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INTRODUCTION

Obesity is diagnosed when the percentage of body fat is high in relation to the lean body mass or when the body mass index (BMI) is 30 kg/m² or more, and individuals with a BMI between 25 and 29.9 kg/m² are considered overweight. According to the Department of Health and Human Services, 60% of the US population in 2001 was either overweight or obese. Such prevalence is much higher among patients with type 2 diabetes, 80% of whom are either overweight or obese (1,2). The situation is almost equally dismal around the globe, including many developing countries, where the adverse health consequences of overweight and obesity have begun to replace undernutrition and infection as the main causes of early death and disability (3).

ASSOCIATION BETWEEN OBESITY AND TYPE 2 DIABETES

It has been quite clear that the prevalence of type 2 diabetes increases with the increasing prevalence of overweight and obesity among different racial and ethnic groups (4). Follow-up of middle-aged women in the Nurses’ Health Study and of men in the Health Professionals Follow-up Study for 10 yr has clearly shown that the risk of developing type 2 diabetes is rising in parallel with increasing severity of overweight and obesity (5). Interestingly, the risk of developing diabetes starts to increase even with modest weight gain (6,7). It has thus been reported that a period of gradual weight gain usually precedes the onset of type 2 diabetes. This observation is evident, e.g., in the Pima Indian population, which has a high prevalence of type 2 diabetes. Body
weight of Pima Indians has been noted to increase by an average of 30 kg above their ideal body weight in the years immediately preceding the diagnosis of diabetes (8). By contrast, weight reduction is associated with decreased incidence of type 2 diabetes. In the Nurses Health Study, a weight loss of 5 kg or more reduced the risk of developing type 2 diabetes by approx 50% (6). This observation was later documented in the Diabetes Prevention Program, in which an approximate 7% of weight reduction maintained for an average duration of 2.8 yr was associated with a 58% reduction in the risk of developing type 2 diabetes in prediabetic individuals with impaired glucose tolerance (IGT) (9). Weight reduction through increased physical activity or bariatric surgery also leads to similar results (10,11). Dixon and O’Brien (12) found that an average weight reduction of 27 kg 1 yr after laparoscopic adjustable gastric band surgery in a group of severely obese patients with type 2 diabetes resulted in remission of diabetes in 64% of them and major improvement in glucose control in another 26%.

Insulin resistance and hyperinsulinemia are often seen in overweight and obese individuals and are by far the best predictors of type 2 diabetes. Both conditions are currently considered an outcome of the interaction between increased body weight and underlying genetic factors. It has also been reported that although the degree of insulin sensitivity may be quite similar between the nondiabetic offspring of parents with type 2 diabetes and the offspring of nondiabetic parents whose body weight is close to the ideal weight, insulin sensitivity declines more rapidly with increasing body weight in those with a family history of diabetes (13).

The development of type 2 diabetes in overweight and obese individuals is characterized by progressive deterioration of glucose tolerance over several years. Cross-sectional and prospective data suggested that weight gain and abnormal or deficient insulin secretion and insulin action together with increased endogenous hepatic glucose production underlie this deterioration (14–17). It has also been observed that these abnormalities are sequential, with impairments of insulin action and insulin secretion occurring earlier during the transition from normal glucose tolerance to IGT and worsening as an individual moves toward diabetes; the increased endogenous hepatic glucose production starts only during the late transition from IGT to diabetes (18). These findings suggest that intervention(s) to prevent diabetes in high-risk individuals with overweight or obesity should start very early, especially in subjects with a positive family history of diabetes among first-degree relatives.

**PATHOGENESIS OF TYPE 2 DIABETES IN OBESITY**

The mechanism through which obesity increases insulin resistance is currently thought to be related to the increased circulating free fatty acids (FFAs), altered levels of adipocytokines, altered body fat distribution, or a combination of the three. Serum FFA levels are frequently high in obese subjects. It has been reported that elevated levels of FFAs could potentially be the major contributor to peripheral insulin resistance in patients with type 2 diabetes mellitus (19,20). Chronically elevated serum FFA levels stimulate gluconeogenesis, induce hepatic and muscle insulin resistance, and impair insulin secretion in genetically predisposed individuals (21). FFAs also tend to increase the accumulation of triglycerides in both liver and skeletal muscle, which correlates with the degree of insulin resistance in these tissues (22,23). In addition, since triglycerides are in a state of constant turnover, their metabolites, such as acyl coenzymes A, ceramides, and diacylglycerol, contribute toward both impaired hepatic and peripheral insulin action. This sequence of events is frequently called lipotoxicity (24). Accumulating