Is Weight Loss Beneficial for Reduction of Morbidity and Mortality?

What is the controversy about?

PETER M. NILSSON, MD

The increase of obesity and type 2 diabetes on a global scale has increased the interest in how to counteract this epidemic. Improved lifestyle in general is a fundamental approach, but other remedies such as specific weight reduction or diabetes preventive drugs and surgery have also been tested. One problem to understand is what really happens after weight loss. Ongoing studies will try to address this question, such as the Swedish Obese Subjects (SOS) surgery study, the Look AHEAD (Action for Health in Diabetes) trial in the U.S. (recruiting obese type 2 diabetic patients), and the Comprehensive Rimonabant Evaluation Study of Cardiovascular End Points and Outcomes (CRESCENDO) trial (by use of rimonabant versus placebo). This is very important, since previously, several observational studies in large population-based cohorts have indicated some detrimental effects of weight loss, even after intentional weight loss, with increased morbidity and mortality rates.

Diabetes Care 31 (Suppl. 2):S278–S283, 2008

Obesity is a well-established risk factor for many chronic disorders such as cardiovascular disease (CVD), type 2 diabetes, and certain cancers, as well as for increased all-cause mortality risk (1–3). It is therefore paradoxical that weight loss, whether only observational or even intentional (in some observational studies) is also associated with an increased mortality risk (4–10). This has now been documented from four Nordic countries (7–10) in recent epidemiological studies based on population-based cohorts followed over time, after an initial assessment of weight loss compared with weight stability or weight increase during the first few years of follow-up. Therefore, a clinical controversy exists.

In Malmö, Sweden, several studies have shown the health hazards related to obesity (11,12), but also have confirmed the association between observational weight loss and increased long-term mortality risk in middle-aged men (7). Why is there such a paradoxical association? Possible explanations could include the following: *1*) an artifact due to residual confounding, *2*) subclinical disease or depression causing both weight loss and increased mortality risk, *3*) true detrimental effects on metabolism by weight loss per se, and *4*) weight loss being a marker of early general aging (biological involution) in susceptible individuals, causing premature morbidity and mortality. It seems that weight loss may well improve medical symptoms, risk factor levels, and quality of life for obese subjects, but the paradoxical finding of an increased mortality risk associated with observational and even intentional weight loss (10) calls for more research efforts and a more cautious attitude toward the healthy but obese subject asking for medical advice. An alternative approach is to promote weight stabilization as a goal for the healthy but overweight or even mildly obese individual, because a stable weight has been associated with less cardiovascular risk and less mortality in observational studies, both in comparison with weight increase and weight loss (7–10).

From the Department of Clinical Sciences, University Hospital, Malmö, Sweden.

Address correspondence and reprint requests to Peter M. Nilsson, Department of Clinical Sciences, University Hospital, S-205 02 Malmö, Sweden. E-mail: peter.nilsson@med.lu.se.

The author of this article has no relevant duality of interest to declare.

This article is based on a presentation at the 1st World Congress of Controversies in Diabetes, Obesity and Hypertension (CODHy). The Congress and the publication of this article were made possible by unrestricted educational grants from MSD, Roche, sanofi-aventis, Novo Nordisk, Medtronic, LifeScan, World Wide, Eli Lilly, Keryx, Abbott, Novartis, Pfizer, Generx Biotechnology, Schering, and Johnson & Johnson.

Abbreviations: CVD, cardiovascular disease; SOS, Swedish Obese Subjects.

