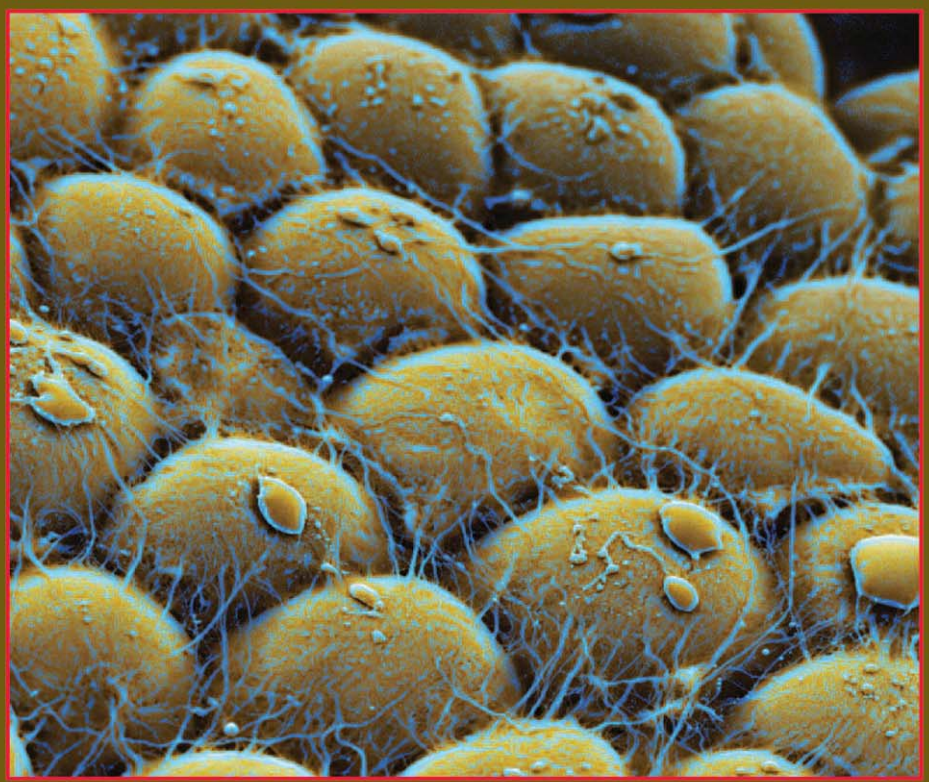
Therapeutic Strategies in METABOLIC SYNDROME

V. Fonseca



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Vivian Fonseca

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Contents

Editor and Contributors vii

Preface ix

1 Lifestyle intervention to reduce metabolic and cardiovascular risks 1
S. Dagogo-Jack

2 Dietary controversies in treatment of the metabolic syndrome 13
N. Davis, N. Tomuta, J. Wylie-Rosett

3 An exercise prescription for the metabolic syndrome 29
R. Bentley-Lewis, M. Pendergrass

4 Impact of hypoglycemic agents on the metabolic syndrome 43
T. K. Thethi, S. Singh, V. Fonseca

5 Weight loss agents and the metabolic syndrome 55
W. T. Cefalu, C. Champagne, F. Greenway

6 Blockage of the renin–angiotensin system in metabolic syndrome: implications for the prevention of diabetes 69
K. Vijayaraghavan, P. C. Deedwania

7 Lipid management in the metabolic syndrome 93
O. P. Ganda

8 A potential role for insulin in management of the metabolic syndrome 111
P. Dandona, A. Chaudhuri, P. Mohanty, H. Ghanim

9 Suppressing inflammation: a novel approach to treating the metabolic syndrome 125
A. D. Rao, V. Fonseca

10 GLP-1 analogues, DPP-IV inhibitors and the metabolic syndrome 137
A. H. Stonehouse, J. H. Holcombe, D. M. Kendall

List of Abbreviations 159

Index 165

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Preface

We are in the midst of a worldwide epidemic of obesity and its consequences, in particular type 2 diabetes and cardiovascular disease. Clinical studies have recognized that risk factors for these conditions frequently cluster in individuals, leading to the development of the concept of the metabolic syndrome. This was soon followed by considerable controversy as to whether the syndrome is a distinct entity or not. In addition, multiple definitions and diagnostic criteria have made interpretation of data occasionally problematic. I expect that this controversy will continue, though all parties on both sides of the argument are clearly in agreement on one thing – we need action to halt the progression from risk factor development to clinical events and death. Despite the controversies on terminology, therefore, it is important to focus on the goal of effective treatment, hence the development of this book.

