Review

Clinical significance of cardiovascular dysmetabolic syndrome
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Abstract

Although diabetes mellitus is predominantly a metabolic disorder, recent data suggest that it is as much a vascular disorder. Cardiovascular complications are the leading cause of death and disability in patients with diabetes mellitus. A number of recent reports have emphasized that many patients already have atherosclerosis in progression by the time they are diagnosed with clinical evidence of diabetes mellitus. The increased risk of atherosclerosis and cardiovascular complications in diabetic patients is related to the frequently associated dyslipidemia, hypertension, hyperglycemia, hyperinsulinemia, and endothelial dysfunction. The evolving knowledge regarding the variety of metabolic, hormonal, and hemodynamic abnormalities in patients with diabetes mellitus has led to efforts designed for early identification of individuals at risk of subsequent disease. It has been suggested that insulin resistance, the key abnormality in type II diabetes, often precedes clinical features of diabetes by 5–6 years. Careful attention to the criteria described for the cardiovascular dysmetabolic syndrome should help identify those at risk at an early stage. The application of nonpharmacologic as well as newer emerging pharmacologic therapies can have beneficial effects in individuals with cardiovascular dysmetabolic syndrome and/or diabetes mellitus by improving insulin sensitivity and related abnormalities. Early identification and implementation of appropriate therapeutic strategies would be necessary to contain the emerging new epidemic of cardiovascular disease related to diabetes.

Although the importance of diabetes mellitus (DM) as a major risk factor for macrovascular and microvascular disease is well recognized, the recent increase in the prevalence of DM, especially in younger individuals, has raised alarm. It is probable that the increased incidence of DM will slow the age-adjusted decline in coronary heart disease (CHD) and will even raise the possibility of a significant increase in the risk of cardiovascular (CV) disease during the next several decades. Recent data from the Center for Disease Control showed that, although there was an increase in the prevalence of DM across all ethnic groups and all ages, the most striking increase (by 70%) was observed in people aged between 30 and 39 years. These data suggest that there is not only an increase in the prevalence of DM, but that the disease is occurring at younger ages and that such trends, if uninterrupted, can potentially lead to a new epidemic of CV disease during this millennium.
CV complications are the leading cause of death and disability in patients with type II DM [1]. The magnitude of CV complications in DM is best illustrated by a recent report demonstrating that the risk of myocardial infarction in diabetic patients with no prior myocardial infarction was as high as that in nondiabetic patients with a history of prior myocardial infarction [2]. Although it has been known for years that DM is a major coronary risk factor, the precise mechanism for the increased risk of CHD in patients with DM has not been well defined [3–6].

Several studies have evaluated the role of potential factors that could increase the risk of atherosclerosis in association with DM [7–10]. The results of these studies demonstrate that there are a number of pathways by which DM increases the risk of CHD. Most diabetic patients frequently have one or more of the well-established risk factors, including hypertension, dyslipidemia, and obesity [7]. Although these are well-established, independent risk factors in nondiabetic patients, they can only account for approximately one-half of the excess CHD risk associated with DM [6]. The additional risk of CHD must therefore be partly accounted for by the predominant metabolic abnormalities in DM, which are hyperglycemia and hyperinsulinemia due to insulin resistance [7,8].

A number of recent studies have documented a relationship between the risk of CHD events and hyperglycemia, increased levels of glycated hemoglobin (HgA1C), and hyperinsulinemia [2–10]. Whether these metabolic abnormalities play a direct role in the pathogenesis of atherosclerosis or increase the risk of CHD due to other associated risk factors is currently being investigated.

Based on the available information, it appears that hyperinsulinemia secondary to insulin resistance is an important and independent risk factor for CHD [5–12]. The strongest evidence to support the association between hyperinsulinemia and CHD events comes from the prospective study of men from Quebec, which demonstrated a fourfold to fivefold increase in the risk of CHD in individuals with the highest levels of fasting plasma insulin [8].

The precise pathogenetic mechanism by which insulin increases the risk of atherosclerosis and CHD has not been established [1]. However, several possibilities exist. Insulin might contribute to the risk of hypertension by stimulating sympatho-adrenal axes through modulation of cation transport and vascular remodeling by stimulating hypertrophy of vascular smooth cells [9]. Insulin not only enhances the effects of platelet-derived growth factor, but also directly stimulates vascular smooth cell hypertrophy [11]. Hyperinsulinemia can also produce dyslipidemia (e.g. increase triglyceride and decrease high-density lipoprotein cholesterol by increasing catecholamine levels and by increased synthesis of very low-density lipoprotein [7,8,11,12]. In addition, the increased levels of glucose and insulin promote secretion of plasminogen activator inhibitor-1, which increases the risk of thrombosis by producing a prothrombotic state [11]. Diabetic patients also have increased levels of serum fibrinogen and von Willebrand factor, which further enhance thrombosis.

