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Clinical Efficacy of Metformin against Insulin Resistance Parameters

Sinking the Iceberg

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Abstract

It has been increasingly recognised in recent years that type 2 (non–insulin-dependent) diabetes is part of a cluster of cardiovascular risk factors known as the metabolic syndrome, but also endorsed with such names as the deadly quartet, syndrome X and the insulin resistance syndrome. Atherosclerosis is the most common complication of type 2 diabetes among Europeans, and coronary artery, cerebrovascular and peripheral vascular disease are 2 to 5 times more common in people with this condition than in those without diabetes.

These observations indicate that the treatment of type 2 diabetes requires agents that do more than simply lower blood glucose levels, and a therapy with both antihyperglycaemic effects and beneficial effects on dyslipidaemia, hypertension, obesity, hyperinsulinaemia and insulin resistance is likely to be most useful. In this respect, metformin has an important and established role: this drug has been shown to lower blood glucose and triglyceride levels, and to assist with weight reduction and to reduce hyperinsulinaemia and insulin resistance.

Studies in the Israeli sand rat, *Psammomys obesus*, have indicated hyperinsulinaemia/insulin resistance to be the initial and underlying metabolic disorder in obesity and type 2 diabetes. Thus, the well established effect of metformin in reducing insulin resistance makes this drug an excellent candidate for the prevention of progression of impaired glucose tolerance to type 2 diabetes, and for the reduction of mortality associated with cardiovascular disease.

In a world with a host of new therapies emerging for type 2 (non–insulin-dependent) diabetes, it is remarkable that an agent such as metformin, with a 40-year history, still plays such an important role in the management of this condition and syndromes associated with insulin resistance, including the metabolic syndrome[1,2] and polycystic ovary syndrome.[3] It is now increasingly recognised that type 2 diabetes is part of a cluster of cardiovascular disease (CVD) risk factors generally known as the metabolic syndrome,[4] but also endorsed with such names as the deadly quartet,[5] syndrome X,[6] syndrome X plus[7] and the insulin resistance syndrome.[7] These associations have great relevance, as atherosclerosis is the most common complication of type 2 diabetes among Europeans,[8] and this clustering seems to be the most likely explanation. CVD accounts for at least 66% of deaths in type 2 diabetes,[8,9] and coronary artery, cerebrovascular and peripheral vascular disease are 2 to 5 times more common in persons with diabetes.[8]

1. Type 2 Diabetes and the Metabolic Syndrome: Background and Epidemiology

The clustering of CVD risk determinants representing the metabolic syndrome was first described more than 20 years ago, and the description has been attributed to various people including Vague, Crepaldi, Welborn and Modan.[7] In 1988, Reaven refocused attention on the cluster and named it syndrome X.[6] As central obesity, omitted by Reaven from his original description, is a common component of the cluster, the term metabolic syndrome is now favoured.[4]

Individuals with either type 2 diabetes or impaired glucose tolerance (IGT) associated with hypertension, central (upper body) obesity and dyslipidaemia with or without other characteristics of the metabolic syndrome pose a major diagnostic and therapeutic challenge for the diabetologist (fig. 1). These patients are at very high risk of coronary artery, cerebrovascular and peripheral vascular disease,[8] as each of the risk factors in the metabolic syndrome is an important CVD risk factor in its own right. They also contribute cumulatively to macrovascular disease.[8] Often, a patient with one of these conditions (e.g. type 2 diabetes or central obesity) is found to have at least one or more of the other CVD risk components.[10]

Epidemiological studies confirm that the metabolic syndrome occurs frequently in a variety of ethnic groups, including Europeans, Afro-Americans, Mexican-Americans, Asian Indians, Chinese, Australian Aborigines, Polynesians and Micronesians.[8,11,12] It is clear that type 2 diabetes in these populations is the 'tip of the iceberg' in a cluster of CVD risk factors also described as 'The New World Syndrome'.[11] The type 2 diabetes global epidemic is also the tip of a massive social problem now facing developing and newly industrialised nations and ethnic minorities and the disadvantaged in developed countries.[4] Very high rates of obesity, type 2 diabetes, hypertension and CVD, coupled with cigarette smoking, alcohol abuse and the other effects

