The Metabolic Syndrome as a Clinical Problem

Peter Kopelman

Department of Clinical Medicine, Barts and The London, Queen Mary’s School of Medicine and Dentistry, University of London, London, UK

Why the Metabolic Syndrome?

Insulin resistance is a common metabolic problem characterized by an impaired physiological response to insulin. It is a key factor in the pathogenesis of type-2 diabetes and is present in more than 50% of patients with the condition [1]. Importantly, it may predate the development of hyperglycemia by several years. The clustering of insulin resistance and several other metabolic and vascular disorders is known as the metabolic syndrome or insulin resistance syndrome. Both insulin resistance and the metabolic syndrome are associated with an increased risk of cardiovascular disease.

The characteristic features of the metabolic syndrome include upper body (central) obesity, hypertension, dyslipidemia, glucose intolerance and specific abnormalities of coagulation and endothelial function. In addition, it is frequently associated with fatty infiltration of the liver and the development of non-alcoholic steatohepatitis (NASH).

The precise origins of the metabolic syndrome remain poorly understood. However, they are unquestionably related to increasing body fatness.

Clinicians should be made familiar with the risks associated with insulin resistance and the metabolic syndrome just as they are aware of the established interventions that reduce the risk of heart disease. Early intervention that targets the metabolic syndrome will, if successful, prevent the progression to type-2 diabetes, diminish the risk of coronary heart disease and reduce the future burden to health care.

Despite this, many clinicians continue to consider obesity to be self-inflicted and fail to recognize the metabolic syndrome and its medical significance and, as a consequence, do not seize the early opportunity to intervene.
Clinical Problems Caused by Overweight and Obesity

Increasing body fatness is accompanied by profound changes in physiological function. These changes are, to a certain extent, dependent on the regional location of adipose tissue. This chapter will particularly focus on the intra-abdominal visceral deposition of adipose tissue that characterizes upper body obesity. Intra-abdominal fat is a major contributor to the development of hypertension, elevated plasma insulin concentrations and insulin resistance, hyperglycemia and hyperlipidemia. The alterations in metabolic and physiological function that follow an increase in adipose tissue mass are predictable when considered in the context of normal homeostasis: the intimate relationship between increasing fatness and type-2 diabetes has led some to coin the terms ‘diabesity’ or ‘obesity-dependent diabetes’ [2].

Obesity and the Metabolic Syndrome

In 1988 Reaven [3] coined the term syndrome X to refer to the clustering of (abdominal) obesity, hypertriglyceridemia, reduced levels of high-density lipoprotein (HDL) cholesterol, hyperinsulinemia, glucose intolerance and hypertension. To this basic cluster of abnormalities have been added further metabolic alterations that include increased atherogenic small, dense low-density lipoprotein (LDL) particles, elevated apo B concentrations and raised plasminogen activator inhibitor-1 (PAI-1). The syndrome is now referred to as the ‘metabolic syndrome’ or ‘insulin resistance syndrome’, the latter identifying the likely pivotal biochemical abnormality. Reaven estimated that the prevalence of insulin resistance within the sedentary adult population of North America is approximately 25% and is closely linked to central (visceral) obesity. Several cohort studies have confirmed that upper body (visceral) obesity is associated with greater cardiovascular morbidity and mortality than obesity itself [4].

Obesity and Type-2 Diabetes mellitus

Obesity is characterized by elevated fasting plasma insulin and an exaggerated insulin response to an oral glucose load [5]. Overall fatness and the distribution of body fat influence glucose metabolism through independent but additive mechanisms. Increasing central obesity is accompanied by a progressive increase in the glucose and insulin response to an oral glucose challenge with a positive correlation being observed between increasing upper body (central) obesity and measures of insulin resistance. Post-hepatic insulin delivery is increased in upper body obesity leading to more marked peripheral
insulin concentrations that, in turn, lead to peripheral insulin resistance. Figure 1 illustrates the key role played by insulin within the liver and skeletal muscle in glucose metabolism.