DOI: 10.2337/dc08-s268

POSSIBLE EXPLANATIONS FOR INCREASED HEALTH RISKS ASSOCIATED WITH WEIGHT LOSS

— As weight loss has been associated not only with health benefits, but also with health hazards (Table 1), it is important to find some putative explanations for these paradoxical effects. One explanation is simple; the associations could be the result of residual confounding and therefore be spurious and classified as artifacts. It is well known that chronic devastating disease will lead to weight loss in many patients, for example, cardiac cachexia or advanced chronic obstructive pulmonary disease, and thus associate observational weight loss with increased mortality risk. In the studies from the Nordic countries (7–10), researchers have however tried to avoid this fallacy by excluding unhealthy subjects at baseline for follow-up analyses, as well as excluding the first few years of follow-up regarding mortal events to avoid confounding by subclinical disease. Another explanation is that psychiatric conditions such as depression, eventually leading to suicide, could influence the association between weight loss due to poor appetite in depressed subjects with later mortality risk. This could well be true for some select subjects, but cannot be accepted as a more general explanation for larger groups of people experiencing weight loss. A third explanation is based on the fact that biological involution (e.g., reduced weight and height) in healthy subjects is part of a normal aging process. This is supposed to take a more rapid course in subjects showing signs of early ageing, thereby increasing the risk of early-onset mortality. For CVD, this can be called the early vascular aging syndrome.

Finally, it is difficult to rule out the possibility that weight loss per se could be hazardous to health, at least in some susceptible individuals. One piece of evidence supporting this hypothesis is the well-known risk of cholelithiasis attacks in obese patients after rapid intentional weight loss (13). If correct, this hypothesis based on observation could be extrapolated to other unwanted health risks and

eventually an increased mortality risk in a subset of people, even after intentional weight loss. To settle this research dilemma based on observations, it takes well-designed, randomized, controlled intervention studies in large groups of overweight/obese subjects who are losing weight, either after drug treatment or surgery, or a combination of these modes of interventions.

RISK OF CVD AND DIABETES IN RELATION TO OBESITY

— Overweight and obesity are major contributors to both type 2 diabetes and CVD. Moreover, individuals with type 2 diabetes who also are obese are at particularly high risk for CVD morbidity and mortality, since other risk factors such as hypertension and dyslipidemia tend to cluster with obesity (14). Several studies have shown that obesity gradually increases the risk of type 2 diabetes, especially if located in the abdominal region (15,16). This risk depends on several pathophysiological mechanisms including decreased insulin sensitivity and secondary impairment of β-cell function associated with obesity, the latter often being a consequence of the former when hyperglycemia (glucotoxicity) gradually increases and impairs the function of the β-cell. It is less known that diabetes treatment itself may also increase the degree of obesity. The reason for this is the weight-increasing effects of treatment by various antidiabetes drugs, for example, by insulin and sulfonylureas, as shown in the U.K. Prospective Diabetes Study (17), or by glitazone treatment (18,19). Paradoxically, the increased weight in these patients is associated with a decreased risk of both micro- and macrovascular complications (17,20). Similar findings have been noted for the weight increase, but at the same time, decreased risk after smoking cessation or by use of β-receptor blocking agents after myocardial infarction (secondary prevention) has been noted. In both conditions, the cardiovascular risk is more or less decreased, forming a paradox of weight gain–associated clinical benefits and risk reduction.

WEIGHT CONTROL ACHIEVEMENT IN TYPE 2 DIABETES

— The common practice to advise diabetes patients to lose weight is based on beliefs of potential benefits documented in observational studies only (21,22). In addition, it may also be difficult to combine this goal of weight loss with that of improved glycemic control if weight-promoting antidiabetes drugs are used (insulin, sulfonylureas, or glitazones). Regretfully enough, we presently lack data on clinical end points from randomized intervention trials to really support such common advice to lose weight in these patients. There is no doubt that weight control and weight reduction can reduce the risk of developing diabetes in subjects with impaired glucose tolerance, as shown both by lifestyle interventions (23–25) and by use of drugs such as orlistat (26,27), acarbose (28), and rosiglitazone (29). However, the feasibility and benefits by weight reduction in established type 2 diabetes is less well documented and also sometimes hard to achieve if most antidiabetes drugs act by increasing weight, with metformin being the only exception.