Although our goal is to have an in-depth analysis of treatment strategies, we felt it important to first review the epidemiology and pathophysiology of the syndrome, in order to lay the groundwork for developing treatment concepts. We have also strongly emphasized the importance of lifestyle (and perhaps societal) change that is needed to halt this epidemic. Clearly, preventing and treating obesity effectively should liberate us from the syndrome. However, whether we use population strategies or individualized pharmacotherapy for obesity, the greatest impact is likely to be seen in treatments that alleviate risk factors involved in the pathogenesis of cardiovascular events such as blood pressure, lipids, inflammation and thrombogenesis. To that end, we have focused on the impact of treatment on these factors.

It is also important to recognize the impact of current treatments for individual risk factors on other components of the syndrome. This is most clearly recognizable in the effect of glucose-lowering drugs, particularly insulin sensitizers if insulin resistance is an important underlying feature of the syndrome. Some of these drugs, as well as insulin itself, paradoxically cause weight gain, yet favorably impact other features of the syndrome. Is that good or bad? The answers are currently surrounded by controversy, the essence of which we hope we have captured adequately in the text. We look forward to further clarification from ongoing clinical trials.

I am most grateful to the outstanding group of authors who have contributed scholarly and up-to-date reviews in a timely fashion.

Finally, I would like to dedicate this book to the city of New Orleans and to its fragile recovery from disaster.

Vivian Fonseca
June 2008

1

Lifestyle intervention to reduce metabolic and cardiovascular risks

S. Dagogo-Jack

INTRODUCTION

More than 75% of deaths in people with diabetes are attributable to cardiovascular disease (CVD). Compared with non-diabetic persons, the CVD risk rises exponentially among patients with type 1 and type 2 diabetes [1–3]. Cardiometabolic risk factors, including insulin resistance and its associated manifestations, predispose to the 2–4-fold increased risk for CVD in type 2 diabetes. Strikingly, coronary artery disease (CAD) is ten times more prevalent among patients with type 1 diabetes than age- and gender-matched persons without diabetes [2, 3]. Clearly, insulin resistance is not a characteristic feature of type 1 diabetes, at least not during the initial years. Therefore, the mechanisms underlying the 10-fold increased risk of CAD in type 1 diabetes must involve factors beyond insulin resistance, and hyperglycemia appears to be a mediator. The role of hyperglycemia as a major CVD risk mediator in type 1 diabetes has been strengthened by new data [4] from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC). The strategy for reduction of CVD risk in patients with type 1 or type 2 diabetes must necessarily be comprehensive and multifaceted. At the least, such strategy should include bio-behavioral interventions (smoking cessation, weight reduction, dietary modification, increased physical activity) and pharmacological therapies to control hyperglycemia, hypertension, dyslipidemia, dysfibrinolysis, and other comorbid conditions. This review focuses on the role of lifestyle modification as a primary or adjunctive intervention to prevent or decrease CVD and cardiometabolic risks in persons with diabetes and prediabetes.

CHRONIC COMPLICATIONS OF DIABETES

The prevalence and incidence rates for both type 1 and type 2 diabetes are increasing worldwide, although the rates for type 2 diabetes are disproportionately greater. Diabetes is a major public health problem, largely because of its long-term complications. These complications include microvascular (retinopathy, nephropathy and neuropathy) and macrovascular (CAD, cerebrovascular disease and peripheral vascular disease) categories. Hyperglycemia is the driving force for the development of microvascular complications in patients with type 1 or type 2 diabetes, as has been confirmed in landmark studies [5, 6]. Hyperglycemia is also one of several major etiological factors for macrovascular disease in

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type 2 diabetes. Diabetes leads to accelerated atherosclerosis through a variety of mutually reinforcing mechanisms [7]. For patients with type 2 diabetes, the risk of first myocardial infarction (MI) is similar to that of recurrent MI in non-diabetic persons who have had a previous heart attack [8]. Although no exactly similar data have been reported for type 1 diabetes, the pattern is likely identical or worse, given the known 10-fold increased prevalence of CVD in patients with type 1 diabetes [2, 3].