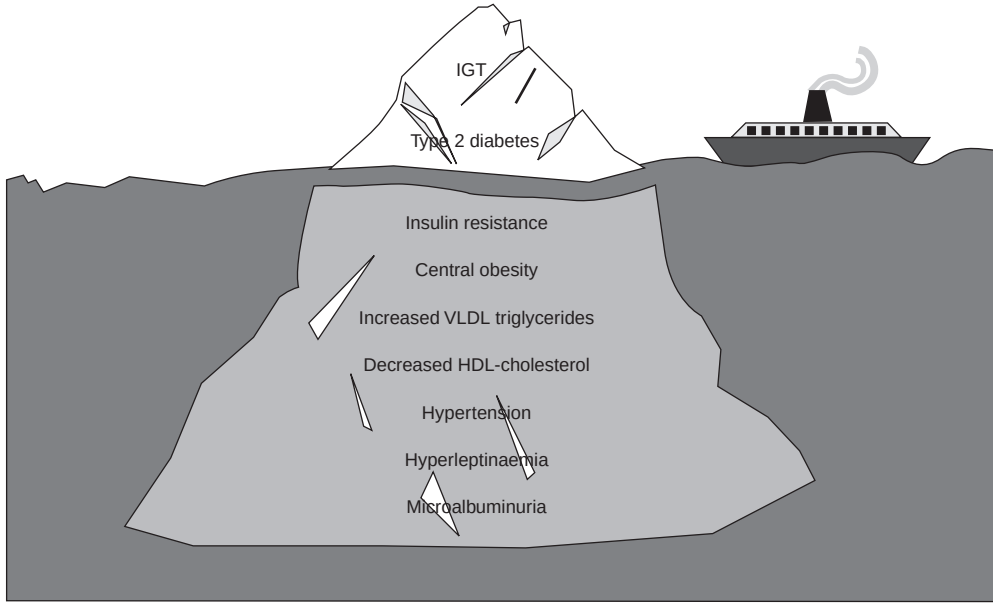

Fig. 1. The iceberg – metabolic syndrome: abnormal glucose tolerance [impaired glucose tolerance (IGT) and type 2 diabetes] is the 'tip of the iceberg' of a cluster of cardiovascular disease risk factors that form the metabolic syndrome.

Table I. Baseline cardiovascular risk factors in 1987 in a population of normoglycaemic Mauritian males and in a subpopulation who developed diabetes by the follow-up survey in 1992 (unpublished observations)

Risk factor	Baseline measurements	
	total population (n = 1029)	subpopulation who developed diabetes (n = 70)
Body mass index (kg/m^2)	22.4	24.3**
Waist-to-hip ratio	0.88	0.91**
Diastolic blood pressure (mm Hg)	78.3	82.0*
Fasting plasma insulin level (mU/L)	4.1	6.5*
2-hour plasma glucose level (mmol/L)	5.6	6.3**
Plasma triglyceride level (mmol/L)	1.3	1.9**

* $p < 0.05$, ** $p < 0.01$ between groups.

and outcomes of affluence are just part of the 'Coca-colonisation' process.[13] We have predicted a global doubling in the number of cases of type 2 diabetes by the year 2010.[14]

Hyperinsulinaemia is a predictor of both type 2 diabetes and coronary artery disease in a number of epidemiological studies.[4,11,12] Evidence is accumulating that insulin resistance and/or hyperinsulinaemia may be the common aetiological factor/s for the components of the metabolic syndrome,[4,6,10] although there appears to be some variation in this relationship between populations, particularly with respect to hypertension.[15]

