

Diabetes - An Evolving Socio-Economic and Public Health Tragedy

Paul Zimmet¹ and Donald Chisholm²

¹International Diabetes Institute, 250 Kooyong Road, Caulfield VIC 3162

²Garvan Institute of Medical Research, 384 Victoria Street, Darlinghurst NSW 2010

Introduction

Diabetes mellitus is a syndrome rather than a single condition, with four major categories (1). Type 1 diabetes (previously designated insulin-dependent or juvenile-onset) is due to destruction of the insulin producing β -cells of the pancreatic islets, most commonly by an autoimmune mechanism, with an immediate and life-long requirement for insulin therapy. Type 2 diabetes (previously designated non-insulin-dependent or mature-onset) is characterised by a combination of a defective end-organ response to insulin (insulin resistance) and a relative deficiency of insulin secretion. It is a heterogeneous disorder with a number of different pathogenetic mechanisms explaining some variation in the phenotype. The third group consists of a small percentage of patients with diabetes who have a specific recognisable cause, for example, Cushing's syndrome or pancreatitis. Finally, gestational diabetes is defined as glucose intolerance with first recognition during pregnancy.

Epidemiological perspective

The dramatic increase in the prevalence of diabetes (mainly Type 2) world-wide is a matter of enormous concern to individuals and public health authorities in both developed and developing nations and the World Health Organisation (WHO). Globally, the percentage of Type 2 diabetes is greater than 90%, as Type 1 diabetes is relatively uncommon in some populations, particularly Asian, Middle Eastern and African (2). At the present time it is estimated that 150 million people worldwide have diabetes and that this will increase to 220 million by 2010 and 300 million by 2025 (2). Not only is the prevalence increasing, but the age of onset of Type 2 diabetes is becoming younger with an increasing, but also poorly quantified number of children and adolescents being diagnosed (2).

The AusDiab Study has demonstrated that there are about 1 million Australian with diabetes, approximately 90% Type 2. It demonstrated that the prevalence of diabetes has trebled over the last 20 years, that 7.5% of Australians over the age of 25 have diabetes and approximately 20% of the population are affected by their late 60s (3,4). The incidence of diabetes has

more than doubled since 1981, and this is only partially explained by changes in age profile and obesity. Almost one in four Australians 25 years and over has either diabetes or a condition of impaired glucose metabolism.

A particularly worrying feature of the epidemiology of diabetes has been the concurrence of diabetes with other cardiovascular risk factors. In the AusDiab Study, the presence of obesity, hypertension, elevated LDL cholesterol, low HDL cholesterol and elevated triglycerides were dramatically increased in the diabetic population compared to those with normal glucose tolerance (Table 1) (3). This concern regarding cardiovascular risk becomes even greater when one considers that people with a lesser abnormality of blood glucose levels (impaired glucose tolerance (IGT) and impaired fasting glucose (IFG)) have a substantial increase in cardiovascular risk factors and an

Table 1. Prevalence (%) of cardiovascular disease risk factors stratified by glucose tolerance status (AusDiab data (3)).

	NGT	IFG	IGT	Diabetes
Obesity (BMI ≥ 30 kg/m ²)	16.2	29.9	31.4	46.2
Hypertension ($\geq 140/90$ mmHg)	21.1	44.4	51.1	68.6
LDL ≥ 3.5 mmol/L	47.3	69.9	62.1	63.8
HDL < 1.0 mmol/L	14.9	27.1	22.5	39.1
Triglycerides ≥ 2.0 mmol/L	19.6	39.9	38.8	56.7

Data are not age or sex adjusted. BMI - body mass index; NGT - normal glucose tolerance; IFG - impaired fasting glucose; IGT - impaired glucose tolerance.

