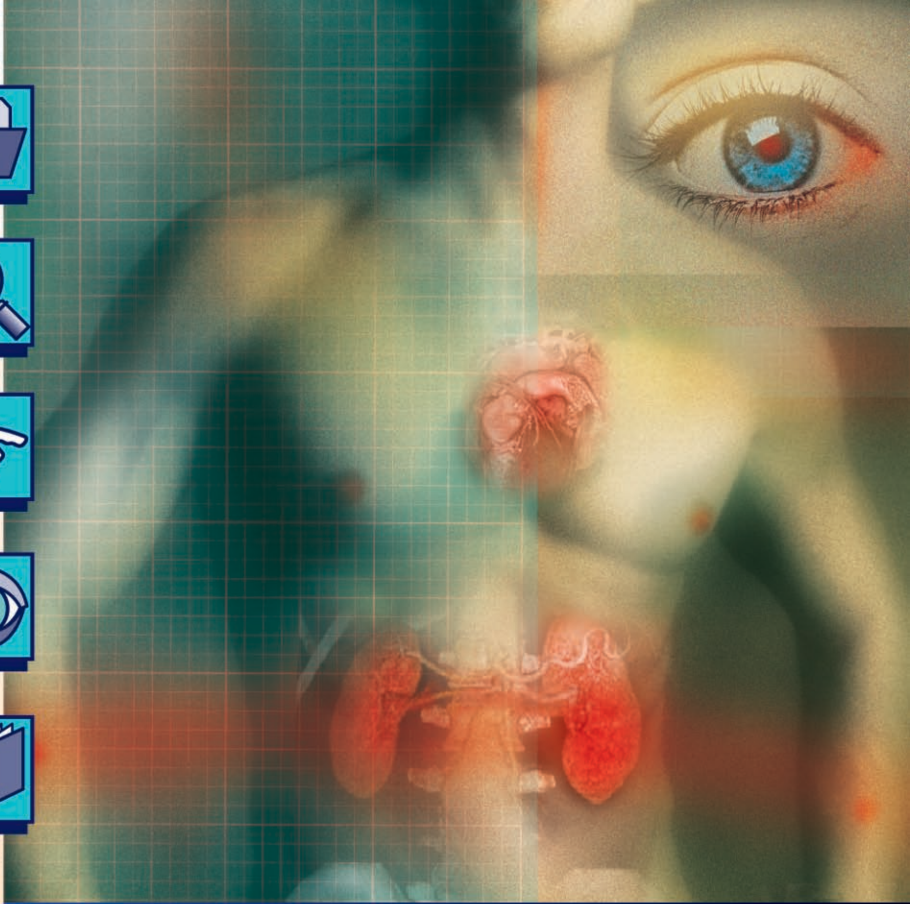

Problem Solving in Diabetes

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CLINICAL PUBLISHING

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Contents

Abbreviations

4S Scandinavian Simvastatin Survival Study
ABCD trial Appropriate Blood Pressure Control in Diabetes Trial
ABPI Ankle–brachial pressure index
ABPM Ambulatory blood pressure monitoring
ACAS Asymptomatic Carotid Atherosclerosis Study
ACE Angiotensin-converting enzyme
ACR Albumin–creatinine ratio
ACHOIS trial Australian Carbohydrate Intolerance Study in Pregnant Women
AER Albumin excretion rate
AHI Apnoea–Hypopnea Index
ALLHAT Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial
AMD Age-related macular degeneration
ANG-1 and ANG-2 Angiopoetin
APT Anti-Platelet Trialists
ARB Angiotensin receptor blocker
ASTRAL trial Angioplasty and Stent for Renal Artery Lesions trial
BARI trial Bypass Angioplasty Revascularization Investigation
BMI Body mass index
BP Blood pressure
CABG Coronary artery bypass grafting
CALM study Candesartan And Lisinopril Microalbuminuria study
CAPD Continuous ambulatory peritoneal dialysis
CAPRIE study Clopidogrel versus Aspirin in Patients at Risk of Ischaemic Events study
CARDS Collaborative Atorvastatin Diabetes Study
CARE study Cholesterol and Recurrent Events study
CAS Carotid artery stenosis
CETP Cholesteryl ester transfer protein
CF Cystic fibrosis
CFRD Cystic fibrosis-related diabetes
CHD Coronary heart disease
CHHIPS Controlling Hypertension and Hypotension Immediately Post-Stroke trial
CI Confidence interval
CK Creatine kinase
CPAP Continuous positive airway pressure
CSII Continuous subcutaneous infusion of insulin
CSMO Clinically significant macular oedema
CT Computed tomography
CWS Cotton-wool spot
DAN Diabetic autonomic neuropathy
DCCT Diabetes Control and Complications Trial
DIGAMI Diabetes and Insulin-Glucose Infusion in Acute Myocardial Infarction study
DIRECT DIabetic Retinopathy Candesartan Trial
DKA Diabetic ketoacidosis
DMa Diabetic maculopathy
DME study Diabetic Macular Edema study
DPN Distal sensory peripheral neuropathy
DPP Diabetes Prevention Program
DPP-IV Dipeptidyl peptidase IV
DPS Diabetes Prevention Study
DRS Diabetic Retinopathy Study
ECG Electrocardiogram
ECST European Carotid Surgery Trial
EDIC Epidemiology of Diabetes Interventions and Complications
ELISA Enzyme-linked immunosorbent assay
ENDIT European Nicotinamide Diabetes Intervention Trial
ETDRS Early Treatment Diabetic Retinopathy Study
ETF Enteral tube feeding
EUCLID study EURODIAB Controlled Trial of Lisinopril in Insulin-Dependent Diabetes Mellitus
FEV(1) Forced expiratory volume in one second
FOOD Feed or ordinary diet trial

