– *Peripheral insulin resistance and hepatic insulin resistance*

– *Insulin deficiency*

– *with consequent decreased glucose utilisation and increased hepatic glucose production.*

While both genetic and non-genetic markers are associated with the development of type 2 diabetes, the non-genetic factors including obesity, sedentary lifestyle, high fat and saturated fatty acid-rich diets have been shown to be particularly important especially in those over 45.

Epidemiological studies have also indicated that the risk of developing type 2 diabetes is increased in people regularly consuming a diet made up of high proportions of animal fats, carbohydrates (especially those with a high glycaemic index e.g. potatoes, white bread, sweets etc) and low fibre foods. Exactly how these factors produce insulin resistance and/or this reduction of insulin secretion is unclear.

The pathophysiological basis of both IFG and IGT are not the same [9]: this is because the determinants of elevated fasting glucose and 2 hour plasma glucose in an oral glucose tolerance test (2-HPG) levels differ. Specifically, these are:

– IFG: raised hepatic glucose output and a defect in early insulin secretion.

– IGT: peripheral insulin resistance and later a defect in insulin secretion.

– The concordance between the categories of IFG and IGT is therefore limited.

However, these conditions are probably heterogeneous regarding pathogenic mechanisms.

Individuals who meet the criteria for IGT or IFG usually have HbA_{1c} values that are within or only just above the normal range. However even this degree of hypergly-

caemia is clearly associated with other metabolic and cardiovascular abnormalities.

Question 3: How prevalent is pre-diabetes in Europe and are we more likely to find it in specific “high risk” groups?

Answer

– *Pre-diabetes is increasing rapidly in Europe*

– *Populations with IGT and IFG are not the same*

– *Pre-diabetes is more common in certain high risk populations*

Type 2 diabetes accounts for between 80% and 90% of all diabetes cases in Europe [12]. Projections for the prevalence of type 2 diabetes in Europe reveal that the number of people with this condition will have increased by almost 6 million between 1995 and 2010 [13].

Table II gives the figures for IGT prevalence in the major European countries. Although there are some inconsistencies in these numbers (particularly in Germany) they do demonstrate the broad split by age and sex and the significant preponderance of pre-diabetes that exists in the 60-79 group. Interestingly, although not shown in this table for simplicity's sake, the percentage of IGT sufferers as a proportion of that population also increases with age.

A survey carried out in Copenhagen (Denmark) [14] showed that 24.7% of males and 17% of females aged 60 years or more had IGT, indicating an increase of 70% and 40% respectively over a 10-year period. The prevalence of Type 2 diabetes in children is also increasing in conjunction with obesity due to environmental and behavioural changes.

The high prevalence of pre-diabetes in Europe is a consequence of the relatively old population – currently over 30% of the region's population is over 50 (and expected to rise to over 40% by 2025) (IDF data).

In all prevalence studies to date, up to half of subjects with IFG have IGT whereas a lower proportion (20-30%) with IGT also have IFG.

In the majority of populations studied, IGT is age-related which means IGT is more prevalent in ageing populations; IFG on the other hand is more prevalent in younger people. This means that IGT is more prevalent than IFG - there is a difference in phenotype and gender distribution between the two categories. IFG is significantly more common among men and IGT slightly more common in women (IDF data).

Significant differences in prevalence among ethnic groups is also well known with Asians, African, and Hispanic populations having significantly higher levels of diabetes (both 1 and 2) than Caucasians. There is also a strong link with the metabolic syndrome.

Table II
IGT prevalence estimates for adults in Europe (2003) (IDF figures).

Country	Pop (20-79) (000's)	IGT Prev alence (%)	Male	Female	No. of people with IGT (000's)						
					20-39 years	40-59 years	60-79 years	Total	%	%	%
B	7,531	6.4	237.8	243.7	54.8	11.38	141.6	29.4	285.0	59.19	481.5
F	42,546	5.6	974.6	1415.2	457.4	19.14	829.3	34.7	1103.1	46.16	2,389.9
D	61,895	6.3	1849.6	2049.5	6.4	0.16	840.5	21.56	3052.2	78.28	3,899.1
I	43,925	5.8	1042.0	1513.3	467.0	18.28	800.6	31.33	1287.6	50.39	2,555.2
NL	11,678	5.9	352.0	334.6	90.5	13.18	232.6	33.88	363.6	52.96	686.6
E	30,329	9.9	1209.7	1794.6	838.4	27.9	973.2	32.39	1192.6	39.7	3,004.3
Sw	6,290	9.0	181.9	383.7	98.9	17.48	169.5	29.97	297.2	52.55	565.6
UK	42,423	5.1	1362.3	783.8	591.3	27.55	904.1	42.13	650.7	30.32	2,146.1
Total	246,617					15.7%		31%		52%	15,727.1

IGT in Europe shows little association with affluence and there is no evidence that any difference in urban/rural prevalence exists.

In summary, groups at high risk of pre-diabetes can be clearly identified as people having one or more of the following conditions including:

- Family history of diabetes
- Excess body weight (high BMI) particularly abdominal adiposity
- Over 45 years
- Gestational diabetes
- High birth weight children
- Certain ethnic groups
- Hypertension
- Physical inactivity

Question 4: Can we quantify the risk of pre-diabetes both in terms of diabetes and cardiovascular disease?

Answer

- People with pre-diabetes are a risk population for the development of type 2 diabetes and cardiovascular disease.
- Approximately 30% of people with IGT will convert to type 2 diabetes within 5 years
- Approximately 40% of people with IGT will revert to normal over a period of years

There is now a clear and strong linkage between glucose levels above normal but below the thresholds diagnostic for diabetes and a substantially increased risk of developing type 2 diabetes, cardiovascular disease [15] (CVD) and death.

