Nutrition in Metabolic Syndrome

Module 24.3

Lifestyle Interventions in Metabolic Syndrome

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Learning Objectives

• Diet modification in overweight and obese individuals;
• Beneficial effects of exercise;
• Prescription of exercise;
• Strategies to improve lifestyle counselling;
• Evidence of lifestyle intervention efficacy;
• Comparison of lifestyle interventions and surgical treatment.

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Key Messages

• Lifestyle modification improves diabetes and cardiovascular risk;
• Modest weight loss and light physical activity significantly reduce insulin resistance;
• Behavioural strategies are necessary to achieve long-term success in maintaining adequate food intake and exercise.
1. Lifestyle Interventions in Metabolic Syndrome

Many authorities consider that we face a global obesity pandemic that demands urgent action to reverse this risk factor for chronic disease in future generations (1, 2). Abdominal obesity is the main aetiological factor in the development of metabolic syndrome (MS). As the syndrome advances many people suffer a cascade of adverse events, such as the development of type 2 diabetes and cardiovascular disease (CVD), as well as complications associated with them. The MS appears to be the link between prediabetes and macrovascular disease.

WHO has identified several leading risk factors for worldwide mortality. Eight risk factors, including high blood pressure, high body mass index, high cholesterol, high blood glucose, low fruit and vegetable intake and physical inactivity account for 61% of cardiovascular deaths. These same risk factors combined account for over three quarters of the leading cause of death worldwide, ischaemic heart disease (3). Many of these factors are included in the definition of MS. The MS and impaired glucose tolerance (IGT) are more prevalent than diabetes and are high-risk conditions for the development of both type 2 diabetes and CVD.

Dietary habits and physical activity are the most important risk factors in the development of MS, even more than genetic disorders. For this reason, the primary intervention for correcting MS is lifestyle therapy (4). It has the potential to reduce the severity, slow the progression of all metabolic risk and delay the need of drug therapy in persons with MS. It consists of weight reduction, increased physical activity, following an anti-atherogenic diet, and smoking cessation (5). Once a person is found to have the syndrome, lifestyle measures should be introduced, reinforced, and monitored. Modest weight loss (5-10% of body weight) and modest physical activity (30 minutes daily) are the recommended goals (6).

2. Diet
The ideal diet for individuals with MS should improve insulin sensitivity and prevent or correct the associated metabolic and cardiovascular abnormalities. Most individuals with MS are overweight and obesity is the main cause of insulin resistance.

Effective weight reduction improves all risk factors associated with the MS and it will further reduce the risk for type 2 diabetes. Weight loss improves insulin sensitivity in a proportion greater than that obtained with insulin-sensitizing drugs. The treatment of obesity consists of diet change, exercise, behavioural modification, and in some patients, drugs or surgery. Dietary intervention to reduce energy intake and physical activity to enhance energy expenditure are basic forms of treatment in any overweight or obese patient. In contrast to drug therapy or surgery, diet and physical activity can be changed by lifestyle modifications. Both weight reduction and increased physical activity are likely to have independent and complementary effects in diabetes prevention.

Many different diets have been proposed for the treatment of obesity (7). These dietary approaches vary in their total energy prescription, macronutrient (fat, carbohydrate, and protein) content, glycaemic index, energy density, and portion control. To date, no single approach has been demonstrated to be significantly better than others and sustained weight reduction is the main factor in achieving the desired outcomes (8).

2.1 Energy Intake
The energy content of a diet is the primary determinant of weight loss. Diets can be classified as

- Low Calorie Diets (LCD): 12-20 kcal/kg ideal body weight/d (50-80 kJ/kg), usually between 800 and 1500 kcal/day
Very Low Calorie Diets (VLCD): < 12 kcal/kg ideal body weight/d (< 50 kJ/kg), usually less than 800 kcal/day

An LCD typically causes approximately 8% loss of body weight at 6 months of treatment. In contrast, the use of a VLCD usually produces a weight loss of 15% to 20% within 4 months. However, VLCDs are associated with poorer weight loss maintenance and a greater weight regain than are LCDs, so weight loss at 1 year after treatment with a VLCD does not differ from treatment with an LCD. Most authorities and clinical guidelines recommend a 500- to 1000-kcal/d deficit diet for obese persons, which will initially result in a weekly weight loss of 0.45 to 0.9 kg. It is important to remember that the relation between weight loss and time is non-linear, with decreasing of the slope of the curve as time goes by.

Patients’ daily energy requirements can be estimated from the equation proposed for obese individuals by the Institute of Medicine's Dietary Reference Intakes for Energy (10):

For men

\[
\text{TEE} = 1086 - (10.1 \times \text{age \ [years]} + \text{AF} \times (13.7 \times \text{weight \ [kg]} + 416 \times \text{height \ [m]})
\]

TEE stands for Total Energy Expenditure

AF (activity factor) depends on the physical activity level (PAL):

- AF = 1 if activity is sedentary: \( \text{PAL} \geq 1 < 1.4 \)
- AF = 1.12 if activity is light: \( \text{PAL} \geq 1.4 < 1.6 \)
- AF = 1.29 if activity is active: \( \text{PAL} \geq 1.6 < 1.9 \)
- AF = 1.59 if activity is very active: \( \text{PAL} \geq 1.9 < 2.5 \)

For women

\[
\text{TEE} = 448 - (7.95 \times \text{age \ [years]} + \text{AF} \times (11.4 \times \text{weight \ [kg]} + 619 \times \text{height \ [m]})
\]

AF (activity factor) depends on the physical activity level (PAL):

- AF = 1 if activity is sedentary: \( \text{PAL} \geq 1 < 1.4 \)
- AF = 1.16 if activity is light: \( \text{PAL} \geq 1.4 < 1.6 \)
- AF = 1.27 if activity is active: \( \text{PAL} \geq 1.6 < 1.9 \)
- AF = 1.44 if activity is very active: \( \text{PAL} \geq 1.9 < 2.5 \)

2.2 Macronutrient Distribution

It is generally accepted that the macronutrient composition of a diet does not affect the rate of weight loss. However, several concepts regarding the main macronutrients have been proposed in diets for obese patients (11):

\textbf{Low fat diet:} a low-fat diet is considered the standard approach for the treatment of obesity. The “classical” distribution of macronutrients in a diet for obesity is shown in Fig. 1, left column, close to the recommendations for a healthy lifestyle. Despite the traditional support that many physicians have given to these diets, weight loss induced by low-fat diets and other weight-reducing diets was similar, especially after 12 months’ follow-up (12). On the other hand, some data
suggest that obese persons who are successful at maintaining long-term weight loss, consume a lower percentage of calories from fats.

![Graph showing dietary distribution for General population and Metabolic Syndrome.](image)

**Fig. 1** Diet for the Metabolic Syndrome

*Low carbohydrate diet:* in recent years, the use of low-carbohydrate diets has become the focus of much research. In all studies, weight loss at 3 and 6 months in subjects randomized to the low-carbohydrate diet was roughly twice (4 to 5 kg greater weight loss) that in those randomized to the low-fat group. However, when patients were followed-up for 1 year, weight loss was not significantly different between groups. It appears that the positive benefits come from a reduction of energy intake, and not from the carbohydrate restriction itself. The low-carbohydrate diet was more beneficial in serum triglyceride and HDL-C concentrations as compared with the low-fat diet, but the low-fat diet was more beneficial in serum LDL-C concentration. It is not known whether these alterations are associated with long-term beneficial effects on CHD. The low content of antioxidant vitamins, dietary fibre and high content in total fat are a cause of concern because their long-term effects, on either global health or cardiovascular health in particular, have not been evaluated (13).

