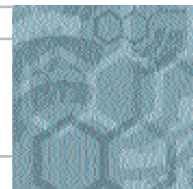


Insulin resistance and vascular disease



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The insulin resistance syndrome comprises a typical cluster of cardiovascular risk factors and is predicted to increase dramatically over the next few decades. The disease process starts many years before the condition is clinically obvious and targets primarily the cardiovascular system. The pathogenesis involves a complex interplay between all the associated cardiovascular risk factors but endothelial dysfunction plays a major role. Management of these patients involves management of all the associated risk factors and should be aimed primarily at early detection and the prevention of vascular morbidity and mortality in the short and long term.

South Africa is already staggering under a quadruple burden of disease including the pre-transitional diseases associated with poverty and underdevelopment, the emerging 'Western' chronic non-communicable diseases, injuries, both intentional and unintentional, and HIV/AIDS.¹ Cardiovascular disease is second to HIV/AIDS in the cause-of-death categories, and diabetes mellitus, a major cardiovascular risk factor in South Africa, is featured as one of the leading non-communicable causes of years-of-life-lost in both women and men.¹ It is predicted that the incidence of obesity and type 2 diabetes mellitus, appropriately referred to as diabetesity,² is to increase dramatically over the next decade to the extent that it is seen as a pandemic.³ A dramatic increase in incidence of diabetesity has already been noted in westernised countries and is a source of great concern.⁴ The burden for developing countries, in human and financial terms, is expected to be enormous and far-reaching.

Dysglycaemia in South Africa

Type 2 diabetes accounts for the vast majority of all diabetes in South Africa⁵ and is extremely common in certain ethnic groups including the South African Indian population.⁶ Whereas the microvasculature is predominantly affected in type 1 diabetes and is related to the years of exposure to dysglycaemia, type 2 diabetes is predominantly a macrovascular disease with a consequent dramatic increase in cardiovascular morbidity and mortality that accounts for up to 75% of all deaths in this group.⁷

All too frequently it is assumed that increases in diabetesity are purely a consequence of affluence, but the projected figures for sub-Saharan and other developing countries are even greater and tell another story.^{5,8} Indeed, there is evidence to suggest that the diabetesity

pandemic is already well established in South Africa^{5,6} and we are bound to see a dramatic rise in the number of patients suffering from the insulin resistance syndrome (IRS) over the next decade.

The progression of insulin resistance

Insulin resistance (IR) is the initial underlying pathogenetic factor in the majority of patients with type 2 diabetes and is modified by numerous genetic and environmental influences, not the least of which is central obesity.⁹ In the face of decreasing insulin sensitivity and in an effort to maintain euglycaemia, the beta cells of the pancreas increase their secretion of insulin and in doing so succeed in keeping the glucose levels normal. This results in a hyperinsulinaemic but euglycaemic state that is now accepted to be associated with many other cardiovascular risk factors and an increased cardiovascular morbidity and mortality.¹⁰ The clustering of these cardiovascular risk factors and IR is now recognised as part of the IRS. It is important to stress that this condition is present before the onset of dysglycaemia, and long before the onset of diabetes, and that presence of type 2 diabetes is not required to make the diagnosis of this extremely common disorder.¹¹ Indeed, type 2 diabetes is only the tip of the IRS iceberg.¹² Ultimately the second requirement for the development of dysglycaemia comes into play, namely beta-cell failure in the pancreas, after which the blood glucose starts to rise. Eventually the patient goes through a phase where the dysglycaemia exceeds the diagnostic criteria for impaired glucose tolerance and impaired fasting glucose, and eventually the hyperglycaemia will be sufficient to make the diagnosis of type 2 diabetes.