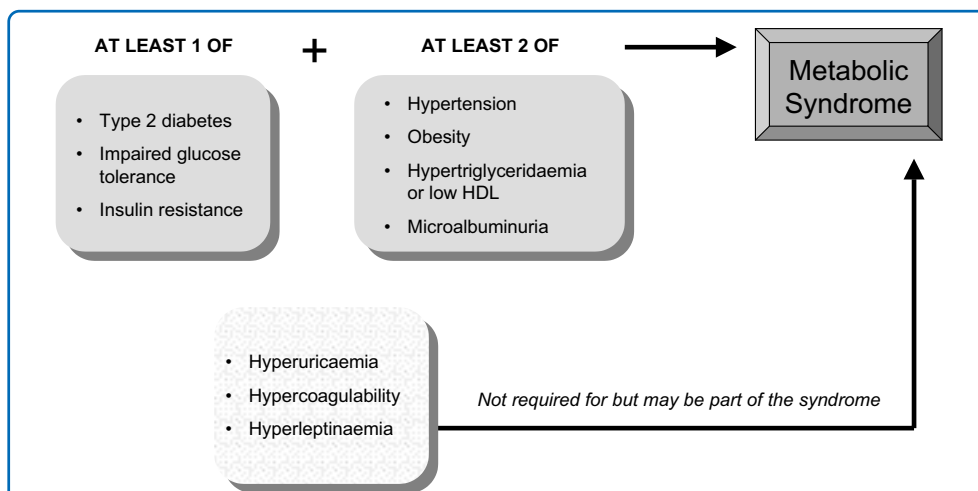


Fig. 1. Metabolic Syndrome as defined by the World Health Organisation (1).

Insulin resistance defined as being within the highest quartile for the relevant population. Hypertension - BP $\geq 140/90$. Obesity - BMI ≥ 30 kg/m² or for males waist hip ratio (WHR) > 0.90 ; for females WHR > 0.85 . Hypertriglyceridaemia - triglycerides ≥ 1.7 mmol/L. Low HDL - < 0.9 mmol/L for men; < 1.0 mmol/L for women. Microalbuminuria - urinary albumin excretion rate ≥ 20 μ g/min or albumin creatinine ratio ≥ 30 mg/min.

approximate doubling of cardiovascular risk (1,5). This is the hidden epidemic – impaired glucose tolerance and impaired fasting glycaemia.

Worldwide it is estimated that more than 250 million people have IGT or IFG and in Australia over 16% of the adult population (additional to those with diabetes) fall into this category. Impaired glucose tolerance (IGT) was considered a class in the previous WHO classification but is now categorised as a stage in the natural history of disordered carbohydrate metabolism (1). A stage called IFG, impaired fasting hyperglycaemia or non-diabetic fasting hyperglycaemia, is now recognised as these people also appear to be at greater risk for progression to diabetes and macrovascular disease, although prospective data are sparse and early data suggest a lower risk of progression than IGT (1,6). IFG refers to fasting glucose concentrations, which are lower than those required to diagnose diabetes mellitus but higher than the “normal” reference range (1).

IGT and IFG are not clinical entities in their own right (mostly in the absence of pregnancy for IGT), but rather, risk categories for future diabetes and/or cardiovascular disease (1,6). IGT and IFG represent impaired glucose regulation in reference to a metabolic intermediate between normal glucose homeostasis and diabetes. Individuals who meet criteria for IGT or IFG may be euglycaemic in their daily lives as shown by normal or near-normal glycated haemoglobin levels (1). IGT is often associated with the Metabolic Syndrome (or Insulin Resistance Syndrome) (Fig. 1) (1,7). An individual with a fasting plasma glucose concentration of 6.1 mmol/L or greater but less than 7.0 mmol/L is considered to have impaired fasting glycaemia. If an oral glucose tolerance test (OGTT) is performed, some individuals with IFG will have IGT. Some may have diabetes but this cannot be determined without an OGTT. If resources allow, it is recommended that those with IFG have an OGTT to exclude diabetes (6).