*High protein diet:* Replacing protein for carbohydrates has also been proposed as a method for weight loss. Several advantages have been pointed out: better conservation of lean body mass, lower postprandial insulin response, higher satiating effect, and decrease in triglyceride levels (14). A recent study, Diogenes (Diet, obesity and Genes), investigated the efficacy of moderate fat diets that vary in protein content and glycaemic index in preventing weight gain and obesity related factors following an initial weight loss phase. A combination of low-protein and low-GI was most beneficial in respect to high sensitivity C Reactive Protein (hs CRP) reduction (15). However, comparison of iso-energetic high protein diets with standard high carbohydrate diets has failed to show differences in weight loss. There is also a concern that these diets could increase urinary calcium excretion and bone turnover. Therefore, they cannot be advocated for long-term treatment of individuals with MS.

It is important to emphasize that total energy intake and compliance with the prescribed nutrition therapy are more important than a particular distribution of macronutrients (16).
2.3 Diet Recommendations for the Metabolic Syndrome

Specific recommendations for subjects with MS have been proposed (Table 1). The main features of these recommendations are (17):

<table>
<thead>
<tr>
<th>Nutrients</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy</td>
<td>↓ Energy intake to ↓ 5-10 % body weight or maintain desirable weight</td>
</tr>
<tr>
<td>Carbohydrate</td>
<td>↑ Low Glycaemic Index foods, ↑ Fibre Intake, Avoid potatoes, bread, pasta, rice, sweetened cereals, soft drinks, sweetened juices</td>
</tr>
<tr>
<td>Proteins</td>
<td>↑ Fish, low dairy and vegetable protein</td>
</tr>
<tr>
<td>Fat</td>
<td>↓ Saturated fat (&lt; 10 % energy) and trans fatty acids (&lt; 2 % energy), ↑ Monounsaturated fatty acids, Use virgin olive oil as a basic cooking fat</td>
</tr>
<tr>
<td>Others</td>
<td>↓ Salt intake to &lt; 6 g/day, ↓ Alcohol intake to &lt; 2-3 drinks/day</td>
</tr>
</tbody>
</table>

Energy: Energy intake should allow patients to maintain weight, if it is acceptable, or otherwise to reduce it by 5 to 10%. It is important that patients learn to make good food choices, such as low-energy-density foods, and to decrease the size of the portions served to decrease the amount of food consumed.

Carbohydrates: Foods with low Glycaemic Index (GI) may have favourable effects on insulin sensitivity and lipid levels. A low-GI diet (high in dairy and fruit, but low in potatoes and cereals) was associated with improved insulin sensitivity and lipid metabolism and with a reduction in chronic inflammatory factors. However, systematic reviews have failed to substantiate these benefits. The glycaemic response to a specific food that is ingested as part of a meal can be altered by many factors, such as the method of preparation and the effect of concomitantly ingested foods on intestinal motility. Nevertheless, fruits, vegetables, legumes, and whole-grain cereals are considered important components of the recommended diet. In contrast, bread, potatoes, pasta, and refined rice, all of them with higher GI, should be sparingly consumed (18). Liquid carbohydrates are associated with lower satiety compared with carbohydrates consumed in solid form. Soft drinks and sweetened juices are considered main culprits of the obesity epidemic and should be avoided or eliminated (19).

Proteins: Fish, low-fat diary, vegetable protein and lean meats are recommended. Some authors entertain the hypothesis that these protein sources reduce insulin resistance in comparison with red meat, but more evidence is necessary.

Fat: Quality of fat is more important than quantity. Following a Mediterranean-diet style, monounsaturated fatty acid (MUFA) intake should constitute 20-25% of total energy. A 60-70% proportion of the energy intake as low glycaemic index carbohydrates together with MUFA should be the best choice in individuals with MS. This approach facilitates compliance with the dietary
recommendations, since it allows a less drastic reduction of the total amount of fat. On the other hand, saturated fat and trans fatty acids should be limited to < 10% and < 2% of energy intake, respectively. A signal coming from a recent systematic review and meta-analyses points to a lack of association of saturated fat with all-cause mortality, cardiovascular disease, stroke or type 2 DM, but the evidence is heterogeneous with methodological limitations. The ω-3 fatty acids have anti-thrombotic effects and can decrease cardiovascular risk. Patients should remember that a food’s energy density is directly correlated with its fat content and inversely correlated with its water content. The use of low-energy-density foods may be an effective approach for treating obesity (20).

Macronutrient distribution: When energy restriction is prescribed, the percentage of protein is frequently higher than 20% of total energy. Fat can be increased up to 35-40%, if MUFA plus low GI carbohydrates add up to 60-70%. In that case, carbohydrates are reduced to 40-45% of total energy (Fig. 1). Some authors have advocated a 30-40-30 diet for patients with MS and type 2 diabetes. Foods included in and excluded from this diet are similar to those recommended above.

Other nutrients: According to the Dietary Approaches to Stop Hypertension (DASH) study, salt intake should be not higher than 6 g of sodium chloride/day. Alcohol intake should be less than 2-3 drinks/day (< 30 g/day) in men and 1-2 (< 20 g) in women. Although modest consumption of alcohol is associated with a decrease in the relative risk of coronary heart disease, alcohol ingestion may worsen other factors linked to MS, such as steatohepatitis or triglyceride levels.

2.4 Specific Dietary Patterns

Many foods are consumed together, leading to many potential interactions between different nutrients and foods. The influence of any of these in the pathogenesis and treatment of MS is less crucial than the effect of the overall dietary pattern. They are not directly measurable, but they are categorized according to different statistical methods, either by dietary indices or by factor and cluster analysis. Several dietary approaches have been advocated for treatment of the metabolic syndrome (21). The following specific dietary approaches have been recommended: The Mediterranean diet may be beneficial for individuals with MS. In studies comparing the Mediterranean diet (high in fruits, vegetables, nuts, whole grains, and olive oil) with low-fat diets, subjects in the Mediterranean diet group had greater weight loss, lower blood pressure, improved lipid profiles, improved insulin resistance, and lower levels of markers of inflammation and endothelial function (22, 23). In the PREDIMED Study, 7,447 participants, who were at high cardiovascular risk but with no CVD at enrolment, were randomized to a control group that received advice to reduce dietary fat or to an energy-unrestricted Mediterranean diet, supplemented with either extra-virgin olive oil or nuts. The Mediterranean Diet was significantly associated with a 30% relative reduction in the risk of major cardiovascular events (myocardial infarction, stroke or death from cardiovascular causes) (24). Supporting the findings of single clinical trial, a meta-analysis that included over 500,000 overweight and obese subjects, showed that, compared with a low fat diet, a Mediterranean diet improved cardiovascular risk factors and vascular inflammatory markers (25).

The DASH diet (Dietary Approaches to Stop Hypertension) is characterized by increased consumption of low-fat dairy, fruit and vegetables, dietary fibre and whole grains and decreased intake of refined grains, saturated fat and total fat. It limits daily sodium intake to 2400 mg and it is higher in dairy intake than the Mediterranean diet. The DASH diet was developed as a means of reducing blood
pressure by dietary patterns as opposed to nutrients alone (26). When compared to a weight reducing diet emphasizing healthy food choices, the DASH diet achieved greater improvements in triglycerides, total, LDL and HDL cholesterol diastolic blood pressure, and fasting glucose, even after controlling for weight loss (27). The DASH diet may prevent the occurrence of T2DM. Therefore, the DASH diet could prevent and treat the risk factors associated with the MS (28). A diet with low glycaemic index foods, replacing refined grains with whole grains, fruits and vegetables, and eliminating high-glycaemic index beverages, may be particularly beneficial for patients with the metabolic syndrome (29, 30).

A different approach is to identify dietary patterns that increases the prevalence of Metabolic Syndrome components and ultimately CVD. In the INTERHEART study diets were classified as “Oriental”, “Western” or “Prudent”. In a very simple way, the content of tofu and soy and various other sauces can define the oriental diet. In contrast, the western diet is high in fried foods, salty snacks, eggs and meat. Finally, the prudent diet includes large amounts of fruit and vegetables. Confirming our current concepts regarding diet and CVD, the western diet was associated with Acute Myocardial Infarct, the oriental diet had no association with it, and the prudent diet had a protective effect at higher levels (31). Similar results regarding the role of a western diet in the incidence of MS were observed in the ARIC study (32).

