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Obesity and Diabetes
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Abstract
Type 2 diabetes mellitus is characterized by hyperglycemia, insulin resistance, and relative impairment in insulin secretion and its possible long term complications. Its pathogenesis is poorly understood, but both genetic and environmental factors, such as obesity and aging, play a key role. “Diabesity” is a new term which refers to diabetes occurring in the context of obesity. In this article, we will discuss the epidemiology and impact of diabetes and obesity and will also outline the components of the metabolic syndrome and the studies that demonstrate that screening and prevention are possible in an attempt to control this epidemic.

Key words: Metabolic syndrome. Type 2 diabetes. Insulin resistance. Obesity.

Abbreviations
MetS: Metabolic syndrome.
DM: diabetes mellitus.
IR: insulin resistance.
BMI: body mass index.
CVD: cardiovascular disease.
ESRD: end-stage renal disease.
IL: Interleuquin.
TNF: tumor necrosis factor.
HT: Arterial Hypertension.
NO: nitric oxide.
CRP: C reactive protein.
WHO: World Health Organization.

Introduction
Type 2 diabetes mellitus (DM) has become a highly prevalent disease all over the world and it has been recognized as a worldwide epidemic. The prevalence of both type 2 DM and obesity has increased worldwide during the last century, not only in developed countries, but also in developing countries, sometimes coexisting with undernutrition. Furthermore, the global prevalence of diabetes in 2010 was 280 million people worldwide (around 6.2% of the world’s total population), and it has been predicted that in 2030 the prevalence will reach more than 7.5% of the world’s total population, paralleling the aging and body mass index (BMI) of the population, thus confirming the relationship between obesity and diabetes. During the last 25 years, the prevalence of diabetes has doubled in the USA and multiplied by three to five times in Asian countries.1 Epidemiological data in Spain has shown a diabetes prevalence of between 5.5-18%, and a glucose intolerance prevalence of between 7.2-18%, depending on geographical location.

Obesity induces insulin resistance and involves a plethora of molecules that predispose individuals to an inflammatory state and metabolic complications. Insulin resistance is determined by genetic factors and also environmental factors as hyper-energetic and saturated and trans-fat high diet, obesity, aging and sedentarism.

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Diabesity is a new term referring to diabetes occurring in obese persons. A direct relationship between BMI and diabetes has been demonstrated. The pathogenesis has been demonstrated to be a resistance to insulin action in peripheral tissues. Insulin resistance can be defined as a state in which greater than normal amounts of insulin are required to produce a normal biological response. Insulin acts through coupling to a membrane cell receptor, a tetrameric protein with 2 identical alpha sub-units and other 2 identical beta sub-units. Alpha sub-units are extracellular and after insulin coupling translate the signal to both intracellular beta sub-units, which have tyrosine kinase activity, and are auto-phosphorylated, with a subsequent increase of their catalytic tyrosine kinase activity. Then, endogenous protein substrates are phosphorylated and activate a cascade of intracellular signals, which in last term induce migration of glucose transporters (Glut-4) from intracellular pools to the cellular surface, to facilitate glucose entry into the cell. So, insulin resistance is due to an impairment in one or more of these steps of this process in the target-tissue, which induces compensating hyperinsulinemia to maintain normoglycemia. But along the years, pancreas gets exhausted and plasmatic glucose levels start to increase. Once glucose has increased, hyperglycemia has a toxic effect over islet cells (glucotoxicity) and has been demonstrated to impair the kinase function of insulin receptor ("down-regulation").

An important consequence of insulin resistance is the increase of free fatty acids, which in turn, impairs even more the insulin resistance (lipotoxicity). Even more, insulin resistance on hepatic, muscular and adipose tissue is associated with overproduction of proinflammatory cytokines, as interleukin-6 (IL-6) and tumor necrosis factor (TNF), and a relative decrease of antinflamatory cytokines, as adiponectin. All these factors contribute to a chronic inflammatory status.