**Clinical relevance of cardiovascular dysmetabolic syndrome**

It is now well recognized that endothelial dysfunction and injury are key initial steps in the process of atherosclerosis. Many of the factors associated with insulin resistance can also lead to endothelial dysfunction directly or indirectly. Although in the normal physiologic state insulin stimulates production of nitric oxide by endothelial cells, recent studies have shown that in a hyperinsulinemic state endothelial response to insulin is impaired [11]. The presence of endothelial dysfunction has also been demonstrated in association with hyperglycemia and in patients with type II DM [11]. In addition, the increased oxidative stress in association with diabetes can further impair endothelial function. It is thus clear that diabetes and the associated insulin resistance have damaging effects on the endothelium that, together with the cluster of associated abnormalities, increase the risk of atherosclerosis and CHD [1].

It has been suggested that as many as 50% of newly diagnosed patients with type II DM might already have evidence of CHD [3–6]. It is therefore conceivable that the insulin resistance that often precedes the development of clinical signs and symptoms of type II DM is responsible for the increased risk of CHD [7–11]. Several studies have demonstrated that insulin resistance and hyperinsulinemia often coexist with other metabolic abnormalities that increase the risk of CHD (Table 1) [7–11]. Although insulin resistance syndrome has been recognized for some time as syndrome X or Reaven’s syndrome, this was recently redefined as cardiovascular dysmetabolic syndrome (CDS) [12,13]. This newly coined term appears to be more logical because it includes all of the important elements of the syndrome and it highlights the involvement of the CV system in this dysmetabolic state.

CDS has four critical elements: dyslipidemia, insulin resistance, obesity, and high blood pressure (easily remembered by the mnemonic DROP) (Table 2) [13]. A diagnosis of CDS requires the presence of at least two of the first three components: dyslipidemia, insulin resistance, and obesity [13]. All components of CDS are risk factors for macrovascular disease (coronary disease, carotid disease, cerebral disease, and peripheral vascular disease). The presence of more than one component confers additive risk, although some components (e.g. diabetes or
insulin resistance) confer more risk than others [13]. It is important to note that, whereas the presence of DM doubles the risk of macrovascular disease in men, this risk is increased by fourfold to fivefold in women. Women with diabetes thus lose the gender protection and are at equally high risk of CHD as men of the same age and risk profile [13].

**When and how to screen for CDS**

Although it is difficult to define insulin resistance (the critical element of CDS) in the clinical setting, it has been suggested that fasting plasma glucose ≥ 110 mg/dl identifies most individuals with an insulin-resistant state [13–15]. The other elements of CDS, such as obesity and hypertension, require only good physical examination and measurement of weight, waist circumference, and blood pressure. Those with an increased waist-hip ratio (> 0.9) and/or truncal obesity can be suspected to have an insulin-resistant state. A simple, fasting lipid panel would identify those patients with most common and critical dyslipidemia.

The new criteria of the American Diabetes Association have also lowered the cut-off point that defines DM to fasting glucose ≥ 126 mg/dl, in recognition of the microvascular disease that is often seen with glucose values above that level [15]. Fasting glucose ≥ 126 mg/dl corresponds to a postprandial glucose ≥ 200 mg/dl, 2 hours after a 75 g glucose load, and either one of these values denotes the presence of DM [14,15]. It has also been recommended that any casual nonfasting blood glucose ≥ 200 mg/dl indicates the presence of DM [14,15]. It is important to note that, although good control of glucose levels decreases the risk of microvascular disease, patients with well-controlled glucose continue to be at increased risk of macrovascular disease due to persistence of insulin resistance, hyperinsulinemia, and associated metabolic and hemodynamic abnormalities [13,14].

Although routine screening for DM should be carried out at 3-year intervals starting at 45 years of age, earlier and more frequent screening is recommended for individuals who have one or more elements of CDS, for those who have a family history of DM, and for members of high-risk ethnic groups (e.g. Hispanics, native Americans, or migrant Southeast Asians) [15].

**Therapeutic strategy in CDS and DM**

There are numerous nonpharmacologic and pharmacologic interventions that can have beneficial effects in individuals with CDS and/or DM. Nonpharmacologic measures should always be the initial therapeutic intervention in individuals with CDS [13]. Although weight reduction by as little as 10% of body weight can improve insulin sensitivity, it is generally desirable to reduce weight to the ideal level, achieving body mass index < 25 kg/m²[13]. Regular aerobic physical exercise can substantially improve insulin sensitivity and, in many cases, improve many of the abnormalities seen in CDS. It has been suggested that even low levels of exercise, such as brisk