We have discussed the recommendations for individual nutrients and specific dietary patterns. However, as we have said above, it is important to stress that the most important factor associated with better long-term results is the motivation of the patient to follow the dietary recommendations. Consequently, the rate of success is proportional to the adherence to the new dietary regimen rather than to any specific macronutrient content or combination. In two important studies comparing four different types of diets, researchers found a strong curvilinear association between self-reported dietary adherence and global weight loss, regardless of the specific diet chosen (16, 33).

3. Exercise

Physical activity is seen as an important modifiable factor, which contributes to the risk of obesity and associated diseases. Sedentary behaviour is a separate important risk factor, which is not avoided by short periods of activity (34). Increased fatness and reduced fitness are associated with increased risks for hypertension, hypercholesterolaemia, and MS, even when accounting for other factors. However, improvements in fitness attenuate the effects of increased body-mass index and percentage body fat, and vice versa. In consequence, it is key to motivate patients with MS both to maintain a normal body weight and to improve their fitness level, not just one or the other (35). Simply prescribing exercise, in a generic sense, to a patient is insufficient guidance and is unlikely to achieve the desired outcomes. Hoffman et al provide precious pieces of advice to health care providers about how to prescribe exercise (36).

3.1 Benefits of Physical Activity

Modern lifestyles are characterized by reduced physical activity at work and during leisure time. Many individuals with MS have a sedentary life. The decrease in physical activity augments the risk of obesity, diabetes, fatal and non-fatal coronary artery disease (CAD), as well as all-cause mortality. In contrast, the most physically active subjects have a reduced incidence of CAD, with a constant inverse correlation: the higher the level of activity the lower the CAD rate. Numerous studies have identified multiple mechanisms that could explain the beneficial consequences of physical activity on the development of these diseases.
Among them are anti-atherogenic, anti-thrombotic, anti-ischaemic, and anti-dysrhythmic effects. Physical activity both prevents and helps treat many established atherosclerotic risk factors (37, 38). In general, the effect of exercise on these risk factors is substantially less than that achieved by pharmacological therapies. However, combined with weight loss and improvements in dietary composition, the effect of exercise may be more relevant (39, 40).

Obesity
Increasing physical activity favours weight loss. Although it is difficult to achieve a significant weight loss from increased exercise alone, when it is combined with diet, individuals lose more weight than with diet alone. Furthermore, this loss is maintained for longer periods of time (41, 42).

Exercise also produces beneficial changes in body composition. Weight loss induced by combining physical activity with diet ameliorates the loss of Fat Free Mass that occurs when weight loss is produced by diet alone. Physically active men and women have a more favourable waist-to-hip ratio than do sedentary individuals, reflecting a decrease of central obesity.

Physical activity is very important for preventing weight regain. Numerous studies confirm that patients who keep up their increased physical activity for longer periods after lifestyle interventions regain less weight, although exercise alone does not completely prevent some weight regain. A combination of aerobic and resistance training programs is more effective than either alone (43, 44).

The weekly amount of calories spent on physical activities is higher in patients that maintain the lost weight (8).

Lipids
Epidemiological studies of physical activity have shown an average reduction in triglyceride and LDL-C of 4-5% and a similar increase in HDL-C. A meta-analysis of 95 studies, most of which were not randomized controlled trials, reported better results, with a reduction of 6.3% in total cholesterol, 10.1% in LDL cholesterol, and 13.4% in total/HDL cholesterol ratio, and a 5% increase in HDL (45). Table 2 shows the reductions observed in the HERITAGE study that included 675 normolipidaemic subjects who participated in 5 months of exercise training (46).

<table>
<thead>
<tr>
<th>Table 2</th>
<th>HERITAGE Study Baseline and Post-training Adjusted Plasma Lipid Levels</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Men</td>
</tr>
<tr>
<td>HDL-c, mg/dl</td>
<td>+ 1.1 (3 %)</td>
</tr>
<tr>
<td>LDL-c, mg/dl</td>
<td>- 0.9 (0.8 %)</td>
</tr>
<tr>
<td>Triglycerides, mg/dl</td>
<td>- 5.9 (2.7 %)</td>
</tr>
</tbody>
</table>

Blood pressure
Physical activity also has beneficial effects on resting blood pressure. The reported average reduction in systolic and diastolic blood pressure is of 3.4 and 2.4 mm Hg, respectively. The decrease in blood pressure is more significant in hypertensive subjects. Average systolic and diastolic blood pressures decreases 2.6 and 1.8 mm Hg in normotensive subjects and by 7.4 and 5.8 mm Hg in hypertensive subjects, respectively (47). Regular exercise reduces the incidence of hypertension. Moderate-intensity dynamic exercise is preferable to vigorous exercise, as moderate-intensity exercise appears to be more effective in reducing blood pressure (48).
Diabetes Mellitus

Physical activity reduces insulin resistance and glucose intolerance, postprandial hyperglycaemia, and possibly hepatic glucose output (49). In a study of 6000 men followed for 14 years, each 500 kcal/week increase in physical activity reduced the age-adjusted risk of diabetes by 6 % (50). Several prevention trials have proven that physical activity and weight loss can decrease the onset of type 2 diabetes in individuals at high risk for this disease (see below).

Recently there have been advances in the knowledge of the hormonal link between physical activity and insulin resistance. A key molecule is PGC1-alfa that is produced by muscles. It has been observed in the mouse that PGC1-α expression in muscle stimulates an increase in expression of FNDC5, a membrane protein that is cleaved and secreted as a newly identified hormone, irisin. This hormone transforms subcutaneous white fat cells into brown fat cells. Even without exercise or decrease in caloric intake, irisin caused weight loss and reduced insulin resistance in mice. In this way glucose homeostasis is improved. Human muscle also produces irisin in response to exercise. Interestingly, human and mouse irisin are identical. The therapeutic use of irisin in humans is still of unproven value (51).

3.2 Characterization of Exercise

From a clinical point of view, any physical activity should be assessed according to five features: intensity, frequency, duration, mode, and progression. In relation to the first concept, it is useful to distinguish between absolute and relative intensity:

Absolute intensity: rate of energy expenditure during exercise. It is usually expressed in METs, where 1 MET equals the resting metabolic rate of ~3.5 mL O₂ · kg⁻¹ · min⁻¹. One MET is the energy consumed during resting conditions, such as television viewing, and is approximately equal to 1 kcal/kg of body weight per hour. On the other hand, brisk walking at 4.8 km/hour (3 miles/hour) has an absolute intensity of 4 METs. Tables 3 and 4 list the energy requirements of various activities of daily life and of leisure time. METs can be transformed into kilocalories with the following formula: kilocalories per minute = [(METs x 3.5 x body weight in kilograms)/200].