The health impact of type 2 DM is due to its long-term complications including cardiovascular diseases (CVD), stroke, peripheral vascular diseases, retinopathy, nephropathy, neuropathy. In Western countries, diabetes is the main cause of blindness and end-stage renal disease (ESRD), accounting for 40-50% of incident ESRD cases, and it doubles the possibility of CVD. It has been anticipated that due to increasing rates of childhood obesity in the USA, we may see the first generation which will be less healthy and have a shorter life expectancy than their parents, because of diabetic complications. Even more, diabetic patients had a significantly lower health-related quality of life in contrast to those without diabetes. The economic burden of diabetes is noteworthy, and it has a real impact on the world economy, as reflected by the consumption of about 14-15% of a country’s total health expenditure, because of diabetic complications, with management of macrovascular disease being the largest and earliest. Even more, the burden of diabetes on the world economy has been increasing during the last decades, reaching at least $376 billion in 2010. Therefore, improving glycemic control of diabetes, or even better, avoiding diabetes by staying thin and fit, will prevent complications, and will reduce these high costs.

**Metabolic Syndrome (MetS)**

The rising prevalence of abdominal overweight and obesity has also a direct correlation with increasing prevalence of hypertension, dyslipidaemia. In 1998, Dr. Reaven defined metabolic syndrome (MetS), also known as X syndrome, as a conglomerate of coronary risk factors. It is characterized by the clustering of abdominal obesity, impaired glucose tolerance, elevated triglyceride levels, reduced high-density lipoprotein (HDL) cholesterol levels, and hypertension, often accompanied by a proinflammatory status that predisposes to CVD. Persons with MetS are at increased risk of type 2 DM and CVD. The waist perimeter can be used as an indirect, but effective marker of intraabdominal fat content, as it has been demonstrated to significantly correlate with it, quantified by radiological techniques. Over the years, several classifications for the MetS have been proposed by experts. The major definitions used are the WHO, National Cholesterol Education Program Adult Treatment Panel (NCEP ATP III), National Heart, Lung and Blood Institute/American Heart Association and International Diabetes Federation (IDF). These definitions differ somewhat in terms of the prerequisite components and the cut-off levels used for each component. WHO, IDF and NCEP ATP III and criteria for Identification of the Metabolic Syndrome are shown in Tables I, II and III, respectively. These last criteria have been widely accepted by its easy clinical applicability.

**Other components of the MetS**

Arterial Hypertension (HT) is often associated with obesity and increases the risk of CVD, even with minor

<table>
<thead>
<tr>
<th>Table 1</th>
<th>WHO Criteria for Identification of the Metabolic Syndrome</th>
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<tbody>
<tr>
<td><strong>At least 1 of the following:</strong></td>
<td></td>
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<tr>
<td>- Type 2 Diabetes</td>
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<td>- Abnormal glucose tolerance</td>
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<tr>
<td>- Insulin Resistance</td>
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<td><strong>At least 2 of the following:</strong></td>
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<tr>
<td>- Hypertension ($\geq 140/90$ mm Hg)</td>
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<tr>
<td>- Obesity ($\text{BMI} \geq 30$)</td>
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<tr>
<td>- Dislipemia:</td>
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<tr>
<td>- $\text{TG} \geq 150$ mg/dl.</td>
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<tr>
<td>- $c-\text{HDL} &lt; 35$ mg/dl (men)</td>
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<tr>
<td>- $&lt; 40$ mg/dl (women)</td>
<td></td>
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<tr>
<td>- Microalbuminuria $\geq 20$ g/min</td>
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</table>

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14. Obesity

Hipertrigliceridemia:

Abdominal obesity:

\[ \geq \]

HT* (\( \leq 130/85 \) mm Hg)

And two more of teh following:

- Hypertrigliceridemia*: TG \( \geq 150 \) mg/dl
- Low HDL-cholesterol*:
  - \( < 40 \) mg/dl (men)
  - \( < 50 \) mg/dl (women)
- Fasting glucose*:
  - \( \geq 100 \) mg/dl
  * Or being under treatment.