The 'ticking clock' hypothesis¹³

It is therefore evident that many years of IR have been present by the time the clinical diagnosis of diabetes is usually made. Data from the UK Prospective Diabetes (UKPD) Study¹⁴ suggest that on average 10 - 12 years of beta-cell failure have elapsed before confirmation of the diagnosis of type 2 diabetes. In addition, years of IR have been present even before the onset of beta-cell failure. It is now evident that endothelial dysfunction and all the other attendant cardiovascular risk factors have been present for many years in the period before the patient is eventually labelled as a type 2 diabetic.^{15,16} Long before hyperglycaemia and diabetes have been diagnosed and long before the hyperglycaemia has started to have its deleterious effect on the microvasculature, the macrovascular disease clock has already been silently ticking away in this 'pre-diabetic phase'.¹³

Therefore it is not surprising that in this 'pre-diabetic' phase of the IRS many patients develop the same macrovascular complications as type 2 diabetics. Indeed, a patient suffering from type 2 diabetes and with no prior history of an acute coronary syndrome has the same chance of having a coronary event as a non-diabetic who has already suffered from an acute myocardial infarction.¹⁷ Accordingly, type 2 diabetes is considered to be a coronary equivalent, and the diabetic should be managed for secondary coronary and atherosclerotic prevention in the same way as any other person who already has clinically evident atherosclerotic and coronary artery disease. Many of these patients never live to develop type 2 diabetes; they succumb prematurely to the effects of the macrovascular pathology associated with IR which precedes the type 2 diabetes. Conceptually it is therefore useful to speak of the vascular disease of IR rather than the vascular disease of type 2 diabetes as this emphasises the early and pre-diabetic onset of the vasculopathy. Indeed, a good argument can be made for the point of view that type 2 diabetes is not a disease in itself, but rather the end result and complication of another disease, namely IR, and later beta-cell failure of the pancreas. The latter two in turn have causes that are diverse and varied, and still need to be clearly defined.¹⁸

The message is clear; the onset of macrovascular disease is well established by the time the diagnosis of type 2 diabetes has been made, and it follows that the concept of 'mild diabetes' is nonsensical and a potentially deleterious platitude to deliver to a newly diagnosed diabetic. It is also evident that the early recognition of these high-risk IR patients before they develop diabetes is mandatory.

Macrovascular disease

Type 2 diabetes is closely associated with macrovascular disease of all vascular systems but this

is particularly true for coronary artery disease. The relative risk of coronary artery disease in 45 - 74-year-old diabetic men and women is 2.4 and 5.1 times greater than in their non-diabetic counterparts respectively.¹⁹ Although typically atherosclerotic, the macrovascular disease of type 2 diabetics differs in many respects from that seen in non-diabetics — the atherosclerosis is more diffuse with a greater plaque burden, involves more organ systems simultaneously, presents at a younger age, abolishes the differences in incidence between males and premenopausal females, abolishes the disparity in incidence between different ethnic groups, and additionally affects arteries of a smaller diameter.

Type 2 diabetes imparts an increased morbidity and mortality for vascular disease in general and for acute vascular incidents of all types. Diabetics have a post-myocardial infarction mortality double that of non-diabetics which is two-fold higher in females than males, they have a higher incidence of complications such as heart failure, recurrent ischaemia, infarct extension and cardiogenic shock, and they are more likely to have recurrent myocardial infarction.²⁰ Although the increased tendency to develop heart failure, or diabetic cardiomyopathy, is thought to be largely vascular in origin, hypertension, acetylated glycation end products, dysautonomia, abnormal intracellular calcium handling, lipotoxicity and apoptosis probably also play a significant role.²¹

The prevalence of dysglycaemia in patients with an acute coronary syndrome may be higher than usually suspected. In patients with an acute myocardial infarction and no previous diagnosis of diabetes, nearly one-third were found to have undiagnosed diabetes and a further third had impaired glucose tolerance.²² Surely few clinical settings exist where the identification of this number of dysglycaemic patients can be exceeded, and not to perform a modified glucose tolerance test on patients during convalescence from an acute coronary syndrome is a valuable opportunity missed.