In terms of diabetes risk, a great deal of heterogeneity exists in the rates of progression to diabetes in different

populations. Recent data suggest that the annual rates of progression to type 2 diabetes from IGT range from 2.3% per year to 11.0% per year with higher rates in non-white racial/ethnic groups. The average conversion rate was estimated at 5.8% per year with wide variations which are likely to depend on differences in age, BMI, ethnicity etc across the studies.

Below are listed the conversion rates from IGT to type 2 in the control group of the key intervention trials:

- 67.7% in the Da Qing study [16] in 6 years
- 58% in the Diabetes Prevention Program (DPP) [17] after 2.8 years
- 23% in the Diabetes Prevention Study (DPS) [18] in 4 years
- 42% in STOP NIDDM study [19,20] in 3.3 years
- 28.8% in the IGT sub-population of the XENDOS study [21] after 4 years

In the Hoorn study [11], the risk of conversion to type 2 diabetes during 6.4 years of follow up was 51.4/1000 person years for IFG compared with 57.9/1000 person years for IGT and 7.0/1000 person years for those with normal glucose levels. The incidence of diabetes after 6.4 years for participants with both IFG and IGT was 64.5% versus 4.5% for those with normal glucose levels and the relative risk of diabetes was four times higher when both IFG and IGT were present as opposed to the risk when only one was there.

However it should be noted that a substantial proportion of people with IGT remain static or even revert back to normal glucose tolerance (although there is no agreement of the exact level) [22,23]. In the Singapore Impaired Glucose Tolerance Follow-Up Study [24] of the IGT subjects, 41.4% reverted to NGT, 23.0% remained glucose intolerant, and 35.1% developed diabetes over 8 years.

In addition, IGT and type 2 diabetes have a number of risk factors in common, including obesity (particularly

abdominal adiposity), advanced age, prior gestational diabetes, family history of type 2 diabetes, a predilection for some racial/ethnic groups, dyslipidemia, hypertension and insulin resistance. This overlap supports the argument that IGT is a precursor of type 2 diabetes, but the specific contribution of each risk factor to progression from IGT to type 2 diabetes has not been quantified in the literature.

Cardiovascular risk

Patients with IGT are at high risk for the development of a cardiovascular disease. The most convincing evidence of increased CVD risk was provided by the DECODE (Diabetes Epidemiology: Collaborative analysis Of Diagnostic criteria in Europe) study [5]. In this study, data from 10 prospective European cohort studies including 15388 men and 7126 women aged 30-89 years were collaboratively analysed. People with IGT had a high risk of death compared with those without IGT, but subjects with IFG did not have increased risk of death compared with those with normal fasting glucose levels. Furthermore, the DECODE study revealed that abnormalities in 2-hour glucose were better predictors of mortality from all cause, CVD and CHD than fasting glucose alone. A high 2-hour glucose concentration was found to be associated with an increased risk of death, independent of the level of fasting blood glucose, whereas mortality associated with the fasting glucose concentration depended on the level of 2-hour glucose).

IGT is not so clearly a risk factor for microvascular complications.

Question 5: What evidence have we that actively managing pre-diabetes is beneficial in preventing diabetes and or CVD?

Answer

– At least 5 well-designed trials now confirm the benefits of intervention in pre-diabetes – the Finnish Diabetes Prevention Study, the Diabetes Prevention Program, the STOP-NIDDM trial, the Da Qing study and the XENDOS study (Table III).

Five well-designed randomized controlled trials have been reported that now categorically confirm the benefits of intervention in pre-diabetes.

In the Finnish Diabetes Prevention study [18], middle-aged (mean age 55 years) obese (mean BMI 31 kg/m²) subjects with IGT were randomized to receive either usual standardized diet and exercise counselling (control group) or intensive individualized instruction on weight reduction, food intake, and guidance on increasing physical activity (intervention group). After an average follow-up of 3.2 years, there was a 58% relative reduction in the incidence of diabetes in the intervention group compared with the control subjects. This appears to be due principally to the improvement of insulin sensitivity when losing weight (goal was 5.0% weight reduction). A correlation was also seen between the ability to stop the progression to diabetes and the degree to which subjects were able to achieve one or more of the following:

Table III
Summary of major findings from key diabetes prevention studies.

Study	Comparators	Follow up (Av.)	Results
Finnish Diabetes Prevention Study (18)	Control group: usual standardized diet and exercise counselling. Intervention group: intensive individualized instruction on weight reduction, food intake, and guidance on increasing physical activity.	3.2 yrs	58% relative reduction in the incidence of diabetes
Diabetes Prevention Program (17)	Intensive lifestyle group: intensive nutrition and exercise counselling. Metformin group (+ brief diet and exercise + counselling). Placebo group (+ diet and exercise + counselling)	2.8 yrs	58% relative reduction in diabetes in the intensive lifestyle group. 31% relative reduction in the metformin group
STOP-NIDDM trial (19)	Acarbose or placebo (+diet and exercise)	3.3 yrs	25% relative reduction in diabetes
Da Qing study (16)	Diet group. Exercise group. Diet plus exercise group	6 years	31% relative reduction in diabetes in diet group. 46% reduction in exercise group and 42% in diet plus exercise group
XENDOS study (21)	Lifestyle changes + orlistat 120mg tds or placebo	4 years	37.3% diabetes risk reduction in orlistat group (difference in diabetes incidence only detectable in IGT subgroup)

- lose weight (goal of 5.0% weight reduction)
- reduce fat intake (goal of < 30% of calories)
- reduce saturated fat intake (goal of < 10% of calories)
- increase fibre intake (goal of [greater than or equal to] 15 g/1,000 kcal)
- exercise (goal of > 150 min/week)

No untoward effects of these lifestyle interventions were observed.