Criteria for Identification of the Metabolic Syndrome

<table>
<thead>
<tr>
<th>Central obesity</th>
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<tbody>
<tr>
<td>Waist circumference</td>
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<tr>
<td>( \geq 94 ) cm (men)</td>
</tr>
<tr>
<td>( \geq 88 ) cm (women)</td>
</tr>
<tr>
<td>Abnormal glucose tolerance</td>
</tr>
</tbody>
</table>

And two more of teh following:

- Hypertrigliceridemia*: TG \( \geq 150 \) mg/dl
- Low HDL-cholesterol*:
  - \( < 40 \) mg/dl (men)
  - \( < 50 \) mg/dl (women)
- HT* (\( \leq 130/85 \) mm Hg)
- Fasting glucose*:
  - \( \geq 100 \) mg/dl
  * Or being under treatment.

Clinical importance of metabolic syndrome

MetS has been criticized because of the different definitions proposed. Since the WHO criteria in 1999, when insulin resistance was primordial, to NCEP ATP III, that prioritizes abdominal obesity, or International Diabetes Federation (IDF) criteria in 2005. It has also been said that the criteria are incomplete and the etiology is not clearly understood. In some of the definitions, type 2 diabetic patients are not included. Even more, a specific treatment of MetS does not exist, but every one of the components must be treated separately. Even more, the cardiovascular risk of persons diagnosed is not higher than the associated to the risk factors. In this context, Dr. Reaven published in 2005 an article titled “Metabolic Syndrome: Requestiem in Pace”.

Nonetheless, the presence of a MetS is associ-
Similar results were obtained in the Diabetes Prevention Program, which aimed to reduce the incidence of diabetes in individuals with impaired glucose tolerance (mean age 55 years, mean BMI 33.2) assigned to a weight-reduction and exercise program. Patients lost 3.5 kg (vs 0.8 kg in the control group) and the cumulative incidence of diabetes was significantly lower in the intervention group (11 versus 23%).

The Finnish Diabetes Prevention Study, patients with impaired glucose tolerance (mean age 55 years, mean BMI 34 kg/m²) subjects, with high risk for diabetes due to impaired glucose tolerance, were randomly assigned to one of the following groups: 1) Intensive lifestyle changes through a low-fat diet and exercise for 150 minutes per week. 2) Treatment with metformin plus information on diet and exercise. 3) Control group with placebo plus information on diet and exercise. The diet and exercise group lost an average 7 percent of weight in the first year, most of which was sustained through the duration of the study. After 3 years, fewer patients in this group developed diabetes (14% versus 22% and 29% in the metformin and placebo groups, respectively). After 2.8 years follow-up, 58% reduction in metformin group was observed. Improvements in insulin sensitivity and insulin secretion, greatest in the intensive lifestyle intervention group, and somewhat lower in the metformin group, correlated directly with decreased risk of diabetes.

Lifestyle intervention may also be effective in individuals without impaired glucose tolerance in the MRFIT. In this large primary prevention trial, an intervention (advice on diet, exercise, giving up smoking, and intensive blood pressure treatment) in men at high risk for coronary heart disease was associated with a lower risk of type 2 diabetes in the nonsmokers.

But, although effectiveness of lifestyle intervention has been clearly demonstrated, the dietary and exercise changes may be difficult to implement in the real world. Long term compliance with dietary interventions has been poor, and new, less expensive strategies must be found to achieve long-term weight loss. The “real-world” implementation of lifestyle interventions is a challenge. The Good Ageing in Lahti Region (GOAL) Lifestyle Implementation Trial was designed for the primary health care setting in Finland, with lifestyle and risk reduction objectives derived from the major diabetes prevention efficacy trials. A total of 352 middle-aged participants with elevated type 2 diabetes risk were recruited. The intervention included six group counseling sessions, delivered by nurses. At baseline, mean BMI was 32 kg/m², and 25% of the participants had impaired glucose tolerance. After 12 months, 20% of participants achieved at least four of five key lifestyle outcomes. Therefore, this trial demonstrates that lifestyle counseling can be effective and is feasible in real-world settings for individuals with elevated risk of type 2 diabetes.