2. Therapy in Type 2 Diabetes

The frequent association of type 2 diabetes with other CVD risk factors means that management needs to be focused not only on tight blood glucose control, but also on strategies for reduction of the other CVD risk factors such as obesity, hypertension, hyperinsulinaemia and dyslipidaemia.[4,6] Strong evidence for this is provided by the recently published findings of the UK Prospective Diabetes Study (UKPDS)[16,17] and the results of the Scandinavian Simvastatin Survival Study.[18]

It is also now well established that the other features of the metabolic syndrome can be present up to 10 years before diagnosis of type 2 diabetes.[8,12] In Mauritius, we found that the major CVD risk factors were present at baseline assessment up to 5 years before the development of the disease (table I).[8] This is of great importance in our understanding of the aetiology of type 2 diabetes and the associated CVD risk, and the potential to prevent CVD and its morbidity and mortality in persons with glucose intolerance. In other words, the risk and the actual development of CVD start many years before the manifestation of glucose intolerance, and Haffner et al.[12] have posed the very relevant question: 'When does the clock start ticking for CVD in persons with type 2 diabetes?'

Thus, paradoxically, the prevention of CVD in persons with type 2 diabetes should actually begin many years before diabetes is diagnosed. Is this really feasible at our current state of knowledge? The diagnosis of the metabolic syndrome without type 2 diabetes denotes a group at very high risk of future type 2 diabetes, and aggressive early management of the syndrome may therefore have a significant impact on both the prevention of type 2 diabetes and CVD mortality.[8,12]

3. Metformin Therapy in Type 2 Diabetes and the Metabolic Syndrome

It is very apparent that the therapy of type 2 diabetes requires more than blood glucose lowering alone. A therapy with effects on both glycaemia and the other CVD risk factors associated with the metabolic syndrome (e.g. dyslipidaemia, hypertension, obesity, hyperinsulinaemia and insulin resistance) is therefore likely to be beneficial in the prevention of macrovascular complications. Associated defects in the fibrinolytic system that result in increased plasma levels of plasminogen activator inhibitor-1 (PAI-1) have been seen in type 2 diabetes and the metabolic syndrome.[1,19] It is

against this background that this article reviews data showing the importance and role of metformin.

The use and efficacy of metformin alone and in combination with other oral hypoglycaemic agents and insulin have been reviewed in detail elsewhere,[1,2,20-23] and reports indicate that metformin has a well established role among drugs that improve insulin sensitivity. In summary, metformin has been shown to lower blood glucose and triglyceride levels in plasma without causing hypoglycaemia, to assist with weight reduction and to reduce hyperinsulinaemia and insulin resistance. Metformin has also been shown to lower plasma PAI-1 levels.[1] By improving the sensitivity of cells to insulin, the drug reduces hepatic glucose production and increases glucose uptake in muscle and other peripheral tissues.[24]

While the improvement of glycaemic control results in improved lipid profiles, metformin has lipid-lowering effects quite independent of its antihyperglycaemic action.[25] Metformin is indicated as initial therapy in obese patients with type 2 diabetes.[25] Sulphonylurea[26] and thiazolidinedione[27] therapy may result in weight gain, an outcome that does not provide optimal therapy for obese patients. On the other hand, weight loss or at least no weight gain is the usual situation with metformin.[1] The data for hypertension vary, with some studies showing reduction of blood pressure and others showing no effect.[22]

These metabolic effects make metformin a logical choice for the treatment of obese patients with type 2 diabetes as well as lean patients who fit the metabolic syndrome phenotype. Table II compares the effect of metformin and troglitazone on the parameters of the metabolic syndrome and clearly demonstrates the advantages of the former agent. The combination of metformin with another thiazolidinedione, rosiglitazone, produces an additive effect, which suggests that these agents act to reduce insulin sensitivity through different pathways (Rebuck, personal communication).