Glucose intolerance and the Metabolic Syndrome

Insulin resistance may be a central issue in the clustering of glucose intolerance and other cardiovascular risk factors, which has led to the terminology of Metabolic Syndrome (Fig. 1) whose features include insulin resistance, central obesity, dyslipidaemia (especially elevated triglycerides and reduced HDL-cholesterol), hypertension, hyperuricaemia, and increased plasminogen activator inhibitor-1 (1,7). The causative mechanisms involved have not been clearly defined but one possibility is that central obesity and excess lipid availability constitutes a major mechanism for many or all of these abnormalities.

Globally there has been a small but important increase in the incidence of Type 1 diabetes, but a massive explosion of Type 2 diabetes (2). Although we do not have all the molecular answers to this conundrum, the epidemiological data seems clear. Type 2 diabetes is a lifestyle disorder, and during the last 30 to 40 years, there have been dramatic changes in the human environment, behaviour and lifestyle, which have resulted in escalating rates of both obesity and diabetes (2). In fact, the term diabetes has been suggested to describe this phenomenon (2). There is every reason to believe that over the next decade the epidemic of Type 2 diabetes will continue to escalate. There is also a contribution from ageing, but it by no means explains the

dramatic rise (4). With improvements in public health, mortality from infectious diseases has fallen dramatically and, paradoxically, there has been a marked increase in the prevalence of non-communicable diseases such as Type 2 diabetes (8).

Genetic influences are clearly important with a strong familial tendency and also major ethnic differences in prevalence (7,9). In our region of the world the Micronesians in the Marshall Islands and Nauru, Polynesians in Samoa and Tonga, and our own Indigenous population have especially high risk – over 35% of adult Nauruans have diabetes (10). Asian Indian and Chinese who have moved to urban centres or to developed nations also have a relatively high risk, though the particular predisposing genes have defied identification (6).

A favourite theory to explain the unduly high risk in some populations relates to a “thrifty genotype” which has historically allowed populations to survive long famines and migration by favouring energy conservation and fat accumulation (11,13). In a situation of plenty, this genetic advantage becomes a disadvantage with excessive accumulation of adipose tissue and a variety of consequences of tissue lipid oversupply (12). An alternative theory, proposed by Hales and Barker (13), suggests that foetal nutritional deprivation, with low birth weight, is a major predisposing factor to the later development of the insulin resistance syndrome and Type 2 diabetes. This proposal is controversial as statistically it may explain only a small proportion of the diabetic risk, and the association of low birth weight with diabetic risk in later life could be on a genetic rather than nutritional basis, being another example of the thrifty gene hypothesis (7).

Epidemiological transition

Clearly the largest contribution to the increase in Type 2 diabetes is the combined environmental influence of changes in nutrition and physical activity (2,7). In most parts of the world, food is more available (with some notable exceptions) and physical activity is declining. The reduction in physical activity seems particularly important in a number of epidemiological studies (9). In Australia, calorie consumption today is not greatly different to that of 50 years ago, but physical activity has halved. It seems probable that the ratio of calories consumed versus calories expended is the critical factor in generating adiposity and insulin resistance. However, it must be noted that lack of physical activity not only contributes to increased adiposity, but particularly to an abdominal (visceral) distribution of fat which is very adverse metabolically (14).

As Type 2 diabetes increases, so does gestational diabetes, with approximately 6% of Australian pregnancies so affected. This is not only a concern in regard to maternal and foetal outcomes of the pregnancy, but recent data suggests that the child of a diabetic pregnancy will probably have a lifetime risk of developing Type 2 diabetes. This is double that which would be explained on their familial genetic risk. Thus, a vicious cycle emerges. Type 2 diabetes occurs at a younger age and is present in an increasing number of pregnancies, so the children of those diabetic pregnancies will be at higher risk of early onset Type 2 diabetes, the females of which being at high risk of gestational diabetes.

Some unusual forms of diabetes may be instructive regarding possible pathogenetic mechanisms. Several

different specific genetic mutations have been identified as causes of dominantly inherited maturity onset diabetes of the young (MODY) (7). One of these (MODY2) involves mutations in the glucokinase gene (13). As glucokinase acts as a glucose sensor in the β -cell, and these mutations result in a changed set point for the insulin response to glucose, so that there is a lesser insulin response to any particular glucose level.