MECHANISMS OF THE CVD RISK IN DIABETES

Cardiometabolic risk factors, including insulin resistance, dysmetabolic syndrome and associated manifestations, predispose to the increased CVD in type 2 diabetes [9]. Features of the dysmetabolic syndrome include visceral obesity, insulin resistance, hypertension, hypertriglyceridemia, decreased high-density lipoprotein (HDL)-cholesterol levels, small dense low-density lipoprotein (LDL)-cholesterol levels, pro-inflammatory state, endothelial dysfunction and a pro-coagulant state, among others [1, 10]. In contrast, insulin resistance is not the dominant feature of type 1 diabetes, at least not during the initial years. It must be noted, though, that a phenotype of insulin resistance can be superimposed upon pre-existing type 1 diabetes, particularly in persons with a family history of type 2 diabetes and those who develop abdominal obesity [11, 12]. Conceptually, the mechanisms underlying the 10-fold increased CVD risk in type 1 diabetes must involve at least two sets of factors: those expressed during the initial years that may be independent of insulin resistance, and factors arising from the insulin resistance that is superimposed in later years. Of course, there is also a multiplicative effect from non-glycemic risk factors (e.g., hypertension, dyslipidemia, smoking etc.).

The pathogenesis of diabetes-specific long-term complications is not fully understood. Some suggested mechanisms include genetic predisposition; hyperglycemia-induced abnormalities in the polyol pathway; toxic effects of advanced glycated end-products; glomerular hyperfiltration; aberrant growth factor expression, inflammation, altered redox state, and abnormal endothelial function [13–18]. Thus, the mechanisms responsible for the initiation of macrovascular complications in type 1 diabetes could well involve hyperglycemia as a direct mediator or trigger. Despite the existing gaps in our knowledge, one can argue that lifestyle measures that decrease CVD risk in type 2 diabetes should prove beneficial in type 1 diabetes also, despite mechanistic differences in the pathophysiology of CVD in the two forms of diabetes. Therefore, the specific lifestyle interventions to be discussed later in this review (consisting of smoking cessation, weight optimization, dietary modification and increased physical activity) constitute a generic strategy for cardiometabolic risk reduction.

PREDIABETES AND THE CONTINUUM OF CARDIOMETABOLIC RISK

The term ‘prediabetes’ refers to impaired glucose tolerance (IGT) and impaired fasting glucose (IFG), two intermediate metabolic states between normal glucose tolerance and diabetes. IGT is defined by a plasma glucose level of 140 mg/dl to 199 mg/dl, 2 h following ingestion of a 75 g oral solution. IFG is defined by a fasting plasma glucose of 100 mg/dl to 125 mg/dl [19]. IFG and IGT are risk factors for type 2 diabetes, and persons with these conditions progress to type 2 diabetes at variable rates. The prediabetic state is associated with numerous CVD risk markers that overlap considerably with components of the metabolic syndrome. Among several definitions of the metabolic syndrome, the one proposed by the National Cholesterol Education Program, Adult Treatment Panel III (NCEP, ATP III) [20] that focuses on abdominal obesity, low HDL-cholesterol (<40 mg/dl in men and <50 mg/dl in women), triglycerides (>150 mg/dl), blood pressure (>130/80 mmHg) and fasting plasma glucose (>100 mg/dl) has the merits of simplicity and specific numerical cut-off points. Estimates using the NCEP criteria for the metabolic syndrome have indicated an alarming prevalence of the syndrome [21]. Components of the metabolic syndrome can