Different fat depots vary in their responsiveness to hormones that regulate lipolysis and this also varies according to fat distribution [6]. In both men and women, the lipolytic response to noradrenaline is more marked in abdominal than gluteal or femoral adipose tissue. Cortisol may also contribute to this enhanced lipolysis by further inhibiting the anti-lipolytic effect of insulin. More recently additional factors have been identified that contribute to the insulin resistance of abdominal adiposity. The increased production of a fat cell-specific protein called resistin by abdominal subcutaneous and omental adipose tissue is associated with decreased cellular insulin sensitivity [7]. By contrast, there is an inverse relationship between adiponectin, an adipocyte-specific secretory protein, and adiposity and insulin sensitivity with type-2 diabetes being characterized by low levels of adiponectin [8]. Adiponectin is similar in structure to tumor necrosis factor-α (TNF-α) which paradoxically appears to be increased in abdominal adipose tissue. All of these factors underline the importance of the adipocyte as an endocrine organ and contribute to the exaggerated release of free fatty acids (FFAs) from abdominal adipocytes into the portal system [6]. FFAs have a deleterious effect on insulin uptake by the liver and

Fig. 1. The key role played by insulin within the liver and skeletal muscle. Insulin increases glycogenesis in the liver, decreases glycogenolysis and suppresses gluconeogenesis. In skeletal muscle, insulin enhances glucose uptake and utilization by increasing GLUT-4 transporter translocation and expression, and increases glucose utilization.
contribute to the increased hepatic gluconeogenesis and hepatic glucose release observed in upper body obesity. Insulin insensitivity is not confined to adipocytes with the process being accentuated by skeletal muscle insulin resistance (fig. 2).

The elevation in plasma FFA concentration, particularly postprandially when they are usually suppressed by insulin, leads to an inappropriate maintenance of glucose production and an impairment of hepatic glucose utilization (impaired glucose tolerance). Reduced hepatic clearance of insulin leads to increased peripheral (systemic) insulin concentrations and to a further downregulation of insulin receptors.

In the initial phases of this process, the pancreas can respond by maintaining a state of compensatory hyperinsulinemia with gross decompensation of glucose tolerance being prevented. With ever increasing plasma concentrations of FFAs, the insulin-resistant individual cannot continue to maintain this state of compensatory hyperinsulinemia, and hyperglycemia prevails.

Hyperinsulinemia and insulin resistance are both significant correlates of a dyslipoproteinemic state and contribute to the characteristic alterations in plasma lipid profile associated with obesity: elevated fasting plasma triglyceride concentration, reduced HDL cholesterol, marginal elevations of cholesterol and LDL cholesterol concentrations and increased number of apo-B-carrying lipoproteins [9]. This abnormal lipid profile in obese subjects may be associated with abnormalities in liver function characterized by elevations in γ-glutamyl transferase, alanine transaminase (ALT) and aspartate transaminase (AST) [10].

**Fig. 2.** Insulin resistance in abdominal visceral adipocytes results in increased lipolysis and increased release of non-esterified fatty acids (NEFA) into the portal vein. This release of NEFA contributes to increased hepatic gluconeogenesis and decreased glucose uptake and utilization by muscle. In addition, increased release of tumor necrosis factor-α (TNF-α) and resistin by fat cells with a reduction in adiponectin secretion further inhibits the action of insulin in skeletal muscle.
Hepatic Function and Obesity

NASH is an emerging clinical problem among obese subjects, particularly those with central obesity. 40% of patients with NASH are overweight or obese, 20% have type-2 diabetes and 20% are hyperlipidemic [11]. The development of the characteristic pathological changes within the liver are intimately related to the various clinical and biological markers of the metabolic syndrome – body mass index, waist circumference, hyperinsulinemia, hypertriglyceridemia, and impaired glucose tolerance. The diagnosis of NASH rests on characteristic histological features that include substantial fat infiltration, necroinflammation and fibrosis in the absence of alcohol as a cause for the disease. In NASH the ratio of serum ALT to AST is always >1 whereas the ratio in alcoholic liver disease is almost always <1 [12]. Histological evidence of fibrosis and/or cirrhosis is seen in up to 50% of patients, with most patients, who initially show fibrosis, developing cirrhosis after 10 years – it has been suggested that ‘cryptogenic cirrhosis’ represents ‘burnt out’ NASH. A liver biopsy is necessary to make a diagnosis and is important for therapeutic and prognostic reasons – ultrasound scanning of the liver is not sufficiently sensitive to be diagnostic.

The causative factors inducing necrosis, inflammation and fibrosis within the liver include oxidative stress and subsequent lipid peroxidation, factors associated with abnormal cytokine production, disordered fat metabolism and insulin resistance.