Various lipodystrophies, where there is usually a loss of peripheral, but not visceral, adipose tissue are associated with insulin resistance, hyperlipidaemia and Type 2 diabetes (16). Such a syndrome also occurs in rodents that are genetically manipulated to deplete white adipose tissue. Animal and human experimental evidence would suggest that the insulin resistance and

dyslipidaemia in this situation is partly related to an inability to store surplus fatty acids "out of harm's way" in peripheral adipocytes. This leads to an increase in circulating lipids and triglyceride content of liver and muscle with consequent insulin resistance and hypertriglyceridaemia. However it is likely that fat cell hormones (adipokines) also contribute to the problem. Leptin and adiponectin cause increased fat oxidation and improve insulin sensitivity; both are low in these syndromes.

In humans it has been shown that leptin administration can markedly improve the lipid and glucose abnormalities (17) and in animals a combination of leptin and adiponectin may restore near metabolic normality (18). Thus, it seems likely that the low levels of these two hormones are of some importance in generating the metabolic disturbance. Until recently, lipodystrophy has been a rare condition, but a lipodystrophy associated with highly active antiretroviral therapy in HIV affected individuals (associated particularly with the protease inhibitor drugs) is now relatively common and of considerable concern in this group of subjects (19).

It was hoped that identification of the genetic causes of some of the unusual diabetic syndromes would lead to identification of similar, but perhaps more subtle, genetic abnormalities in the general Type 2 diabetic population. But at this stage, it does not appear that any of the genetic abnormalities associated with these rare forms of diabetes is a substantial contributor in the overall Type 2 population (7).

Not surprisingly, concern over the magnitude of the health problem of Type 2 diabetes and its consequent costs has generated a major interest in primary prevention. Several recent studies (Table 2) have clearly demonstrated that lifestyle modification (calorie restriction and increased physical activity) can dramatically reduce the incidence of Type 2 diabetes in high risk subjects (6). Unfortunately,

Table 2. Intervention Studies to Reduce Incidence of Type 2 Diabetes

Name	Number of subjects	Characteristics of subjects	Mean duration (years)	Intervention	% reduction in incidence	Incidence of diabetes (% p.a.)
Diabetes Prevention Program (USA)	3234	IGT mean age 50.6 mean BMI 34	2.8	Control		11.0
				Lifestyle*	58%	4.8
				Metformin	31%	7.8
Finnish Study	522	IGT mean age 55 mean BMI 31	3.2	Control		7.8
				Lifestyle [▼]	58%	4.8
Da Qing IGT and Diabetes	577	IGT mean age 45 mean BMI 26	6	Control		13.3
				Diet [†]	33%	8.3
				Exercise [#]	47%	5.1
				Diet & exercise	38%	6.8
STOP-NIDDM Acarbose	1429	IGT mean age 54 mean BMI 31	3.3	Placebo		12.7
				Acarbose	25%	9.7

* at least 7% weight loss and 150 minutes physical activity per week

▼ at least 5% weight loss and 210 minutes physical activity per week

† target BMI of 23

increase exercise by at least 1 unit per day (e.g. extra 30 minutes of slow walking or 5 minutes of swimming)

the intensity of effort and associated costs in the two major studies in developed countries (the Finnish Diabetes Prevention Study and the American Diabetes Prevention Program) would not allow implementation on a community-wide basis (6). However many authorities believe it is time for a concerted effort by commonwealth, state and local government with employers, unions and non-government groups to create a changed attitude to diet and exercise in the overall community.

The use of pharmacological agents for Type 2 diabetes prevention is also on the agenda and, while contrary to an appropriate community health strategy, may be contemplated where lifestyle intervention fails or is difficult from a socio-cultural perspective (6). Both metformin (which improves insulin sensitivity, particularly at the liver) and acarbose (which impairs carbohydrate absorption from the gut) have been shown to produce a moderate reduction in incidence of Type 2 diabetes in high risk individuals. The outcome of prevention trials using the thiazolidinedione drugs (which improve insulin sensitivity by stimulation of the PPAR γ receptor) are awaited with great interest (6). The cost-effectiveness of pharmacological intervention is currently the subject of several studies.