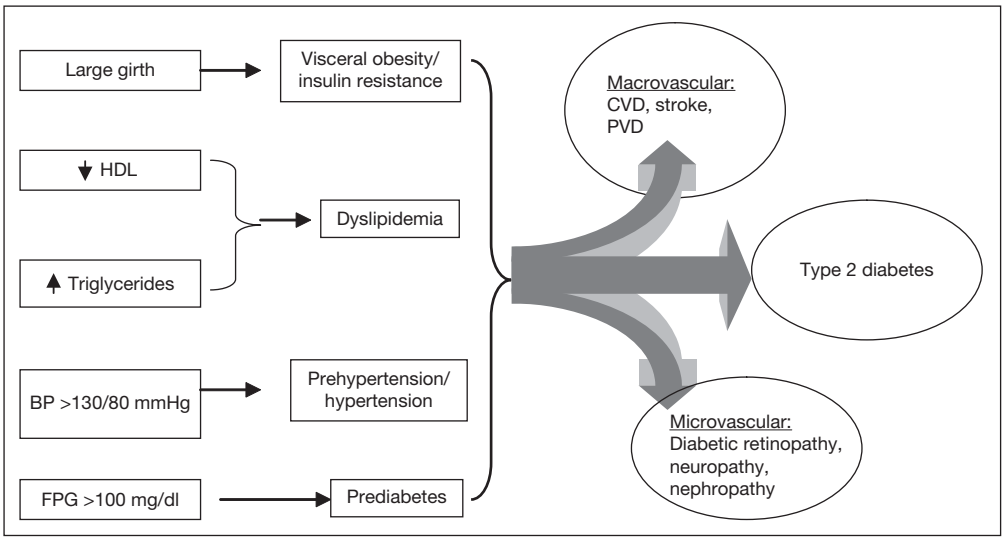

Figure 1.1 Sequelae of the metabolic syndrome. Individual components of the syndrome are risk factors for type 2 diabetes and CVD. Progression to diabetes initiates susceptibility to microvascular complications and further exacerbates the risk for CVD. Lifestyle prevents or delays progression to type 2 diabetes and ameliorates each of the cardiometabolic risk factors. BP = blood pressure; CVD = cardiovascular disease; FPG = Fasting plasma glucose; PVD = Peripheral vascular disease.

be identified in prediabetic subjects several years before the diagnosis of type 2 diabetes, are significantly associated with expression of pro-inflammatory cytokines, and are predictive of future risk of incident diabetes and CVD [22].

Furthermore, the individual components of the metabolic syndrome represent pre-nosologic or prodromal states for subsequent disease states (Figure 1.1). Thus, dyslipidemia and hypertension lead to CVD; obesity and IGT/IFG lead to type 2 diabetes, and also predict increased CVD risk. In the Paris Prospective Study [23], a prediabetes status at baseline conferred a doubling of the 10-year risk for CVD mortality. In the EPIC-Norfolk study [24], the degree of glycemia (as assessed by glycosylated hemoglobin [HbA1c]) emerged as an independent predictor of CVD mortality. The relationship between HbA1c and CVD mortality was evident as a continuum of risk, beginning well before the glycemic threshold for the diagnosis of diabetes is reached (Figure 1.2). These data indicate that macrovascular disease manifests during the prediabetic stage, thus arguing for early intervention. The insulin resistance (metabolic) syndrome appears to be the link between prediabetes and macrovascular disease. Therefore, interventions that reduce insulin resistance and attenuate expression of the metabolic syndrome can be expected to reduce the metabolic and cardiovascular consequences of the syndrome. The stark reality from long-term follow-up of prediabetic subjects assigned to a placebo arm is that spontaneous recovery from prediabetes rarely occurs [25]. This realization makes early lifestyle intervention a clinical imperative and a compelling public health priority.

LIFESTYLE INTERVENTION FOR PREVENTION OF CVD IN DIABETES

The multifactorial origin of CVD in diabetes compels a comprehensive approach that incorporates lifestyle modification with an appropriate selection of medications for glucoregulation, control of hypertension, dyslipidemia, antiplatelet therapy and other comorbid conditions [26] (Table 1.1).

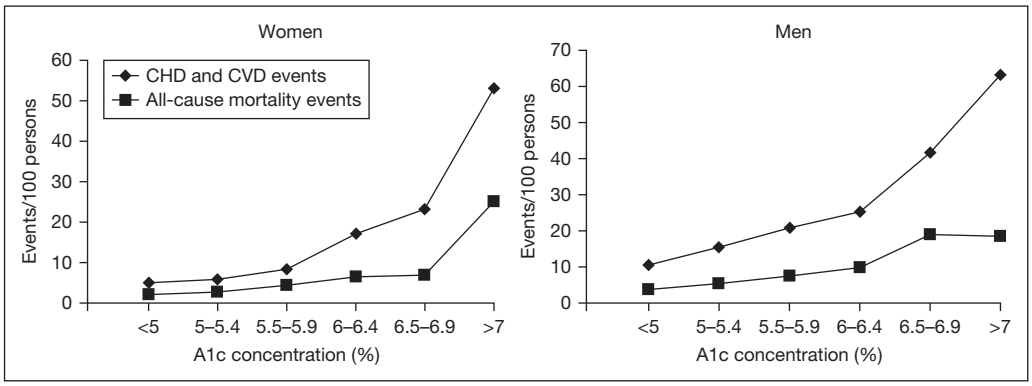

Figure 1.2 Hemoglobin A1c and CVD events and mortality in the EPIC-Norfolk study. An increase in A1c of 1% was associated with a 20% to 30% increase in cardiovascular events or mortality. CHD = coronary heart disease; CVD = cardiovascular disease. Reproduced with permission from [7].

