

The Diabesity Epidemic

a report by

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Prognostic Importance of Obesity

The worldwide prevalence of diabetes has increased over the past 40 years. Estimates vary, but it is incontrovertible that the increase has reached epidemic proportions (see *Figure 1*).^{1–4} An extrapolation of World Health Organization (WHO) estimates on diabetes prevalence from all 191 WHO member states suggested the global prevalence to be 2.8% in 2002 and projected an increase to 4.4% by 2030.¹ Others have projected an increase to 300 million, or 5.4% of the world population, by 2025,² the majority of which (>90%) will be type 2 diabetes.^{2,3} There is a well-established link between diabetes incidence and the adoption of a western lifestyle;^{5,6} thus, prevalence is increasing particularly rapidly in the industrialising nations of Asia.^{2,3,7} Rapid westernisation has created a large disparity in the rate of increase between the developed and developing nations. Between 1995 and 2025, diabetes is projected to increase by 170% in the developing world compared with a projected increase of 42% in developed nations.⁴

Increases in the prevalence of diabetes and pre-diabetes are paralleled by, and closely linked to, a marked increase in obesity (see *Figure 2*).⁸ The two conditions are so closely tied that their joint increase has been referred to as the 'diabesity epidemic'.³ In 1999–2002, 65.1% of US adults ≥ 20 years of age were overweight or obese (body mass index [BMI] $\geq 25\text{kg/m}^2$), 30.4% were obese (BMI $\geq 30\text{kg/m}^2$) and 4.9% were extremely obese (BMI $\geq 40\text{kg/m}^2$).⁹ Among children aged 6–19 years, 31% were at risk of overweight or obesity and 16% were overweight.⁹

Obesity lies in the causative pathway to glucose intolerance, and is a major factor in the progression from impaired glucose tolerance (IGT) to type 2 diabetes. Every 1kg increase in weight is associated with a 9% relative increase in diabetes prevalence.¹⁰ Obesity also worsens the metabolic and physiological abnormalities associated with diabetes. IGT is associated with a six- to 10-fold increased overall risk in progression to type 2 diabetes compared with individuals without IGT,¹¹ and approximately 40% of people with IGT will progress to type 2 diabetes over five to 10 years.² The conversion rate from isolated IGT to type 2 diabetes is about 5–6% annually.^{11–13}

Burden of Obesity and Diabetes

This projected future burden of obesity-associated diabetes has rightly been described as a ticking time bomb¹⁴ that will burden world healthcare infrastructure and affect economic productivity in a multitude of ways. Consider the following:

- Obesity in children in the US and other developed nations has increased to approximately 30%, and rates among Latino- and African-Americans are even higher.⁹ In some nations, obesity is increasing at a faster rate in children than in adults.¹⁵

- At least 80–90% of people with type 2 diabetes are obese.¹⁰
- Diabetes accounts for 2–7% of the total national healthcare budgets of western European countries.¹⁶
- Diabetes is already the most common reason for end-stage renal disease requiring expensive dialysis. The healthcare infrastructure is poorly prepared to accommodate a significant increase in the number of people requiring such care.¹⁷
- Age-adjusted mortality among adults with diabetes is about twice that of those without diabetes.¹⁸
- The risk factors for cardiovascular disease, already the single leading cause of mortality in the general population, occur to a significantly greater degree when obesity and insulin resistance are present.¹⁹

Obesity, Impaired Glucose Tolerance, Insulin Resistance and Type 2 Diabetes

The relationship between obesity, IGT, insulin resistance and diabetes is complex. Obesity is a primary contributor to insulin resistance and IGT, and is also a major risk factor for progression from IGT to type 2 diabetes in susceptible individuals with a propensity for β -cell failure.²⁰ Insulin resistance impedes glucose disposal and disrupts lipid metabolism in insulin-sensitive tissues (liver, muscle, adipose). When present in those susceptible, insulin resistance contributes to β -cell failure and progression of type 2 diabetes. The majority of insulin-resistant persons are overweight or obese.^{19,21,22} It also appears that much insulin resistance is due to acquired factors rather than just genetic factors, as weight loss will normalise insulin sensitivity completely and oppose progression from IGT to type 2 diabetes in obese insulin-resistant individuals.²³ This conclusion was supported by the results of a study of insulin response in monozygotic twin pairs who were discordant for obesity.²⁴ However, other studies of twins estimate that the heritability of insulin resistance may be as high as 47–66%.²³