FSH Follicle-stimulating hormone
GABA Gamma-aminobutyric acid
G-CSF Granulocyte–colony stimulating factor
GDM Gestational diabetes mellitus
GFD Gluten-free diet
GFR Glomerular filtration rate
GI Glycaemic index
GIK Glucose insulin potassium
GIST Glucose Insulin in Stroke Trial
GLP-1 Glucagon-like peptide-1
HAAF Hypoglycaemia associated autonomic failure
HAIR-AN syndrome HyperAndrogenism, Insulin Resistance and Acanthosis Nigricans
HbA1c Glycosylated haemoglobin
HDL High-density lipoprotein
HELLP syndrome Haemolysis, Elevated Liver enzymes, Low Platelets
HERS Hormone Estrogen-Progestin Replacement Study
HHS Hyperosmolar hyperglycaemic state
HLA Human leucocyte antigen
HOPE Heart Outcomes Protection Evaluation study
HOT study Hypertension Optimal Treatment study
HPS Heart Protection Study
HRT Hormone replacement therapy
ICU Intensive care unit
IFG Impaired fasting glucose
IGF Insulin-like growth factor
IgG Immunoglobulin G
IGT Impaired glucose tolerance
IHD Ischaemic heart disease
IMT Intima–media thickness
INR International normalized ratio
IRS Insulin resistance state
IRMA Intraretinal microvascular abnormality
ISDN Isosorbide dinitrate
IV Intravenous
IVF in vitro fertilization
LAD Left anterior descending
LDH Lactate dehydrogenase
LDL Low-density lipoprotein
LIFE study Losartan Intervention For Endpoint reduction in hypertension
LIPID study Long-term Intervention with Pravastatin in Ischaemic Disease study
LH Leuteinizing hormone
MA Microaneurysm
MDI Multiple daily injections
MDRD study Modification of Diet in Renal Disease Study
MIDD Maternally inherited diabetes and deafness
MO Macular oedema
MODY Maturity-onset diabetes of youth
MRA Magnetic resonance angiography
MRFIT Multiple Risk Factor Intervention Trial
MRI Magnetic resonance imaging
MRSA Methicillin-resistant *Staphylococcus aureus*
NAOIN Non-arteritic optic ischaemic neuropathy
NASCET North American Symptomatic Carotid Endarterectomy Trial
NGF Nerve growth factor
NHANES National Health and Nutrition Evaluation Study
NMR Nuclear magnetic resonance
NO Nitric oxide
NTD Neural tube defects
NRT Nicotine replacement therapy
OAD Oral antidiabetic agent
oGTT Oral glucose tolerance test
OSA Obstructive sleep apnoea
PAD Peripheral arterial disease
PARP Poly-ADP-ribose polymerase
PCI Percutaneous coronary intervention
PCOS Polycystic ovarian syndrome
PDE Phosphodiesterase
PDGF Platelet-derived growth factor
PEDF Pigment Epithelial-Derived Factor
PEG Percutaneous endoscopic gastrostomy
PKC Protein kinase C
PPAR Peroxisome proliferator-activated receptor
PPP Primary Prevention Project
PROGRESS Perindopril PROtection aGainst Recurrent Stroke Study
RAS Renin–angiotensin system
RANKL Receptor Activator of Nuclear factor Kappa B Ligand