Table 1.1 Targets of intervention for CVD risk reduction

Overweight/obesity
Physical inactivity
Cigarette smoking
Dyslipidemia
Hypertension
Insulin resistance/IFG/IGT
Hyperglycemia
Microalbuminuria
Platelet aggregation/dysfibrinolysis
Atheroinflammatory cytokines
Other

IFG = impaired fasting glucose; IGT = impaired glucose tolerance

Smoking cessation

The use of tobacco products exacerbates adverse metabolic and cardiovascular outcomes among diabetic patients [7, 9, 27]. Studies have found that cigarette smoking is associated with up to four-fold additional increase in the risk of cardiovascular death among people with diabetes, depending on the amount smoked [7]. Diabetic patients with a current history of cigarette smoking have been reported to have higher HbA1c and lipoprotein levels compared with non-smokers [9, 27]. Cigarette smoking is also a risk factor for the metabolic syndrome [28]. The mechanisms for the association between smoking and increased metabolic and CVD risks include induction of insulin resistance, increased hepatic lipase activity and dyslipidemia [29–31]. Other contributory factors include the chronic elevation of stress hormones, endothelial dysfunction and the vasoconstrictive effect of nicotine [30]. It is reasonable to expect that smoking cessation would improve cardiometabolic risk through the amelioration of these noxious effects of nicotine.

Despite evidence supporting their efficacy, smoking cessation counseling and interventions are offered to only about 50% of diabetic smokers [32]. Clearly, smoking cessation counseling must become standard practice in the management and prevention of CVD and diabetes complications. As already discussed, there are several putative mechanisms whereby smoking cessation could improve cardiometabolic risk. The observation that blood pressure, heart rate, blood flow and skin temperature of hands and feet return to normal within 20 min after smoking cessation suggests rapid reversal of the acute vasoconstrictive effects of nicotine. However, rigorous intervention studies testing the effect of smoking cessation on progression of prediabetes and metabolic endpoints are yet to be reported. Nonetheless, there are compelling reasons for promoting smoking cessation counseling in clinical practice. These include the expected reduction in the risks for emphysema, lung cancer, CAD and stroke following smoking cessation; cleaner air and improved blood oxygenation; and overall improvement in quality of life [33]. Furthermore, exercise tolerance is expected to improve in ex-smokers, which should improve fitness and potentiate adherence to the exercise habit.

Interestingly, the standard lifestyle interventions (increased physical activity and caloric restriction) have been shown to enhance successful abstinence from smoking. In one randomized controlled trial, a regimen of three exercise sessions per week for 12 weeks plus a cognitive behavioral program improved continuous abstinence from smoking at 12 months compared with behavioral program alone [34]. The actual approach to smoking cessation in a given patient should be individualized. However, common elements of any specific approach include application of the transtheoretical model of readiness for change [35], periodic reinforcement of key messages, cognitive behavioral therapy, use of tapered transdermal or buccal nicotine, and prescription medications (bupropion, varenicline) to decrease craving during the transitional period. Referral to a specialized smoking cessation center, where available, is an efficient way of accomplishing the desired goal.

Physical activity and dietary modification

Increased physical activity and dietary modification are the cornerstones of non-pharmacological intervention for glycemic control. These lifestyle measures also provide broad benefits toward reducing cardiometabolic risk. Regular physical activity improves insulin action, blood pressure and lipid levels, and decreases obesity, among other benefits. Notably, the pro-atherogenic visceral fat compartment has been reported to be quite sensitive to physical activity [36], and decreases in waist circumference often occur early during lifestyle change. Moreover, exercise conditioning that improves cardiorespiratory fitness significantly predicts longevity [37]. The recommended goal for most people is 30–60 min of moderate-intensity aerobic exercise, repeated three or more times per week. Programs should be tailored to individual patients' physical condition, and should always include warm-up and cool-down periods. Cardiac screening is advisable for patients aged 35 years or older, especially if they have been sedentary.