In the DPP [17], the 3,234 enrolled subjects were slightly younger (mean age 51 years) and more obese (mean BMI 34 kg/m²) but had nearly identical glucose intolerance compared with subjects in the Finnish study. About 45% of the participants were from minority groups (e.g. African-American, Hispanic), and 20% were > 60 years of age. Subjects were randomized to one of three intervention groups, which included the intensive nutrition and exercise counseling (“lifestyle”) group or either of two masked medication treatment groups: the metformin group or the placebo group. The latter interventions were combined with standard diet and exercise recommendations. After an average follow-up of 2.8 years (range 1.8-4.6 years), a 58% relative reduction in the progression to diabetes was observed in the intensive “lifestyle” group (absolute annual incidence 4.8%), and a 31% relative reduction in the progression of diabetes was observed in the metformin group (absolute annual incidence 7.8%) compared with control subjects (absolute annual incidence 11.0%). On average, 50% of the “lifestyle” group achieved the goal of - greater than or equal to - 7% weight reduction, and 74% maintained at least 150 min/week of moderately intense activity. No serious side effects were seen in any group.

In the STOP-NIDDM trial [19,20], 1,429 participants with IGT were randomized in a double-blind fashion to receive either the alpha-glucosidase inhibitor acarbose or a placebo. The subjects had a mean age of 55 years and a mean BMI of 31 kg/m². After a mean follow-up of 3.3 years, a 25% relative risk reduction in progression to diabetes, based on one OGTT, was observed in the acarbose-treated group compared with the placebo group. If this diagnosis was confirmed by a second OGTT, a 36% relative risk reduction was observed in the acarbose group compared with the placebo group. The absolute risk reduction in the acarbose-treated group was 9%. The effect of acarbose was consistent among all age groups, between both sexes and irrespective of BMI values (but gone after wash out).

The Da Qing study [16] was also a multi-centre randomised study that assessed the effect of intervention with diet, exercise or diet plus exercise, relative to control, in 530 Chinese subjects with IGT. Subjects were middle aged individuals with a mean age of 45 years, a BMI of 26 kg/m², IGT, and a mean FPG of 5.59 mmol/L. Follow up was conducted over a period of 6 years. The cumulative incidence of diabetes in the diet (43.8%), exercise (41.1%) or diet plus exercise (46.0%) group was significantly lower when com-

pared with the control group (67.7%; $P < 0.05$). After adjusting for differences in baseline BMI and fasting glucose, this corresponded to significant reductions in risk of developing diabetes of 31% ($P = 0.03$), 46% ($P < 0.0005$) and 42% ($P < 0.005$) in the diet, exercise, and diet plus exercise interventions respectively.

The Xendos study [21] looked at the effect of adding a weight reducing agent (orlistat) to lifestyle changes in obese patients thus reducing diabetes incidence through a reduction in weight. In a 4 year, double blind, prospective study, 3,305 obese patients were randomised to lifestyle changes plus either orlistat 120 mg or placebo three times daily. Participants had a BMI ≥ 30 kg/m² and normal (79%) or impaired (21%) glucose tolerance test. Primary endpoints were time to onset of type 2 diabetes and change in body weight. Of orlistat treated patients, 52% completed treatment compared with 34% of placebo recipients ($P = 0.0001$). After 4 years treatment, the cumulative incidence of diabetes was 9.0% with placebo and 6.2% with orlistat corresponding to a risk reduction of 37.3% ($P = 0.0032$). The preventive effect was explained by the difference in subjects with IGT. In patients with IGT at baseline, orlistat plus lifestyle changes significantly decreased the progression to type 2 diabetes when diagnosed on the basis of a single test ($P = 0.0024$). Cumulative incidence rates after 4 years were 18.8% with orlistat and 28.8% with placebo corresponding to a 45% risk reduction. In addition, orlistat plus lifestyle changes significantly decreased the progression to type 2 diabetes when diagnosed by repeat positive testing in this subgroup with IGT. Cumulative incidence rates after 4 years were 8.3% with orlistat versus 14.2% with placebo, corresponding to a 52% risk reduction.

Based on these studies it appears that the active management of pre-diabetes is highly effective in preventing the progression of diabetes. Accordingly the number of IGT subjects needed to treat in order to prevent one case of diabetes is really low, as shown in Table IV.

Table IV
Number of IGT patients to treat in order to prevent one case of diabetes.

Study	Modality	NPT*	Duration
DPS (18)	Lifestyle	5	5
DPP (17)	Lifestyle	6.9	3
	Metformin	13.9	3
STOP-NIDDM (19)	Acarbose	11	3.3
Da Qing (16)	Lifestyle	6	6
XENDOS (21)	Orlistat	10	4

*NPT = Number of Patients to Treat.

Question 6: What strategies should we adopt to identify pre-diabetes?

Answer

– Detection of pre-diabetes should be based upon either a population based strategy or by opportunistically or systematically looking for pre-diabetes in at risk individuals.

Currently there are no universally accepted approaches to detecting pre-diabetes.

Detection can realistically be approached in two ways:

– population-based strategy

– high risk strategy

- systematically
- opportunistically

The goal of the population-based strategy is to prevent obesity and metabolic syndrome in all age groups. The target group is an entire national population and all the stakeholders have responsibilities in the process. Action must be taken both at societal and individual level.

The high risk strategy aims to prevent the onset of type 2 diabetes in people belonging to risk groups [25]. Screening of people in these groups is central to this strategy.

Current evidence suggests that opportunistic screening to detect IFG or IGT should be considered in individuals > 45 years of age and is strongly recommended in those > 45 years of age and overweight (BMI ≥ 25 kg/m²). Opportunistic screening should also be considered if a cardiovascular event occurs since IGT may be detected after acute MI in around one third of patients [26]. Screening should also be considered for people who are < 45 years of age and are overweight if they have another risk factor, such as a first-degree relative with diabetes or previous gestational diabetes or macrosomia in one or more children or if they are of an ethnicity other than Caucasian [27] or have hypertension or dyslipidemia. Asians should be considered for screening at lower levels of BMI (e.g., 23 kg/m²). There are no data that support screening of children for IFG or IGT, although there are recommendations for screening children for diabetes. Lastly, patients with thyroid dysfunction should also be tested.

