Diabetes and Cardiovascular Disease
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Diabetes mellitus is a major risk factor for cardiovascular disease, contributing to its devastating economic consequences. Metabolic syndrome and abdominal obesity are an increasing health problem, often linked to diabetes (and glucose intolerance). The atherosclerotic plaque is not only contributing to these conditions, but also being a link between them. Indeed, several pathways suggest interaction between the metabolic and immune-inflammatory system, indicating that these processes are not different mechanism but different manifestation of the same process. Cardiovascular, non-invasive imaging has emerged as an accurate tool for assessing burden of atherosclerosis. Magnetic resonance imaging has been revealed as an accurate tool for assessing burden of atherosclerosis. Molecular imaging. One day update in diabetes and cardiovascular diseases
Consequences of the modern lifestyle?

Cardiovascular disease (CVD) has long been the leading cause of mortality and morbidity in developed countries. The recognition and management of cardiovascular risk factors led to a decline in CV mortality rates in the 1960s. Despite this progress in the battle against CVD, the socioeconomic impact of this disease is still monumental. It is estimated that every year more than 1 million people in the United States and more than 19 million others worldwide experience an acute coronary syndrome or sudden cardiac death.

The health status and disease profile of a society have been linked to its economic status. Following industrialization, the major causes of death and disability in developed countries have changed from a preponderance of nutritional deficiencies and infectious diseases, to degenerative diseases such as CVD and diabetes. Paradoxically, these diseases are associated with over-nutrition. CVD is becoming the number one killer in both developed, and developing countries. This shift in CVD incidence and prevalence in developing countries is attributable to the increasing rates of urbanization and higher risk factor levels (diabetes, dyslipidemia, obesity, hypertension, etc.).

The rates of urbanization are increasing globally, from 37% of the world population living in urban areas in 1970, to 45% in 1994. Urbanization is associated with a radical change in lifestyle, with a marked increase in consumption of energy-rich foods and a decrease in energy expenditure, through less physical activity.

Diabetes mellitus is a well-known cardiovascular risk factor. Diabetes mellitus is not only a current common disease but its prevalence is expected to increase, especially in developing countries. In 1995, 135 million people worldwide were affected by diabetes, but alarmingly it is expected that by the year 2025 the prevalence will increase to approximately 300 million. More than 90% of diabetic patients suffer from type 2 diabetes mellitus, which is a progressive disorder with a slow and subtle onset. Consequently, type 2 diabetes is an under reported condition and, of the estimated 15.6 million adult diabetic patients in the United States, an anticipated 5.4 million cases remain undiagnosed.

ECONOMIC IMPACT OF CARDIOVASCULAR DISEASE AND DIABETES

As has been stated above, CVD is the most relevant health problem in developed countries in the 21st century, and is becoming similar in developing countries. The magnitude of this epidemic is so significant that many countries are heading toward an actual crisis. CVD cost the health care systems of the European Union (EU) approximately €105 billion in 2003. This represents a cost per capita of €230 per year, around 12% of the total health care expenditure across the EU. The cost of inpatient hospital care for people with CVD accounted for about 57% of these costs, while drugs accounted for about 27% (Figure 1). Coronary heart disease and stroke represent almost half of the health care expenditure on CVD in the EU (22% and 20% respectively). These numbers illustrate the huge cost secondary to CVD in the developed countries, and the expectations are similar for the countries in development.

Throughout the world, one of the economic sectors with the largest expenditure increase over the last 30 years is the medical sector. It is estimated that the care of people with diabetes mellitus accounts for 5% of the total health budget of the United Kingdom. In the US, diabetes accounted for $44 billion in direct healthcare expenditures in 1997, with $17.0 billion from lost productivity due to premature mortality. CVD and diabetes are clearly associated. In fact, CVD is the diabetes complication with greatest proportion of direct costs and more than half the mortality-related costs of diabetes mellitus. It has been recently shown that the annual costs associated with type 2 diabetes increased by more than 50% when cardiovascular complications started to appear, and by 360% when a major cardiovascular event occurred. Hence, the economic burden of CVD and diabetes cannot be taken as different "budgets" but as co-morbidities frequently associated with exponential effects on economic expenditures. Due to the large number of complications associated with diabetes, diabetic patients account for 1 in every $7 spent on healthcare in the United States. In the EU, the average cost per patient due to type 2 diabetes is estimated to be approximately €2,834 a
year. Of these costs, hospitalizations account for the half of the expenses. It is estimated that hospitalizations for type 2 diabetic patients average 23 days per year.12 Taken together, these data clearly show the disastrous economic burden of CVD and diabetes mellitus.