Adiposity, Lipotoxicity and Insulin Resistance

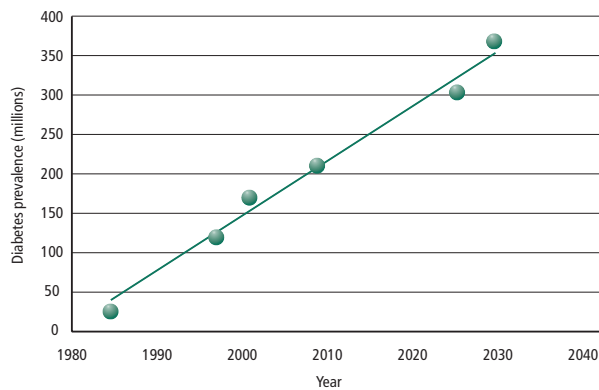
Visceral adiposity is a major determinant of insulin resistance in both obese and non-obese individuals.²⁵ Visceral adipocytes have a higher turnover rate than subcutaneous adipose tissue, and free fatty acids (FFAs) released from these cells drain via the portal vein directly into the liver, where they act to decrease insulin clearance and increase hepatic glucose output.²³



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Figure 1: Estimated and Projected World Prevalence of Diabetes¹⁻⁴



Furthermore, visceral adipocytes are inherently more resistant to the anti-lipolytic actions of insulin than adipocytes in other body fat.²³ Elevated FFAs (i.e. lipotoxicity) can also impair β -cell function, which may partially explain how long-term obesity leads to the progression of glucose intolerance.^{20,25}

Another undesirable consequence of central adiposity, insulin resistance and hyperinsulinaemia is that they are tightly correlated with many other metabolic derangements, including hyperlipidaemia, hypertension, hypercoagulability – known collectively as the insulin-resistance syndrome, dysmetabolic syndrome or metabolic syndrome²⁶ – which lead to a variety of adverse health outcomes.

Importance of Weight Control

Weight control is critical for limiting the development of glucose intolerance and progression from IGT to diabetes, as well as for optimal disease management in those who develop diabetes. Compelling reasons for greater attention to weight control include the following:

- weight loss has beneficial effects on β -cell function and improved glycaemic control;^{27,28}
- both glucotoxicity and lipotoxicity are potentially reversible with weight loss;²³
- the implications of weight control are more serious for persons with diabetes. Studies suggest that these persons tend to lose less weight than people without diabetes and regain weight even more rapidly;²⁹ and
- weight loss may reduce risk factors other than obesity, such as blood pressure and elevated lipids.¹⁴

Efficacy of Weight-loss Interventions

The two primary weight-loss strategies are lifestyle modifications (e.g. exercise, behaviour and diet) and pharmacotherapy, the latter often being used in conjunction with lifestyle modifications.

Pre-diabetes or Type 2 Diabetes Populations

Weight gain exacerbates existing problems with insulin resistance and can contribute to further β -cell deterioration. In contrast, deterioration in glucose tolerance can be mitigated by minimising weight gain and obesity. For example, in the severely obese the rate of conversion from IGT to overt diabetes was reduced 30-fold with significant weight loss versus comparable controls without weight loss.³⁰ Even when irreversible diabetes is diagnosed, weight loss is beneficial. This is shown by the fact that people with diabetes who actively lose weight improve their risk profile³¹⁻³³ and their longevity.^{34,35}

Lifestyle interventions for weight loss have been extensively studied in cohorts with pre-diabetes or type 2 diabetes. One systematic review indicated that dietary interventions alone produced a weight loss of about 9kg, in contrast to a loss of about 3kg when behavioural interventions were used, in patients with type 2 diabetes.³⁶ These results reflected only short-term follow-up, as few studies examined outcomes beyond six months. A meta-analysis of 22 studies indicated that lifestyle modifications were associated with modest reductions: a pooled weight loss of 1.7kg (95% confidence interval [CI] 0.3–3.2kg), or about 3.1% of bodyweight.²⁹