<table>
<thead>
<tr>
<th>Table 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy Requirements of Selected Daily Activities, METs</td>
</tr>
<tr>
<td>• Gardening (no lifting) 4.4</td>
</tr>
<tr>
<td>• Household tasks, moderate effort 3.5</td>
</tr>
<tr>
<td>• Lifting items continuously 4.0</td>
</tr>
<tr>
<td>• Loading/unloading car 3.0</td>
</tr>
<tr>
<td>• Lying quietly 1.0</td>
</tr>
<tr>
<td>• Mopping 3.5</td>
</tr>
<tr>
<td>• Mowing lawn (power mower) 4.5</td>
</tr>
<tr>
<td>•</td>
</tr>
</tbody>
</table>
Table 4
Energy Requirements of Selected Leisure Activities, METs

<table>
<thead>
<tr>
<th>Activity</th>
<th>METs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Climbing hills (no load)</td>
<td>6.9</td>
</tr>
<tr>
<td>Climbing hills (5 kg load)</td>
<td>7.4</td>
</tr>
<tr>
<td>Dancing (ballroom)</td>
<td>2.9</td>
</tr>
<tr>
<td>Jogging (10 min mile)</td>
<td>10.2</td>
</tr>
<tr>
<td>Golf (with cart)</td>
<td>2.5</td>
</tr>
<tr>
<td>Cycling (leisurely)</td>
<td>3.5</td>
</tr>
<tr>
<td>Horseback riding (walking)</td>
<td>2.3</td>
</tr>
<tr>
<td>Cycling (moderately)</td>
<td>5.7</td>
</tr>
<tr>
<td>Walking (2 mph)</td>
<td>2.5</td>
</tr>
<tr>
<td>Skiing (water or downhill)</td>
<td>6.8</td>
</tr>
<tr>
<td>Walking (3 mph)</td>
<td>3.3</td>
</tr>
<tr>
<td>Swimming (slow)</td>
<td>4.5</td>
</tr>
<tr>
<td>Walking (4 mph)</td>
<td>4.5</td>
</tr>
<tr>
<td>Swimming 7.0</td>
<td></td>
</tr>
<tr>
<td>Tennis (doubles)</td>
<td>5.0</td>
</tr>
<tr>
<td>Squash 12.1</td>
<td></td>
</tr>
</tbody>
</table>

Relative intensity: relative percentage of maximal aerobic power that is maintained during exercise. It is expressed as a percentage of maximal heart rate (maximum heart rate equals 220 minus age) or a percentage of VO$_2$max.

Table 5 shows a classification of activities and their corresponding percentages of both VO$_2$max and maximum heart rate, as well as METs. As it can be seen, METs attributed to the different classes of activities (light, moderate, etc) are lower in older than in young persons. Therefore, in relative terms, the intensity depends on the age of the person. Brisk walking could be considered as a vigorous exercise for an 80 year-old person, but a light activity for a 20-year-old individual (52).

Table 5
Classification of Physical Activity Intensity

<table>
<thead>
<tr>
<th>Intensity</th>
<th>VO$_2$ max %</th>
<th>Max Heart Rate %</th>
<th>Young (20-39)</th>
<th>Middle-Aged (40-64)</th>
<th>Old (65-80)</th>
<th>Very-Old (80+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very light</td>
<td>&lt; 20</td>
<td>&lt; 35</td>
<td>&lt; 2.4</td>
<td>&lt; 2.0</td>
<td>&lt; 1.6</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>Light</td>
<td>20-39</td>
<td>35-54</td>
<td>2.4-4.7</td>
<td>2.0-3.9</td>
<td>1.6-3.1</td>
<td>1.1-1.9</td>
</tr>
<tr>
<td>Moderate</td>
<td>40-59</td>
<td>55-69</td>
<td>4.8-7.1</td>
<td>4.0-5.9</td>
<td>3.2-4.7</td>
<td>2.0-2.9</td>
</tr>
<tr>
<td>Hard</td>
<td>60-84</td>
<td>70-89</td>
<td>7.2-10.1</td>
<td>6.0-8.4</td>
<td>4.8-6.7</td>
<td>3.0-4.25</td>
</tr>
<tr>
<td>Very hard</td>
<td>&gt; 85</td>
<td>&gt; 90</td>
<td>&gt; 10.2</td>
<td>&gt; 8.5</td>
<td>&gt; 6.8</td>
<td>&gt; 4.25</td>
</tr>
<tr>
<td>Maximum</td>
<td>100</td>
<td>100</td>
<td>12.0</td>
<td>10.0</td>
<td>8.0</td>
<td>5.0</td>
</tr>
</tbody>
</table>

3.3 Prescription of Exercise
Promotion of physical activity to sedentary adults recruited in primary care significantly increases physical activity levels at 12 months, as measured by self report (53). Exercise does not need to be of high intensity to achieve the benefits associated with it. The total amount of activity is more important than the performance of high-intensity exercise. On the other hand, vigorous exercise performed by untrained individuals predisposes them to orthopaedic injuries and higher dropout rates (54).
In current living conditions, individuals have few opportunities to do exercise in their jobs. Therefore, they should turn to physical activities during their leisure time, with a minimum goal of 700 to 1000 kcal/week. A consensus has been reached that a minimum of 30 minutes of moderate intensity physical activity, such as a brisk walking, is required on most, and preferably all, days of the week to obtain the clinical benefits described before. This is equivalent to ≈2.4 km (1.5 miles) per day of brisk walking at an energy cost of 150 kcal per day for an average-sized person (8).

In the Diabetes Prevention Program (see below) the goal for physical exercise was selected to approximate to expenditure of at least 700 kcal/week from physical activities. This goal was described as at least 150 minutes each week of moderate physical activities similar in intensity to brisk walking. Other activities that are usually equivalent are aerobic dance, bicycle riding, and swimming (55). Alternatively, it has been reported that the intensity of activity needed to improve physical conditioning may be as low as 40% of VO_{2}max for 20 minutes 3 times per week. However, there is still debate about a possible activity threshold for benefit and the general recommendation is to exercise daily.

A summary of the main components of the exercise prescription, according to the FITT principle, is provided in Table 6 (56). The effect of intensity and duration of physical activity over weight loss as described in clinical guidelines is summarized in Table 7 (57). Individuals should follow some general guidelines when programming physical activity (Table 8).

### Table 6
The FITT Principle

<table>
<thead>
<tr>
<th>Component</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency</td>
<td>3-5 days/week. More frequent exercise is desirable, but make sure that a regular exercise habit is acquired</td>
</tr>
<tr>
<td>Intensity</td>
<td>Start at a low to moderate intensity and gradually progress over the course of several weeks or months. Emphasis should be on increasing duration rather than intensity</td>
</tr>
<tr>
<td>Time</td>
<td>30 to 60 minutes, using a gradual progression. Multiple short bouts produce similar benefits as a single long bout of the same total duration</td>
</tr>
<tr>
<td>Type</td>
<td>Low-impact activities (e.g., walking, cycling, low-impact aerobics, water exercise) that are convenient, accessible, and perceived as enjoyable by the participant</td>
</tr>
</tbody>
</table>
### Table 7
Guidelines for Physical Intervention for Weight Loss

<table>
<thead>
<tr>
<th>Goal</th>
<th>Activity Intensity</th>
<th>Minutes/week</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prevent gain &amp; modest weight loss</td>
<td>Moderate</td>
<td>150-250</td>
</tr>
<tr>
<td>Clinically significant weight loss</td>
<td>Moderate</td>
<td>&gt; 250</td>
</tr>
<tr>
<td>Significant weight loss</td>
<td>Moderate</td>
<td>225-420</td>
</tr>
</tbody>
</table>

### Table 8
General Guidelines for Individual Exercise Programming

<table>
<thead>
<tr>
<th>• Exercise only when feeling physically well</th>
<th>• Understand personal limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Do not exercise vigorously soon after eating</td>
<td>• Select appropriate exercises</td>
</tr>
<tr>
<td>• Drink fluids</td>
<td>• Slow down for hills</td>
</tr>
<tr>
<td>• Adjust exercise to the weather</td>
<td>• Be alert for symptoms</td>
</tr>
<tr>
<td>• Wear proper clothing and shoes</td>
<td>• Watch for signs of over-exercising</td>
</tr>
<tr>
<td></td>
<td>• Start slowly and progress gradually. Allow time to adapt</td>
</tr>
</tbody>
</table>

A more active lifestyle may also be developed through changing daily activities (e.g., walking instead of riding, using stairs instead of escalators/elevators, using public transportation instead of a private car in cities). These routines reliably help to increase overall physical activity, without them being considered as an added time investment or occupation. Good exercise adherence and long-term weight loss has also been observed in users of home exercise equipment such as a treadmill. Along with hobbies and sports, more formal exercise training may be useful to reduce the risk of injury or cardiovascular events associated with sudden onset of activity, increase functional capacity and muscular strength, improve the ability to sustain activities of daily living, and promote personal independence and positive self image. These activities consist of periods of warm-up and cool down, endurance exercise, flexibility exercise, and resistance training (52). A meta-analysis has proved that structured exercise training that consists of aerobic exercise, resistance training, or both combined, is associated with HbA1c reduction in patients with type 2 diabetes. The benefits were observed with structured exercise training of more than 150 minutes per week, with greater HbA1c reductions than with 150 minutes or less per week. In contrast, physical activity advice alone was associated with a lower HbA1c, but only when combined with dietary advice (58, 59).