Challenges and opportunities

Prevention of diabetes is crucial to lowering diabetes incidence, and thus minimizing the health burden. At the time of diagnosis, 50% of patients have macrovascular complications (retinopathy, neuropathy or nephropathy) and twice the risk of macrovascular complications compared to the general population. Obesity is the most important modifiable factor, accounting for...
more than half of new diabetes’ cases. Even modest weight loss has a favorable effect in preventing the appearance of diabetes. Also, physical exercise with or without diet contributes to a healthier lifestyle, and is important for lowering risk. The best way to contain this epidemic is to screen for early detection, prevention and management of obesity, especially in younger individuals, before the development of type 2 DM. In table IV the American Diabetes Association recommendations for type 2 DM screening are shown. Risk factors include family history, hypertension, obesity, sedentary lifestyle, smoking and hyperlipidaemia. Screening should be done for high risk individuals using fasting plasma glucose (FPG). An FPG <126 mg/dL (7.0 mmol/L) in an individual with a high suspicion for diabetes should be followed by a OGTT to confirm diabetes.

In 2010 the American Heart Association (AHA) announced its new Strategic Impact Goals: “by 2020, to improve the cardiovascular health of all Americans by 20% while reducing deaths from cardiovascular diseases and stroke by 20%” 24 The novel aspect of the 2020 goals is the promotion of “cardiovascular health”, a new, positive approach to prevention of CVD, including smoking status, BMI, dietary content, participation in physical activity, and levels of blood pressure, blood glucose, and total cholesterol. Hopefully, these goals will imply a decrease in obesity, type 2 DM, and MetS.

### Table IV

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<tr>
<th>Recommendations for Screening for Pre-Diabetes and Diabetes</th>
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<tbody>
<tr>
<td>Testing should be considered in all adults who are overweight (BMI &gt; 25 kg/m²) and have additional risk factors:</td>
</tr>
<tr>
<td>• Physical inactivity</td>
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<td>• First-degree relative with diabetes</td>
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<tr>
<td>• Members of a high-risk ethnic population (e.g., African American, Latino, Native American, Asian American, Pacific Islander)</td>
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<tr>
<td>• Women who delivered a baby weighing &gt; 4 kg or were diagnosed with gestational diabetes mellitus</td>
</tr>
<tr>
<td>• Hypertension (&gt;140/90 mmHg or on therapy for hypertension)</td>
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<tr>
<td>• Women with polycystic ovary syndrome</td>
</tr>
<tr>
<td>• HDL cholesterol level &lt; 35 mg/dl and/or a triglyceride level &gt; 250 mg/dl</td>
</tr>
<tr>
<td>• A1C ≥ 5.7%, impaired glucose tolerance or impaired fasting glucose on previous testing</td>
</tr>
<tr>
<td>• other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans polycystic ovarian syndrome)</td>
</tr>
<tr>
<td>• History of cardiovascular disease</td>
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</tbody>
</table>

In the absence of the above criteria, testing for pre-diabetes and diabetes should begin at the age of 45 years. If results are normal, testing should be repeated at least at 3-year intervals, with consideration of more frequent testing depending on initial results and risk status.

### Conclusion

Diabetes and MetS have become a worldwide epidemic with a significant health and economic burden affecting both developed and developing countries. It seems possible to reduce the burden of diabetes. Clinical trials have convincingly shown that lifestyle modification is the most effective tool in the prevention or delay of type 2 diabetes. For overweight and obese patients, a modest weight-loss goal of 5-10% can substantially reduce diabetes risk. Moderate-intensity physical activity such as brisk walking for at least 150 minutes per week also plays an important role in reducing diabetes risk, even in the absence of weight loss. Therefore, prevention of diabetes should be a priority, and successful implementation of these proven strategies should be the focus of our efforts. We have a lot to do.

### References