LIFESTYLE INTERVENTION TO DECREASE RISK OF DIABETES

— In the Finnish Diabetes Prevention Study, 522 subjects with impaired glucose tolerance participated (23). The intervention group showed significantly greater improvement in each intervention goal of weight loss and physical exercise. After 1 and 3 years, weight reductions were 4.5 and 3.5 kg in the intervention group and 1.0 and 0.9 kg in the control group, respectively. Measures of glycemia improved more in the intervention group. The intensive lifestyle intervention produced long-term beneficial changes in diet, physical activity, and clinical and biochemical parameters. It also substantially reduced the risk of diabetes by 58%, an effect that was at least partly preserved during long-term post-trial follow-up, as recently described (24). This is a proof of concept that an effective intervention, including weight loss, could improve glucose metabolism. However, it is difficult to disentangle beneficial effects associated with weight loss from effects caused by other simultaneous interventions, especially that of increased physical activity.

DRUG INTERVENTION TO DECREASE THE RISK OF DIABETES: ONE EXAMPLE

— A reduction in the incidence of type 2 diabetes with lifestyle changes has previously been demonstrated in several studies, based on, for example, physical exercise. Addition of a weight-reducing drug to lifestyle changes may lead to an even greater decrease in body weight and thus the incidence of type 2 diabetes in obese patients. In a 4-year double-blind prospective study, 3,305 patients were randomized to lifestyle changes plus either

Table 1—*The pros and cons of weight loss based on observational and intervention studies*

Health benefits of weight loss
Lower levels of cardiovascular risk factors, e.g., blood pressure, lipids, and glycemia
Less abdominal obesity increases adiponectin levels and insulin sensitivity
Lower incidence of new-onset type 2 diabetes in subjects with impaired glucose tolerance or impaired fasting glucose when combined with physical activity
Reduced symptoms of musculoskeletal and joint pain, obstipation, and psychological complaints
Improved quality of life in very obese subjects
Health hazards of weight loss
Increased mortality risk in observational studies, even in subjects with the intention to lose weight. Controversies still exist based on lack of information, e.g., on the intentionality of weight loss in other studies with opposite findings
Increased risk of osteoporotic fractures in lean elderly subjects
Increased risk of gallstone attacks if (intentional) weight loss is rapid
Loss of muscle tissue if weight loss is only based on dieting and not the combination with increased physical activity

120 mg orlistat or placebo, three times daily (27). Participants had a BMI ≥30 kg/m^2 and normal (79%) or impaired (21%) glucose tolerance. Primary end points were time to onset of type 2 diabetes and change in body weight. Of orlistat-treated patients, 52% completed treatment compared with 34% of placebo recipients ($P < 0.0001$). After 4 years' treatment, the cumulative incidence of diabetes was 9.0% with placebo and 6.2% with orlistat therapy ("intention to treat"), corresponding to a risk reduction of 37% ($P = 0.0032$). The preventive effect was explained by the difference in subjects with impaired glucose tolerance. Mean weight loss after 4 years was significantly greater with orlistat (5.8 vs. 3.0 kg with placebo; $P < 0.001$) and similar between orlistat recipients with impaired (5.7 kg) or normal glucose tolerance (5.8 kg) at baseline. Compared with lifestyle changes alone, orlistat plus lifestyle changes thus resulted in a greater reduction in the incidence of type 2 diabetes over 4 years and produced greater weight loss in this obese population. However, a difference in diabetes incidence was detectable only in the impaired glucose tolerance subgroup.

EFFECTS OF RIMONABANT ON WEIGHT LOSS AND CLINICAL EFFECTS

— A new alternative to lose weight and to improve risk factor control is the endocannaboid-1 receptor antagonist rimonabant. Clinical studies in abdominally obese subjects have documented weight loss, improved glucose metabolism, and lipid control, as well as reduced blood pressure in patients with type 2 diabetes (30–33). Some adverse effects on mental function have been noticed in some patients, and that is why this drug should not be prescribed to patients with a medical history of depression or pronounced mental symptoms. Other effects seen in some but not all studies include increased rates of smoking cessation. It is important that rimonabant is currently being evaluated for effects on cardiovascular morbidity and mortality end points versus placebo in a randomized controlled study, the Comprehensive Rimonabant Evaluation Study of Cardiovascular End Points and Outcomes (CRESCENDO) study, with expected results in 2011 (34). This trial is recruiting patients ≥55 years, with inclusion criteria: waist circumference >102 cm (40 inches) in males, >88 cm (35 inches) in females, with one coronary heart disease equivalent or two major risk factors for CVD.