RArtS Renal artery stenosis
RIO Rimonabant In Obesity trial
rTPA Recombinant tissue plasminogen activator
RR Relative risk
SDB Sleep-disordered breathing
SHBG Sex-hormone binding globulin
SR Sustained release
STOP-NIDDM Study to Prevent Non-Insulin-Dependent Diabetes Mellitus
SHHS Sleep Heart Health Study
SSRI Selective serotonin reuptake inhibitor
SUR Sulphonylurea receptor
SWAN Study of Women's health Across the Nation
T1DM Type 1 diabetes
TCC Total contact casting
TIA Transient ischaemic attack
TNT study Treating to New Target study
UAE Urinary albumin excretion
UKPDS United Kingdom Prospective Diabetes Study
VAT Visceral adipose tissue
VA-HIT Veterans Affairs High-Density Lipoprotein Intervention Trial
VEGF Vascular endothelial growth factor
VLDL Very-low-density lipoprotein
VO_2max Maximal oxygen uptake
WHI Women's Health Initiative
WOSCOPS West of Scotland Coronary Prevention Study
XENDOS study XENical in the prevention of Diabetes in Obese Subjects study

SECTION ONE 01

Prevention and Diagnosis

PROBLEM

1 Preventing Type 1 Diabetes

Case History

The parent of a 4-year-old boy with type 1 diabetes consults you wanting to know if there is anything he can do to prevent a future child developing the condition. He already has an 8-year-old daughter with diabetes and there is a strong family history of autoimmune thyroid disease on both his and his wife's side of the family. They are contemplating having a third child.

Is there any evidence that type 1 diabetes is preventable?

Is there any general advice the parents can usefully follow?

Can we predict the onset of type 1 diabetes?

Background

Preventing or curing type 1 diabetes is one of the holy grails for those who research autoimmune disease or treat patients with diabetes. The disease typically presents in childhood, currently necessitates lifelong use of insulin injections and exposes the individual to increased risk of vascular complications. The risk of type 1 diabetes in the general population is about 1 in 300, and this is increased up to 20-fold in first-degree relatives. Genetic markers do not provide an accurate prediction of diabetes, with only 5% of those with susceptibility markers actually developing the disease. However, the fact that the disease has a long latent period and that the pre-diabetic phase can be identified by measuring islet cell antibodies or by assessing beta cell function yields an opportunity for preventative therapy. The results of trials using non-specific immunosuppression in the 1980s were disappointing with only temporary improvements in insulin production demonstrated.

Type 1 diabetes in children became much more common in the course of the 20th century.[1] In fact, available evidence suggests that the disease was quite uncommon, although generally fatal, in children during the 19th century. This, along with the geographical variation in the prevalence of childhood diabetes that is not accounted for by variations in the prevalence of susceptible genotypes, strongly suggests that environmental factors are important.[2] The wide variation in incidence rates applies much more to childhood than to adult type 1 diabetes.[3] It is not surprising that there has been intensive research into environmental triggers for diabetes that might be modified, or into safe and effective nutritional or immunological manipulations that might decrease risk of developing the disease (Figure 1.1). Recent evidence suggests that most parents of children at risk of type 1 diabetes will attempt preventative measures,[4] and it is increasingly important for health professionals to be able to enter into a balanced discussion with parents and would-be parents.

Both macronutrient and micronutrient components of the diet have received attention.[5] A protective effect of breast-feeding has been proposed, but not confirmed in all

Factors Predisposing To Type 1 Diabetes	**Level of Evidence**
Genetic (including HLA)	***
Non-breast-fed	*
Early exposure to cows' milk	*
Low vitamin D status	**
Viral infection	*
Rapid weight gain in childhood	*

The Following Do Not Appear To Modify Risk

Childhood vaccination
Treatment with nicotinamide
Oral insulin therapy

***	Strong evidence supported by multiple well-conducted and randomized clinical studies
**	Reasonable evidence supported by clinical studies (not randomized)
*	Some evidence supported by observational studies and expert opinion

Fig.1.1 Factors predisposing to type 1 diabetes. HLA = human leucocyte antigen.