Screening should be performed using either the FPG test or 2-hour OGTT. It is preferable that the FPG test be given in the morning because afternoon values tend to be lower [28]. Although it is clear that the 2-hour OGTT will detect more cases of glucose intolerance and undiagnosed diabetes than the FPG test at current cut points, the proportion who progress to diabetes from IFG or IGT is similar. Given the age-related incidence of diabetes and the rate of progression to diabetes in normoglycemic middle-aged subjects, repeat testing at 3-year intervals should be considered.

The case for screening is strengthened by the fact that this will not only detect cases of IFG or IGT, but also cases of undiagnosed diabetes [29]. Thus, policies to identify indi-

viduals for whom it is appropriate to initiate a diabetes prevention strategy will also identify individuals who should receive immediate treatment for diabetes. Furthermore, because individuals with IFG, IGT, or undiagnosed diabetes are at high risk for CVD, their identification should herald increased surveillance and treatment for hypertension, dyslipidemia, and tobacco use.

Initiatives to screen for diabetes or pre-diabetes, either opportunistically in defined high-risk groups or in more general populations, are already underway in a number of countries.

Question 7: What screening tests could we use?

Answer

Blood glucose testing

– There is general agreement both in Europe and the USA that either an FPG test or fasting and 2-hour OGTT can be used to screen effectively for IFG or IGT.

Three studies (including the Hoorn study) have examined whether the FPG test or 2-hour OGTT is a better predictor of future diabetes. In each study, a fasting and 2-hour OGTT value was obtained at baseline and follow-up. The cumulative incidence of diabetes over 5-6 years was low (4-5%) in those individuals starting with a normal fasting and normal 2-hour OGTT value; intermediate (20-34%) in those with IFG and a normal 2-hour OGTT or IGT and a normal FPG; and highest (38-65%) in those with combined IFG and IGT. There was virtually no difference in the rate of progression to diabetes if a person had IFG or IGT. In the USA Harris et al. [30] reported that some individuals with a normal FPG level will have IGT or diabetes if a 2-hour OGTT is performed, but fewer people (usually older individuals) with a normal 2-hour OGTT will have IFG or diabetes if an FPG test alone is done. These observations have been confirmed repeatedly in virtually every population that has been studied.

Using the current definitions of IFG, IGT, and diabetes [31], the 2-hour OGTT appears to identify more people who have impaired glucose homeostasis and thus, more people who will progress to diabetes. However, Gabor et al. [32] pointed out that the differences in the proportion of subjects with IGT or IFG “reflect the fact that they represent different proportions of the glucose distributions rather than that FPG or the 2-hour OGTT value per se are inherently different in their sensitivity, specificity, or predictive power.” It has been suggested, therefore, that if the cut off point of IFG were lowered to 5.5 mmol/L (1.0 g/l), the FPG and 2-hour OGTT would have similar sensitivity and positive predictive values (but they would not necessarily include the same individuals) [33,34].

In November 2003, the American Diabetes Association expert committee on the diagnosis and classification of diabetes mellitus [10] suggested just such a revision of the diagnostic criteria for IFG, lowering the diagnostic threshold from 6.1 to 5.6 mmol/l. Borch-Johnsen et al [35] showed that this proposed change would identify 60% of all subjects with IGT compared to 29.2% with the old criteria, but among individuals with the new IFG category only 18.5% would also have IGT. Thus the proposed revision would lead to a dramatic increase in the prevalence of IFG, but the concordance rate with IGT would remain low. This new IFG group will also have a more favourable cardiovascular risk profile than the current IFG group (as defined by the WHO). In addition they say, "this seriously questions whether the existing intervention strategies are applicable to the new category of individuals with IFG."

Regarding the tests themselves, the FPG test is more convenient to patients, less costly, and easier to administer than the 2-hour OGTT.

For all the above reasons, either plasma glucose measurements only at fasting or at fasting and with 2 hour OGTT added can be used to screen for IFG and IGT. But doing both measurements increases the likelihood of diagnosis. Alternatively, some investigators have proposed logistic regression models using multiple risk factors, from which a "risk score" can be created. If this work can be confirmed and the sensitivity, specificity, and predictive value is acceptable, such an approach would have great advantages and utility.

Diabetes Risk Scoring

– *Risk scoring tests have been shown to be very useful in the detection process [31,32].*

– *That developed by the National Public Health Institute in Finland is a good example of best practice.*

A scoring system has been developed by the National Public Health Institute in Finland and also in Denmark [27,36,37] and Germany.

The Finnish Risk Test Form has eight scored questions, with the total test score providing a measure of the probability of developing type 2 diabetes over the following 10 years. The reverse of the form contains brief advice on what the respondent can do to lower their risk of developing the disease, and whether they should seek advice or seek medical attention. The test takes only a couple of minutes to complete and can be easily done on the internet www.diabetes.fi/diabetiet/d2testi/ (Questions are in Finnish), in pharmacies or at various public campaign events. Risk Test Forms are available in Finnish and Swedish from the Finnish Diabetes Association. The Risk Test is based on a highly representative random sample of the Finnish population, derived from the FINRISK 1987 and FINRISK 1992 surveys [35]. The incidence of diabetes in these people was monitored until the end of 1997 through the Register

on Preferential Drug Reimbursement kept by the Social Insurance Institution.

Seven variables clearly correlated with the risk of developing diabetes were chosen for the test: age, bodymass index, waist circumference, use of antihypertensive medication, history of elevated blood glucose, meeting the criterion for daily physical activity and daily intake of fruit or vegetables. It proved impossible to determine the use of fats with a single question, and this item had to be omitted. The variables were assigned scores according to the relative risk conferred by each, yielding a range of 0-21 for the total score. On the basis of other studies, history of diabetes in the family was incorporated in the final Risk Test, which made the maximum score 26. The respondent's likelihood of developing diabetes is higher, the more points scored in the test.