### 3.4 Risks of Exercise
The main risks of exercise are musculoskeletal injuries, sudden cardiac death and myocardial infarction (60). These complications are more frequent in subjects who are not generally physically active, perform unaccustomed vigorous physical activities, or have previous cardiovascular disease. Musculoskeletal lesions are common in inactive people and individuals who suffer them may stop exercising. In general, a gradual increase of exercise over time is advised to reduce injury risk. Sedentary subjects should avoid vigorous physical activity (39 The American Heart
Association has established a classification of risk associated with exercise, according to the individual’s cardiovascular status (Table 9), as well as providing recommendations for the type of exercise and the medical supervision that is prudent for patients with cardiovascular disease (52).

**Table 9**

<table>
<thead>
<tr>
<th>Class</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Apparently Healthy Individuals</td>
</tr>
<tr>
<td>B</td>
<td>Presence of Known, Stable Cardiovascular Disease With Low Risk for Complications With Vigorous Exercise, but Slightly Greater Than for Apparently Healthy Individuals</td>
</tr>
<tr>
<td>C</td>
<td>Those at Moderate-to-High Risk for Cardiac Complications During Exercise and/or Unable to Self-Regulate Activity or to Understand Recommended Activity Level</td>
</tr>
<tr>
<td>D</td>
<td>Unstable Disease With Activity Restriction</td>
</tr>
</tbody>
</table>

A systematic review for the U.S. Preventive Services Task Force came to the conclusion that stress tests should usually not be recommended to detect ischaemia in asymptomatic individuals at low CAD risk (<10% risk of a cardiac event over 10 years) because the risks of subsequent invasive testing triggered by false-positive tests outweighed the expected benefits from detection of previously unsuspected ischemia (61, 62).

4. **Lifestyle-Counselling**

Health professionals need to convince patients that effective lifestyle interventions will help prevent the development of the MS. Manson and colleagues have suggested that the stages of behaviour for intended weight loss and increased physical activity are:

1. pre-contemplation, in which desired behaviours are not occurring and the patient does not intend to initiate them;
2. contemplation, in which desired behaviours are not occurring but the patient intends to initiate them;
3. preparation, in which the patient is exploring options;
4. action, in which the patient has begun lifestyle modification and engaged in it for < 6 months;
5. maintenance, in which the patient has engaged in lifestyle modification for > 6 months (63).

Several external barriers to lifestyle modification for patients have been identified in the ATP III report (64):

- Increased consumption of foods prepared away from home
- Lack of time both to eat correctly and to exercise
- Lack of third-party reimbursement for nutritional counselling
- Lack of adequate strategies for referral to registered dietitians and exercise trainers
- Perception that drug therapy is easier and, in all cases, more effective.
These and other obstacles have to be overcome by patients and health providers. Foreyt has proposed the concept of a "toolbox" of strategies that can be used to aid patients to introduce lifestyle changes (65). These strategies include:

**Setting goals:** The average weight loss is 8% to 10% of baseline weight. Patients and health professionals should avoid unrealistic goals, such as trying to achieve a 20% reduction from their current weight in two months. Easy short-term goals can effectively motivate patients to comply with recommendations. They can be formulated as contracts that patients commit themselves to carry out. Goals should be re-evaluated regularly, adapting them depending on the patient’s achievements.

**Raising awareness:** If patients are to change their lifestyle, they have to recognize what they are eating and how much they are exercising. Food and exercise diaries are essential to collect this information, along with daily or weekly body weight recording. Patients should be instructed how to keep these diaries. It may also be useful to teach them how to transform food and physical activity into calories consumed and spent. Health professionals should encourage patients to keep these diaries, convincing them that they are an important means to long-term success. Under-reporters of energy intake have a higher prevalence of MS than those who do not under-report (66).

**Confronting barriers:** Health professionals should help patients to devise strategies to solve the problems that they will confront, such as coping with psychological stress, eating away from home, travelling and vacation, changing schedules, attending celebrations, etc.

**Changing eating behaviours and routines:** Patients should have a plan with a fixed number of meals. They should strive to acquire new habits, such as eating slowly, using small dishes and portions, avoiding watching TV as they eat, not repeating a dish without feeling hungry, adopting new forms of cooking that are healthier, reading food labels, understanding portion size and energy intake during meals and snacks, etc.

**Organizing support:** family members, friends, and colleagues can be very helpful in encouraging patients to persevere with their efforts to modify their lifestyles. They should avoid suggestions to make transgressions - just this once - shopping wisely for food and beverages, arranging for attractive and healthy leisure activities, etc.

There is a dissociation between food availability and the basic nutritional information already offered to citizens in developed countries, and the food and physical activity choices these citizens make. Attempts to increase public awareness of the best ways to eat more healthily have not substantially changed patterns of food purchase and consumption. More attention must be given to finding ways to increase people’s motivation, abilities and opportunities to make healthy choices (67). To do this effectively, research is needed to discover why consumers make certain choices; what they understand about food; what type of information is lacking; how this information can best be presented; what factors prevent individuals and populations from exercising a healthy lifestyle; and what changes in the food and nutrition environment can ‘nudge’ us towards more healthy choices. Research has shown that knowledge is often not a direct determinant of eating behaviour. Although some nutrition knowledge appears necessary, effective health behaviour changes need a more comprehensive set of measures.

Different approaches can be used for the delivery of lifestyle counselling. The more demanding a lifestyle change programme regarding health care provider time, the more expensive and the more difficult to implement. For this reason, different initiatives have been studied to decrease these requirements. Examples of technical methods include pedometers, self-tracking Web sites, Web-based education, e-mail feedback, telephone counselling and text messaging. Overall, methods that involve human contact are more effective than those based in a technology-based approach.
for achieving successful lifestyle change. Participation at group counselling sessions and a team-approach were strongly correlated with the amount of weight loss, irrespective of the diet recommended (33). Even among methods based in technology, those with more human involvement, as human e-mail counselling versus automated e-mail counselling, or telephone intervention versus e-mail communication, resulted in significantly more weight loss after the intervention with personal contact.

In an attempt to formulate some features of the best approach to lifestyle change programmes, it can be proposed that they should be carried out by a multidisciplinary team trained in motivational feedback, adjusted to individual patient characteristics and preferences, utilizing group support, with Internet monitoring or pedometer usage that does not replace the human contact, and regular personal feedback (59).

5. Benefits of Weight Loss

Intentional weight loss, even a modest deficit of \( \approx 5 \% \) of initial weight, can improve or prevent many of the obesity-related risk factors: insulin resistance, MS and type 2 diabetes mellitus, dyslipidaemia, hypertension, pulmonary disease and inflammation. There has been less information coming from randomized clinical trials that have studied whether intentional weight loss affects CVD mortality (86). As weight loss modifies many cardiovascular disease risk factors, it could however reasonably be assumed that weight reduction would decrease cardiovascular events or mortality.

A few years ago, we learnt the results of the LOOK AHEAD (Action for Health in Diabetes) trial. It was a multicentre study performed on 5145 overweight or obese men and women with type 2 diabetes. The main goal was to test the hypothesis that lifestyle intervention may reduce the incidence of major CVD events in these patients. Of course, this study was not intended to observe the effect of lifestyle intervention on patients at risk of developing DM, because they already had this disorder.