studies. Breast-feeding may afford protection through early oral exposure to human milk (inducing tolerance to insulin; see below), through protection against infectious agents, and by decreasing the risk of excessive weight gain in infancy. The latter is also probably a trigger for diabetes during adolescence. On the other hand, early exposure to cows' milk may increase risk through exposure to bovine insulin or β-casein, the latter being a known immunomodulatory protein contained in cows' milk. Bottle-feeding can also be associated with excessive weight gain. Amongst micronutrient components of the diet, nitroso compounds (related to streptozotocin), nitrates and nitrites, all used as preservatives in meat products, have been considered. Variations in vitamin D status may be another reason for the geographical variation in the incidence of type 1 diabetes. Vitamin D has important regulatory effects on the immune system. A protective effect of cod liver oil (a source of both vitamin D and long-chain n-3 fatty acids, which are also anti-inflammatory) was shown against childhood diabetes in the recent study reported by the Norwegian Childhood Diabetes Study Group.[6]

Certain infectious agents, including enteroviruses, have been associated with development of diabetes in animal models and in rare cases of human diabetes. This has led to worries that childhood vaccination, particularly with live attenuated vaccines, may be a risk factor for type 1 diabetes. A Danish study, along with other recent evidence, has gone a long way to dispel worries on this score; Hviid and colleagues[7] studied a cohort including all Danish children born between 1990 and 2000, and found no evidence of any association between childhood vaccinations and diabetes. On the contrary, the vaccines may be protective by limiting the effect of potentially diabetogenic infections, particularly rubella.

Recent Developments

1 Vitamin B_3 (niacin) consists of nicotinic acid and nicotinamide. The latter is tolerated in high doses, and has been shown to decrease the incidence of diabetes in streptozotocin-treated animals, and in non-obese diabetic mice. Some early preclinical studies showed promise for the agent. The vitamin inhibits poly-ADP-ribose polymerase (PARP), an enzyme involved in DNA repair. Activation of PARP leads to depletion of intracellular nicotinamide adenine dinucleotide. This depletion of cellular energy stores may predispose to cell damage, including in the pancreatic beta cell. The European Nicotinamide Diabetes Intervention Trial (ENDIT)[8] was a randomized, double-blind, placebo-controlled trial in which 552 islet cell antibody-positive first-degree relatives of patients with diabetes took either nicotinamide or placebo. There was no difference in the incidence of diabetes during the five years of the trial (82 vs 77 cases, respectively).

2 Autoimmunity directed at insulin epitopes is one of the critical driving forces in the pathogenesis of type 1 diabetes. In animal models, exposure to mucosal insulin induces tolerance and thus decreases risk of diabetes. This mechanism is of particular interest because of the recent developments of insulin formulations which are active after oral or nasal administration. The Diabetes Prevention Trial-Type 1 reported recently.[9] In this trial, a large number of first- and second-degree relatives of patients with diabetes were screened for pre-diabetes. Those found to be positive were ran-

domized to receive either oral insulin or placebo. Again, there was no difference in the incidence of new diabetes between the control and the treatment groups.

3 The prospects of gene therapy for diabetes are improving rapidly. Approaches to introduce a functioning insulin-producing mechanism in glucose-responsive cells have been considered. The genetic susceptibility to diabetes is mainly through class II histocompatibility alleles. Recent experiments in non-obese diabetic mice have been carried out to replace diabetes-prone genes with those that are protective.[10]

Conclusion

There is not, currently, any way to accurately predict which individuals are going to get diabetes, or to prevent its occurrence. Family history is a major risk factor, increasing susceptibility by up to 20-fold, and there might be a slight bias towards males developing diabetes. Epidemiological data strongly support a role for environmental influences, especially for childhood diabetes. There is no evidence currently to support specific preventative measures. Breast-feeding should be promoted for its possible role in preventing type 1 diabetes, as well as its other health benefits. Efforts to limit excessive weight gain in infancy and adolescence should be promoted, as high body weight at these times may favour development of type 1 diabetes. Among the other nutritional factors, the best evidence is for a protective effect of vitamin D and supplementation should be considered (perhaps as cod liver oil) in areas where sunlight exposure is low. Finally, parents should be encouraged to have their children vaccinated as per normal childhood schedules—there is no evidence that vaccination predisposes to diabetes and it may be that, by decreasing infection with some agents, it actually protects.

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PROBLEM

2 Preventing Type 2 Diabetes

Case History

You are consulted by a 43-year-old man who has a strong family history of diabetes. He is concerned because his father developed diabetes at the age of 56 and has recently (aged 60 years) had a lower limb amputation. Your patient is generally in good health. He has a body mass index of 28 kg/m^2 and takes very little exercise as he has a busy job and a young family. He smokes 20 cigarettes per day, and has been noted to be mildly hypertensive although not requiring treatment at present.

How would you advise him?

Are we able to prevent development of type 2 diabetes?