The two metabolic abnormalities most strongly associated with NASH are insulin resistance and an increased supply of FFAs from visceral adipocytes via the portal vein directly to the liver. There is evidence that NASH associated with obesity and type-2 diabetes is due primarily to peripheral insulin resistance and consequential hyperinsulinemia [13]. Insulin blocks hepatic mitochondrial fatty acid oxidation and results in an increased concentration of intracellular fatty acids that may be directly toxic or lead to oxidative stress. The link between central obesity and liver injury may be explained by the fact that fatty acids are mobilized more rapidly from visceral (central) than subcutaneous fat and drain directly to the liver via the portal vein (fig. 3).

Weight loss is generally associated with a reduction in the severity of the biochemical abnormalities and a regression of the steatosis. Nevertheless, sudden weight loss or ‘weight cycling’ (weight loss followed by weight regain) may predispose to NASH [14].

Hemostasis and Obesity

The hemostatic system plays an important role in the pathogenesis of atherosclerotic plaques and associated complications. A pro-thrombotic environment and/or a situation in which the thrombus is not cleared will predispose to the development of atherosclerosis and its clinical sequelae.
Plasminogen activator inhibitor-1 (PAI-1) is the main inhibitor of fibrinolysis. PAI-1 binds to and inactivates tissue plasminogen activator and urokinase-like plasminogen, the main activators of plasminogen. As PAI-1 levels increase, plasminogen activation is reduced and consequently fibrin accumulates. In this situation the balance is in favor of thrombosis – high concentrations of PAI-1 are likely to favor the development of atherosclerosis and its acute complications. Furthermore, the prognostic value of PAI-1 appears to be related to its association with the metabolic syndrome [15]. Results from animal and human studies suggest that adipose tissue may be an important source of PAI-1 and be responsible for elevated concentrations in obese subjects; as fat mass increases so does PAI-1 production. There is evidence that elevated adipose TNF-α, as found in obesity, may increase PAI-1 mRNA expression in adipose tissue. Moreover, the production of PAI-1 from the liver appears to be regulated by insulin – chronic hyperinsulinemia is associated with increased PAI-1 mRNA expression [16].

PAI-1 levels are positively correlated with the degree of obesity as judged by body mass index and waist circumference. This correlation is confirmed by computerized tomography measurements of visceral fat mass. PAI-1 concentration is additionally positively correlated with each of the variables that make up the metabolic syndrome: central obesity, hypertension, hypertriglyceridemia and low HDL cholesterol concentration.

**Clinical Management of the Metabolic Syndrome**

Effective management of the metabolic syndrome is a clinical priority. Nevertheless, many clinicians avoid this challenge partly as a result of not
appreciating the importance of managing each of its components, and partly as the result of poor knowledge of effective interventions. Clinical management of the metabolic syndrome entails three strategies: (1) lifestyle interventions that include weight management and physical activity to limit insulin resistance; (2) aggressive treatment of identified coronary risk factors that include dyslipidemia, hypertension and thrombotic risk, and (3) treatment of impaired glucose tolerance and type-2 diabetes.

Figure 4 outlines a scheme for the management of the metabolic syndrome and underlines the importance of aggressive treatment targets.

**What Is the Evidence that Weight Reduction Leads to Medical Benefit?**

Lifestyle modification remains the single most important tool for the management of the metabolic syndrome. Physical inactivity is a major risk factor for the development of type-2 diabetes. Prospective studies suggest that the more weekly exercise taken, the lower the risk of developing type-2 diabetes [17]. People who are physically inactive are more likely to have
impaired glucose tolerance, and type-2 diabetes is more common among people who are physically inactive [18]. Intervention studies have demonstrated that a program of lifestyle change focusing on improved diet and increased activity can delay, or possibly prevent, the development of type-2 diabetes in people with impaired glucose tolerance. The Diabetes Prevention Program in North America involved 3,234 men and women with impaired glucose tolerance (mean age 50 years; mean body mass index 34 kg/m²) randomized either to placebo, metformin treatment, or an intensive lifestyle intervention, with goals of at least 7% weight reduction from starting weight and 150 min of physical activity each week. The individualized intensive lifestyle intervention resulted at 3 years in a 58% reduction in the incidence of type-2 diabetes in the lifestyle intervention group compared to a 33% in the metformin-treated group [19]. These highly significant results led to the cessation of the trial (fig. 5). Interestingly, identical results were demonstrated by a similar study in Finland. Such findings strongly support the hypothesis for reversibility of the vicious cycle of events that follow increasing adiposity with increasing insulin resistance and systemic hyperinsulinemia provided that the lifestyle changes occur sufficiently early and prior to islet cell failure. Preliminary publications of the results from the use of the anti-obesity drug orlistat in patients with impaired glucose tolerance and/or established metabolic syndrome indicate a benefit from the addition of orlistat to a program of lifestyle change. The results from the XENDOS study show a 37% reduction in relative risk for all subjects, and 45% reduction in subjects with impaired glucose tolerance alone. Subjects with the metabolic syndrome showed a 36% reduction in risk of developing type-2 diabetes at 4 years [20]. These results suggest a role for orlistat in certain patients with the metabolic syndrome in combination with lifestyle change.