Risk factors in the development and progression of atherosclerosis

The IRS comprises a characteristic collection of cardiovascular risk factors that individually and collectively make patients with this syndrome extremely prone to develop atherosclerosis. Many of the traditional risk factors are incorporated in the somewhat varying diagnostic criteria for what others also refer to as the metabolic syndrome.¹¹ Of these different sets of criteria, those of the third Adult Treatment Panel (ATPIII) of the National Cholesterol Education Program (NCEP)²³ have now eventually recognised the importance of the IRS and are likely to be the diagnostic criteria with the greatest clinical utility. The ATPIII criteria regard the IRS as being present if three of the following five criteria are present:

(i) central obesity as measured by a waist circumference exceeding 102 cm in males and 88 cm in females, but there is evidence that an increased waist/hip ratio of more than 1 in males and greater than 0.8 in females may more accurately predict cardiovascular disease;²⁴ (ii) serum triglyceride levels greater than 1.7 mmol/l; (iii) a high-density lipoprotein (HDL) cholesterol level less than 1 mmol/l in males and less than 1.3 mmol/l in females; (iv) a blood pressure greater than 130/80 mmHg; and (v) a fasting plasma glucose greater than 6.1 mmol/l. Of note is that diabetes or dysglycaemia need not be present to make the diagnosis. The IRS is a characteristic phenotype and in many cases recognisable at a distance and it must be exceptional that additional biochemical parameters, including insulin estimations, are required to confirm this diagnosis and institute management.

The prevalence of IR increases in correlation with the increasing combinations of dysglycaemia, dyslipidaemia, hyperuricaemia and hypertension²⁵ and, as expected, the cardiovascular risk and mortality of the IRS rises in correlation with the number of associated traditional and non-traditional risk factors.²⁶ Insulin resistance predicts cardiovascular risk independently of the presence of any other risk factors, and by most definitions IR is present in all those with the IRS and probably underpins all the associated vascular risk factors associated with this syndrome; such a correlation can be shown for all the traditional and non-traditional risk factors.²⁷ It is tempting to ascribe the increased cardiovascular risk associated with IR to a direct effect of the associated compensatory hyperinsulinaemia but although there is a clear association between hyperinsulinaemia and cardiovascular disease, satisfactory data to prove a cause and effect relationship between hyperinsulinaemia and vascular disease are lacking. The causes of IR are not clearly defined and probably vary in different populations.¹⁸ There may be something inherent in the underlying cause of IR which in its own right increases cardiovascular risk either directly or via other associated risk factors in a complex interplay of different mechanisms.²⁸

The association with hypertension and hyperinsulinaemia has long been known²⁹ and the link between hypertension and IR has been clearly demonstrated.³⁰ Considerable data exist to support the deleterious role that hypertension plays in the genesis of the vascular disease, especially in the presence of dysglycaemia. Indeed the combination of IR and hypertension powerfully predicts the presence of coronary artery disease.³¹

Obesity is an important if not integral part of the IRS. The presence of central or visceral adiposity in particular is one of the hallmarks of this disease. In most cases this is visually obvious but it can be measured by an abnormal waist-to-hip ratio (> 1 in males and > 0.8 in females) or simply an increased waist circumference (> 88 cm in females and > 102 cm in males). Not only is

central obesity a precipitating or aggravating factor, but many regard it as an integral part of the disease process and not merely a manifestation of wilful overeating, which may be one of the reasons that it is so difficult to treat.

Insulin has an important antilipolytic effect and accordingly plays a fundamental role in lipid metabolism. It is therefore not surprising that dyslipidaemia is an important feature of the IRS.³² The dyslipidaemia is characterised by hypertriglyceridaemia in association with a decreased HDL cholesterol level. Typically the triglyceride level is only slightly increased (> 1.7 mmol/l) and often passes the notice of clinicians; exceptionally, under circumstances of additional metabolic stress such as uncontrolled diabetes, excessive caloric intake, hypothyroidism or drugs, and in genetically susceptible individuals, the triglyceride level increases to be noticed as milky serum, or the chylomicronaemia syndrome. Usually the total cholesterol and low-density lipoprotein (LDL) cholesterol are normal or only slightly increased, and accordingly a fasting serum cholesterol may be a poor screening test for this form of dyslipidaemia. Some of the IR patients additionally inherit some of the cluster of genes that determine the spread of cholesterol and hypercholesterolaemia in the general population; these patients, in addition to the above lipid consequences of their insulin-resistant genes, may also have increased (LDL) cholesterol. Patients with the IRS also fail to clear triglyceride-rich particles from their circulation following a meal which manifests as postprandial lipaemia and which is an independent cardiovascular risk factor.³³