The Intensive Lifestyle Intervention group was compared to the Diabetes Support and Education control group. Subjects randomized to the active arm had approximately weekly group or individual treatment in year 1; continued but less frequent contact was provided in years 2 to 4. The standard diabetes support participants received three group educational sessions in all years. The study was planned to run for 13.5 years, but it was interrupted after a median follow-up of 9.6 years, because the number of CV events did not differ between the groups (68, 69, 70, 71, 72).

Several reasons have been proposed to explain the negative findings. CVD event rates were much lower than expected, and therefore reduced the power of the study to demonstrate differences between the groups. This low rate of CVD events may be explained because the patients with type 2 diabetes participating in the trial were at relatively low CVD risk (73). They were highly motivated, with good glycaemic control at the beginning of the trial, and there was a higher use of statins in the control group accompanied by more successful lowering of LDL Cholesterol levels in these patients. The dietary intervention aimed at weight loss has also been criticized because it reduced fat intake and used meal replacements, but it did not go further to specific modifications regarding types of fat, carbohydrates and food groups.

Many other risk factors were positively influenced, such as weight loss, diabetes remission, blood pressure control, with reduction of diabetes and antihypertensive drugs, improvement of hepatic steatosis, obstructive sleep apnoea, depression, urinary incontinence in women and erectile dysfunction in men, with lower concentrations of high sensitivity C Reactive Protein, Plasminogen activator inhibitor-a (PAI-1) and HDL Cholesterol, and eventually better quality of life. These changes constitute substantial health benefits of lifestyle modifications worth pursuing (74).
6. Evidence of Lifestyle Intervention Efficacy

Several randomized controlled trials have demonstrated the efficacy of lifestyle modification or glucose-lowering drugs in preventing diabetes (Tables 10 and 11). Dietary modification, weight loss and increased physical activity are effective in reducing the progression from IGT to type 2 diabetes and in reducing several CVD risk factors over a defined period of observation (3–6 years) in the intervention arm versus a comparison group. However, the effectiveness of lifestyle modification programmes to reduce CVD events has not been proved specifically. A common observation in all these trials was that substantial efforts were necessary to achieve only modest changes in weight and exercise, but those changes were sufficient to attain an important reduction in the incidence of diabetes (75).

Table 10
Diabetes Prevention Trials: lifestyle interventions

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (y)</th>
<th>Population/BMI</th>
<th>Duration</th>
<th>Intervention</th>
<th>RRR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Da Qing</td>
<td>44</td>
<td>IGT/&gt; 25</td>
<td>6 y</td>
<td>G-Diet ± Exercise</td>
<td>31–46</td>
</tr>
<tr>
<td>FDPS</td>
<td>55</td>
<td>31</td>
<td>3,2 y</td>
<td>I-Diet + Exercise</td>
<td>58</td>
</tr>
<tr>
<td>DPP</td>
<td>51</td>
<td>IGT/34</td>
<td>3 y</td>
<td>I-Diet + Exercise</td>
<td>58</td>
</tr>
<tr>
<td>Toranomonon Study</td>
<td>55</td>
<td>IGT/24</td>
<td>4 y</td>
<td>I-Diet + Exercise</td>
<td>67</td>
</tr>
<tr>
<td>Indian DPP</td>
<td>46</td>
<td>IGT</td>
<td>2,5 y</td>
<td>I-Diet + Exercise</td>
<td>29</td>
</tr>
<tr>
<td>Look AHEAD</td>
<td>59</td>
<td>DM 2/36</td>
<td>4 y</td>
<td>Diet + Exercise</td>
<td></td>
</tr>
</tbody>
</table>

Table 11
Diabetes Prevention Trials: pharmacologic interventions

<table>
<thead>
<tr>
<th>Study</th>
<th>Age (y)</th>
<th>BMI</th>
<th>Duration</th>
<th>Intervention</th>
<th>RRR %</th>
</tr>
</thead>
<tbody>
<tr>
<td>XENDOS</td>
<td>43</td>
<td>37</td>
<td>4 y</td>
<td>Orlistat</td>
<td>37</td>
</tr>
<tr>
<td>STOP-NIDDM</td>
<td>54</td>
<td>IGT</td>
<td>3,2 y</td>
<td>Acarbose</td>
<td>25</td>
</tr>
<tr>
<td>DPP</td>
<td>51</td>
<td>IGT/34</td>
<td>3 y</td>
<td>Metformine</td>
<td>31</td>
</tr>
<tr>
<td>Indian DPP</td>
<td>46</td>
<td>IGT</td>
<td>2,5 y</td>
<td>I-Diet + Exercise</td>
<td>29</td>
</tr>
<tr>
<td>DREAM</td>
<td>55</td>
<td>IGT/IGF</td>
<td>3 y</td>
<td>Rosiglitazone 8 mg</td>
<td>60</td>
</tr>
<tr>
<td>Voglibose</td>
<td>56</td>
<td>3 y</td>
<td>3 y</td>
<td>Voglibose 0,2 mg</td>
<td>40</td>
</tr>
</tbody>
</table>

The first large, randomized trial to show the impact of diet and exercise on the development of diabetes in high-risk individuals was the Da Qing Study. 577 men...
and women from 33 health care clinics in the city of Da Qing, China, were screened with oral glucose tolerance test (OGTT), and those with impaired glucose tolerance (IGT) were randomized by clinic to a control group or to one of three active treatment groups: diet only, exercise only, or diet plus exercise. For the intervention group, a diet of 25 to 30 kcal/kg (55-65 % carbohydrates, 25-30 % fat and 10-15 % protein) was designed. Participants were encouraged to increase their daily intake of vegetables, and to reduce the consumption of simple sugars. They were asked to increase the activities of daily living, and by participating in moderate intensity exercise equivalent to brisk walking for at least 30 minutes daily.

Subjects were seen by local physicians every 2 weeks during the first 3 months, every 3 months thereafter and then re-examined biannually by the research staff. After an average of 6 years' follow-up, the diet, exercise, and diet plus exercise interventions were associated with 31, 46, and 42% relative reductions in risk of developing type 2 diabetes, respectively (76). Important traits of this clinical trial were firstly that no added effect of diet plus exercise over either diet or exercise alone was found, and secondly that this lifestyle modification intervention could be carried out in an outpatient clinic setting. The group also demonstrated that this intervention has a long-term effect on the risk of diabetes: group-based lifestyle interventions over 6 years can prevent or delay diabetes for up to 23 years after the active intervention. There was also significant difference between the intervention and control groups in the rate of first CVD events, CVD mortality, and all-cause mortality (77).

In the Finnish Diabetes Prevention Study, 522 middle-aged obese subjects with IGT were randomized to receive either brief diet and exercise counselling (control group) or intensive individualized instruction on weight reduction (target: at least 5 % of body weight), food intake (fat and saturated fat < 30 % and < 10 % total calories, respectively, fibre > 15 g/1000 kcal), and guidance on increasing physical activity. Moderate exercise, such as brisk walking, for 30 min/day was suggested. Supervised resistance-training sessions were also offered. Dietary advice was tailored by trained dietitians for each subject based on 3-day food diaries that were completed quarterly. An oral glucose-tolerance test was performed annually; the diagnosis of diabetes was confirmed by a second test. The mean duration of follow-up was 3.2 years. Weight loss averaged 4.2 kg at 1 year, and 3.5 kg after 2 years in the intervention group, versus 0.8 kg in the control group. There was a direct relationship between adherence to the lifestyle intervention and the reduced incidence of diabetes. After an average follow-up of 3.2 years, there was a 58% relative reduction in the incidence of diabetes in the intervention group compared to the control subjects (78). The beneficial effects of the lifestyle intervention were maintained after discontinuation of the study, with an overall 43 % risk reduction after a median of 3 years of follow-up (79). After follow-up of 13 years he corresponding HR for diabetes during the post-intervention was 0.672 (95% CI 0.477, 0.947; p = 0.023) (80). The Finnish protocol was also applied to a cohort of Spanish patients attending primary care clinics. In this high-risk Mediterranean population a group-based or an individual intervention (intensive reinforced DE-PLAN [Diabetes in Europe-Prevention using Lifestyle, Physical Activity and Nutritional] intervention) led to a 36.5% relative risk reduction of the incidence of diabetes in 4.2 year median follow-up (81).