P. Valensi et al. recently conducted a cross-sectional survey in a population of patients consulting a General Practitioner in France, without known diabetes, having at least one risk marker for diabetes according to the ANAES 2003 guidelines** and having at least one fasting plasma glucose measurement within the previous three years. They confirmed the high prevalence of unknown type 2 diabetes (10.8%) and impaired fasting glucose (23.4%) in this population and thus the relevance of these screening criteria [38].

Age considerations and frequency of review

No study has explicitly addressed the age at which screening should begin, the optimal frequency of screening, or other indications for screening. In the Finnish, DPP, and STOP-NIDDM trials, participants were much older and heavier than the population initially screened, suggesting that individuals > 45 years of age and who are substantially overweight are most likely to have IGT (or IFG). In a cross-section of U.S. adults tested between 1988 and 1994 [39], the prevalence of IFG or undiagnosed diabetes in people 40-74 years of age was 14.5%. The prevalence of IGT or undiagnosed diabetes (by 2-hour OGTT) in people from the same population was 22%.

The prevalence of IFG or undiagnosed diabetes (by FPG) increases greatly between age 20 and 39 years and age 40 and 49 years and reaches a peak in people aged 60-74 years. The prevalence of IFG, IGT, or undiagnosed diabetes in those > 45 years of age and who are overweight (BMI > 25 kg/m²) are 9.3%, 12.8%, and 7.3%, respectively (M.I. Harris, personal communication).

These data suggest that IFG or IGT is much more likely to be detected in overweight middle-aged individuals than in younger lean individuals. Finally, in a subset analy-

** Subjects over age of 45 and presenting at least with at least one risk factor: - metabolic markers (BMI ≥ 28 kg/m², hypertension, HDL-cholesterol ≤ 0.35 g/l or triglycerides ≥ 2 g/l or treated dyslipidemia), or a history of temporarily induced diabetes, family history of diabetes (first degree relative) or gestational diabetes or child birth weight ≥ 4 kg.

sis of the DPP, there was a trend toward greater success of the lifestyle intervention among the elderly than among those < 45 years of age. This provides further support for initiating screening at middle-age when the intervention to be implemented is more effective.

Excess in abdominal adiposity

A number of studies have found that BMI and fat distribution are independent risk factors for diabetes particularly in men. In a US study the relative risk of diabetes was correlated with BMI after multivariate adjustment (Fig 1). Central abdominal adiposity in particular has been shown to be a strong indicator of diabetes risk. An analysis of a cohort of over 50,000 US male health professionals [40] 40-75 year of age followed for 5 years showed that waist circumference is a better indicator than waist to hip ratio (WHR) of the risk of diabetes (272 cases of type 2 diabetes developed) (Table V).

Although early obesity, absolute weight gain throughout adulthood and waist circumference are good predictors of diabetes, attained BMI is the dominant risk factor for

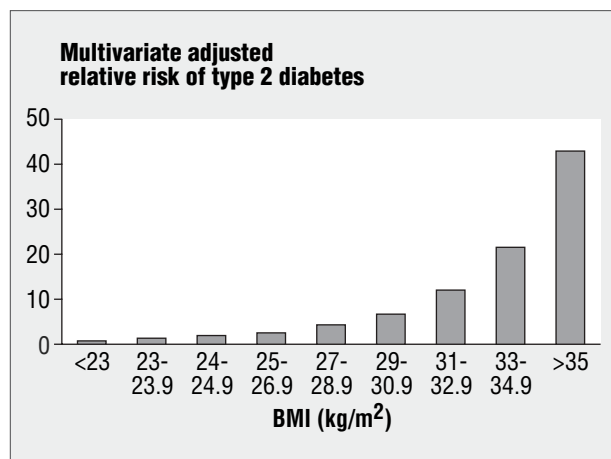


Figure 1 Obesity as a risk factor for type 2 diabetes in men after adjustment for age, family history and smoking status (40).

Table V

Influence of waist circumference on development type 2 diabetes in men (40).

Waist (cm)	<88	88-91	92-96	97-101	>102
RR** of type 2 diabetes	1.0	2.0	2.2	3.3	12.0
After adjustment*	1.0	1.7	1.7	1.9	3.5
Waist to Hip Ratio	<0.9	0.9-0.92	0.93-0.95	0.96-0.99	>1.0
RR for type 2 diabetes	1.0	0.9	1.9	2.5	4.6
After adjustment*	1.0	0.8	1.3	1.4	1.7

**RR = Relative Risk. *For family history of diabetes, BMI, smoking.

type 2 diabetes; even men of average relative weight have significantly elevated relative risk. Even in youth, abdominal obesity is an important signal of future risk [41].

Question 8: How should we be managing pre-diabetes in clinical practice?

Answer

- Diet and lifestyle modification are without the doubt the first line of management
- These interventions must be intensive and persist lifelong to achieve their effects, be regularly monitored and supported by diabetes healthcare professionals
- Despite this effort, a large proportion do not achieve the necessary targets to reap the benefits of their changes in behaviour; furthermore most healthcare systems do not reimburse for such activities
- Effective pharmacological interventions must therefore be actively explored

The strategies shown to be effective in preventing diabetes rely on lifestyle modification or glucose-lowering drugs that have been approved for treating diabetes. The DPP is the only study in which a comparison of the two was made, and intensive lifestyle modification was nearly twice as effective in preventing diabetes (58 vs 31% relative reductions, respectively) [17]. However, the greater efficacy of metformin in younger, severely obese individuals compared with older, less overweight subjects strongly suggests that this pharmaceutical intervention may be particularly effective in this subset of patients. Furthermore, given the difficulty most individuals had in maintaining lifestyle modifications, pharmacological intervention combined with diet and exercise counselling may be the most realistic option for achieving real reductions in diabetes incidence in all age groups.