IR patients also have some qualitative lipid changes. They develop small cholesterol-rich LDL-like particles referred to as 'small-dense LDL'.³³ These particles are especially atherogenic because they are easily modified by oxidation and hence more easily engulfed by macrophages. Each LDL particle has only one ApoB apoprotein attached to it. It therefore follows that persons with predominantly small-dense LDL will have more LDL particles per unit volume than normal people and consequently also more ApoB particles. This is referred to as hyper-ApoB, is a feature of the dyslipidaemia of IR and is an even greater predictor of vascular disease than LDL cholesterol.³⁴ The ratio of ApoB to LDL cholesterol may be an indirect marker of the presence of small-dense LDL.³⁵

Endothelial dysfunction plays a pivotal role in the initiation and progression of atherosclerosis. It is one of the earliest manifestations of the IRS and consequently there are early alterations in vascular reactivity and the coagulation and thrombolytic pathways.³⁶ Nitric oxide (NO) plays a pivotal role in the maintenance of vascular health. NO maintains normal guanyl cyclase-mediated vasoreactivity and protects blood vessels from atherosclerosis; it mediates signals that prevent

platelets and leucocytes from interacting with the vessel wall and inhibits vascular smooth-muscle cell proliferation and migration. A deficiency of NO leads to an increase in proinflammatory signals via the transcription factor nuclear kappa B (NF- κ B) which in turn results in an increased expression of leucocyte adhesion molecules and production of various inflammatory chemokines and cytokines.^{37,38} The bioavailability of NO is a balance between its production by NO synthase and its destruction, particularly by free oxygen radicals. A deficiency of NO-mediated signalling results from hyperglycaemia, excess free fatty acid production and IR, and underpins the abnormalities of endothelial function observed in the IRS resulting in a proinflammatory milieu.³⁹ It is now accepted that inflammation plays a central role in the progression of atherosclerosis and genesis of the vulnerable plaque.^{40,41} Nowhere is this more evident than in the IRS which has been referred to as an inflammatory metabolic condition.⁴² There is a close relationship between highly sensitive CRP (hsCRP), other inflammatory markers, and the IRS,^{16,43} and remnant triglyceride-rich particles seem to play an important role in linking the IRS to the inflammatory process and even activate inflammatory cascades during postprandial lipaemia.⁴⁴

Microalbuminuria is associated with atherosclerotic vascular disease and various cardiovascular risk factors.⁴⁵ There is a particularly strong association with the IRS and its components. It is thought that microalbuminuria is a marker of endothelial dysfunction induced by numerous insults but whether microalbuminuria is a true risk factor or just a marker of vascular disease is uncertain.

The IRS is associated with hyperfibrinogenaemia which appears to be modifiable in pace with those interventions that favourably modify the dyslipidaemia, especially fibrates. Whether these decreases in fibrinogen levels result in a decrease in cardiovascular endpoints, and whether to specifically target the increased fibrinogen levels remains to be proved.

Blood levels of plasminogen activator inhibitor type I (PAI-1), an important inhibitor of the fibrinolytic system, are increased in virtually all patients with the IRS and may be amenable to treatment by drugs that improve IR such as the thiazolidinediones.⁴⁶ It is intriguing that obesity and IR can be prevented in mice lacking the PAI-1 gene!⁴⁷

Hyperhomocysteinaemia has been reported in association with an IR model and has been suggested to be a component of the IRS, but others have not been able to confirm this association.^{48,49} Increased homocysteine levels occur independently of the IR and should be managed as such.