OBSERVATIONAL STUDY ON THE EFFECTS OF WEIGHT LOSS IN DIABETES

— If randomized controlled intervention studies are not available, the second best option on which to base decisions in clinical medicine are well-designed and large observational studies. In one such study, medical records were reviewed of all 263 patients with type 2 diabetes from a diabetes clinic in Scotland who were known to have died in the mid-1980s (22). Mean age was 65 years (range 57–75) at diagnosis and 72 years (range 66–80) for men and 75 years (range 72–83) for women, at death. Analysis of survival in 233 patients who lived >1 year (189 overweight), using stepwise multiple regression analysis, indicated the following as significant ($P < 0.05$) adverse independent variables: age at diagnosis, presence of clinical ischemic heart disease at diagnosis, and plasma glucose at diagnosis. Significant favorable variables were oral hypoglycemic drug therapy, weight loss in the first year, and an interaction between weight loss and BMI for patients with BMI >25 kg/m^2. Changes in treatment over the years are likely to have biased these results toward including oral hypoglycemic therapy and excluding the expected adverse effect of smoking. Mean weight loss at 1 year was 2.6 kg for individuals with BMI 25–30 kg/m^2 and 6.8 kg for individuals with BMI >30 kg/m^2, following dietary advice. For the average patient, each 1-kg weight loss was associated with 3–4 months' prolonged survival. Some rest confounding could, however, be present as this was not a randomized, controlled study.

ROLE OF LIFESTYLE AND EMPOWERMENT OF DIABETIC PATIENTS

— The efforts to help patients with established type 2 diabetes to improve their lifestyle must often be combined with methods to increase self-efficacy and the empowerment of the patient (35). There could be obstacles to this ambition, such as poverty or poor education on behalf of the patient, or a lack of social support. One project evaluated lifestyle interventions for patients with diabetes living in poor rural communities. It was a 12-month randomized clinical trial ($n = 152$) of "intensive-lifestyle" and "reimbursable-lifestyle" (intensive-lifestyle intervention delivered in the limited time associated with Medicare reimbursement for diabetes education related to nutrition and physical activity) interventions, with usual care as a control group (36). Modest weight loss occurred after 6 months among intensive-lifestyle participants and was greater than the weight loss among usual-care participants (2.6 vs. 0.4 kg, $P < 0.01$). At 12 months, a greater proportion of intensive-lifestyle participants had lost ≥2 kg than the usual-care participants (49 vs. 25%, $P < 0.05$). No differences in weight change were observed between reimbursable-lifestyle and usual-care participants. Glycated hemoglobin was reduced among all groups ($P < 0.05$) in the same way. In conclusion, this study showed that improvement in both weight and glycemia are indeed attainable by lifestyle interventions designed for individuals with type 2 diabetes living in rural communities, often in less favorable social conditions.

However, we need data from larger studies on the methodology and clinical outcomes of intentional weight loss in at-risk individuals with diabetes. Fortunately, a few clinical trials are now ongoing and will hopefully be able to increase the knowledge on how to achieve weight loss in obese subjects and diabetic patients, as well as the long-term consequences of this achievement for clinical end points.