Although preventive action will not be easy or cheap, the magnitude of the problem we face with diabetes and its complications demands serious action.

References

1. World Health Organisation. (1999) Definition, Diagnosis and Classification of Diabetes Mellitus and its Complications; Part 1: Diagnosis and Classification of Diabetes Mellitus. Department of Noncommunicable Disease Surveillance, Geneva
2. Zimmet, P., Alberti, K., and Shaw, J. (2001) *Nature* **414**, 782-787
3. Dunstan, D., Zimmet, P., Welborn, T., Sicree, R., Armstrong, T., Atkins, R., Cameron, A., Shaw, J., and Chadban, S. (2001)

• *The Tragedy of Diabetes*

References (*contin.*)

1. Diabetes & associated disorders in Australia 2000: the accelerating epidemic. International Diabetes Institute, Melbourne, Australia
4. Dunstan, D., Zimmet, P., Welborn, T., Shaw, J., de Courten, M., Cameron, A., Sicree, R., Dwyer, T., Colagiuri, S., Jolly, D., Kuiman, M., and Atkins, R. on behalf of the AusDiab Steering Committee. (2002) *Diabetes Care* **25**, 829-834
5. Zimmet, P., and Alberti, K. (1997) *Lancet* **350**, S1-S4
6. Unwin, N., Shaw, J., Zimmet, P., and Alberti, K.G.M.M. (2002) *Diabetic Med.* **19**, 708-723
7. Zimmet, P. (1999) *Diabetologia* **42**, 499-518
8. Zimmet, P. (2000) *J. Internal Med.* **247**, 301-310
9. de Courten, M., Bennett, P., Tuomilehto, J., and Zimmet, P. (1997) Epidemiology of NIDDM in non-Europids, John Wiley & Sons, 143-170
10. Zimmet, P., Taft, P., Guinea, A., Guthrie, W., and Thoma, K. (1977) *Diabetologia* **13**, 111-115
11. Neel, J. (1962) *Am. J. Human Genetics* **14**, 353-362
12. Dowse, G., and Zimmet, P. (1993) *Br. Med. J.* **306**, 532-533
13. Hales, C., Desai, M., and Ozanne, S. (1997) *Diabetic Med.* **14**, 189-195
14. Montague, C.T., and O'Rahilly, S. (2000) *Diabetes* **49**, 883-888
15. Hattersley, A.T. (1998) *Diabetic Med.* **15**, 15-24
16. Reitman, M.L., Arioglu, E., Gavrilova, O., and Taylor, S.I. (2000) *Trends Endocrinol. Metab.* **11**, 410-416
17. Oral, E.A., Simha, V., Ruiz, E., Andewelt, A., Premkumar, A., Snell, P., Wagner, A.J., DePaoli, A.M., Reitman, M.L., Taylor, S.I., Gorden, P., and Garg, A. (2002) *N. Eng. J. Med.* **346**, 570-578
18. Yamauchi, T., Kamon, J., Waki, H., Terauchi, Y., Kubota, N., Hara, K., Mori, Y., Ide, T., Murakami, K., Tsuboyama-Kasaoka, N., Exaki, O., Akanuma, Y., Gavrilova, O., Vinson, C., Reitman, M.L., Hagechika, H., Shudo, K., Koda, M., Nakano, Y., Tobe, K., Nagai, R., Kimura, S., Tomita, M., Froguel, P., and Kadowaki, T. (2001) *Nature Med.* **7**, 941-946
19. Carr, A., Samaras, K., Thorisdottir, A., Kaufmann, G.R., Chisholm, D.J., and Cooper, D.A. (1999) *Lancet* **353**, 2092-2099