Is there a role for drug therapy?

Background

Once the condition is established, it is extremely difficult to maintain tight control of blood glucose and other vascular risk factors in patients with type 2 diabetes. A number of very important studies have been published in the past three years demonstrating the potential for lifestyle interventions and drugs to either prevent diabetes, or at least to delay its onset. These studies, along with the acknowledged costs of managing patients with type 2 diabetes, have heightened awareness of the value of preventative measures.

The best-known of the prevention studies is the Diabetes Prevention Program (DPP), carried out in 27 North American centres.[1] In this study, 3234 non-diabetic patients with impaired glucose tolerance were randomly assigned to placebo, metformin (850 mg twice daily) or lifestyle intervention. The latter consisted of dietary advice plus at least 150 minutes of physical activity per week. After 2.8 years of follow-up, the incidence of diabetes was 11.0, 7.8 and 4.8 cases per 100 patient-years in the placebo, metformin and lifestyle groups, respectively. Metformin reduced the incidence of new diabetes by 31%, while lifestyle intervention reduced it by 58%. Some of the benefit associated with metformin use is lost after the drug is stopped. However, a recent washout study using the DPP cohort confirms that much of the benefit persists.[2] A very recent cost–benefit analysis of this study confirmed that both interventions were cost effective.[3] However, lifestyle intervention was much more cost effective with a cost, relative to placebo, of $1100 per quality-adjusted life-year, compared with $31 300 for metformin.

The benefit of lifestyle intervention was confirmed in the Finnish Diabetes Prevention Study (DPS).[4] Usual diabetes care was compared with a lifestyle intervention programme in 522 overweight, middle-aged subjects with impaired glucose tolerance. The lifestyle intervention group experienced greater weight loss and improved glycaemic and lipid parameters. The STOP-NIDDM trial[5] (Study to Prevent Non-Insulin-Dependent Diabetes Mellitus) randomized 714 patients with impaired glucose tolerance to either placebo or acarbose, and followed them up for over three years. Forty-two per cent of patients in the placebo wing and 32% of patients taking acarbose developed diabetes. The decrease in new diabetes was highly significant, although the study has been criticized because of possible bias due to the large proportion of patients that did not complete their treatment regime. There is further evidence that drug treatment can prevent, or delay the onset of, diabetes from small studies using either sulphonylureas or the thiazolidinedione drug, troglitazone.[6]

One in five of the population in most developed countries is now obese, and this is the major factor underlying the global increase in diabetes prevalence in recent years. It is not surprising, therefore, that obesity has become an increasing focus for treatment and prevention of diabetes and cardiovascular disease. In the XENDOS study (XENical in the prevention of Diabetes in Obese Subjects), 3305 patients were treated with lifestyle intervention and randomized either to placebo or to treatment with the gastrointestinal lipase inhibitor, orlistat.[7] After four years' treatment, diabetes had developed in 9.0% of placebo patients and in 6.2% of orlistat-treated patients. Patients treated with orlistat also lost more weight and had improved lipid profiles. Again, and as with many long-term studies in this area, a relatively large proportion of patients did not complete the study.

In summary, a number of recent studies confirm that both lifestyle interventions and drug treatments can reduce the incidence of new diagnoses of diabetes, and also improve some of the associated cardiovascular risk factors (Figure 2.1). Lifestyle intervention is clearly preferable, particularly if changes can be sustained long-term. Diet and exercise can also be cost-effective interventions. For those who do not succeed with lifestyle management, drug treatment appears to be both a safe and an effective option.

Recent Developments

1 Other drug groups used in the prevention of cardiovascular disease may affect the development of diabetes.[6] Blockade of the renin–angiotensin system has now been shown in several studies, including the Heart Outcomes Protection Evaluation (HOPE) study, to modestly decrease incidence of diabetes. Lipid-lowering drugs may have a similar effect, perhaps by decreasing insulin resistance. For some patients, vig-