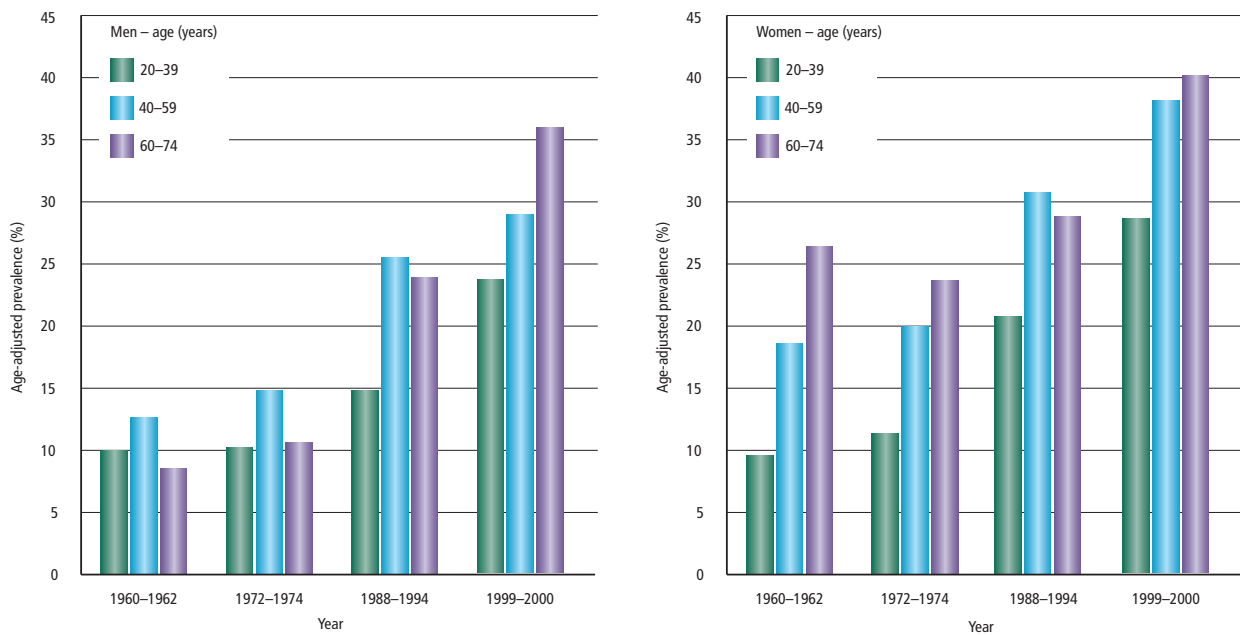
There are reasons for optimism regarding the efficacy of lifestyle interventions in people with pre-diabetes. A meta-analysis of nine randomised clinical trials indicated that diet, exercise or behavioural interventions produced weight loss of 2–3kg (~3% of initial bodyweight) at one- and two-year follow-up.³⁷ In two studies in which weight was examined for up to 10 years, these reductions were maintained. It would be encouraging if these results were applicable to the general population of people with IGT because other studies have shown that when weight loss is achieved in this population, it can limit progression from IGT to type 2 diabetes by as much as 58%.^{12,13} Weight-loss pharmacotherapy is also of uncertain benefit. For example, a meta-analysis of 14 randomised, controlled trials involving orlistat, fluoxetine or sibutramine indicated that weight reductions were modest (2.6–5.8kg at 26–52 weeks), and side effects were common (gastrointestinal effects with orlistat, tremor, somnolence and sweating with fluoxetine and palpitations with sibutramine).¹⁰ The authors concluded that pharmacotherapy was no more effective than behavioural therapy at one year.

The Challenge of Intensifying Therapy and Limiting Weight Gain

Due to progressive β -cell failure, many patients with type 2 diabetes become unable to adequately control their blood glucose with lifestyle interventions alone.²⁷ Typically, conventional treatment involves a stepwise progression from lifestyle interventions, oral antidiabetic drug (OAD) monotherapy, multiple OAD therapy and, finally, OADs plus insulin.²⁷ Stepwise treatment appears inconsistent with what is known about the pathogenesis of type 2 diabetes and the known failure rates of monotherapy. Results of the UK Prospective Diabetes Study (UKPDS) clearly indicated that monotherapy addressing either of the two major defects in type 2 diabetes (insulin resistance or inadequate β -cell function) is doomed to fail.²⁰

Diabetes may be viewed as a manifestation of much broader metabolic derangements,³⁸ and there is increased recognition that optimal treatment must address a broad array of risk factors, including obesity, address them earlier and attack them more aggressively.^{17,25,27,39-43} However, meeting the dual goals of achieving recommended glycaemic targets and preventing weight gain is difficult because drugs used to control hyperglycaemia, e.g. sulphonylureas, non-sulphonylurea secretagogues and insulin, tend to increase weight, thereby causing a vicious cycle. In addition, weight gain can act as a psychological barrier to the initiation or intensification of diabetes treatment.⁴⁴ The paradox is that some of the weight gain is likely due to caloric retention resulting from improved glycaemic control. This helps to explain why intensification of therapy, as demonstrated in the UKPDS, can further exacerbate weight gain.⁴⁵

The disadvantage of therapeutic regimens that may progressively increase weight, even by a small amount, in a population already likely to be insulin-resistant is compounded by the implications of having to initiate therapy at

Figure 2: Trends in Age-adjusted Prevalence of Obesity for US Adults Aged 20–74 Years, 1960–2000^a

increasingly younger ages. With the current epidemiological trend of an earlier age at onset of diabetes, patients will potentially be exposed to weight-promoting therapies for considerably longer than ever before. However, there are potential solutions. Selection of insulin-sparing OADs such as metformin may limit weight gain in patients who require pharmacotherapy.⁴⁰ For many OADs, using 50% of the maximal dose will produce close to maximum blood glucose reduction.⁴⁶ Therefore, use of combination therapy can decrease the required dose of any individual drug, thus minimising side effects such as weight gain without sacrificing glycaemic control.