4. Hyperinsulinaemia, Hyperleptinaemia and the Metabolic Syndrome

Although attention has focused on the fact that insulin resistance and/or hyperinsulinaemia may be the common aetiological factor/s for the components of the metabolic syndrome,[4,28] there appears to be considerable heterogeneity between populations in this relationship.[15] More recently, we suggested that hyperleptinaemia rather than hyperinsulinaemia may be one of the central driving forces of the metabolic syndrome.[29] Another, more recent, study from the UK supports this contention,[30] and we have shown that plasma leptin levels in normal individuals are directly related to insulin sensitivity when measured by the euglycaemic clamp technique.[31] We have also suggested that hyperleptinaemia/leptin resistance is an important new component of the metabolic syndrome.[29]

This debate is still wide open, with some *in vitro* and *in vivo* studies having shown disparate and sometimes opposing effects of leptin on glucose uptake and insulin action. As many of the human studies have been carried out in small groups of patients, their findings are open to question. Certainly, epidemiological data[29,32] and certain *in vivo* studies in the Israeli sand rat *Psammomys obesus* (an excellent animal model of obesity, insulin resistance and type 2 diabetes)[33] keep alive the possibility of a role for peripheral leptin in either insulin resistance or the modulation of insulin sensitivity.

Table II. Comparison of the actions of metformin and troglitazone on the various components of the metabolic syndrome

Component	Metformin	Troglitazone
Hyperglycaemia	↓	↓
Insulin resistance	↓	↓
Dyslipidaemia	↓	↓
Obesity	↓	→↑
Hypertension	?↓	→
Platelet aggregation	↓	→

↓ = decreases; → = no effect; ↑ = increases.

It will therefore be interesting to see whether metformin has any effect on plasma leptin levels that are independent of its other actions. We intend to examine this in *Psammomys obesus*. These animals, when placed on an *ad libitum* laboratory diet, develop hyperinsulinaemia, insulin resistance, IGT and diabetes, together with hyperleptinaemia and leptin insensitivity.[33] This is therefore an excellent polygenic model for the study of obesity and diabetes.[34] The metabolic characteristics and the heterogeneous development of defects, including elevated leptin levels, mimic those found in susceptible human populations.[33,35-40] The inverted U-shaped curve that describes the relationship between fed glucose and insulin levels in *Psammomys* (fig. 2) is similar to Starling's curve of the pancreas as described by DeFronzo in human populations.[41] Studies in this model suggest hyperinsulinaemia/insulin resistance to be the initial metabolic lesion in the development of obesity and type 2 diabetes.[34]

When comparing animals separated on the basis of glucose and insulin levels into normal and diabetic groups, the diabetic animals are hyperglycaemic, hyperinsulinaemic, and have elevated plasma levels of triglyceride and cholesterol, increased fat stores and increased bodyweight (fig. 3). These metabolic changes constitute some of the major features of the metabolic syndrome as seen in humans. Interestingly, at weaning, animals that go on to develop obesity and hyperinsulinaemia are indistinguishable on the basis of metabolic characteristics such as bodyweight, glucose, insulin and triglycerides from those that remain lean throughout life.[39] However, at an early stage, some animals overeat and develop subsequent metabolic disturbances that include hyperleptinaemia. Furthermore, high plasma leptin levels in *Psammomys* are associated with insulin resistance independently of bodyweight, a phenomenon we have also described in humans.[32] Thus, one may speculate that hyperleptinaemia and leptin resistance may be central in the development of the metabolic syndrome.[29,31]