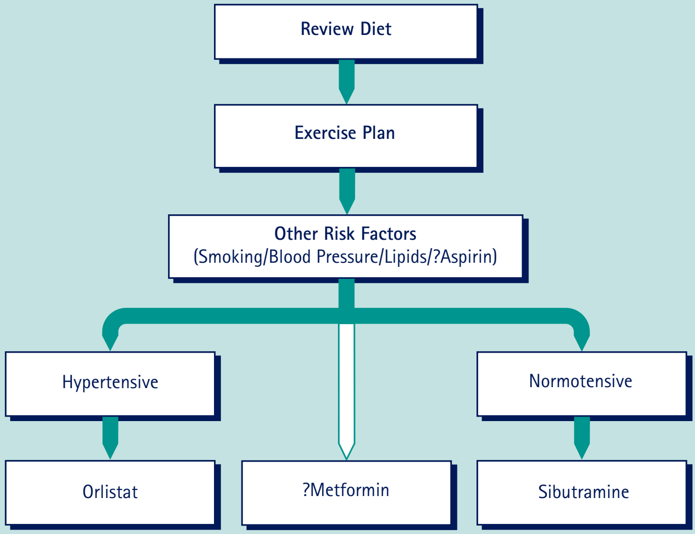

Fig. 2.1 Figure shows suggested scheme for prevention of type 2 diabetes using lifestyle interventions and anti-obesity drugs.

orous treatment of cardiovascular risk factors may be the best line of attack, and decreased risk of diabetes an important secondary benefit of treatment.

2 Individuals at high risk of vascular disease should have vigorous management of their multiple risk factors wherever possible. One of the largest randomized trials of lifestyle intervention conducted is the Multiple Risk Factor Intervention Trial (MRFIT). Recent data[8] from nearly 13 000 men followed for up to seven years show, again, that diet and exercise can prevent diabetes. However, there were interesting differences between smokers and non-smokers; with lifestyle intervention, diabetes incidence was 18% lower in non-smokers but 26% higher in smokers. The exact reasons for this are not clear but use of antihypertensive drugs in smokers and weight gain associated with attempts to quit smoking are possible confounding factors.

3 The role of exercise in improving glucose tolerance is now well established. Traditionally, vigorous aerobic exercise was recommended but was often unpalatable or unachievable for overweight and untrained subjects. Now, almost any type of exercise—depending on the patient's preferences and capabilities—is regarded as beneficial. Recent data from the Finnish Diabetes Prevention Study have confirmed the link between leisure-time physical activity and reduced risk of diabetes.[9] Even low-intensity and walking activity were associated with improved glucose tolerance.

4 There is currently great focus on the effects of diets with differing macronutrient contents. Diets that are low glycaemic index, high in fibre and rich in wholegrain foodstuffs can improve glucose tolerance and diminish the risk of developing diabetes. These findings have been confirmed in a number of substantial studies published in the past two years. In one recent study involving over 36 000 Australian men,[10] consumption of a low glycaemic diet correlated strongly with a decreased risk of diabetes. Also, and in keeping with other studies, low dietary magnesium intake was also associated with increased risk of diabetes.

Conclusion

Given the difficulty experienced in reducing the risk associated with type 2 diabetes once the condition has developed, it seems imperative to try to prevent the condition whenever the opportunity arises. Although the above patient is fit and healthy at present, he is at risk in the future of developing type 2 diabetes. Initial management should be with dietary advice from a registered dietician and the patient should be advised about the benefits of exercise. Even a modest increase in low-intensity activity might be of benefit. He should have a thorough assessment of his overall cardiovascular risk and, if necessary, receive treatment for poorly controlled risk factors. Given that he is healthy and young, he should be strongly advised to keep his weight down and to engage in regular physical activity. Once he commences drug therapy, he is likely to take it for life. He should be advised to stop smoking and offered smoking cessation support if needed. This will reduce his risk of cardiovascular events and may also decrease his risk of diabetes. His glycaemic status should be assessed by fasting blood glucose and, preferably, also with a random or postprandial measurement. Drug therapy—for example with metformin—could be considered if he has impaired glucose tolerance. The benefit is not likely to be as great as that with diet and exercise, and this should be repeatedly emphasized to the patient.

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PROBLEM

3 Diabetes Risk after the Menopause

Case History

A 54-year-old Afro-Caribbean woman is referred to you. She is two years post-menopausal and type 2 diabetes was diagnosed eight months ago. Despite having visited the dietician three times since then, her body mass index remains high at 30 kg/m^2. She takes atenolol 50 mg/day for hypertension, which is well controlled. Diabetes is treated by diet alone, and her glycosylated haemoglobin (HbA1c) is reasonable at 7.1%. Fasting cholesterol is 5.8 mmol/l and triglycerides 2.5 mmol/l. She has a strong family history of type 2 diabetes.

How would you manage her diabetes and hypertension?

Is her age and menopausal status relevant to her management?

Is her racial background important?