LOOK AHEAD: INTERVENTION FOR WEIGHT LOSS IN TYPE 2 DIABETES

— Although short-term weight loss has been shown to ameliorate obesity-related metabolic abnormalities and CVD risk factors, the long-term consequences of intentional weight loss in obese individuals with type 2 diabetes have previously not been adequately examined. The primary objective of the ongoing Look AHEAD (Action for Health in Diabetes) clinical trial (37) is to assess the long-term effects (up to 11.5 years) of an intensive weight loss program delivered over 4 years in overweight and obese individuals with type 2 diabetes. Approximately 5,000 male and female participants (45–74 years old) who have type 2 diabetes and a BMI ≥25 kg/m^2 have been randomized to one of the two groups. The study is now fully recruited and ongoing. The intensive lifestyle intervention is designed to achieve and maintain weight loss through decreased caloric intake and increased physical activity, by support of trained instruc-

tors. This program is compared to a control condition (standard care) of diabetes support and education. The primary study outcome variable is time to incidence of a major CVD event. The study is designed to provide a 0.90 probability of detecting an 18% difference in major CVD event rates between the two groups. Other outcomes include components of CVD risk, cost and cost-effectiveness, diabetes control and complications, hospitalizations, intervention processes, and quality of life. In summary, the Look AHEAD trial is an important clinical trial and a step toward increased evidence-based knowledge on how to handle obesity problems in patients with established type 2 diabetes.

IS WEIGHT-REDUCING SURGERY THE SOLUTION?

— Another approach for weight reduction is to use surgical intervention, such as gastric bypass or gastric banding. The Swedish Obese Subjects (SOS) study is conducted to determine whether obese patients actually can improve their mortality risk by losing weight (38,39). After an initial screening study, a total of 6,328 subjects were recruited and extensively characterized for background factors and other medical treatments. In the following intervention study, 2,010 of the subjects underwent surgery for obesity (gastric banding, gastroplasty, gastric bypass), while 2,037 chose a conventional form of treatment and acted as control subjects (matched pairs) during a period of up to 20 years. Thus, the study was nonrandomized but well controlled, even for personality and psychological factors. After 10 years, the control subjects had gained an average of 1.4 kg in weight. The surgical subjects, in contrast, showed a substantial and persisting decrease in weight, averaging 20–30 kg, differing with the surgical methods used. In comparison with the control group, this surgical intervention group showed a clear decrease in the incidence of cardiovascular risk factors (among others, hypertension, hypertriglyceridemia, and diabetes) as well as an improvement in cardiac function parameters and health-related quality of life. Compared with weight stability, large intentional weight loss thus resulted in substantial reductions in the 2-year incidence of several cardiovascular risk factors. After 8 years, there was still a reduced risk of developing diabetes (odds ratio [OR] 0.16, 95% CI 0.07–0.36) in the surgical group, while the incidence of hypertension, remarkably enough, was equal in the two treatment groups (OR 1.01, 95% CI 0.61–1.67). The reason for this is not clear but could because weight loss in grossly obese people in adult life may not be able to fully abolish the pathophysiological mechanisms regulating blood pressure control, set at a much younger age, possibly during childhood. After 8 years, the maintained weight loss was still 20.1 ± 15.7 kg (16.3 ± 12.3%). Thus, a differentiated risk factor response was identified based on the fact that a maintained weight reduction of 16% strongly counteracted the development of diabetes over 8 years but showed no long-term effect on the incidence of hypertension. Many patients with diabetes taking part in the study have also been able to reduce or completely stop their medication (38,39) because of improved glycemic control after surgery. In 2007, the main SOS study was published (40). It showed that following bariatric surgery in obese subjects with BMI >35 kg/m^2, total mortality and myocardial infarction, and also cancer events, were significantly reduced but surprisingly not stroke incidence. The authors concluded that bariatric surgery for severe obesity is associated with long-term weight loss and decreased overall mortality. Surgical intervention is, however, less well proven in other categories of overweight or in patients not as obese as those recruited in the SOS study.

CONCLUSIONS AND IMPLICATIONS

— A controversy still exists regarding the role of intentional weight loss for prognosis in nondiabetic healthy subjects, as well as in patients with type 2 diabetes, when weight loss is often a contradiction to the weight increase followed by use of some antidiabetic drugs. Without evidence from trials, we will never be able to make justified clinical decisions on how and when weight loss should be recommended to risk patients and which methods should be preferred—lifestyle, drugs, or surgical intervention. Observational studies only represent one first step and are not fully reliable, since rest confounding may sometimes bias the outcome. For example, the background drug medication given to patients losing weight may either increase or decrease the likelihood of achieving weight loss, but at the same time reduce risk of morbidity and mortality. One well-known example of this is the use of β-receptor blockers for secondary prevention after myocardial infarction (41). Even if a weight increase is likely to occur after the use of these drugs, thus providing harder conditions for any weight loss, the cardiovascular risk is decreased and that is what matters the most.

