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New options for the treatment of obesity and type 2 diabetes mellitus (narrative review)☆,☆☆,★

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ABSTRACT

Moderate weight loss (>5%), which has been associated with improvements in glycemic parameters in patients with dysglycemia, also reduces the presence of other comorbidities, including dyslipidemia and hypertension, culminating in a reduced risk of cardiovascular disease. Lifestyle changes are the recommended preliminary approach to weight loss, with an initial weight-loss goal of 10% of body weight achieved over 6 months at a rate of 1–2 pounds per week selected as an appropriate target to decrease the severity of obesity-related risk factors. Implementing and maintaining the lifestyle changes associated with weight loss can, however, be challenging for many patients. Therefore, additional interventions sometimes may be necessary. Bariatric surgery can also be a highly effective option for weight loss and comorbidity reduction, but surgery carries considerable risks and is still applicable only to selected patients with type 2 diabetes. Thus, attention is turning to the use of weight-loss medications, including 2 recently approved compounds: twice-daily lorcaserin and a once-daily combination of phentermine and topiramate extended-release, both shown to be safe and effective therapies in the management of obesity in patients with type 2 diabetes.

1. Introduction

Overweight and obesity are global epidemics affecting about 70% and 35% of the US population, respectively (Flegal, Carroll, Kit, & Ogden, 2012). Both are associated with type 2 diabetes mellitus (T2DM), which itself increases the risk of weight gain (Flegal et al., 2012; Reaven, 2003; Siram, Yanagisawa, & Skamagas, 2010; Tzotzas, Evangelou, & Kiortsis, 2011). Type 2 diabetes mellitus and overweight/obesity both increase risk of cardiovascular disease (CVD) and other comorbidities (American Diabetes Association, 2012; National Heart, Lung, & Blood Institute. The Clinical Guidelines on the Identification, 1998). The American Diabetes Association (ADA) suggests that management of T2DM in overweight/obese patients should focus on control of hyperglycemia (HbA_{1c} goal <7%) via antidiabetic pharmacotherapy, together with moderate weight loss (~7%) (American Diabetes Association, 2012), since the latter is associated with improvements in glycemic parameters in patients with dysglycemia and may subsequently reduce the need for antidiabetic medications (American Diabetes Association, 2012).

While lifestyle changes (dietary modification focused on caloric reduction, increased physical activity, and behavior therapy) (National Heart, Lung, & Blood Institute. The Clinical Guidelines on the Identification, 1998) can produce weight loss in overweight and obese individuals, sustained adherence to these changes and maintenance of weight reduction is often challenging (Greenberg, Stampfer, Schwarzfuchs, Shai, & DIRECT Group, 2009; Mata, Todd, & Lippke, 2010). This review will discuss T2DM and its comorbidities as they relate to obesity and the need for treatment options to address the associated risks. Two compounds that were recently approved by the US Food and Drug Administration (FDA) for the chronic management of obesity or overweight in the presence of ≥1 weight-related comorbidity as adjuncts to a reduced-calorie diet and increased physical activity will be described: twice-daily (BID) lorcaserin (BELVIQ 2012), and once-daily (QD) phentermine and extended-release topiramate (PHEN/TPM ER) (QSYMIA 2012).

2. Obesity-related complications of type 2 diabetes

2.1. Pathophysiology of obesity and T2DM

Although obesity is fundamentally related to an imbalance between energy intake and energy expenditure, it is estimated that genetic

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variability accounts for around 50% of the variation in body mass within a population (de Ferranti & Mozaffarian, 2008; Lyon & Hirschhorn, 2005) via impact on hormone levels, body composition, and energy metabolism (Lentes et al., 1999). Additional factors leading to alterations in metabolism and/or appetite, such as a lack of sleep, illness, and choice of macronutrients, can also contribute (de Ferranti & Mozaffarian, 2008). The resultant energy imbalance leads to hypertrophy and hyperplasia of adipocytes (de Ferranti & Mozaffarian, 2008). Adipose tissues modulate metabolism by releasing non-esterified fatty acids (NEFAs), glycerol, hormones (e.g., leptin and adiponectin) (Lara-Castro, Fu, Chung, & Garvey, 2007), and proinflammatory cytokines (such as interleukin [IL]-6, and insulin growth factor [IGF]-1) (de Ferranti & Mozaffarian, 2008; Kahn, Hull, & Utzschneider, 2006; Scherer, 2006; Shoelson, Lee, & Goldfine, 2006; Wellen & Hotamisligil, 2005). The expansion of adipose tissue in obese patients is associated with changes in the release of numerous adipokines from adipocytes, as well as from macrophages and other cells that populate adipose tissue.

In particular, NEFAs, which are released from adipocytes, have been shown to induce insulin resistance and impair β-cell function, with increased levels observed in both obesity and T2DM (Boden, 1997; Kahn et al., 2006; Reaven, Hollenbeck, Jeng, Wu, & Chen, 1988). Insulin resistance has also been shown to arise in healthy subjects in response to high plasma NEFA levels induced through diet (Roden et al., 1996), suggesting an association between insulin resistance and obesity (Kahn et al., 2006). A possible mechanism for the β-cell dysfunction associated with obesity (Kahn et al., 2006) that may also contribute to the pathogenesis of T2DM (Schaffer, 2003) is lipid (triglyceride) accumulation in pancreatic β-cells (de Ferranti & Mozaffarian, 2008). In addition, the secretion of an adipokine, adiponectin, which is associated with positive metabolic and vascular effects, is reduced in obesity and may contribute to the pathogenesis of metabolic syndrome, T2DM, and atherosclerosis (Lara-Castro et al., 2007). Finally, it has been suggested that proinflammatory cytokines, such as TNF-α secreted by macrophages present in adipose tissue, play a significant role in obesity-related insulin resistance (Kern, Ranganathan, Li, Wood, & Ranganathan, 2001).