She wants to know whether she should consider hormone replacement therapy

Background

Compared with men, women are relatively protected from cardiovascular disease except when they are post-menopausal or they have diabetes. Sex steroids have important roles in regulating lipid metabolism, endothelial function, blood vessel tone and other aspects of vascular function. Menopause is associated with a relatively abrupt decrease in circulating oestrogen. There is no comparable process in men. Since the general population is aging, and women spend an increasing proportion of their life in an oestrogen-deficient state in which they are at risk of atherosclerotic disorders, management of cardiovascular risk in the peri- and post-menopausal periods is of particular importance.

The period of declining ovarian function leading up to the menopause, the peri-menopause, is associated with declining sex steroid levels and important alterations in body composition. Thus total and visceral adiposity increase, and bone mineral density decreases. The change in fat mass and distribution may relate to decreased lipolysis and increased activity of lipoprotein lipase. Weight gain around the menopause is greater in women from more deprived socio-economic backgrounds and in those who do not smoke, do not exercise regularly and have never used HRT. In a prospective 9-year study of women during the menopausal transition, Guthrie *et al.*[1] demonstrated that mood changes and decreased quality of life appeared to contribute to the changes in body composition and cardiovascular risk profile around the menopause.

HRT is not currently recommended for prevention of cardiovascular disease. Although benefits in risk-markers have been documented, there is debate about which oestrogen, which progestogen, or which combination, and which route of administration. Set against the possibility of a marginal benefit in cardiovascular disease prevention, there is undoubtedly increased risk of thromboembolic events and breast cancer. Moreover, two important trials—the Women's Health Initiative (WHI) and the Hormone Estrogen-Progestin Replacement Study (HERS)—actually reported increased cardiac events in the short term. A recent large, Swedish study[2] appears to confirm that oestrogen use can improve cardiovascular risk profile and there are now several lines of evidence that either oral or transdermal oestrogen may improve insulin sensitivity and slow the progress of the metabolic syndrome, thus retarding development of diabetes in those at risk.[3]

The impact of diabetes on cardiovascular risk is higher for women than it is for men. In a recent Finnish study,[4] the event rate per 1000 patient-years was 11.6 for non-diabetic men and 1.8 for non-diabetic women, while comparable event rates for males and females with diabetes were 36.3 and 31.6, respectively. In the recent Study of Women's health Across the Nation (SWAN),[5] differences between insulin sensitivity and beta cell function were compared in groups of pre- or peri-menopausal women from differing racial backgrounds. Insulin sensitivity was lower in African-Americans compared with other racial groups, while beta cell function was relatively preserved in this group. Thus measures to improve insulin sensitivity, including weight loss, should be the approach of choice in this group.

Recent Developments

1 Increased abdominal obesity in women is linked with insulin resistance and with markers of inflammation that predispose to ischaemic heart disease and other complications of obesity (Figure 3.1).[6] Although visceral obesity does not account for all of the increased risk associated with the post-menopausal state, it is an important therapeutic target, and regular exercise goes a long way to ameliorate the fat accumulation and accompanying risk factors.[7]

2 Attempts to improve health and deal with cardiovascular risk factors should not wait until the menopause. Recent data from the Nurses Health Study[8] demonstrate that

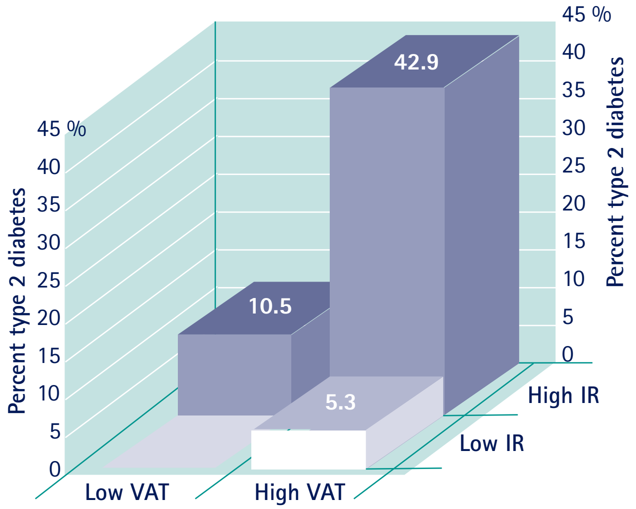

Fig. 3.1 Contributions of visceral adipose tissue (VAT) and insulin resistance (IR) to risk of diabetes. Post-menopausal women were screened for diabetes using an oral glucose tolerance test. Diabetes was particularly prevalent in women who had both increased visceral adipose tissue and insulin resistance. *P<0.0001. *Source*: Piché *et al.* 2005.[6]

increasing obesity in the pre-menopause is associated with increased levels of inflammatory markers (tumour necrosis factor-receptor, interleukin-6 and C-reactive protein), and these markers are predictive of the development of diabetes.