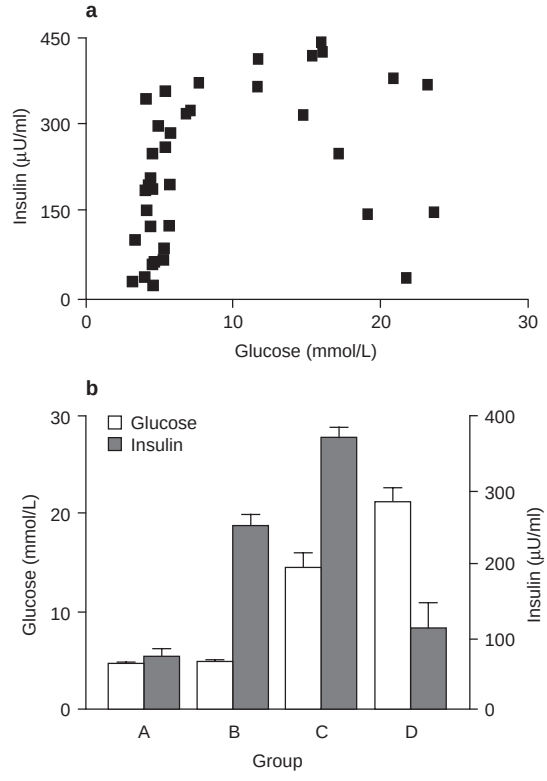

Fig. 2. (**a**) The inverted U-shaped curve describing the relationship between plasma glucose and insulin levels in Israeli sand rats (*Psammomys obesus*) in the fed state (n = 37). (**b**) Plasma glucose and plasma insulin levels in 4 separate groups of Israeli sand rats in the fed state. Results are expressed as mean ± standard error. Group A, normoglycaemic and normoinsulinaemic (n = 10); group B, normoglycaemic and hyperinsulinaemic (n = 13); group C, hyperglycaemic and hyperinsulinaemic (n = 11); group D, hyperglycaemic and normoinsulinaemic (n = 7) [adapted from Cusi & DeFronzo[2]].

In previous studies examining the role of leptin treatment in energy balance in *Psammomys*, we have clearly demonstrated a relative leptin resistance in hyperleptinaemic, obese animals. Only the lean animals responded to exogenous leptin by decreasing food intake and body fat mass. Even with supraphysiological doses, obese animals remained resistant to the anorectic effects of leptin.[40]

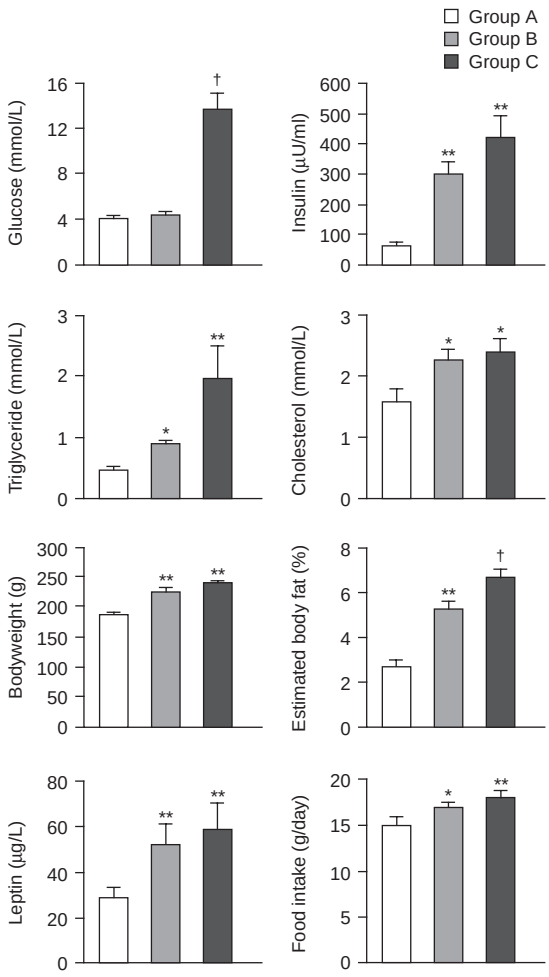

Fig. 3. Data collected from 3 groups (each n = 8) of 18-week-old Israeli sand rats (*Psammomys obesus*). Results are expressed as mean ± standard error. * p < 0.05, ** p < 0.005 *vs* group A; † p < 0.05 *vs* groups A and B.