Lifestyle modification

In the two well-controlled studies that included an intensive lifestyle intervention arm, substantial efforts were

necessary to achieve only modest changes in weight and exercise, but those changes were sufficient to achieve an important reduction in the incidence of diabetes. In the Finnish study, weight loss averaged 4.17 kg at 1 year, 3.49 kg after 2 years, and 2.09 kg after 5 years [18]. The exercise component of the intervention called for “moderate exercise” of 30 min/day. In the DPP, the intensive lifestyle group lost 5.44 kg at 2 years and 4.08 kg at 3 years (mean weight loss for the study duration was about 5.44 kg or 6% of initial body weight) [17]. In both of these studies, most of the participants were obese (BMI > 30 kg/m²).

In the Finnish study [18], the intervention group had seven sessions with a nutritionist during the first year of the study and one session every 3 months thereafter. They also received individualized guidance on increasing physical activity, and over 50% of the participants in the first year of the study received supervised progressive individually tailored physical training sessions. Free membership to an exercise club was also offered.

In the DPP [17], participants in the lifestyle arm met with a case manager 16 times over the first 6 months and then generally monthly thereafter. They made telephone contact at least monthly. Group courses on exercise and weight loss taking place regularly over 4-6 weeks were offered every 3 months. Also, two supervised exercise sessions were offered each week. Moreover, anyone having difficulty achieving or maintaining the study's goals for weight loss or exercise were offered incentives, such as exercise tapes or equipment, free enrolment in exercise facilities, free low-calorie foods, more structured eating plans, and home visits for encouragement and counselling.

Bearing in mind the modest lifestyle goals of both studies (5% reduction in body weight and 150 min moderate exercise/week in the Finnish Study and 7% weight reduction and 150 min/week self-reported moderate physical activity in the DPP) and the fact that the participants were already motivated to join a clinical trial, it is discouraging that the substantial levels of effort described above were only partially successful in achieving the desired objectives. In the Finnish study, only 43% achieved the weight reduction goal, and 36% of subjects increased their physical activity. In the DPP, only 50% reached the weight loss goal, and 74% reached the exercise goal. In both studies, some weight was regained despite the continuation of intensive strategies. Those that did attain the weight loss goal however tended to keep it off for the duration of the study.

The intensive lifestyle intervention used in the DPP appeared to prevent or delay the onset of diabetes for 3 years. Although not designed to determine directly whether there was also CVD benefit, both the Finnish study and the DPP reduced the magnitude of some CVD risk factors. Lifestyle intervention appears to be very safe, and, therefore, regular monitoring for untoward effects is unnecessary. Because ~3-5% of the lifestyle cohort and 6-11% of the control group in the studies developed diabe-

tes per year, which mirrors the rate of progression in other studies, monitoring for the development of diabetes every 1-2 years in patients who have IFG or IGT seems warranted.

Low-cost ways to reinforce lifestyle goals are greatly encouraged, and low-cost community-based programs to increase physical activity and avoid unhealthful lifestyle choices offer potential benefits for people who are at risk for diabetes. This reinforces the fact that positive lifestyle practices must be supported continuously – a lifelong commitment.

A health economic study in the USA of the within trial cost effectiveness of the DPP study showed that intensive lifestyle counselling costs \$2269 more per patient over three years compared with standard lifestyle advice with direct costs per type 2 diabetes case prevented of \$4-15,000. Costs for quality adjusted life year gained during the 3 year period were calculated to be \$8100 to \$31,700 for intensive lifestyle counselling versus control [42,43]. More work is needed to be done to compare the effectiveness and cost effectiveness of various intensive lifestyle and dietary programmes and pharmacological regimens to identify the most efficient diabetes prevention strategy.

Although many lifestyle change strategies have been developed in people with type 2 diabetes, almost all have been difficult to accomplish and maintain [44-48].

In one study, however, it was possible to show the long-term effectiveness of a structured counseling strategy to promote the adoption and maintenance of physical activity by people with type 2 diabetes. After two years from the behavioral intervention, 69% of study patients still achieved the target weekly energy expenditure (> 10 METs Δ h/week*) versus 18% in the control group. The average energy expenditure was 27.1 and 4.1 METs Δ h/week* in the study and in the control groups respectively [49]. A post-hoc analysis of the long-term effects of different amounts of increased energy expenditure has shown an improvement of Hb A_{1c}, blood pressure, total serum cholesterol, triglycerides and estimated % 10-year CHD risk, associated to an energy expenditure > 10 METs Δ h/week*. For an energy expenditure > 20 METs Δ h/week*, there was also an improvement of body weight, waist circumference, heart rate, fasting plasma glucose, serum LDL and HDL cholesterol. The amount of METs Δ h/week* correlated positively with the improvement of all measured variables. The cost analysis showed that per capita/year costs of medications decreased proportionally to the energy expenditure, from 10 to about 30 METs Δ h/week*. The counselling intervention is judged by the authors to be relatively simple and little time consuming, but requiring trained and motivated personnel [50].

*Metabolic equivalent: 1 MET = 3.5 ml O₂/kg body weight/min.

Many individuals have achieved and maintained appropriate lifestyle changes, and some have done so without health care system interventions. Even so, better strategies are needed to help people lose weight, maintain that weight loss and exercise more often. Moreover, most European health care systems are not structured to provide or reimburse for regular lifestyle counselling. Also, the current absence of published data demonstrating the cost-effectiveness of early intervention to prevent diabetes-related complications will dampen support for widespread implementation of costly intervention policies.

There is robust epidemiologic evidence that physical activity and weight loss are of medical benefit, not just for preventing diabetes but also for improving other risk factors like dyslipidaemia and hypertension [51, 52], cardiovascular health and quality of life. Health care policymakers and health care systems should aggressively explore low-cost methods which promote physical activity and weight loss. At the same time, cost-effective patient education and counselling interventions should continue to be developed and tested. For example, in the UK the NHS recommends the issuing of "exercise prescriptions" which outline exercise and lifestyle changes and in some health districts even entitle attendance at health clubs, gyms etc. Also in France where the Programme National Nutrition-Santé (National Programme for Nutrition and Health) makes similar recommendations.