3 Micronutrient status also changes around the time of the menopause and there is considerable evidence now that some of these changes may relate to risk of diabetes and cardiovascular disease. Thus, decreased magnesium levels are more common after the menopause, and predispose to insulin resistance and the metabolic syndrome.[9] Increased iron stores are associated with increased cardiovascular risk factors,[10] and this may be a factor in the peri-menopausal period for many women.[11]

Conclusion

This woman is at increased risk on the grounds of age, ethnicity, menopausal status and the fact that she has diabetes. She should try hard with diet and exercise to manage her weight and glycaemic control (Figure 3.2). Given her imperfect glycaemic control at present, she might consider metformin to help preserve her beta cell function long term. Her hypertension is well controlled but atenolol might not be the ideal agent given her weight and imperfect glycaemic control. An angiotensin-converting enzyme inhibitor or angiotensin II receptor blocker might be preferable. HRT is not routinely recommended for cardiovascular disease prevention but patient choice is important, and she may consider this if she is experiencing menopausal symptoms. She may benefit from aspirin treatment (see Chapter 33).

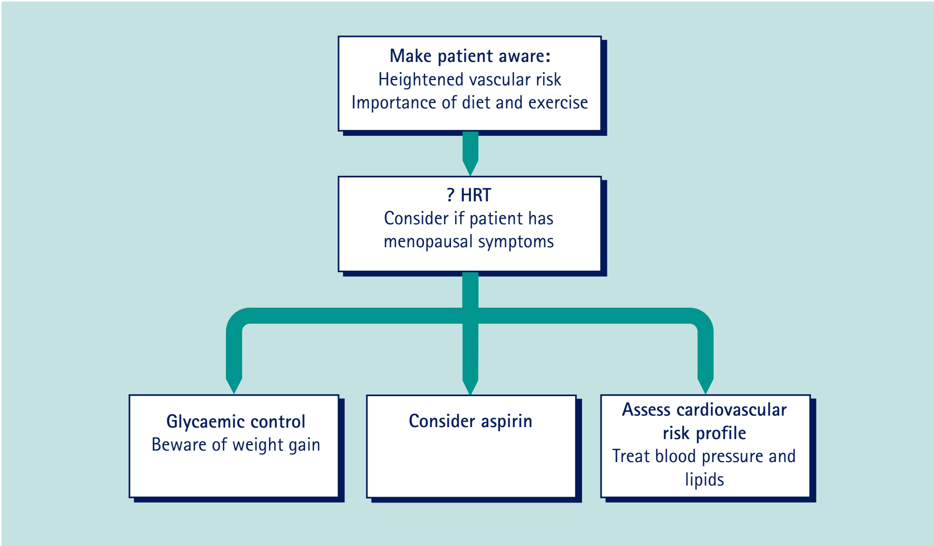

Fig. 3.2 Figure suggests a scheme for managing cardiovascular risk in a patient approaching, or soon after, the menopause. HRT = hormone replacement therapy.

Further Reading

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PROBLEM

4 Genetic Diabetes Syndromes (MODY)

Case History

A 24-year-old woman attends your clinic for annual diabetes review. She was diagnosed with diabetes at the age of 18 years. She is not overweight. She checks her blood sugar two days per week and fasting values are always below 7.0 mmol/l and her glycosylated haemoglobin (HbA1c) is 5.8%. She takes gliclazide 80 mg/day. Checking her eyes, you find that she has moderate diabetic retinopathy. Her blood pressure is 138/92 mmHg. She has a brother who was diagnosed with diabetes at the age of 18 and commenced on insulin.

What type of diabetes does she have?

How would you manage her?

What is her prognosis regarding diabetic complications?

Background

Maturity-onset diabetes of youth (MODY) is an unusual cause of diabetes, and accounts for 1–2% of all cases of diabetes. The fact that the diagnosis is seldom made in clinical practice almost certainly reflects the fact that there is no simple clinical test for the syndrome and it is, therefore, under-diagnosed. It is important to recognize MODY for a number of reasons: the syndrome is usually diagnosed in adolescence or early adulthood and patients may thus have diabetes for a substantial portion of their life; there is an appreciable risk of diabetic complications even though the degree of hyperglycaemia may be mild; the approach to treatment is different to that to either type 1 or type 2 diabetes; and other family members are usually affected. Diabetes usually develops before the age