5. Prevention of Type 2 Diabetes

Perhaps leptin resistance at the central nervous system level is an expression of the 'thrifty gene' described almost 40 years ago by Neel.[42] This would predispose some animals and humans to obesity and diabetes. The ability to develop leptin resistance would be a survival advantage to the animal that would allow consumption of large amounts of food without the suppression of appetite by leptin. Subsequently, with overfeeding, these animals would develop metabolic disturbances, including obesity and diabetes.

With respect to prevention of type 2 diabetes, the thrifty gene scenario as seen in *Psammomys obesus* provides a basis for better understanding.[33,35] A trait that was previously advantageous and allowed survival during famine (i.e. favoured conservation and storage of energy as fat) now leads to insulin resistance, type 2 diabetes and obesity in times of affluence.[33,35] Thus, healthy nutrition along with exercise, resulting in reduced energy intake and increased energy expenditure, provide the logical means of prevention. This is supported by the only major type 2 diabetes intervention yet reported, the Da Qing study in China.[43] Here, the incidence of IGT converting to type 2 diabetes was reduced by a third in the intervention group compared with controls. Given the projected epidemic of diabetes in China, the largest population in the world, such a cost-effective intervention is of great importance. We have also recently shown that a similar community-based lifestyle approach in Mauritius could reduce some of the key risk factor determinants for type 2 diabetes and CVD such as eating behaviour, sedentary lifestyle, plasma lipid profiles and cigarette smoking.[44] The study has yielded additional information on 'when the clock starts ticking' for CVD in type 2 diabetes and on the potential for early intervention (both primary and secondary) to reduce the huge burden of CVD in this disorder. This research could have been directed only by the results of well planned longitudinal epidemiological studies such as those in Mexican-Americans,[12] and in Rancho Bernado[45] and Mauritius.[46]

It is likely that a similar sequence of events to that in *Psammomys obesus* occurs in the transition from the prediabetic state to type 2 diabetes in humans. Thus, the established effect of metformin in reducing insulin resistance makes this drug an excellent candidate for the prevention of progression of IGT to type 2 diabetes, and for the reduction of

mortality associated with CVD. A recent study has demonstrated an additional beneficial effect of metformin in reducing hyperinsulinaemia (increased ovulatory response in obese women with polycystic ovary syndrome).[3]

The efficacy of primarily nonpharmacological interventions such as those used in the Chinese IGT intervention study[43] provides support for the view that interventions in IGT should be given a high priority. The US National Institutes of Health have risen to the challenge and have funded a major multicentre IGT intervention study to examine the potential for type 2 diabetes prevention.[47] The role of pharmacological intervention with metformin will also be assessed (notwithstanding the termination because of potential hepatotoxicity of troglitazone treatment in this study).