METABOLIC SYNDROME AND OBESITY
Diabetes mellitus—inflammation connection. Is abdominal obesity the link?

The incidence of obesity worldwide has increased drastically during recent decades. The World Health Organization estimates that more than 1 billion adults worldwide are overweight.11 Especially shocking is the equally marked increase in childhood obesity.11 Obesity is associated with many heath problems including increased risk of insulin resistance, type 2 diabetes, fatty liver disease, atherosclerosis, and some others.11

Metabolic syndrome is defined as the clustering of risk factors often accompanying obesity and associated with increased risk for both type 2 diabetes and cardiovascular disease.11 Clinical criteria for metabolic syndrome include increased waist circumference, hypertriglyceridemia, low levels of HDL-cholesterol, hypertension, and high glucose levels. Treatment for any of these conditions is also considered a clinical criterion. Today, it is well recognized that metabolic syndrome is a major and prevalent CVD risk factor.16

The hyperglycemic status observed in type 2 diabetes seems to be only the tip of a huge dysmetabolic iceberg, mostly resulting from a combination of factors found in overweight patients with an excess in abdominal fat and insulin resistance.11 Abdominal obesity (as measured by waist circumference) plays an important role in metabolic syndrome. Interestingly, for any given quantity of total body fat, the individuals with a selective excess of intra-abdominal (visceral) adipose tissue are at substantially higher risk of being characterized by insulin resistance and metabolic syndrome.11,12 Impaired non-esterified fatty acid metabolism is suggested as a main contributor to the insulin-resistance observed among patients with visceral obesity. This turns especially important, when we know that insulin resistance is directly implicated in the development and perpetuation of atherosclerosis.13

In fact, insulin has many effects beyond its hypoglycemic effect (Figure 2). The adipose tissue is not only a lipid storage area but it is also an important paracrine “organ” that releases numerous cytokines. Among those cytokines, interleukin (IL)-6 and tumour necrosis factor-α (TNF-α) are proinflammatory molecules produced by the adipose tissue that has vital importance as follows. Obesity is characterized by macrophage infiltration of the adipose tissue14, which could contribute to the inflammatory profile reported in patients with visceral-abdominal obesity.12 Another important inflammatory substance, the C-reactive protein (CRP), is a well-established marker of cardiovascular risk that is also increased in patients with abdominal obesity.12 Adipose tissue synthesizes also anti-inflammatory substances, like adiponectin.24,25 Interestingly, the production and release of adiponectin is reduced in patients with visceral obesity.26 Adiponectin has been shown to have many effects compatible with improved insulin signaling and potential protection against atherosclerosis.27,28 The reduced levels of adiponectin observed in abdominally obese patients could, therefore, represent a key factor responsible for the increased risk of atherosclerosis and diabetes observed in these patients. Hence, patients with excess visceral fat have an excess in circulating CRP, IL-6 and TNF-α levels, associated with reduced adiponectin concentrations29 that may explain the high risk observed in this population (Figure 3).

Excess intra-abdominal fat accumulation represents a marker of the relative inability of subcutaneous adipose tissue to act as an “energy sink” when an individual has to handle a energy/calorie surplus due to excess energy intake and/or reduced energy expenditure.29 Such a relative deficit in the capacity of subcutaneous fat to store excess energy would result in increased intra-abdominal fat accumulation (surrounding various organs), a phenomenon that is
called ectopic fat deposition. Glitazones increases fat deposition in the "right place," the subcutaneous tissue. This fat redistribution following treatment with glitazones might explain the beneficial effects of this class of drug on insulin sensitivity. Thus, weight loss has been reported to induce a selective mobilization of abdominal and visceral adipose tissue, explaining, at least in part, the improvement in the metabolic profile of most patients with metabolic syndrome following moderate weight loss.