**Treatment of Dyslipidemia**

In all patients, lifestyle and dietary interventions, as well as weight management, are equally important in the management of lipid disorders. However, in many patients, additional pharmacological therapy is indicated to achieve treatment targets. In general, an HMG CoA reductase inhibitor (statin) should be considered in every patient with the metabolic syndrome. Results from the Heart Protection Study in people with diabetes has indicated benefit in those without manifest coronary artery disease (CAD) or raised cholesterol concentrations [21].

Treatment of elevated LDL cholesterol does not by itself target the most characteristic lipid abnormality associated with the metabolic syndrome, as previously described in this chapter (elevated triglycerides and low HDL cholesterol). Thus both lifestyle interventions and the use of drug therapy designed to target these specific abnormalities are appropriate. Data from the
Veterans Affairs HDL Intervention Trial confirm that fibrate therapy reduces the risk of coronary events in patients with known heart disease and low HDL concentrations, patients with type-2 diabetes and those with the highest plasma insulin concentrations [22].

**Hypertension**

It is generally accepted that more stringent goals for blood pressure control are required for the treatment of hypertension in people with diabetes in order to reduce the risk of CAD and other cardiovascular events [23]. A level of 130/80 mm Hg or less is associated with significant reductions in morbidity and mortality in high-risk subjects. However, such a level may be difficult to achieve in some patients in clinical practice. The recent Anti-hypertensive and Lipid Lowering Treatment to Prevent Heart Attack trial (ALLHAT) suggests that a thiazide diuretic is at least as good as an angiotensin-converting enzyme inhibitor and calcium-channel blocker as the initial treatment for hypertension, but it is unclear whether this is specifically relevant to patients with the metabolic syndrome [24]. Of interest is the apparent reduction in insulin resistance and new-onset diabetes seen in the LIFE trial that compared Losartan (angiotensin-receptor blocker) with atenolol (β-blocker) [25].
Thrombotic Risk

Anti-platelet therapy (usually low-dose aspirin) is indicated for anyone at significant risk for CAD, which includes patients with the metabolic syndrome, providing that there are no contraindications.

Treatment of Insulin Resistance and Glucose Intolerance

Glucose intolerance is one of the defining features of the metabolic syndrome. Although much is known of the benefits of glycemic control in those with diabetes, the impact of intensive glucose lowering on cardiovascular disease risk remains unclear. Epidemiological studies indicate that blood glucose concentrations of $>6$ mmol/l are associated with an increased risk of CAD, but long-term studies of glucose lowering have not demonstrated a significant reduction in cardiovascular disease risk. By contrast, lifestyle and pharmacological interventions can limit the risk of developing type-2 diabetes. They should be considered in any patient with the metabolic syndrome. Therefore patients should be treated on the basis of individual assessment of risk and evidence for progression to diabetes and CAD. The use of drugs such as metformin and thiazolidinediones (TZDs) for non-diabetic patients is presently considered off-license – such therapy is clearly indicated in anyone found to be hyperglycemic and in patients with lesser degrees of glucose intolerance.

Metformin

Metformin is effective for the treatment of type-2 diabetes. It acts primarily by reducing hepatic glucose production. It additionally has a limited effect on peripheral insulin resistance. Metformin reduces the risk of developing diabetes in people with the metabolic syndrome. Metformin was associated in the United Kingdom Prevention of Diabetes Study (UKPDS) with lower all-cause mortality and a reduction in the risk of myocardial infarction for obese (and likely insulin-resistant) individuals compared with other oral anti-diabetic agents and insulin [26]. The mechanisms through which metformin achieves these effects are not well understood although its use does lower serum triglycerides and LDL cholesterol and concentrations of PAI-1.