References

1. Grant PJ. The effects of metformin on cardiovascular risk factors. Diabetes Metab Rev 1995; 11: S43-50
2. Cusi K, DeFronzo RA. Metformin: a review of its metabolic effects. Diabetes Rev 1998; 6: 89-131
3. Nestler JE, Jakubowicz DJ, Evans WS, et al. Effects of metformin on spontaneous and clomiphene-induced ovulation in the polycystic ovary syndrome. N Engl J Med 1998; 338: 1876-80
4. Zimmet P. The pathogenesis and prevention of diabetes in adults. Genes, autoimmunity, and demography. Diabetes Care 1995; 18: 1050-64
5. Kaplan NM. The deadly quartet: upper-body obesity, glucose intolerance, hypertriglyceridaemia, and hypertension. Arch Intern Med 1989; 149: 1514-20
6. Reaven GM. Role of insulin resistance in human disease. Diabetes 1988; 37: 1595-607
7. Zimmet P. Non-insulin-dependent (type 2) diabetes mellitus – does it really exist? Diabet Med 1989; 6: 728-35
8. Zimmet P, Alberti KGMM. The changing face of macrovascular disease in non-insulin dependent diabetes mellitus in different cultures: an epidemic in progress. Lancet 1997; 350 Suppl. 1: S1-4
9. Panzram G. Mortality and survival in type 2 (non-insulin-dependent) diabetes mellitus. Diabetologia 1987; 30: 123-31
10. Zimmet PZ, Collins VR, Dowse GK, et al. Is hyperinsulinaemia a central characteristic of a chronic cardiovascular risk factor syndrome? Mixed findings in Asian Indian, Creole and Chinese Mauritians. Diabet Med 1994; 11: 388-96
11. Zimmet P. Challenges in diabetes epidemiology – from West to the rest. Diabetes Care 1992; 15: 232-52
12. Haffner SM, Stern MP, Hazuda HP, et al. Cardiovascular risk factors in confirmed prediabetic individuals. Does the clock for coronary heart disease start ticking before the onset of clinical diabetes? JAMA 1990; 263: 2893-8
13. Zimmet P, Dowse G, Finch C, et al. The epidemiology and natural history of NIDDM – lessons from the South Pacific. Diabetes Metab Rev 1990; 6: 91-124
14. McCarty D, Amos A, Zimmet P. The rising global burden of diabetes and its complications: estimates and projections to the year 2010. Diabet Med 1997; 14 Suppl. 5: S1-85
15. Collins VR, Dowse GK, Finch CF, et al. An inconsistent relationship between insulin and blood pressure in three Pacific island populations. J Clin Epidemiol 1990; 43: 1369-78
16. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). Lancet 1998; 352: 854-65
17. UK Prospective Diabetes Study Group. Tight blood pressure control and risk of macrovascular and microvascular complications in type 2 diabetes (UKPDS 38). BMJ 1998; 317: 703-13
18. Pyorälä K, Pedersen TR, Kjeksus J, et al. Cholesterol lowering with simvastatin improves prognosis of diabetic patients with coronary heart disease: a subgroup analysis of the Scandinavian Simvastatin Survival Study (4S). Diabetes Care 1997; 20: 614-20
19. Vague P, Juhan-Vague I, Alessi MC, et al. Metformin decreases the high plasminogen activator capacity, plasma insulin and triglyceride levels in non-diabetic obese subjects. Thromb Haemost 1987; 57: 326-8
20. Bailey CJ, Nattras M. Treatment – metformin. Bailliere's Clin Endocrinol Metab 1988; 2: 455-76
21. Reaven GM. Effect of metformin on various aspects of glucose, insulin and lipid metabolism in patients with non-insulin-dependent diabetes mellitus with varying degrees of hyperglycaemia. Diabetes Metab Rev 1995; 11: S97-108
22. Palumbo PJ. Metformin: effects on cardiovascular risk factors in patients with non-insulin-dependent diabetes mellitus. J Diabetes Complications 1998; 12: 110-9
23. DeFronzo RA, Goodman AM, and the Multicenter Metformin Study Group. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. N Engl J Med 1996; 333: 541-9
24. Stumvoll M, Nurjahan N, Perriello G, et al. Metabolic effects of metformin in non-insulin-dependent diabetes mellitus. N Engl J Med 1995; 333: 550-4
25. Wu MS, Johnson P, Sheu WH-H, et al. Effect of metformin on carbohydrate and lipoprotein metabolism in NIDDM patients. Diabetes Care 1990; 13: 1-8
26. Standl E. New drugs for diabetes. In: Marshall SM, Home PD, Rizza RA, editors. The Diabetes Annual 10. Amsterdam: Elsevier, 1996: 225-49
27. Olefsky AR, Olefsky JM. Perspectives in diabetes. Thiazolidinediones in the treatment of insulin resistance and type II diabetes. Diabetes 1996; 45: 1661-9
28. Ferrannini E, Haffner SM, Mitchell BD, et al. Hyperinsulinaemia: the key feature of a cardiovascular and metabolic syndrome. Diabetologia 1991; 34: 416-22
29. de Courten M, Zimmet P, Hodge A. Hyperleptinaemia: the missing link in the metabolic syndrome? Diabet Med 1997; 14: 200-8
30. Donahue RP, Prineas RJ, De Carlo Donahue R, et al. Elevated leptin associated with insulin resistance among nondiabetic persons. The Miami Community Health Study. Diabetes Care. In press
31. Leyva F, Godsland IF, Ghatei M, et al. Hyperleptinemia as a component of a metabolic syndrome of cardiovascular risk. Arterioscler Thromb Vasc Biol 1997; 18: 928-33
32. Zimmet PZ, Collins VR, de Courten MP, et al. Is there a relationship between leptin and insulin sensitivity independent of