Although there are many plausible theories as to the cause of the underlying IR, and also the later

progression to beta-cell failure, an accepted unifying explanation for the process remains elusive.⁵⁰ The peroxisome proliferator activated receptors (PPAR)-gamma nuclear receptors undoubtedly play an important role.⁵¹ The PPAR- γ receptors have an important influence on IR whereas the PPAR- α receptors influence lipid metabolism. Additionally these PPAR receptors also have powerful regulatory effects on inflammation. It will therefore not be surprising if haplotypes of the genes of these receptors, or of any of the numerous co-activators or co-repressors of these genes, may account for the variability of insulin sensitivity in given populations, and differences between populations.⁵²

Lipotoxicity, or the accumulation of lipids in non-adipocyte cells, together with leptin resistance seems to play a central role but other hormones and cytokines released by adipocytes have also been implicated.^{53,54} More recently, a more central neurological mechanism has been suggested to be active.⁵⁵ Indeed, more than one mechanism is likely to play a role and there is some evidence to support the fact that the underlying biomolecular mechanism of IR differs between different ethnic groups.⁵⁶

It is unfortunate that the UKPD study⁵⁷ showed that intensive glucose control was not associated with a statistically significant effect on endpoints attributable to macrovascular disease. Consequently too many have adopted the attitude that strict glucose control is not all that important in dysglycaemic patients. However, the opposite is suggested by numerous studies that have related hyperglycaemia to the subsequent development of macrovascular disease. Even post-challenge hyperglycaemia, or postprandial hyperglycaemia, is independently related to mortality.⁵⁸ One cannot underplay the role of hyperglycaemia as a cardiovascular risk factor.

Management of the IRS and prevention of macrovascular disease

Management of the patient with IRS is emphasised over mere treatment of the IRS. The aim of treatment should be the prevention of vascular disease and not only the control of the risk factor — this should be repeatedly stressed!

The patient requires a holistic approach; the patient with the disease should be managed rather than only the individual risk factors. There can be no justification for patients to have their obesity treated in one clinic, their hypertension controlled in another, their dyslipidaemia corrected in a third, their diabetes managed in still another clinic and finally, to have their angina and coronary artery disease attended to elsewhere. This on top of having their smoking-cessation and exercise programmes managed at other venues. All the patient's risk factors must be treated together. It makes no sense

to concentrate on treating one aggressively while leaving the others unattended.

Early diagnosis of these patients is imperative. Clearly there is a group of patients who are at great risk for developing type 2 diabetes and who warrant extra surveillance and screening. These patients include those with: (i) impaired fasting glucose; (ii) impaired glucose tolerance; (iii) first-degree relatives of type 2 diabetics; (iv) previous gestational diabetes; and (v) other features diagnostic of IRS. It has been proposed that these patients be referred to as having 'prediabetes', a term similar to but not identical with its previous usage and a term that is conceptually easier to understand by medical and lay persons alike.⁵⁹

Once dysglycaemia has developed patients should be regarded as having a coronary equivalent and managed with secondary prevention of cardiovascular disease. Once the components of IRS are evident it is imperative that the condition be discussed with patients and they should be empowered to make decisions regarding their own health. To underplay their risk factors with comments like 'you are a bit overweight', 'you have a bit of blood pressure' or, even worse 'you have mild diabetes' will not be in the patients' best interests — they must realise the gravity of their diagnosis.

These patients can be very difficult to manage — they look so well because they eat so well because they live so well. A sound doctor-patient relationship is imperative and regular follow-up has a therapeutic effect in its own right. The aims of management include optimal control of all the cardiovascular risk factors collectively, and in the non-diabetic patient prevention of the onset of type 2 diabetes mellitus. Spelling out these aims to the patient will foster better compliance and adherence to advice.

Lifestyle changes

Lifestyle changes affect many aspects of the patient's life. Changes include: (i) smoking cessation; (ii) adjusting the diet to reduce intake of excess calories in order to modify obesity and correct the underlying dyslipidaemia while following other sound dietary advice; and (iii) increasing the amount of exercise.