The largest and best described diabetes prevention trial has been the Diabetes Prevention Program (DPP). In this 3-year study, carried out in the US, 3234 subjects were randomized to one of three intervention groups, which included an intensive nutrition and exercise counselling ("lifestyle") group or either of two masked medication treatment groups: the metformin group, 850 mg twice a day, or the placebo group. The latter interventions were combined with standard diet.
and exercise recommendations. There was a fourth arm that used troglitazone, 400 mg/d, but it was stopped when liver toxicity was observed with this drug. A low-fat (<25% fat) intake was recommended; if reducing fat did not achieve the weight loss goal, calorie restriction was also recommended. Participants weighing 54-78 kg at baseline were instructed to follow a 1,200-kcal/day diet (33 g fat), those 79-99 kg a 1,500-kcal/day diet (42 g fat), those 100-113 kg an 1,800-kcal/day diet (50 g fat), and those > 114 kg were instructed to follow a 2,000-kcal/day diet (55 g fat).

Participants in the lifestyle modification group received an individualized 16-lesson curriculum that covered diet, exercise and behaviour modification, during the first 24 weeks. Subsequently, individual sessions occurred monthly and group sessions were used to reinforce behavioural changes.

On average, 50% of the lifestyle group achieved the goal of ≥7% weight reduction and 74% maintained at least 150 minutes of moderately intense activity each week. The lifestyle group lost ~5.5 kg at 2 years and 4.1 kg at 3 years (mean weight loss for the study duration was ~5.5 kg or 6% of initial body weight).

After an average follow-up of 2.8 years, a 58% relative reduction in the progression to diabetes was observed in the lifestyle group and a 31% relative reduction in the metformin group compared with control subjects. The benefit of lifestyle change over metformin was more apparent in older individuals and those who had lower BMI. Additional data show that part of the effect of metformin actually was treating some cases of already established diabetes more than preventing it (82). Weight loss was a better predictor for reduced risk of progression to diabetes than lowering the percentage of dietary calories from fat and increased physical activity. After controlling for these 2 factors, diabetes risk was reduced by 16% for every kilogram of weight lost (83). Other variables associated with reduction of diabetes risk were decrease of intra-abdominal fat and older age (> 60 years of age) (84, 85). Along with the reduction of diabetes risk, there was an improvement in the control of blood pressure and lipid concentrations, which were accompanied by a reduced need for antihypertensive and lipid-lowering medications among subjects assigned to the intensive lifestyle arm.

What was the benefit of the DPP in the prevention of MS? In those subjects who did not meet the ATP-III criteria for metabolic syndrome at baseline, treatment with metformin resulted in a 17 % risk reduction, whereas the lifestyle intervention produced a 41 % risk reduction, which was significantly greater than in either the placebo or metformin groups. Besides, the lifestyle intervention program resulted in reversal of the metabolic syndrome in 38% of those subjects who had it at randomization (86).

The investigators of the DPP studied the persistence of the positive effects found in the long term. On the basis of the benefits from the intensive lifestyle intervention in the DPP, all three groups were offered group-implemented lifestyle intervention. Metformin treatment was continued in the original metformin group (850 mg twice daily as tolerated), with participants unmasked to assignment, and the original lifestyle intervention group was offered additional lifestyle support. During the 10-year follow-up since randomisation to DPP, the original lifestyle group lost, then partly regained weight. The modest weight loss with metformin was maintained. Diabetes incidence in the 10 years since DPP randomisation was reduced by 34% in the lifestyle group and 18% in the metformin group compared with placebo. Thus, prevention or delay of diabetes with lifestyle intervention or metformin can persist for at least 10 years (87, 88, 89).

Alongside these trials of primary prevention of diabetes carried out in multiethnic American, Finnish and Chinese populations, Indian investigators tested the same hypothesis in a prospective community-based study in native Asian Indians with IGT who were younger, leaner and more insulin resistant than the above
They randomized 531 subjects into four groups, control lifestyle intervention, metformin and both. The relative risk reduction of diabetes was 28.5%, 26.4% and 28.2%, respectively, for each active group as compared with the control group. Therefore, lifestyle intervention was slightly better than metformin and the combination of both approaches was not better than the single approach (90).

A different international experience was analyzed in Japan. Male subjects with IGT recruited from health-screening examinees were randomly assigned in a 4:1 ratio to a standard intervention group (control group) and intensive intervention group (intervention group). The final numbers of subjects were 356 and 102, respectively. The lifestyle intervention was less intense than in other trials: detailed instructions on lifestyle were repeated every 3-4 months during hospital visits, in the intervention group. The cumulative 4-year incidence of diabetes was 9.3% in the control group, versus 3.0% in the intervention group, and the reduction in risk of diabetes was 67.4%. Body weight decreased by 0.39 kg in the control group and by 2.18 kg in the intervention group (91).

Controlled trials of glucose-lowering drugs have shown that they may also be beneficial in preventing diabetes. In the STOP-IDDM trial, participants with IGT were randomized in a double-blind fashion to receive either the α-glucosidase inhibitor acarbose or a placebo. Lifestyle intervention had little intensity. Mean bodyweight decreased from 87.6 kg to 87.1 kg during the study in patients given acarbose and increased from 87.0 kg to 87.3 kg in those on placebo. Participants were instructed on a weight-reduction or weight-maintenance diet, and encouraged to exercise regularly. All participants met with a dietician before randomisation and yearly thereafter. Participants also completed a 3-day nutritional diary filled in at the time of eating, and recorded their physical activities over 3 days (2 weekdays, 1 weekend day) in the last month before each yearly visit. After a mean follow-up of 3.3 years, a 25% relative risk reduction in progression to diabetes, based on one OGTT, was observed in the acarbose-treated group compared with the placebo group. If this diagnosis was confirmed by a second OGTT, a 36% relative risk reduction was observed in the acarbose group compared with the placebo group. Acarbose therapy was associated with a relative reduced risk of 49% for the development of cardiovascular events (2.5% absolute risk reduction). However, 25% of individuals discontinued their participation early as a result of gastrointestinal adverse events (92). Voglibose, another α-glucosidase inhibitor, in addition to lifestyle modification, has been shown to reduce the development of type 2 diabetes in high-risk Japanese individuals with impaired glucose tolerance (93).

In the XENDOS study (XENical in the prevention of Diabetes in Obese Subjects), orlistat was examined for its ability to delay type 2 diabetes when added to lifestyle change in a group with BMI ≥30 kg/m² with or without IGT. 3,305 study participants were randomized to treatment with orlistat plus lifestyle changes (n = 1,650) or placebo plus lifestyle changes (n = 1,655). All patients were prescribed a reduced-calorie diet (~800 kcal/day deficit) containing 30% of calories from fat and not more than 300 mg of cholesterol per day. The prescribed energy intake was readjusted every 6 months to account for any weight lost during the preceding months. Participants received dietary counselling every 2 weeks for the first 6 months and monthly thereafter. Patients were also encouraged to walk at least 1 extra kilometre a day in addition to their usual physical activity. All patients kept physical activity diaries. Mean weight loss was significantly greater with orlistat than placebo at 1 year (10.6 vs. 6.2 kg) and remained significantly greater at the end of the 4-year study (5.8 vs. 3.0 kg). For those patients who completed 4 years of treatment (52% of the orlistat patients and 34% of the placebo patients initially randomized), weight loss
was significantly greater with orlistat than placebo at year 1 (11.4 vs. 7.5 kg) and year 4 (6.9 vs. 4.1 kg). During 4 years of treatment, orlistat plus lifestyle changes significantly decreased the progression to type 2 diabetes compared with placebo plus lifestyle changes. Cumulative incidence rates after 4 years were 6.2 vs. 9.0%. The hazard ratio corresponds to a 37.3% decrease in the risk of developing diabetes with orlistat compared with placebo. The effect of orlistat addition corresponded to a 45% risk reduction in the IGT group, with no effect observed in those without IGT (94).