obesity? A population-based study in the Indian Ocean nation of Mauritius. Int J Obesity 1998: 21: 171-7
33. Collier G, Walder K, Lewandowski P, et al. Leptin and the development of obesity and diabetes in *Psammomys obesus*: Obesity Res 1997; 5: 455-8
34. Shafrir E, Gutman A. *Psammomys obesus* of the Jerusalem colony: a model for nutritionally induced, non-insulin dependent diabetes. J Basic Clin Physiol Pharmacol 1993; 4: 83-9
35. Barnett M, Collier GR, Collier FM, et al. A cross-sectional and short-term longitudinal characterization of NIDDM in the sand rat. Diabetologia 1994; 37: 671-6
36. Habito RC, Barnett M, Yamamoto A, et al. Basal glucose turnover in *Psammomys obesus*: an animal model of NIDDM. Acta Diabetol 1995; 36: 1-6
37. Barnett M, Habito R, Cameron-Smith D, et al. The effect of inhibiting fatty acid oxidation on basal glucose metabolism in *Psammomys obesus*. Horm Metab Res 1996; 28: 165-70
38. Walder K, Willet M, Zimmet P, et al. Ob (obese) gene expression and leptin levels in *Psammomys obesus*. Biochem Biophys Acta 1997; 1354: 272-8
39. Collier GR, De Silva A, Sanigorski A, et al. Development of obesity and insulin resistance in the Israeli sand rat (*Psammomys obesus*): does leptin play a role? Ann NY Acad Sci 1997; 827: 50-63
40. Walder K, Lewandowski P, Sanigorski A, et al. Leptin administration has no effect on food intake, body weight or diabetic status in a multigenic model of obesity: *Psammomys obesus*. Int J Obesity 1998; 22: 1-7
41. DeFronzo RA. The triumvirate: β-cell, muscle, liver. A collusion responsible for NIDDM. Diabetes 1988; 37: 667-87
42. Neel JV. Diabetes mellitus: a thrifty genotype rendered detrimental by 'progress'? Am J Hum Genet 1962; 14: 353-62
43. Pan X, Li G, Hu Y, et al. Effect of diet and exercise in preventing NIDDM in people with impaired glucose tolerance: the Da Qing IGT and Diabetes Study. Diabetes Care 1997; 20: 537-44
44. Dowse GK, Gareeboo H, Alberti KGMM, et al. Changes in population cholesterol concentrations and other cardiovascular risk factor levels after five years of the non-communicable disease intervention programme in Mauritius. BMJ 1995; 311: 1255-9
45. McPhillips JB, Barrett-Conner E, Wingard DL. Cardiovascular disease risk factors prior to the diagnosis of impaired glucose tolerance and non-insulin-dependent diabetes mellitus in a community of older adults. Am J Epidemiol 1990; 131: 443-53
46. Dowse GK, Gareeboo H, Zimmet PZ. High prevalence of NIDDM and impaired glucose intolerance in Indian, Creole and Chinese Mauritians. Diabetes 1990; 39: 390-6
47. Eastman R, Javitt J, Herman W, et al. Prevention strategies for non-insulin-dependent diabetes mellitus: an economic perspective. In: Le-Roith D, Taylor S, Olefsky J, editors. Diabetes mellitus: a fundamental and clinical text. New York: Lippincott-Raven, 1996: 621-30

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