Pharmacological interventions

– Evidence now points to pharmacological intervention being a worthwhile step beyond diet and lifestyle modification

– A number of drugs appear to have an effect: primarily metformin, acarbose and orlistat.

– Early use of metformin appears to be the strategy of choice in a significant proportion of patients, particularly those who are younger (age 24-44) and obese.

While intensive lifestyle interventions have the potential to reduce insulin resistance and prevent or delay the onset of type 2 diabetes [19,21] many patients find these interventions difficult to sustain over the long term [52].

Thus in the real world of clinical practice where the level of support for and adoption of intensive (or indeed any level) lifestyle change may not be optimal, pharmacologic therapy ideally combined with dietary and exercise modification is critically important.

A number of clinical trials have looked at the role of pharmacologic therapy in diabetes prevention and several are ongoing.

1. Metformin

Metformin acts as an insulin sensitiser and thus increases the muscle uptake of glucose and reduces hepatic

glucose output. Clearly beneficial glycaemic effects have been demonstrated in the UKPDS in patients with type 2 diabetes and BMI over 27 kg/m² in the prevention of cardiovascular disease [53]. These are supported and extended by the Diabetes Prevention Program (DPP) in individuals with IGT [17]. The trial recruited groups known to be at higher risk for type 2 diabetes, including individuals age 60 and older, women with a history of gestational diabetes, and people with a first-degree relative with type 2 diabetes.

Volunteers were randomly assigned to one of the following groups:

- Intensive lifestyle changes with the aim of reducing weight by 7 percent through a low-fat diet and exercising for 150 minutes a week.
- Treatment with the drug metformin (850 mg twice a day), approved in 1995 to treat type 2 diabetes. Number of patients in this arm – 1073
- A standard group taking placebo pills in place of metformin.

The latter two groups also received information on diet and exercise.

A fourth arm of the study, treatment with the drug troglitazone combined with standard diet and exercise recommendations, was discontinued due to the potential for liver toxicity.

Metformin significantly reduced the conversion of impaired glucose tolerance to type 2 diabetes by 31% relative to placebo. Metformin was also shown to be effective in delaying the onset of diabetes overall (but less so than intensive diet and exercise). Importantly however, metformin was as effective as intensive lifestyle modification in individuals aged 24-44 years or in those with a BMI greater than or equal to 35 kg/m². Thus there is a severely obese population in whom treatment alone has equal benefit to that of a lifestyle intervention alone.

The evidence base currently available for metformin is strong across the full range of dysglycaemia [54]: As well as showing significantly reduced conversion of IGT to type 2 diabetes in the DPP, forced withdrawal of metformin for periods of up to 2 weeks at the end of DPP in line with the protocol confirmed a sustained protective effect with reduced risk of conversion to type 2 diabetes relative to placebo maintained at 25%.

2. Acarbose

Acarbose, a drug that acts by inhibiting intestinal alpha glucosidase and reducing glucose absorption, was shown to be effective at preventing type 2 diabetes in the STOP-NIDDM trial [19] but the relative risk reduction of developing diabetes under acarbose was only 24%. Although the numbers were smaller than DPP (714 patients with IGT were randomised to either acarbose and 715 to placebo) and there was no comparison with the effect of intensive life-

style or dietary changes, the results were significant: 221 (32%) patients randomised to acarbose and 285 (42%) randomised to placebo developed diabetes ($P = 0.0015$). Acarbose was also shown to decrease the incidence of hypertension and cardiovascular complications in patients with IGT [20]. Almost one third of patients (31%) taking acarbose withdrew from the trial as a result of side effects (primarily flatulence).

3. Orlistat

The XENDOS study [21] examined 3,305 patients randomised to lifestyle changes plus either orlistat 120 mg or placebo, three times daily. Participants had a BMI ≥ 30 kg/m² and normal (79%) or impaired (21%) glucose tolerance.

After 4 years' treatment, the cumulative incidence of diabetes was 9.0% with placebo and 6.2% with orlistat, corresponding to a risk reduction of 37.3% ($P = 0.0032$).

Compared with lifestyle changes alone, orlistat plus lifestyle changes resulted in a greater reduction in the incidence of type 2 diabetes and produced greater weight loss in a clinically obese population. However the difference in diabetes incidence was detectable only in the IGT subgroup; weight loss was similar in subjects with IGT or NGT.

Orlistat-treated patients also showed significant improvements in cardiovascular risk factors such as blood pressure and lipid profiles compared with the placebo treated patients.

The beneficial effects of orlistat are entirely due to the greater weight loss these patients achieved over and above that with diet and lifestyle changes.

4. Thiazolidinediones

The effects of thiazolidinediones on diabetes prevention look promising but to date there are no studies that show an unequivocal benefit in a broad group of high risk subjects. Indeed within the DPP a fourth study arm of patients randomised to receive troglitazone had to be stopped because of the fear of liver complications. More studies are ongoing. The one study that did demonstrate an effect was the Troglitazone in Prevention of Diabetes (TRIPOD) study [55] that looked only at the effect in Hispanic women with previous gestational diabetes. Here troglitazone treatment was associated with a 56% relative reduction in progression of diabetes.

5. Other drugs

In studies performed for other reasons, ACE inhibitors, sartans and statins have shown a decreased incidence of diabetes in hypertensive or hypercholesterolaemic patients e.g. HOPE and SOLVD (ACE-I); LIFE and VALUE (sar-

tans); and 4S (statins). Consider using these drugs in patients with metabolic syndrome.

6. Summary

The evidence supports the use of drug therapy, particularly metformin, when used in addition to lifestyle modification to prevent diabetes (Fig 2). More studies are needed to show the cost-effectiveness of using such pharmacological agents.

