Beta-Cell Preservation…Is Weight Loss the Answer?

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■ Abstract

Obesity is associated with an increased risk of type 2 diabetes (T2D). Pancreatic beta-cell failure is an early event in the development of glucose dysregulation and diabetes. Interventions to halt beta-cell failure in T2D include diet modification, exercise, and use of pharmacologic agents. There is evidence that abdominal obesity may contribute to diabetes through insulin resistance and beta-cell impairment. Pivotal long-term studies into the prevention of T2D have shown the importance of weight loss beside diet, lifestyle, and medication. The Finnish Diabetes Prevention Program (DPP) showed that weight loss gradually reduces the risk of diabetes, and that even modest weight loss can significantly reduce the incidence of T2D. Similarly, in the US DPP, weight loss as part of intensive lifestyle modification was the major factor in reducing the incidence of T2D in high-risk subjects, being more effective than drug intervention. While understanding the relationship between obesity and diabetes is complex, we know that weight loss has positive effects on adipose tissue. It causes an increase in the beneficial fat cell hormone adiponectin, and a decrease in adipose tissue inflammation. Also, it is associated with reduced insulin resistance and a consequential reduction in glucolipotoxicity, which can improve beta-cell function. In summary, weight loss improves glycemic control and thereby mitigates diabetes symptoms and complications, possibly through the preservation of beta-cell function. Therefore, efforts to prevent diabetes and preserve beta-cell function in patients with T2D should more consequently emphasize and target weight loss.

Keywords: type 2 diabetes · obesity · beta-cell dysfunction · weight loss · glucotoxicity · insulin resistance · prediabetes · insulin sensitivity · disposition index · Matsuda index

Introduction

Obesity is a considerable risk factor for various diseases, including diabetes, and has reached epidemic dimensions. Current approaches to treatment and prevention of prediabetes (defined as having either impaired fasting glucose (IFG), or impaired glucose tolerance (IGT), or both) are mainly directed towards drug- and insulin-related glucose control. However, increasing evidence suggests that preservation of pancreatic beta-cell function in type 2 diabetes (T2D) may be possible with strategies other than antidiabetic drug or external insulin administration. In this regard, weight loss could become a focus for preventative measures and early treatment of diabetes [1]. The effectiveness of rigorous weight loss has been demonstrated impressively by studies on gastric surgery to reduce weight and induce remission of T2D [2].

Beta-cell dysfunction occurs early and long before the actual diagnosis of hyperglycemia. In T2D, disorders in beta-cell function acts in concert with insulin resistance [3]. Beside insulin resistance, it is supposed that obesity plays a major role in early beta-cell loss. In many cases, insulin resistance is

related to excess adiposity, which is linked to several abnormalities, and impact beta-cell function. These abnormalities include glucotoxicity, lipotoxicity, increased oxidative stress, and inflammation [4, 5].

However, a basic knowledge of the physiology of normal insulin secretion is necessary to fully understand the changes in beta-cell function and glucose dysregulation, When isolated beta-cells are exposed to glucose, the appropriate response is a biphasic pattern of insulin release: first an acute response, which has been termed the rapid priming phase, followed by a slower second phase of insulin secretion, after continued exposure to glucose. An important factor for maintenance of normal glucose is that the insulin secreted is proportional to the tissue insulin sensitivity. The "disposition index" (DI), the product of insulin secretion and insulin sensitivity, is an integrated measure of the ability to clear glucose in response to a meal. This concept has been critical in the current understanding of insulin resistance and T2D. Nor-

mally, beta-cells compensate for insulin resistance to maintain normal blood glucose levels. The DI should remain constant if variations in insulin action are compensated for by changes in insulin secretion to maintain glucose stability. At first glance, this suggests similar islet function in normal and compensated insulin secretion scenarios, but the advantage of the DI is to normalize this response to the amplitude of third trimester insulin resistance, revealing severe beta-cell deficiency [6].

Insulin action and beta-cell function improve with weight loss [7], whereas insulin sensitivity decreases with weight gain [8]. Insulin action evaluated via hyperinsulinemic clamp and insulin secretion evaluated via intravenous glucose challenge were longitudinally measured (over an average of 2.6 ± 2.0 years) in 209 Pima Indians, a population known for a high prevalence of obesity and T2D [9]. Insulin action improved with weight loss and deteriorated with weight gain in persons with both normal glucose tolerance (NGT) and IGT (Figure 1). The benefits of improved insulin action and glucose tolerance are preserved if the weight reduction is maintained.

To date, a number of large-scale, long-term studies consistently support our central theme: weight loss in obese individuals with prediabetes improves glycemic control and preserves pancreatic beta-cell function (Table 1). These studies support the hypothesis that the present approach to preventing prediabetes and treating T2D by focusing on blood glucose control only is inappropriate. It should also focus on weight loss to remodel adipose tissue and preserve beta-cell mass and function.