There is no doubt that lifestyle modification is effective. The Diabetes Prevention Programme (DPP)⁴ showed a 58% reduction of newly diagnosed type 2 diabetes with lifestyle changes alone, whereas metformin had a 31% reduction. Similarly the Diabetes Prevention Study (DPS)⁴ showed a 58% reduction of diabetes in those treated with lifestyle changes. It is noteworthy that the average weight loss in these two studies was small.⁴ Also, those who increased their exercise but did not lose weight experienced no reduction in diabetes.⁴ However, it is difficult to achieve this degree and

intensity of intervention outside a clinical trial setting.⁴ The patients were given frequent motivational sessions regarding diet, exercise and the cessation of smoking, and were offered incentives for achieving goals. Indeed, the cost-effectiveness of these intensive lifestyle measures has been questioned.⁴

One of the aims of lifestyle change is to get the patient to lose weight, and a dietician's advice may be invaluable. It is important to set realistic goals that are achievable and sustainable. Shedding 10% of the patient's weight over the first year, which translates into about 1 kg per month, is achievable and this should be soundly praised when achieved. The dietary changes should be primarily quantitative and incorporate a reduction of kilojoule intake. Qualitative changes in the diet are tempered by the presence of dyslipidaemia or dysglycaemia. The dyslipidaemia of insulin resistance is manifested by the high-triglyceride/low-HDL complex for which many advise a low-fat diet but which is accompanied by an increase in carbohydrate intake. There are examples of patients who paradoxically increase their triglycerides on this regimen.⁶¹ Others claim success with a low-carbohydrate diet, for which there is also theoretical support.⁶¹ Modest weight loss pays large dividends in correcting the insulin-resistant dyslipidaemia, reducing blood pressure, improving dysglycaemia and reducing cardiovascular events.^{4,62}

An increase in physical activity must be instituted. Patients should aim for 3½ hours of some kind of exercise, divided over at least four sessions per week, and enough to raise the pulse rate and a slight sweat. It appears that exercise does not have an all-or-nothing effect and there does not appear to be a threshold. Patients should do as much as they can within their capabilities, and a little exercise is better than nothing. There is no doubt that switching the television off is a good start. The gains from an increase in exercise are reflected in an improvement in many of the risk factors for the IRS.⁶²

Although not part of the IRS, a large proportion of patients with this syndrome smoke. The benefits of smoking cessation are substantial in the short and long term and go beyond a reduction in cardiovascular risk. Smoking must be recognised as a very potent addiction and it is extremely difficult for a patient to overcome the addiction voluntarily. There can be little justification for denying patients their other usual risk reduction care because they continue to smoke. The need to stop smoking must be reinforced forcefully at each visit but not in an acrimonious manner. More reliance should be placed on smoking cessation clinics, nicotine replacement therapy and other drugs that appear to improve the success rate. The amount of money and effort devoted to smoking cessation by the medical fraternity is inordinately small when compared with that spent on other risk factors!

Once patients have grasped the severity and magnitude of their problem it is important to illustrate to them that their unfavourable lifestyle habits extend beyond themselves to other members of their families, including their children. They are role models for their children. Very often this is motivation enough for the patient to change his or her ways. Bad habits learnt in childhood are difficult to unlearn as adults and it makes sense to foster healthy living in children while they are at home and still imprintable.

Dyslipidaemia

The dyslipidaemia of insulin resistance typically manifests as a raised triglyceride level and a decreased HDL cholesterol.^{62,63} These patients tend to respond well to diet, weight reduction and the control of other metabolic factors such as diabetes. The fibrates are now known to be PPAR- α agonists and they predominantly decrease triglycerides and increase HDL cholesterol. Logic dictates that they should be the drugs of first choice in treating this form of dyslipidaemia. However, they are still reserved for patients where the triglyceride exceeds 5 mmol/l or as part of combination therapy with statins. Statins are recommended as the drugs of first choice in part because they have the pleiotropic effect of improving endothelial dysfunction.⁶⁴ If the triglycerides or HDL cholesterol are not improved sufficiently then the cautious combination of a statin and a fibrate may be considered — cautious because of the real danger of rhabdomyolysis. Some advise combination therapy with nicotinic acid. However, one of the side-effects of this drug is the appearance of IR, including acanthosis nigricans, the principal clinical marker of IR. It makes no sense to use this medication in those where IR is the prime underlying problem.