Dietary practices that restrict saturated fat intake, with augmentation of dietary fiber, fruits and vegetables, offer distinct metabolic and cardiovascular benefits [38]. Fat intake should be limited to ~30% of total calories (saturated fat should be <7%). The intake of trans fatty acids should be reduced drastically to <1% of energy consumption [26]. The so-called Mediterranean diet, based on generous servings of fruits, vegetables and nuts, has been shown to reduce CVD risk factors, reverse components of the metabolic syndrome, and improve morbidity and mortality [39–41]. Although lifestyle interventions that target the metabolic syndrome are most germane to type 2 diabetes, the cardioprotective benefits of exercise and dietary modification should extend to patients with type 1 diabetes and even persons without diabetes. Despite the intuitive appeal of the lifestyle approach, it must be acknowledged that randomized controlled trials are needed to demonstrate unique, independent benefits on CVD. One such study is the ongoing LOOK-Ahead project, funded by

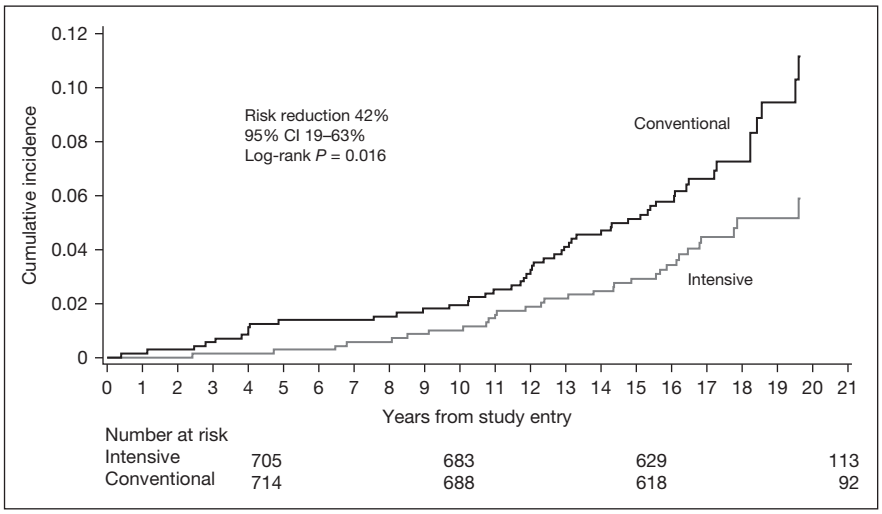

Figure 1.3 Cumulative incidence of the first of any cardiovascular disease event in the DCCT/EDIC cohort. CI = confidence interval. Reproduced with permission from [4].

the National Institutes of Health. LOOK-Ahead is a multicenter longitudinal study that has enrolled persons with type 2 diabetes with two or more additional CVD risk factors. The study subjects are randomized to a lifestyle intervention to induce ~10% weight loss vs no weight loss intervention, on a background of optimized pharmacotherapy for diabetes and comorbid conditions. The primary goal of the study is to determine whether weight loss *per se* results in CVD risk reduction in persons with diabetes.

REDUCTION OF CVD RISK THROUGH CONTROL OF HYPERGLYCEMIA IN DIABETES

The DCCT [4] showed that achievement of near-normoglycemia using insulin therapy prevented long-term microvascular complications in patients with type I diabetes. The United Kingdom Prospective Diabetes Study (UKPDS) [6] demonstrated similar benefits of intensive glycemic control on microvascular endpoints in type 2 diabetes. However, the effect of glycemic control on the occurrence of CVD in type 1 or type 2 diabetes has been an unsettled question. *Post hoc* analysis of the UKPDS data demonstrated a linear relationship between glycemic control and the rate of MI [42]. In the DCCT/EDIC study, intensive glycemic control significantly reduced the risk of any CVD event by 42% (Figure 1.3) and the risk of non-fatal MI, stroke, or death from CVD by 57% [4]. In a multivariate analysis, the decrease in HbA1c values significantly predicted the cardioprotective effect of intensive treatment, and the cardiovascular benefits persisted after adjusting for blood pressure, proteinuria, use of angiotensin inhibitors or lipid-lowering medication [4].

The patients assigned to intensive therapy in the DCCT used a regimen of multiple (four or more) daily insulin injections or continuous subcutaneous insulin infusion, whereas the control group used a conventional insulin regimen comprising two daily injections of a mixture of regular insulin and intermediate-acting insulin. Thus, improved control of post-prandial glucose among patients in the intensive therapy arm possibly contributed to the cardiovascular benefits. In the STOP-NIDDM trial, reduction of post-prandial glycemia with acarbose treatment in subjects with IGT was associated with a reduction in CVD risk

[43]. Although long-term maintenance of glycemic control is not feasible using lifestyle measures alone, the adjunctive role of dietary modification and physical activity in optimizing glycemic control cannot be overstated. At every stage of the disease, institution of the dietary principles discussed earlier leads to improvement in glycemic control, whereas *ad libitum* feeding escalates hyperglycemia. Similarly, exercise improves glycemic control in patients with type 1 or type 2 diabetes, in addition to the other well-known metabolic and cardiovascular benefits.