Thiazolidinediones

The TZDs (rosiglitazone and pioglitazone) specifically target insulin resistance. This class of medication is effective for the management of type-2
diabetes and is known to retard the rate of progression to type-2 diabetes in people with insulin resistance. The glitazones are true insulin-sensitizing medications that may additionally modify other components of the metabolic syndrome. Studies with Troglitazone, prior to its withdrawal due to concerns about hepatotoxicity, indicated a significant reduction in the risk of diabetes in the short term in patients with impaired glucose tolerance [27]. TZDs favorably affect lipid profiles in patients with type-2 diabetes and insulin resistance and reduce concentrations of inflammatory cytokines implicated in atherosclerosis. As with metformin, treatment with TZDs reduces concentrations of PAI-1 in the blood.

Conclusions

This chapter has linked the biochemical and physiological changes that accompany the metabolic syndrome to alterations in lipid metabolism, hepatic function and hemostasis. The important clinical message, based on compelling evidence, must be that such maladaptation is avoidable providing intervention strategies are implemented at an early stage for those at particular risk. This requires a better understanding of the mechanisms involved in the metabolic syndrome by both clinician and patient alike, and earlier recognition. Clinicians must be aware of the benefits of lifestyle intervention regardless of the stage of the disease and be prepared to manage each of its elements aggressively. Community-based programs focusing on education and lifestyle change are required to support the prevention of type-2 diabetes and CAD. Finally, clinicians must appreciate that the risk of cardiovascular complications and type-2 diabetes is greatest in certain populations that include south-east Asians, Afro-Americans and Hispanics.

References

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Discussion

Dr. Wasantwisut: Thank you very much for your excellent presentation. I have a question and a comment. The question has do with the point raised earlier by Dr. James about finding type-2 diabetes in younger and younger populations, and my scary thought would be that at some point it will be found in infants. Has there been
any attempt to diagnose or have an earlier marker so that we could define an at-risk population so that we could do something and intervene as early as possible, or do we have to look at every child that comes along and say this is a potential subject for type-2 diabetes? The second question has to do with your remarks about prevention and with health education and the education of health professionals. I think that the key to this has to do with counseling skills. It is not knowledge that is the problem, it is how this is being delivered effectively and communication strategies that could induce changes for patients. I think that is one of the things that we still haven’t worked enough on.

**Dr. Kopelman:** In answer to your first question about identifying those at risk, I think it is very difficult because one doesn’t want to start doing a whole series of investigations in relatively young children or adults. But I would say, and again I relate to where I work in East London, if you take a good medical history, and you take a good medical history of family risk or family diabetes or coronary heart disease, you can actually anticipate and predict very closely who is at risk. There is the group which I think we need to focus on and intervene early, and intervention is really primary prevention. In relation to education, I would suggest that health professionals are not so well informed. If you talk to colleagues in endocrinology or diabetes they don’t actually appreciate the metabolic syndrome. We avoid the term syndrome X, because if you talk to a cardiologist that is something very different. I also would take the experience with cardiologists, and many of them are close friends, but in the coronary care unit in the hospital where I work at least 50% of the patients have the metabolic syndrome: they have type-2 diabetes and they are dyslipidemic. My cardiology colleagues would recommend statin and β-blockers and so forth, and send them off for coronary rehabilitation, which is excellent, but we still don’t focus on the fact that they are overweight. Coronary rehabilitation tackles sedentariness to a certain extent but we need to be much more focused on the secondary intervention as we were with cigarette smoking. We need to do that in relation to the metabolic syndrome.

**Dr. James:** I am very intrigued by your analysis. You put in family history and so on and I suddenly remember there is a Finnish paper on the metabolic syndrome that showed an interesting conjunction with the family history as you described it plus a much bigger increased risk if those individuals had been overweight in childhood. So I guess you might be saying that if a pediatrician sees a child who comes from those sort of families and is overweight already in early adolescence, then I think the Finnish data suggest that there is a phenomenally increased risk of the metabolic syndrome. I then suppose that, given your practice, you would have to be particularly on the alert if the patient comes from particular ethnic groups, for complex reasons which we have discussed?

**Dr. Kopelman:** Yes, you are quite right. What I should have said is that it is not simply the history, it is actually the growth charts and if it is a child in relation to where the weight is and the height is. It is also a physical measure because certainly as you progress into adulthood, measuring the waist circumference is a very good predictor of problems.