Randomized controlled trials such as Look AHEAD (37) and CRESCENDO (34) will hopefully contribute to our understanding of the effects of intentional weight loss and thereby resolve the controversy that exists. Surgical interventions cannot and will never be a remedy for the vast majority of overweight/obese subjects, who have increased risks for diabetes, CVD, and early mortality. Still, surgery is useful for subjects from the far end of the obese distribution of BMI, providing them with improved quality of life, symptom relief, and a better prognosis, according to findings in the SOS study (40). In the end, we need several options for weight loss strategies, based on evidence, in patients in need of these interventions. However, a strategy of weight stabilization, with conversation of muscle tissue that is sometimes endangered by weight loss and weight cycling, might still be a reasonable and achievable goal for many overweight or even mildly obese subjects who are otherwise healthy.

References

1. Stamler J, Vaccaro O, Neaton JD, Wentworth D: Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. *Diabetes Care* 16:434–444, 1993
2. Yusuf S, Hawken S, Ounpuu S, Bautista L, Franzosi MG, Commerford P, Lang CC, Rumboldt Z, Onen CL, Lisheng L Tanomsup S, Wangai P, Razak F, Sharma AM, Anand SS, INTERHEART Study Investigators: Obesity and the risk of myocardial infarction in 27,000 participants from 52 countries: a case-control study. *Lancet* 366:1640–1649, 2005
3. Bray GA, Bellanger T: Epidemiology, trends, and morbidities of obesity and the metabolic syndrome. *Endocrine* 29:109–117, 2006
4. Andres R, Muller DC, Sorkin JD: Long-term effects of change in body weight on all-cause mortality: a review. *Ann Intern Med* 119:737–743, 1993
5. Pamuk ER, Williamson DF, Serdula MK, Madans J, Byers TE: Weight loss and subsequent death in a cohort of U.S. adults. *Ann Intern Med* 119:744–748, 1993
6. Corrada MM, Kawas CH, Mozaffar F, Paganini-Hill A: Association of body mass index and weight change with all-cause