Potential pharmacological therapies in development for pre-diabetes and diabetes may potentially improve glycaemic control without weight gain. Incretin mimetics are of particular interest as their novel mechanisms of action may have great utility in the management of type 2 diabetes and obesity.⁴⁷ For example, glucagon-like peptide 1 (GLP-1) is a potent insulinotropic gut hormone with a variety of antidiabetic and anti-obesity effects.⁴⁸ It has been shown to decrease food intake and induce weight loss in 19 healthy, obese subjects following subcutaneous infusion.⁴⁹ Native GLP-1 has limited utility because it is rapidly degraded *in vivo* after systemic administration.⁵⁰ A once-daily human GLP-1 analogue, liraglutide, can be administered by subcutaneous injection,⁵¹ and was used in a randomised clinical trial in patients with type 2 diabetes. Liraglutide reduced the glycated haemoglobin (HbA_{1c}) levels of allocated patients by 1.74% from an average baseline of 8.5%, and lost 1.21kg compared with placebo ($p=0.0390$).⁵²

Insulin and Weight Gain

For the foreseeable future, insulin therapy will remain a mainstay of treatment for advanced type 2 diabetes. New analogue insulins, which recreate a more physiological insulin profile, show promise in overcoming the well-known limitation of weight gain associated with insulin therapy. For example, insulin detemir has been compared with neutral protamine Hagedorn (NPH) insulin as the basal component of basal-bolus therapy in type 1 diabetes in a series of comparative trials.^{53–57} The new analogue provided equivalent glycaemic control to NPH insulin in each of these, but in every case this was accomplished without causing weight gain, in contrast

to NPH insulin. A significantly lower degree of weight gain compared with NPH insulin has also been shown in type 2 diabetes.^{58,59} When used in basal-bolus therapy,⁵⁸ six-month weight gains with insulin detemir and NPH insulin were 1 and 1.8kg, respectively ($p=0.017$). When used as add-on therapy to oral agents in a goal-directed titration protocol to achieve HbA_{1c} values of less than 7%,⁵⁹ six-month weight gain averaged 1.2kg with insulin detemir and 2.8kg with NPH insulin ($p<0.001$).

Insulin detemir also demonstrates weight advantages versus insulin glargine in patients with type 2 diabetes. In one study comparing insulin detemir and insulin glargine for insulin-naïve individuals already taking glucose-lowering drugs, HbA_{1c} reductions were comparable in both groups, but reductions in weight gain were observed with detemir versus glargine (2.7 versus 3.5kg; $p=0.03$).⁶⁰ A meta-analysis comparing insulin detemir and insulin glargine with NPH insulin demonstrated that the insulin analogues achieved comparable HbA_{1c} control to NPH insulin with significant reductions in overall, nocturnal and symptomatic hypoglycaemia.⁶¹ However, insulin detemir, but not insulin glargine, was associated with a significantly smaller weight gain than human insulin, even after adjusting for variations in HbA_{1c} in a multivariate analysis ($p<0.05$).⁶¹ The Predictable Results and Experience in Diabetes through Intensification and Control to Target: an International Variability Evaluation (PREDICTIVE™) is a multinational, open-label, prospective, uncontrolled observational study that provides an insight into 'real-life' clinical responses to insulin outside the intensive support structure provided by a typical clinical trial. In the European cohort of over 20,000 patients who transferred from an OAD plus NPH insulin or insulin glargine to an OAD plus insulin detemir, mean bodyweight was significantly reduced in the group that previously received NPH (-0.7kg; $p<0.01$) and the group that previously received glargine (-0.5kg; $p<0.05$).⁶² These weight improvements were observed in conjunction with improved HbA_{1c} control and reduced rates of total and nocturnal hypoglycaemic events following transfer to insulin detemir plus an OAD.⁶²

Conclusions

Diabetes is becoming more prevalent as lifestyles change. Weight control is critical. While modifying diet and increasing physical activity are

important, many patients find it hard to maintain weight loss over the long term using these interventions. In addition, weight-loss pharmacotherapy is also of uncertain benefit. While some treatment options for diabetes, such as sulphonylureas, non-sulphonylurea secretagogues and certain insulins, are associated with weight gain, other treatment choices such as metformin may offer weight benefits. In addition, insulin detemir has been shown to be weight-sparing versus

NPH insulin in type 1 and type 2 diabetes, and versus insulin glargine in type 2 diabetes. ■

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