LIFESTYLE INTERVENTION FOR PRIMARY PREVENTION OF DIABETES

Three landmark studies have demonstrated the efficacy of lifestyle intervention in preventing the development of type 2 diabetes in high-risk individuals [44–46]. All studies targeted persons with prediabetes (IGT). The lifestyle interventions applied in these studies generally involved a modest weight loss (~5% to <10%) through dietary modification and increased physical activity. The dietary modification involved reduction in caloric consumption, selective reduction in saturated fat calories, and increased intake of complex carbohydrates. The physical activity component involved accrual of additional 150–240 min per week of voluntary, moderate-intensity (~55% VO_2 max) physical activity above routine levels [44–46]. The primary outcome measure was the rate of progression from IGT to type 2 diabetes over a defined period (~3–6 years) of observation in the intervention arm versus a comparison group.

Investigators in the Da Qing study [44] enrolled 577 Chinese adults (mean age 45 years; mean body mass index [BMI] 26 kg/m^2) who had IGT at baseline. The subjects were randomized by clinic to a control group or to one of three active treatment groups: diet only, exercise only, or diet plus exercise. The dietary policy had a target BMI of <23 kg/m^2; the exercise goal was an increase in physical activity of 210 min per week (30 min daily). The follow-up schedule was approximately every 2 weeks during the initial 3 months and quarterly thereafter. The cumulative incidence of diabetes at 6 years was 67.7% in the control group compared with 43.8% in the diet group, 41.1% in the exercise group and 46.0% in the diet-plus-exercise group. Cox's proportional hazards analysis, adjusted for differences in baseline BMI and fasting glucose, showed that the diet, exercise, and diet-plus-exercise interventions resulted in 31%, 46% and 42% reductions in risk of developing diabetes, respectively, compared with the control group. Surprisingly, the Da Qing study failed to show an additive effect of diet plus exercise on the primary endpoint.

In the Finnish Diabetes Prevention Study [45], 522 middle-aged IGT subjects (172 men and 350 women; mean age 55 years; mean BMI 31 kg/m^2) were randomly assigned to either an intervention or control group. Each subject in the intervention group received individualized lifestyle counseling aimed at inducing ~5% weight loss and increasing physical activity by ~210 min per week. The mean weight loss by the end of the second year was ~3.5 kg in the intervention group and ~0.8 kg in the control group. The cumulative incidence of diabetes after 4 years was 11% in the intervention group and 23% in the control group, a significant 58% reduction in diabetes incidence.

THE DIABETES PREVENTION PROGRAM

The lifestyle intervention arm of the Diabetes Prevention Program (DPP) enrolled 1079 subjects with IGT (out of the 3234 participants enrolled in the study) drawn from all ethnic and racial groups in the US population [46]. The goals for the participants assigned to the intensive lifestyle intervention were to achieve and maintain a weight reduction of at least 7% of initial body weight through modest caloric restriction (500–700 fewer calories per day) and to engage in physical activity of moderate intensity, such as brisk walking, for at least 150 min per week. After an average follow-up period of 2.8 years, the participants randomized to

lifestyle intervention showed a 58% reduction in the incidence of diabetes, as compared with placebo [46]. This beneficial effect of lifestyle intervention was seen in all age, gender, racial and ethnic subgroups of the DPP participants. Furthermore, reversion to normal glucose tolerance (NGT) occurred in ~30% of subjects in the lifestyle intervention arm, as compared with ~18% in the control arm. Thus, caloric restriction and increased physical activity not only prevented progression from IGT to diabetes but were also effective in restoring NGT in a substantial proportion of subjects with initial IGT [46].