mortality in the elderly. *Am J Epidemiol* 163:938–949, 2006
7. Mikkelsen KL, Heitmann BL, Keiding N, Sorensen TI: Independent effects of stable and changing body weight on total mortality. *Epidemiology* 10:671–678, 1999
8. Nilsson PM, Nilsson J-Å, Hedblad B, Berglund G, Lindgärde F: The enigma of increased mortality associated with weight-loss in middle-aged men: the Malmö Prevention Project. *J Intern Med* 252:70–78, 2002
9. Dröyvold W, Lydersen S, Midthjell K, Nilsen TIL, Nilsson PM, Nilsson J-Å, Holmen J: Weight change and mortality: the Nord-Trøndelag Health Study. *J Intern Med* 257: 338–345, 2005
10. Sorensen TI, Rissanen A, Korkeila M, Kaprio J: Intention to lose weight, weight changes, and 18-y mortality in overweight individuals without co-morbidities. *PLoS Med* 2:e171, 2005
11. Jonsson S, Hedblad B, Engström G, Nilsson P, Berglund G, Janzon L: Influence of obesity on cardiovascular risk: twenty-three year follow-up of 22 025 men from an urban Swedish population. *Int J Obes Relat Metab Disord* 26:1046–1053, 2002
12. Hedblad B, Jonsson S, Nilsson P, Engström G, Berglund G, Janzon L: Obesity and myocardial infarction: vulnerability related occupational level and marital status: a 23-year follow-up of an urban Swedish population. *J Intern Med* 252: 542–550, 2002
13. Tsai CJ, Leitzmann MF, Willett WC, Giovannucci EL: Weight cycling and risk of gallstone disease in men. *Arch Intern Med* 166:2369–2374, 2006
14. Lebovitz HE: Insulin resistance: a common link between type 2 diabetes and cardiovascular disease. *Diabetes Obes Metab* 8:237–249, 2006
15. Björntorp P: Body fat distribution, insulin resistance, and metabolic diseases. *Nutrition* 13:795–803, 1997
16. Björntorp P: Regional fat distribution: implications for type II diabetes. *Int J Obes Relat Metab Disord* 16 (Suppl. 4):S19–S27, 1992
17. UK Prospective Diabetes Study (UKPDS) Group: Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352:837–853, 1998
18. Yki-Järvinen H: Thiazolidinediones. *N Engl J Med* 351:1106–1118, 2004
19. Hedblad B, Nilsson PM, Zambanini A, Berglund G: Rosiglitazone reduces carotid intima-media thickness progression over 1 year in patients with type 2 diabetes but not in non-diabetic people who have insulin resistance alone. *J Intern Med* 261: 293–305, 2007
20. Dormandy JA, Charbonnel B, Eckland DJA, Erdmann E, Massi-Benedetti M, Moules IK, Skene AM, Tan MH, Lefebvre PJ, Murray GD, Standl E, Wilcox RG, Wilhelmsen L, Betteridge J, Birkeland K, Golay A, Heine RJ, Koranyi L, Laakso M, Mokan M, Norkus A, Pirags V, Podar T, Scheen A, Scherbaum W, Schernthaner G, Schmitz O, Skrha J, Smith U, Taton J, PROactive Investigators: Secondary prevention of macrovascular events in patients with type 2 diabetes in the PROactive Study (PROspective pioglitAzone Clinical Trial In macroVascular Events): a randomised controlled trial. *Lancet* 366:1279–1289, 2005
21. Mayer-Davis EJ, Costacou T: Obesity and sedentary lifestyle: modifiable risk factors for prevention of type 2 diabetes. *Curr Diab Rep* 1:170–176, 2001
22. Lean ME, Powrie JK, Anderson AS, Garthwaite PH: Obesity, weight loss and prognosis in type 2 diabetes. *Diabet Med* 7:228–233, 1990
23. Lindström J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, Uusitupa M, Tuomilehto J, Finnish Diabetes Prevention Study Group: The Finnish Diabetes Prevention Study (DPS): lifestyle intervention and 3-year results on diet and physical activity. *Diabetes Care* 26:3230–3236, 2003
24. Knowler WC, Barrett-Connor E, Fowler SE, Hamman RF, Lachin JM, Walker EA, Nathan DM: Diabetes Prevention Program Research Group: Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 346:393–403, 2002
25. Lindstrom J, Ilanne-Parikka P, Peltonen M, Aunola S, Eriksson JG, Hemio K, Hamalainen H, Harkonen P, Keinanen-Kiukaanniemi S, Laakso M, Louheranata A, Mannelin M, Paturi M, Sundvall J, Valle TT, Uusitupa M, Tuomilehto J, Finnish Diabetes Prevention Study Group: Sustained reduction in the incidence of type 2 diabetes by lifestyle intervention: follow-up of the Finnish Diabetes Prevention Study. *Lancet* 368:1673–1679, 2006