Based on probabilities from the DPP and other published data, incorporation of the interventions such as those outlined in the DPP into clinical practice is projected to lead to an increase in diabetes-free years of life, improvements in life expectancy, and either cost savings or minor increases in costs compared with standard lifestyle advice in a population with IGT.

Question 9: How can diagnosis and management be organised to provide the highest quality care?

Answer

- *Pre-diabetes must be addressed in a structured manner both on a national and a local basis with quality assurance.*
- *This is an important public health issue.*
- *In those countries where National Diabetes Plans exist, it should be included.*
- *A multi-disciplinary approach is essential to achieve the desired reductions in diabetes and CVD morbidity and mortality.*

A structured plan for the use of this European statement and subsequent management of pre-diabetes should now be considered in every country in Europe. This is an important public health issue. Governments, professional and patient organisations must come together to develop a flexible national strategy and to place pre-diabetes detection at the forefront of public health initiatives.

Germany is already developing a quality controlled and continuously evaluated system. Individuals are approached by letter and the measurement of a number of parameters agreed e.g. blood pressure, body weight and HbA1c. These are measured by the patient themselves. Other countries or institutions may wish to choose other criteria and other means of communicating with the individual e.g. via a website.

The USA already has a major multidisciplinary Diabetes Prevention and Control Program (DPCP) in place, run and organised by the Centres for Disease Control (CDC). Among other parameters they give special focus to ethnic groups at high risk.

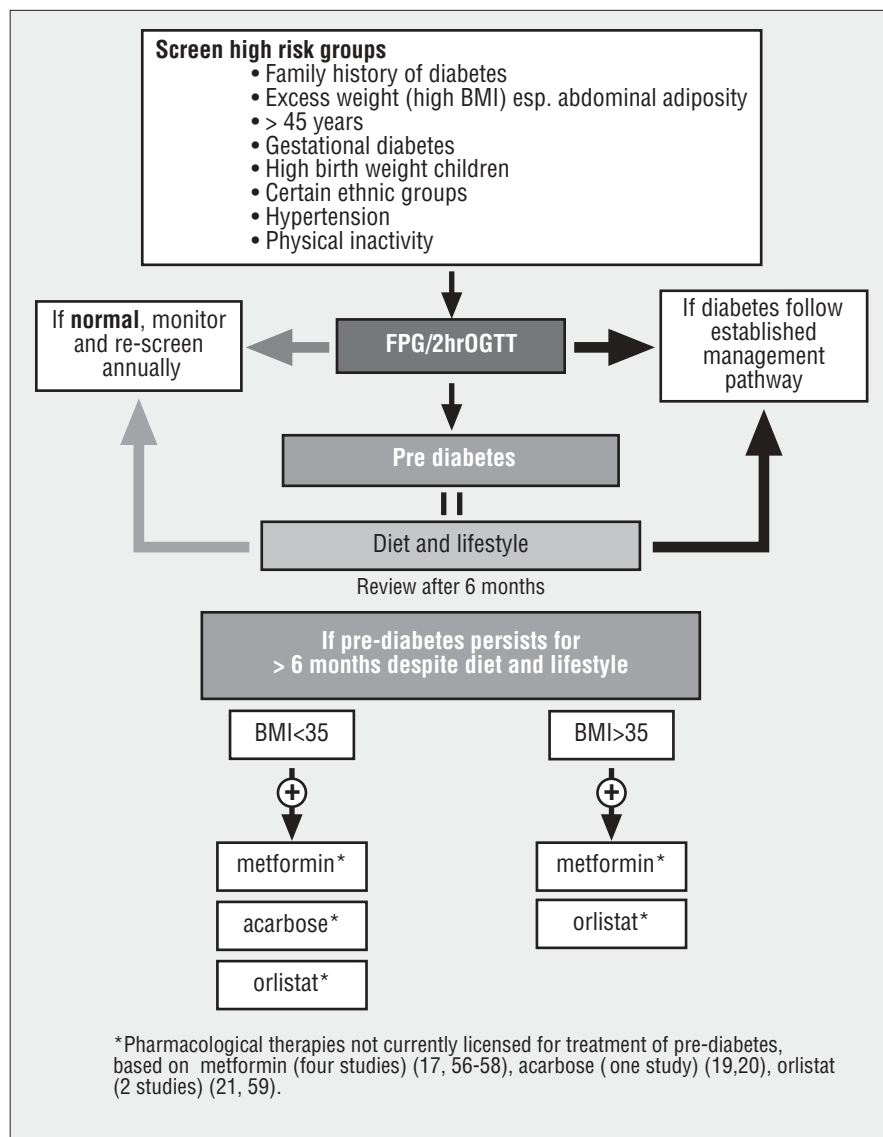


Figure 2
Pre-diabetes management algorithm.

Question 10: How do we ensure that a diagnosis of pre-diabetes does not stigmatise these people?

Answer

- Public awareness campaigns should be introduced to coincide with screening and management programmes.
- Should screening for pre-diabetes become more common, there is an onus on healthcare providers and health insurers not to stigmatise those who are diagnosed as having it, but also not to falsely reassure.

It is clear that should screening for pre-diabetes become widespread then many individuals will potentially find themselves labelled (not least by health insurance companies) as having the potential to develop a number of serious morbidities. Without interpretation this information could have a negative effect on that individual’s employment and

insurance prospects and potentially on his or her social relationships too. It is imperative therefore that confidentiality about an individual’s pre-diabetic status is maintained.

However it is equally important not to falsely reassure individuals who have a negative screen. If they have metabolic syndrome for example but normal blood glucose levels on screening, they must continue to be screened to ensure other morbidities do not develop.

Public awareness campaigns highlighting the importance of detecting pre-diabetes and its health effects are now critically important.

Once diagnosed there should be minimal delay in providing intervention and support. Management should focus on balancing side effects against treatment benefits taking account not only of direct costs, but also of the often hidden long-term savings that effective long-term management can deliver.

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