PRIMARY PREVENTION OF CVD IN PREDIABETES

The DPP investigators [47] assessed the effects of lifestyle intervention, metformin and placebo on CVD risk factors and markers of the metabolic syndrome among subjects with IGT. Compared with the placebo and metformin arms, subjects assigned to lifestyle intervention showed decreased blood pressure, increased HDL-cholesterol levels, and lower triglyceride levels during approximately 3 years of follow-up. Moreover, there was a reduced need for antihypertensive and lipid-lowering medications among subjects assigned to the intensive lifestyle arm. Besides reducing the need for antihypertensive medications, lifestyle intervention reduced the crude incidence of hypertension by 33% in the DPP lifestyle group [47, 48]. The level of LDL-cholesterol was not significantly altered by lifestyle intervention, although a reduction in the more atherogenic small, dense LDL particles was observed [47]. Because total LDL particles, rather than subclasses, have been the standard measurement for landmark outcome trials, early initiation of therapy with an HMG-CoA reductase inhibitor (statin) may be indicated, to reach protective levels of LDL in high-risk subjects. The favorable effects of lifestyle intervention on blood pressure and the levels of HDL-cholesterol, triglycerides, and small dense LDL particles suggest that the overall risk for CVD ought to be decreased. The DPP Outcomes Study is tracking the original cohort for another decade, to determine whether the aforementioned improvements in risk factors would translate to reduction in clinical events.

EMERGING MOLECULAR MECHANISMS

The emerging data on the interactions between lifestyle intervention and incident diabetes suggest possible epigenetic effects at the molecular level that translate to prevention of diabetes [49, 50]. In the Finnish Diabetes Prevention Study, a significant interaction was reported among weight change, progression from IGT to type diabetes, and the G308A polymorphism of the tumor necrosis factor alpha (TNF-α) gene among subjects randomized to the intensive lifestyle intervention arm [49]. Also, the DPP investigators have reported intriguing data that suggest possible epigenetic interactions between lifestyle modification on the transcription factor 7-like 2 gene (*TCF7L2*) [50]. Previously, genotyping of microsatellite markers throughout a 10.5-Mb interval on chromosome 10q in an Icelandic cohort with type 2 diabetes had revealed a microsatellite within intron 3 of *TCF7L2* (formerly known as *TCF4*) that was associated with diabetes [51]. Compared with non-carriers, heterozygous and homozygous carriers of the at-risk alleles (38% and 7% of the Icelandic population, respectively) have relative risks of 1.45 and 2.41 (population attributable risk of 21%) [52]. The TCF7L2 gene product has been implicated in blood glucose homeostasis, probably through the regulation of proglucagon gene expression in enteroendocrine cells [51].

Two of the most strongly associated *TCF7L2* variants (rs12255372 and rs7903146) have been examined in the DPP, to determine whether they predict progression from IGT to type 2 diabetes [50]. Both variants were genotyped in 3548 DPP participants, and Cox regression analysis was performed using genotype, intervention, and their interactions as predictors. During ~3 years of follow-up, subjects harbouring the rs7903146 risk-conferring TT genotype were more likely to have progressed from IGT to type 2 diabetes than were CC

homozygotes (hazard ratio [HR] 1.55; confidence interval [CI] 1.20–2.01; $P < 0.001$). Interestingly, the predictive effect of the TT genotype was strongest in the placebo group (HR 1.81) and weakest among subjects randomized to intensive lifestyle modification (HR 1.15). Further analysis revealed that the TT genotype was associated with decreased insulin secretion but not increased insulin resistance at baseline [50]. The data obtained from analysis of the rs12255372 variant were concordant with the findings from analysis of the rs7903146 variant.

SUMMARY

Dietary modification, regular physical activity, smoking cessation and other lifestyle changes have been shown to exert favorable effects on glycemia, blood pressure, body weight, fat distribution, lipid and lipoprotein profiles, among other metabolic and psychological benefits. Lifestyle interventions have also been demonstrated to be effective in primary prevention of type 2 diabetes. These consistent metabolic and cardiovascular benefits make the implementation of lifestyle intervention a public health imperative. In the DPP, the benefits of lifestyle change were observed universally across all age and BMI groups, whereas the effect of metformin was restricted to young obese persons [46, 52]. The fascinating observations that suggest possible modulation of pro-inflammatory and glucoregulatory genes by lifestyle intervention [49, 50] provide a novel insight into how behavioral interventions can alter the expression of genetic diseases. This area of study into epigenetic influences in behavioral metabolism is still in its infancy, and can be expected to advance rapidly in coming years. Among patients with isolated diabetes, hypertension, dyslipidemia, or the metabolic syndrome, lifestyle change is an important adjunct to medications. For the millions of people who have prediabetes, lifestyle modification is especially compelling because of its non-toxicity and superb efficacy, compared with medications.

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