26. Holt R: Orlistat reduces features of the metabolic syndrome: the XENDOS study. *Diabetes Obes Metab* 5:356, 2003
27. Torgerson JS, Hauptman J, Boldrin MN, Sjöström L: XENical in the prevention of diabetes in obese subjects (XENDOS) study: a randomized study of orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 27:155–161, 2004
28. Chiasson JL, Josse RG, Gomis R, Hanefeld M, Karasik A, Laakso M: STOP-NIDDM Trail Research Group: Acarbose for prevention of type 2 diabetes mellitus: the STOP-NIDDM randomised trial. *Lancet* 359:2072–2077, 2002
29. DREAM (Diabetes REduction Assessment with ramipril and rosiglitazone Medication) Trial Investigators, Gerstein HC, Yusuf S, Bosch J, Pogue J, Sheridan P, Dinccag N, Hanefeld M, Hoogwerf B, Laakso M, Mohan V, Shaw J, Zinman B, Holman RR: Effect of rosiglitazone on the frequency of diabetes in patients with impaired glucose tolerance or impaired fasting glucose: a randomised controlled trial. *Lancet* 368:1096–1105, 2006
30. Van Gaal LF, Rissanen AM, Scheen AJ, Ziegler O, Rossner S, RIO-Europe Study Group: Effects of the cannabinoid-1 receptor blocker rimonabant on weight reduction and cardiovascular risk factors in overweight patients: 1-year experience from the RIO-Europe study. *Lancet* 365: 1389–1397, 2005
31. Despres JP, Golay A, Sjöström L: Rimonabant in Obesity-Lipids Study Group: Effects of rimonabant on metabolic risk factors in overweight patients with dyslipidemia. *N Engl J Med* 353:2121–2134, 2005
32. Pi-Sunyer FX, Aronne LJ, Heshmati HM, Devin J, Rosenstock J, RIO-North America Study Group: Effect of rimonabant, a cannabinoid-1 receptor blocker, on weight and cardiometabolic risk factors in overweight or obese patients: RIO-North America: a randomized controlled trial. *JAMA* 295:761–775, 2006
33. Scheen AJ, Finer N, Hollander P, Jensen MD, Van Gaal LF, RIO-Diabetes Study Group: Efficacy and tolerability of rimonabant in overweight or obese patients with type 2 diabetes: a randomized controlled study. *Lancet* 368:1660–1672, 2006
34. CRESCENDO Comprehensive Rimonabant Evaluation Study of Cardiovascular ENDpoints and Outcomes. Clinical Trials.gov Identifier: NCT00263042 (sanofi-aventis). http://clinicaltrials.gov/ct/show/NCT00263042
35. Narayan KM, Hoskin M, Kozak D, Kriska AM, Hanson RL, Pettitt DJ, Nagi DK, Bennett PH, Knowler WC: Randomized clinical trial of lifestyle interventions in Pima Indians: a pilot study. *Diabet Med* 15:66–72, 1998
36. Mayer-Davis EJ, D'Antonio AM, Smith SM, Kirkner G, Levin Martin S, Parra-Medina D, Schultz R: Pounds Off With Empowerment (POWER): A clinical trial of weight management strategies for black and white adults with diabetes who live in medically underserved rural communities. *Am J Public Health* 94:1736–1742, 2004
37. Ryan DH, Espeland MA, Foster GD, Haffner SM, Hubbard VS, Johnson KC, Kahn SE, Knowler WC, Yanovski SZ: Look AHEAD Research Group: Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Control Clin Trials* 24:610–628, 2003

38. Sjöström CD, Peltonen M, Wedel H, Sjöström L: Differentiated long-term effects of intentional weight loss on diabetes and hypertension. *Hypertension* 36:20–25, 2003
39. Torgerson JS, Sjöström L: The Swedish Obese Subjects (SOS) study: rationale and results. *Int J Obes Relat Metab Disord* 25 (Suppl. 1):S2–S4, 2001
40. Sjöström L, Narbro K, Sjöström CD, Karason K, Larsson B, Wedel H, Lystig T, Sullivan M, Bouchard C, Carlsson B, Bengtsson C, Dahlgren S, Gummesson A, Jacobson P, Karlsson J, Lindroos AK, Lönroth H, Näslund I, Olbers T, Stenlöf K, Torgerson J, Agren G, Carrlsson LM: Swedish Obese Subjects study: effects of bariatric surgery on mortality in Swedish obese subjects. *N Engl J Med* 357:741–752, 2007
41. Fonarow GC: Beta-blockers for the post-myocardial infarction patient: current clinical evidence and practical considerations. *Rev Cardiovasc Med* 7:1–9, 2006