2.2. Comorbidities of T2DM and obesity

The association between obesity and cardiometabolic risk factors, such as dyslipidemia and hypertension (National Heart, Lung, & Blood Institute. The Clinical Guidelines on the Identification, 1998), may lead to further complications in patients with T2DM (American Diabetes Association, 2012; Eckel et al., 2011). For example, it has been reported that even newly diagnosed T2DM is associated with a 25% increase in risk of CVD, emanating from numerous contributors (Wilson & Kannel, 2002). Since obesity often precedes the development of T2DM, common pathogenic mechanisms (Eckel et al., 2011) and comorbidities may already be present (National Heart, Lung, & Blood Institute. The Clinical Guidelines on the Identification, 1998; Wilson & Kannel, 2002).

Obese patients with T2DM have been reported to show significantly increased serum levels of total cholesterol, low-density lipoprotein (LDL) cholesterol, very-low-density lipoprotein (VLDL) cholesterol, and triglycerides and decreased high-density lipoprotein (HDL) cholesterol compared with non-obese patients with T2DM (Saxena, Agrawal, Gautam, Bid, & Banerjee, 2009). Research in monozygotic twins has shown that acquired obesity is associated with increased activity of fibrinogen and coagulation markers, which are strongly correlated with inflammation and insulin resistance and, as such, may increase risk of thrombosis and cardiovascular events (Kaye et al., 2012).

Hypertension is also commonly seen with both T2DM and obesity and is a major risk factor for CVD and microvascular complications. Due to the synergistic effects of hypertension and T2DM, the diagnostic cutoff for hypertension is lower for those with concurrent T2DM (≥130/80 mm Hg) vs those without (≥140/90 mm Hg) (American Diabetes Association, 2012; Chobanian et al., 2003).

3. Effects of intentional weight loss on T2DM

Studies have shown that moderate weight loss in obese patients with T2DM leads to decreased insulin resistance, improvements in glycemic parameters, and reductions in T2DM-related complications as well as in several CVD risk factors, including dyslipidemia and elevated blood pressure (BP) (American Diabetes Association, 2012; National Heart, Lung, & Blood Institute. The Clinical Guidelines on the Identification, 1998). Even modest reductions in risk factors can have a substantial impact on mortality – for example, reductions in systolic BP (SBP) of 5 mm Hg can reduce the risk of mortality from stroke by 14% and coronary heart disease (CHD) by 9% (Fig. 1) (Whelton et al., 2002). In this article, we discuss the relative merits of different approaches to intentional weight loss: lifestyle changes, bariatric surgery, and pharmacotherapy. It is important to remember that some medications used to treat T2DM may induce weight gain (insulin, sulfonylureas, glinides, thiazolidinediones), while others are reported to be weight neutral (DPP-4 inhibitors, acarbose, miglitol, bromocriptine) (Bray & Ryan, 2012). There are also a few antidiabetic medications that may lead to a modest degree of weight loss (metformin, pramlintide, exenatide, liraglutide) (Bray & Ryan, 2012). These effects should be considered when determining treatment options for obese patients with T2DM.

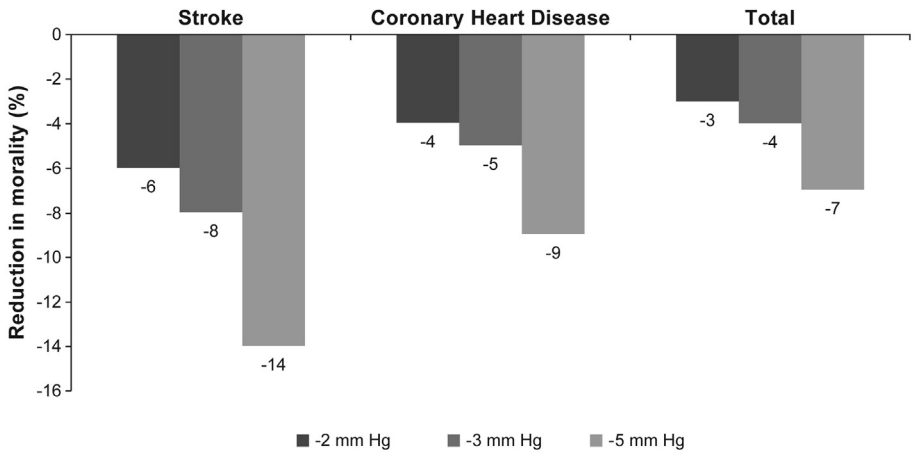

Fig. 1. Reductions in mortality by reduction in systolic blood pressure (SBP) (Chobanian et al., 2003; Whelton et al., 2002). Figure adapted from Whelton et al., 2002.