**Dr. Tan:** A comment and a question regarding the use of bed-time insulin. You said that you use this because it shows that there is no effect in terms of weight gain, and side effect of thiazolidinediones (TZDs) would be weight gain. We all know that in terms of obesity TZD in itself has been shown to reduce peripheral insulin resistance while metformin as a drug has been shown to reduce hepatic glucose output. So the combination of these two drugs would most likely be better off compared to a metformin-based treatment already and you start right away on insulin. The other comment I have is what do you think about the effect of TZD on fat topography because you mentioned that the weight gain may be harmful, and TZDs have been...
shown to reduce or there is a change in fat differentiation from a decrease in subcutaneous but an increase in intrahepatic fat which is a marker of visceral fat.

Dr. Kopelman: Two very good points. When I was talking about the use of bedtime insulin I was talking in relation to patients with established type-2 diabetes. In Europe we haven’t been able to use TZDs as a first-line monotherapy until now. Having said that, the disappointment with the glitazones in second- or third-line treatment has been that by that stage endogenous insulin production has failed and so, even though you increase the peripheral insulin sensitivity, it is not going to make any difference. That is why I think bed-time insulin suppressing hepatic gluconeogenesis is beneficial, so that is slightly different from the suggestion of using it earlier on. I am not aware of published information about the combination of metformin and glitazones as yet. The downside from that is of course, as in North America, the glitazones are extremely expensive, metformin is relatively cheap. In relation to your second good point, there is now good evidence of a differential effect of the glitazones in relation to fat deposition and it does seem to mobilize and reduce visceral fat, and the fat or the weight gain you get in association with their use seems to be related to increased subcutaneous fat. It may well be that there will be benefits. The downside is of course that the patients don’t like putting weight on, particularly when you keep telling them that they must lose weight, and although they may not appreciate the metabolic benefit, it may be that the metabolic benefit is something that we should look at more closely in the future.

Dr. James: You are proposing that we should go in for counseling skills and you are highlighting the fact that we medics are completely useless at it. But let me put a proposition to you. A long time ago I looked up the analysis of the effectiveness with which dieticians treat people with weight gain and obesity, and I found practically nothing in the literature. So I run special courses for dieticians and they spent 80% of their time on diabetes and/or obesity, and we could only find one paper by Foster at that stage that had any analysis of their effectiveness and when I asked them about elementary things, admittedly they were British dieticians, 9 of 10 could not answer the majority of fundamental questions about the management of obesity except in very vague personalized terms. So I am much more depressed than you are in the sense that you tell me that doctors are incompetent, I claim that dieticians are incompetent and I hope there aren’t any dieticians here. How are we going to begin to make progress? You might then say that it is physical activity. Everybody in the United States is saying that the Diabetes Prevention Program trials are incredibly intensive and extremely difficult, whereas in the Xendos trial, which you highlighted, I was told by the investigators that all they told their patients to do was to walk an extra kilometer a day, and therefore presumably the effectiveness of their intervention was on diet, so it sounds to me as though the Swedish doctors are the only people who know anything about how to change people’s diet.

Dr. Kopelman: Thank you for that challenge late in the afternoon. Firstly I said my talk was in two parts: act 1 and act 2. In relation to your first point about the dieticians, I think you are being a little bit disingenuous because you spend most of your life going around and telling governments they have got to change society’s perception and governmental policy in relation to preventing obesity. I mean that is the only way we are going to reduce the incidence and prevalence of the metabolic syndrome, we have to induce a change across society. So that is the prevention message. In relation to intervention, I didn’t want to marginalize, the whole point of my talk was that if you are going to treat the metabolic syndrome you need to treat each element of it. The danger we face is that the public wish is for the single pill to achieve everything, and if you want to get on the front page of the Daily Mail, which is the most prestigious scientific journal in England at the present time, you simply announce
that you have found the cure for obesity and you are guaranteed publicity because that is what patients want to hear. What I meant to say was that we need to simplify the therapeutic intervention to ensure that the patients take the tablets that we prescribe, otherwise the gain from the intervention is going to be minimalized for the longer term.