### Table 1: Frequently observed metabolic, hemostatic, and other abnormalities in cardiovascular dysmetabolic syndrome

| ↑ | Insulin |
| ↑ | Levels of insulin growth factor |
| ↑ | Intra-abdominal fat |
| ↑ | Fatty acids |
| ↑ | Triglycerides |
| ↓ | High-density lipoprotein cholesterol |
| ↑ | Small dense low-density-lipoprotein cholesterol |
| ↑ | Apolipoprotein B |
| ↑ | Tissue angiotensin II levels |
| ↑ | Serum fibrinogen |
| ↑ | Plasminogen activator inhibitor-I |
| ↓ | Oxidative stress |
| ↓ | Synthesis of endothelial derived relaxation factor (nitric oxide) |

↑, increased; ↓, decreased

### Table 2: Cardiovascular dysmetabolic syndrome

| Dyslipidemia | Fasting triglycerides > 140 mg/dl, or High-density lipoprotein cholesterol < 40 mg/dl, or Low-density lipoprotein particle size < 260 Å |
| Insulin resistance | Fasting plasma glucose ≥ 110 mg/dl, or Type 2 diabetes mellitus |
| Obesity | Body mass index > 25 kg/m², or Waist-hip ratio > 0.85, or Waist > 100 cm |
| High blood pressure | Systolic blood pressure ≥ 140 mmHg, or Diastolic blood pressure ≥ 90 mm Hg |

### Table 3: Effects of thiazolidinedione insulin sensitizers

| ↓ | Insulin resistance |
| ↓ | Hyperinsulinemia |
| ↓ | Fasting blood sugar in type 2 diabetes mellitus |
| ↓ | Free fatty acids |
| ↓ | Triglycerides |
| ↑ | High-density lipoprotein cholesterol |
| ↑ | Plasminogen activator inhibitor-I activity |
| ↑ | Vascular compliance |
| ↓ | Blood pressure/vascular resistance |
| ↓ | Macrophage inflammatory activity |

Direct vascular effects

↑, increased; ↓, decreased
walking for 30–45 min three to five times a week, are useful in improving insulin sensitivity.

There are several pharmacologic modalities that can be used for patients with DM and CDS. In patients with DM, although exogenous insulin supplements endogenous production by the pancreas, it does not improve insulin resistance and it often causes hunger and additional weight gain. Sulfonylureas work by stimulating production of insulin and would have the same metabolic drawbacks as exogenous insulin. Alpha-glucosidase inhibitors, such as acarbose, delay carbohydrate absorption and decrease the stimulation for endogenous insulin secretion [16]. Their use is limited due to gastrointestinal side effects.

Biguanides, such as metformin, primarily decrease hepatic glucose production and, to a lesser extent, reduce insulin resistance [17]. Although rare, metformin can cause fatal lactic acidosis, particularly in patients with renal or hepatic dysfunction. However, it can improve insulin sensitivity and can help reduce weight in some individuals [18].

The thiazolidinediones, such as pioglitazone or rosiglitazone, reduce insulin resistance in muscle [19] and, to a lesser extent, reduce hepatic glucose production [20]. These actions lower both plasma glucose and insulin. This class of agents also has other beneficial effects. Thiazolidinediones inhibit cell growth and migration in the setting of vascular injury [21]. The thiazolidinediones can decrease blood pressure by reducing peripheral vascular resistance due to improved endothelial function [22]. Some of these agents can increase high-density lipoprotein cholesterol and decrease triglyceride levels [22]. Low-density lipoprotein cholesterol might increase without an increase in apolipoprotein B in some cases, indicating an increase in low-density lipoprotein particle size without an increase in number of particles, which may have an antiatherogenic effect [23,24]. A number of ongoing studies are now evaluating the CV benefits of treatment with thiazolidinediones (pioglitazone and rosiglitazone) in patients with type II DM. Although improvement in insulin sensitivity with these agents might be beneficial in the short term, we need to evaluate their long-term safety and efficacy, especially in light of the serious adverse experience observed with troglitazone.

In summary, treatment of type II DM should emphasize improvement in insulin sensitivity, a decrease in hepatic glucose production, and a decrease in stimulation of endogenous insulin production, rather than increased endogenous insulin production or exogenous administration of insulin. Future drug development in this area should focus on drugs that can improve several of these abnormalities. It is only through development of such therapy, as well as public health measures directed to reducing obesity in the population at large, that we will be able to control this emerging epidemic of the 21st century.

Conclusion
Recent data show that the prevalence of type II diabetes is rapidly increasing in the world. People are also developing DM at a younger age, and this trend is likely to continue with increased prevalence of obesity in the adolescent and youth years. DM has clearly become a major public health issue and it is likely to result in a new epidemic of premature coronary artery disease in the new millennium. It is therefore critical to identify those individuals at future risk of developing DM. Early identification by regular evaluation for CDS in susceptible individuals should help to identify the high-risk individuals who will benefit from aggressive nonpharmacologic as well as pharmacologic measures (when necessary) directed toward decreasing their risk for developing DM and CV disease.

Competing interests
None declared.

Abbreviations
CDS = cardiovascular dysmetabolic syndrome; CHD = coronary heart disease; CV = cardiovascular; DM = diabetes mellitus.

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