Dysglycaemia and diabetes

The onset of diabetes must be treated in its own right. It is beyond the scope of this article to repeat the proper treatment of type 2 diabetes and it is better defined elsewhere.⁶⁵ Metformin improves IR and it should be included in the first line of oral antidiabetic agents, certainly in the centrally obese patients. Others argue for the early use of metformin in all those with the IRS and who are destined to get type 2 diabetes.^{66,67}

Primary prevention of type 2 diabetes

Data indicate that the primary prevention of diabetes may be achievable.⁴ Optimally this requires a national population approach and it is doubtful whether this can be achieved in South Africa in the short term. At the individual level it is feasible to target the high-risk group of patients for the primary prevention of type 2 diabetes. The DPP⁶⁸ showed a 58% and 31% risk reduction for developing diabetes in the groups treated

with lifestyle changes and metformin respectively. Similarly the DPS⁶⁸ resulted in a 58% reduced risk with lifestyle intervention. These studies clearly show what can be achieved with lifestyle changes.

Drugs as a primary prevention tool are starting to show their probable benefit. The effectivity of metformin in the DPP study is convincing.⁶⁹ The use of metformin in non-diabetic patients with IRS has much to recommend it and is recommended by many.^{66,67} This will probably have to be debated by special interest groups in South Africa before it can be generally recommended.

Other drugs also have potential. The Swedish Trial in Old Patients (STOP)⁶⁹ showed a 25% reduction in the probability of developing diabetes in those patients treated with acarbose. The thiazolidinediones are PPAR agonists with varying degrees of PPAR- α or PPAR- γ affinity. These drugs, including pioglitazone and rosiglitazone, have been shown to improve IR.^{70,71} They prevent progression to diabetes, have a favourable effect on lipotoxicity,⁷² and consequently have been shown to prevent the decline in beta-cell function.⁷³ Although these drugs are currently only recommended late in the treatment of diabetes when other antidiabetic drugs have failed, data increasingly indicate that these drugs should be used much earlier in type 2 diabetes and a sound argument can be made for their use even before the onset of diabetes in IR patients.

Other drugs not primarily designed for the treatment of dysglycaemia have a role to play in the primary prevention of diabetes. In the HOPE Study⁷⁴ the number of new diabetics was less in the angiotensin-converting enzyme (ACE) inhibitor (ramipril) arm of the study compared with placebo. In the XENDOS Study,⁷⁵ orlistat plus lifestyle intervention resulted in 37% lower incidence of type 2 diabetes. A post hoc analysis of the WOSCOP Study⁷⁶ showed that use of pravastatin resulted in a 30% reduction in type 2 diabetes. There are various currently ongoing studies looking at the primary prevention of diabetes. These include the DREAM Study⁷⁷ looking at the use of ramipril and rosiglitazone, the NAVIGATOR⁷⁷ Study looking at the effect of valsartan and nateglinide, and the currently ongoing ORIGIN Study looking at the effect of glargine insulin with or without the addition of n-3 polyunsaturated fatty acids (PUFAs).

Other treatment

The management of hypertension in diabetics has been covered extensively elsewhere and should be familiar to all those interested in the IRS.⁷⁸ Many antihypertensive medications have an adverse effect on the IRS and this should be considered when making a choice.^{79,80} Care should be taken that patients are not denied some of the benefits of these medications; type 2 diabetics have much to benefit from the use of beta-blockers.

The vascular risk profile of patients with IRS is such that they should all be treated with aspirin.⁸¹

It has become evident that the polycystic ovary syndrome (PCOS) is an extremely IR condition.⁸² PCOS should always be considered in females presenting with IRS and managed appropriately, including measures to reduce vascular risk.

Many patients receiving highly active antiretroviral therapy (HAART), primarily the protease inhibitors, develop IR.^{83,84} Manifestations include lipodystrophy and the typical and rather severe dyslipidaemic changes described above. It appears that HAART may eventually be used more widely in South Africa and this problem is going to surface more frequently in metabolic clinics.

Conclusion

The IRS is already a commonly seen phenomenon — it only takes an observant eye to see the large number of these patients with the typical ‘braaivleis physique’ walking around in our shopping malls. There can be few in the medical profession who will not encounter this condition in their daily activities, and accordingly it behoves us all to know more than the rudiments of this condition.

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