**Dr. Rock:** We actually have an enormous amount of knowledge at this point about how to effect behavior change, and I am involved in a couple of studies. I am going to talk a little bit about some of the ones relating to hypertension tomorrow. I think the take-home lesson is that you really can’t expect someone to change lifestyle behavior by one visit to the dietician and in fact in the United States, for example, you would be lucky to get that covered through health care. We also have different levels of dietetic training much as we have different levels of medical training and there are differences across countries, and even within the United States there are huge differences across the levels of training. If you are interested I can share examples of similar large skill intervention studies that have shown long-term sustained weight loss, and more important than that exercise, and I am involved in some relating to cancer prevention right now. If you use the proper tools and go forward with the proper training we know that we can in fact change, but if you simply give someone a diet sheet that has ‘This is your menu for tomorrow’, you can expect that he won’t even take it home. Any physician will realize that you don’t just see a patient once and say well lose 5 kg, come back and see me next week, that is an effective way of eliminating your practice because no one will come back and see you. So I think we need to realize, and this will be my last point, that it takes some intensive intervention. It is not easy to change one’s lifestyle and, as you brought up earlier, it isn’t all associated with the effected behavior change. You have to give someone the tool box and you have to show them how to use those tools. That is something that our health care in the United States has not invested a lot in.

**Ms. Easaw:** I would like to argue with Dr. James. I think you are talking about dieticians 20 years ago. The current dieticians are not like that in practice anymore. I agree with Dr. Rock and I think that changing someone’s behavior is not easy. At the National Heart Institute in Kuala Lumpur we make sure our patients come back the same day to see the cardiologist. So they see the cardiologist and the dietician, and we target them for 4 visits a year, and when they have achieved their target they come once every 6 months. At the same time they see their doctor. They would see their doctor but they would not see the dietician; so if they see the doctor the same day they will have to see the dietician. We have actually achieved quite a lot of success in weight management and diabetes in the sense that I must admit cardiologists manage diabetes very differently. So the role of the dietician is not useless and we progress and play an important role in patient’s education these days.

**Dr. Njenga:** I would like to make a comment on the many pills that we have now for metabolic syndrome. Coming from an economically handicapped region of the world we have problems with patients who cannot afford what you have on that list, which gives us no option but to go fully for education and prevention of the metabolic syndrome rather than wait for the pills because most likely by the time they come we would not be able to afford them. We have a major problem in that some of our patients are covered by insurance groups because they have a chronic or preexisting condition, but those with the metabolic syndrome are not covered by the insurance companies. So we do have a major issue and we are going to educate our patients and educate our professionals and also educate our policymakers, and that is what we are working on now.

**Dr. Kopelman:** That is a very good point and I think one of the factors we must not overlook is the poor understanding of patients about the link between increasing body weight with the metabolic syndrome and the development of type-2 diabetes.
In my own practice I am always amazed by the ignorance, I suppose I should not be, but the ignorance of people with university degrees and they cannot see why we are focusing on weight reduction because they have developed diabetes – they don't see the link. We need to get it across in very simple language to whatever the population.

Dr. Battandier: I have a comment about a study which was started 10 years ago in France in two small cities in the north of France, each with 10,000 inhabitants. The way to change behavior and the way the food is seen is to teach the children, and the children then teach the parents. Since the beginning of this study 10 years ago, there has been no increase in obesity in these two cities. In the other cities around these two cities, in the departments around, there has been a 30–40% increase in obesity as in the rest of France. So to teach the children is a very efficient way to prevent an increase in obesity; at least in this study.

Dr. Allison: Lenin understood this, that if you get them young you can change them. If you wait until our age, we are hopeless. It is pediatricians and schoolteachers for whom this is a problem, and parents. By the time they are referred to me it is too late. It is not the geriatricians, it is the pediatricians we need.

Ms. Mace: In the Sibutramine Trial on Obesity Reduction and Maintenance study [1] did you see a difference in carbohydrate or fat intake between the placebo and the sibutramine-treated people?

Dr. Kopelman: From my memory, no, we didn’t. We just saw an overall reduction in the calorie intake of those who were taking sibutramine. Dr. James, perhaps you can correct me.

Dr. James: I think you are right. The question was whether there was a selective drive for carbohydrates or fat, and the full analyses have not been done but our preliminary analyses suggest that we did not see that. It was based on diarrhea and so on. We are actually in the process of doing a sub-analysis of the 3 or 4 centers that kept the metabolic rate measurements going, and perhaps then we will find differences in respiratory quotients which will imply that there has been a selective drive for carbohydrates or fat, but that has not been done as yet.

Reference