Despite the evidence that metabolic syndrome and type 2 diabetes are linked to inflammation, the linkage is still striking to understand. The ability to withstand starvation and the capacity to mount an effective immune response to pathogens are among the processes most critical to species survival. The first mechanism promotes the storage of excess calories when food is scarce. However, in the presence of a continuous nutritional surplus, this once beneficial metabolic mechanism turns disadvantageous by promoting excess adiposity. Interestingly, the functional units controlling metabolic and immune functions in higher organisms have evolved from common ancestral structures. It is suggested that the organs descendant from the former unique unity still have common or overlapping signaling pathways, regulating the immune and metabolic functions.

The Toll-like receptors (TLR) represent the classical clue for this theory. TLR are pathogen-sensing systems that, upon contact with some nutrients, particularly fatty acids, unleash metabolically or nutritionally induced inflammatory responses. Metabolic, inflammatory and immune processes are also regulated by lipids. Several transcription factors, particularly those in the peroxisome-proliferator activated receptor (PPAR) and liver X receptor (LXR) families, seem to be crucial for modulating the intersection of these pathways. Ligands to all three PPAR family members suppress production of proinflammatory cytokines through suppression of NF-κB. Interestingly, signaling from TLRs inhibits LXR activity in macrophages, promoting cholesterol accumulation in macrophages.
and accounting, at least in part, for the pro-atherogenic effects of infection.46

Deleterious defense mechanisms implicated in the generation and perpetuation of atherosclerosis, like macrophage infiltration of the vessel wall, have a counterpart in the adipose tissue. The morphology of adipose tissue in obese patients illustrates the convergence of macrophages on necrotic adipocytes, suggesting that their presence in adipose tissue might be predominantly for clearance purposes,47 as it is in the atheromatous vessel wall. All the inflammatory responses triggered by macrophages may also be present in the adipose tissue of obese patients.

Thus, it is clear that inflammation is a major player in patients with obesity, metabolic syndrome, and diabetes. Several pathways suggest interaction between the metabolic and immune-inflammatory system, indicating that these processes are not different mechanism but different manifestation of the same process.

**ROLE OF IMAGING MODALITIES IN CARDIOVASCULAR DISEASE AND DIABETES**

**Beyond the anatomy: functional imaging (inflammation)**

Cardiovascular, noninvasive imaging has emerged as an accurate tool for assessing not only the anatomy and function of the heart,48 but also that of the arterial vessels, being feasible to study the burden of atherosclerosis.49,50 Magnetic resonance imaging (MRI) has been demonstrated to be an extremely accurate tool for assessing the effectiveness of interventions aimed toward plaque regression,51,52 (Figure 4). Our group pioneered the concept that atheroma deposition within the vessel wall was not a “one-way” phenomenon, showing for the first time the effect of apoA-I/HDL on atheroma burden.53 Later, the development of MRI allowed us to demonstrate that diverse interventions targeting different mechanisms
were able to regress the already established atherosclerotic plaques. Recent efforts are focusing on the imaging of biologic processes (functional imaging) in addition to anatomy. The understanding of the mechanism involved in plaque development, inflammation and instability led to the concept of functional imaging. Inflammation within the atherosclerotic plaque can be quantified by $^{18}$F fluorodeoxyglucose (FDG) positron-emission tomography (PET), since FDG uptake is confined to areas rich in macrophages. To overcome the limitations of PET scanning in terms of anatomical resolution, the merging of FDG-PET and high-resolution MRI allowed an astonishing combination of plaque size characterization and inflammation quantification. (Figure 5). Therefore, much effort is focused on the detection of high risk areas (plaques). Plaque vulnerability has been largely associated with a plaque’s macrophage content. Plaque composition has been a target of vast research. Despite our demonstration that novel contrast agents can be helpful in detecting lipid-rich plaques by MRI, the sensitivity and specificity of these “non-targeted” contrast agents are far from desirable. New advances in molecular imaging using targeted contrast agents have permitted the noninvasive characterization of plaque composition. Very recently it has been shown that macrophage targeted immunomicelles enhance the atherosclerotic vessel wall of ApoE knockout mice in vivo, suggesting that the amount of enhancement seen with MRI could be directly related to the macrophage content of the atherosclerotic vessel. (Figure 6). These preliminary results increase the likelihood of accurate plaque composition imaging. One issue that remained unaddressed is whether serial functional and anatomical imaging studies of high-risk patients can monitor the effectiveness of interventions. In a substudy of the Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) trial we are testing whether MRI merged with PET-CT can identify the inflammatory vessel wall burden of diabetic patients, and whether an aggressive management of these patients will result in cessation of the inflammatory process (or even a regression of it), as assess by these new high-resolution modality (Figure 7).