The pharmacologic reduction of insulin resistance may also prevent the development of type 2 DM. There has been a large randomized trial with rosiglitazone, 8 mg/day for 3 years. 5269 adults aged 30 years or more with either IFG or IGT, or both, and no previous cardiovascular disease were recruited from 191 sites in 21 countries. A decrease of 60 % of the relative risk reduction was observed with rosiglitazone. However, the cardiovascular adverse events of this drug have forced its withdrawal from the market in Europe and restricted its use in other countries, which eliminate it as a potential drug for the prevention of DM (95). Pioglitazone can also reduce the risk of type 2 DM (96).

Glucagon-like peptide-1 (GLP-1) exerts glucoregulatory and insulinotropic actions. GLP-1 agonists are used in the treatment of Diabetes Mellitus. In addition these drugs have cardioprotective actions. They may improve risk factors such as body weight, blood pressure, heart rate and lipid profiles, as well as their potential consequences on cardiovascular events, such as arrhythmias, heart failure, myocardial infarction and death. However, in contrast to their proven anti-hyperglycaemic efficacy, there is less evidence for their role in the treatment of metabolic syndrome, although it can be hypothesized that they could be also useful in this disorder. Recently, in a 56-week, double-blind trial involving 3731 patients who did not have type 2 diabetes and who had a body-mass index of at least 30 or a BMI of at least 27 plus treated or untreated dyslipidaemia or hypertension, 3.0 mg of liraglutide, as an adjunct to diet and exercise, was associated with reduced body weight and improved metabolic control (97). This can be an effective therapy for obesity and metabolic syndrome, but the higher cost of these agents has to be taken into consideration by clinicians.

Overeating and insufficient physical activity can lead to changes in gene expression and epigenetic alterations. A few of the clinical trials on lifestyle intervention have also studied the influence of genetic variants on the efficacy of the measures taken to prevent the development of DM (98). Significant gene-lifestyle interactions in predicting progression from prediabetes to type 2 diabetes have been identified for the tumour necrosis factor alfa gene (TNF-α) (99), the transcription factor 7-like 2 (TCF7L2) gene (100), the ectoenzyme nucleotide pyrophosphatase phosphodiesterase 1 (ENPP1) gene (101), peroxisome proliferator-activated receptor-gamma (PPAR-γ) gene (102), fat mass and an obesity-associated gene (FTO) (103) and Mitochondrial Translational Initiation Factor 3 (MTIF3) (104). These studies explore the different risks of progression from prediabetes to diabetes or insulin secretion in carriers of different alleles of these genes. Interestingly, the effect of lifestyle intervention varies across the carriers of these alleles. The main findings are summarized in Table 12. The mechanisms translating these polymorphisms into clinical differences are associated with different responses to lifestyle interventions of body fat, modulation of proglucagon gene expression, incretin processing and insulin secretion. However, the investigators of the Look AHEAD trial found that the genetic burden associated with T2D risk does not undermine the effect of lifestyle intervention. There may be additional genomic regions, distinct from the T2D-susceptibility loci, which may enhance or mitigate weight loss (105). This has been the objective of a recent Conference organized by the USA National Institute of Health (106).
Table 12
Gene/lifestyle interactions in diabetes prevention studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Gene</th>
<th>Association</th>
<th>Risk reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>DPP</td>
<td>TCF7L2</td>
<td>type 2 diabetes</td>
<td>66 %</td>
</tr>
<tr>
<td>DPP</td>
<td>ENPP1</td>
<td>type 2 diabetes</td>
<td>55%</td>
</tr>
<tr>
<td>DPP</td>
<td>PPARG (Pro12A1a genotype)</td>
<td>obesity</td>
<td>20 %</td>
</tr>
<tr>
<td>FDPS</td>
<td>TNF-α (-308A allele vs. G308G genotype)</td>
<td>type 2 diabetes</td>
<td>–</td>
</tr>
</tbody>
</table>

7. Bariatric Surgery and Metabolic Syndrome

Bariatric surgery has been shown to resolve or improve CVD risk factors to varying degrees. Most studies have reported significant postoperative decreases in the prevalence of CV risk factors, including hypertension, diabetes, dyslipidaemia, elevated C-reactive protein, and disturbed endothelial function. A 40% relative risk reduction for 10-year coronary heart disease risk was observed, as determined by the Framingham risk score (107). There are new data on clinical outcomes (e.g. myocardial infarction, stroke, death) showing an improvement with bariatric surgery (108). Until recently a significant proportion of the included data came from studies of gastric bypass or biliopancreatic diversion, so the impact of sleeve gastrectomy and gastric banding could not be extrapolated from these studies. It is accepted that there are procedure-specific variations in efficacy and risks. Gastric banding reduced weight to a lower extent than gastric bypass and sleeve gastrectomy and resulted in shorter operating times, fewer serious complications, lower weight loss efficacy, and more frequent reoperations compared to gastric bypass. Sleeve gastrectomy and gastric bypass reduced weight to a similar extent (109).

In relation to MS, there have been studies showing decreased frequency of this syndrome in the follow-up of bariatric surgery, with larger reductions with more restrictive surgery and with greater weight loss. In a surgical series, after seven years of follow-up, metabolic syndrome was present in 6% of patients in the biliopancreatic diversion group, in 30% in the gastric by-pass group, and 41% in the vertical gastroplasty group (110). A similar experience has been reported by the investigators of the Swedish Obesity Study. They found both an improvement of risk factors in the surgical group compared to the medically treated or non-surgical group, along with a clear rebound of some of the risk factors from 2 to 10 years of follow-up after bariatric surgery (111). For those individuals with MS and severe obesity, surgery may be a very efficacious therapeutic option if patients also adhere to significant changes in lifestyle that are maintained over many years. Therefore, lifestyle intervention is mandatory both in the medical and surgical management of patients with MS. Any surgical programme that omits it is heading for a partial or total failure in the long term (112).
8. Summary

We can conclude that lifestyle and pharmacological interventions reduce the rate of progression to Type 2 Diabetes in people with impaired glucose tolerance. Lifestyle interventions seem to be at least as effective as drug treatment (96).

The American Diabetes Association standards of care 2016 state that lifestyle modification should be the first choice to prevent or delay diabetes. Metformin therapy for prevention of type 2 diabetes may be considered in those at the highest risk for developing diabetes, such as those with multiple risk factors, especially if they demonstrate progression of hyperglycaemia (e.g., A1C ≥6%) despite lifestyle interventions (113). Health care providers and patients can discuss preferences between lifestyle changes and drugs.

There have been some reservations about the feasibility of applying the results of lifestyle intervention trials to real world clinical practice. The reasons cited are that: 1) patients who were recruited to these clinical trials may not be representative of the general prediabetic population; 2) adherence to lifestyle changes would be lower in routine practice with patients less committed and with less access to nutritional counselling and exercise programmes; 3) educational efforts to help patients accomplish the predefined goals were significantly higher than the standard of care. Furthermore, the effectiveness of lifestyle modification programmes to reduce CVD events has not yet been adequately determined. And, finally, despite the encouraging long-term outcomes described in the lifestyle trials, the success can be less spectacular in the clinical setting. When MS is associated with severe obesity, surgery may be a good option. In the long term, only those patients who really change their lifestyle will maintain the initial positive effects on weight, blood pressure and metabolism.

Therefore, lifestyle intervention is the first and basic approach to treat the MS, independently from the potential benefits of added drug treatment that may be proven in the future. Clinical practice should adapt to the results of lifestyle modification trials. Health authorities should review financial and human resources to allow the development of preventative programmes for sedentary overweight adults.
9. References


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