Neovascularization within the atherosclerotic plaque is another feature recently associated with lesion vulnerability. Even though this hypothesis has not been universally accepted, certain studies suggest that vasa vasorum-derived microvessels nurture the atherosclerotic plaque, facilitating their progression by providing a permanent communication between the systemic circulation and the atheroma, increasing leukocyte, albumin, and red blood cells extravasation. It is also well known that intraplaque hemorrhage leads to plaque rupture and thrombosis. The subsequent iron deposition may increase oxidation and inflammation within the atherosclerotic plaque. Haptoglobin is the protein responsible for the defense against hemoglobin injury. It has been demonstrated that haptoglobin polymorphism plays a critical role in the oxidative and inflammatory response to intraplaque hemorrhage. Novel imaging techniques are aimed at the direct visualization of plaque neo-vessels. Other known markers of plaque instability, like tissue factor plaque content and macrophage apoptosis within atheroma are future targets for imaging risk stratification.

Fig. 5. High Resolution Magnetic resonance imaging (HRMRI) and fluorodeoxyglucose (FDG) positron-emission tomography (PET) scans taken from a patient after a right carotid territory stroke. Top panels: transaxial images taken at the level of the proximal right internal carotid (RIC) artery. There is a large atherosclerotic plaque in the RIC artery causing severe luminal stenosis (arrows). Despite its size, only low FDG uptake is demonstrated (arrows). Bottom panels: axial images taken at the level of the proximal common carotid arteries (CCA). The arrows highlight a nonstenotic plaque in the wall of the right CCA. Middle panel’s arrow points to an area of high FDG uptake, the location of which is confirmed on the fused scan as the right CCA (bottom right panel). Taken from Davies et al.57

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38C  Rev Esp Cardiol Supl. 2008;8:30C-41C
CONCLUSIONS

Cardiovascular disease is an increasing health problem of epidemic magnitude worldwide. Several factors influence this astonishing growth, with changes in lifestyle secondary to urbanization being one of the major players. Changes in lifestyle have shifted the once advantageous mechanism of energy surplus storage into the deleterious mechanism responsible for the exponential increase in obesity, metabolic syndrome and diabetes. There is a strong interplay between cardiovascular-metabolic disease and the inflammatory state. The important interaction between the immune-inflammatory apparatus and the metabolic system implies that obesity (specifically abdominal obesity) is associated with a highly inflammatory status, increasing the risk of cardiovascular manifestations.

Noninvasive imaging modalities have proven to be highly accurate in the anatomical study of atherosclerotic patients, but more interestingly, such modalities are also becoming a precise tool for the functional and biological study. Inflammation can be accurately quantified by the fusion of novel imaging modalities. Targeted contrasts for noninvasive imaging are also promising tools for plaque characterization.

Fig. 6. In vivo magnetic resonance images obtained pre- and post-injection of macrophage-targeted immunomicelles (A and B), untargeted micelles (C), and gadolinium (D) in ApoE knockout mouse. Taken from Amirbekian et al.59
REFERENCES