Evidence for a promising weight-centric treatment of diabetes

The China Da Qing Diabetes Prevention Study

The China Da Qing Diabetes Prevention Study (CDQDPS) was the first large scale evaluation of over 570 individuals with IGT [10]. The primary question posed was "how long does a reduction in diabetes persist?", by using a 20 year follow-up longitudinal design. Patients were recruited, starting in 1986, and randomized to 4 groups: usual care, diet, exercise, and diet plus exercise. Active intervention lasted for 6 years with patients reassessed at 2-year intervals. During the active intervention, the cumulative diabetes incidence was 43% in the intervention group versus 66% in the control group (hazard rate ratio (HRR) 0.49; 95%

Abbreviations:

ACT NOW - Actos Now for the Prevention of Diabetes
AIR - acute insulin response
BMI - body mass index
CDQDPS - China Da Qing Diabetes Prevention Study
CI - confidence interval
CVD - cardiovascular disease
DI - disposition index
DPP - Diabetes Prevention Program
DPPOS - Diabetes Prevention Program Outcomes Study
DREAM - Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication
EBMS - estimated metabolic body size
FINDRISC - Finnish Diabetes Risk Score
GDM - gestational diabetes mellitus
HOMA-IR - homeostasis model assessment of insulin resistance index
HRR - hazard rate ratio
IFG - impaired fasting glucose
IGI - insulinogenic index
IGT - impaired glucose tolerance
ILS - intensive lifestyle
IVGTT - intravenous glucose tolerance test
M - insulin action
NAVIGATOR - Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research
NGT - normal glucose tolerance
OGTT - oral glucose tolerance test
PI - proinsulin
PIPOD - Pioglitazone in the Prevention of Diabetes
SI - insulin sensitivity
T2D - type 2 diabetes
TRIPOD - Troglitazone in the Prevention of Diabetes
TZD - thiazolidinedione
XENDOS - XENical in Prevention of Diabetes in Obese Subjects
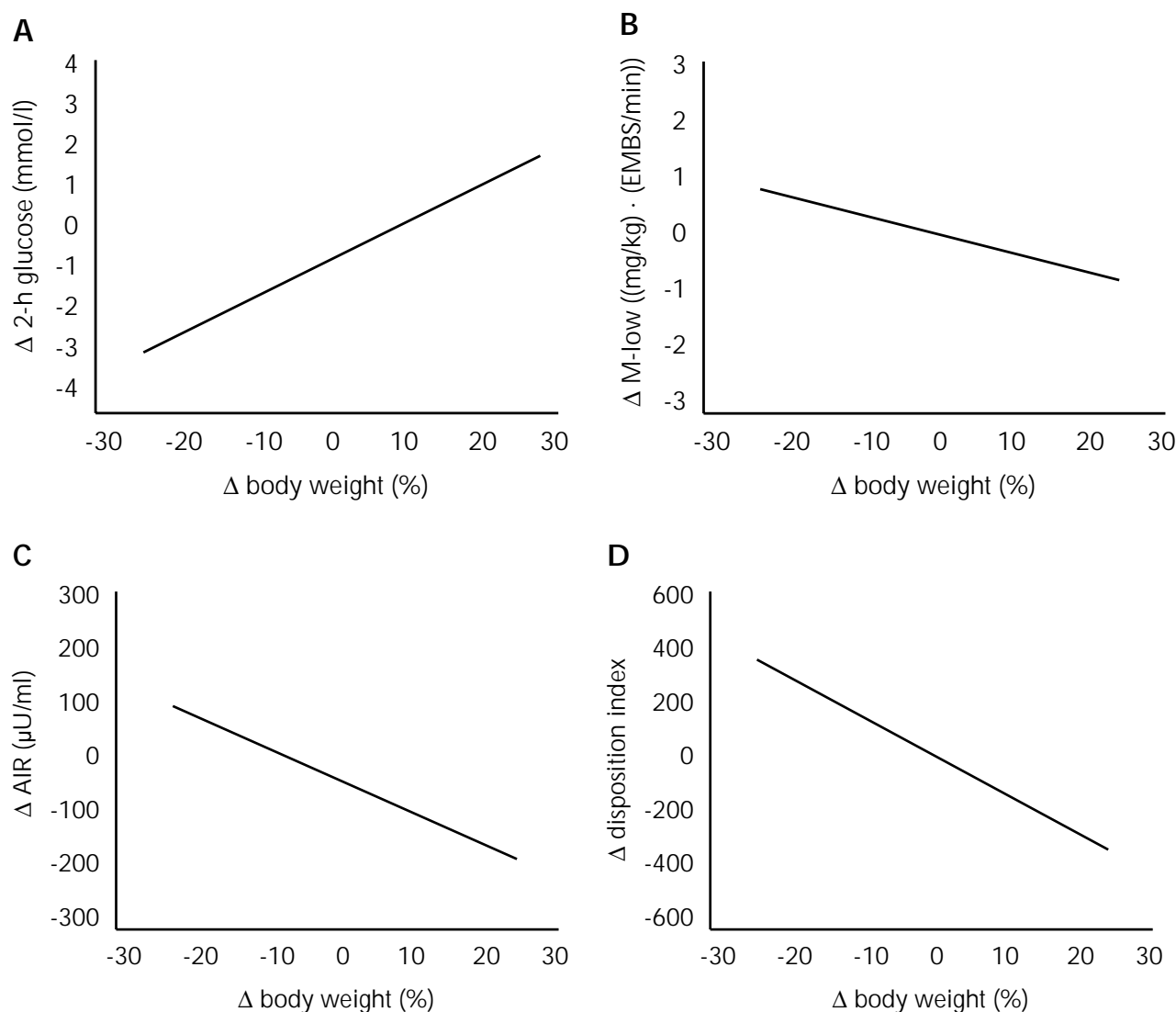
Figure 1. Relation of changes in 2-h glucose concentration (**A**), insulin action (Δ M-low) (**B**), insulin secretion (Δ AIR) (**C**), and disposition index (**D**) to change in body weight (Δ weight) in 209 Pima Indians with impaired glucose tolerance, who either lost or gained weight over an average of 2.6 ± 2 years. **Abbreviations**: AIR - acute insulin response. EBMS - estimated metabolic body size. M - insulin action. Reproduced according to Weyer et al. [9].

confidence interval (CI)). During the 20 year follow-up, the incidence of diabetes was 80% in the intervention group versus 93% in the control group (HRR 0.57; 95% CI). Although not statistically significant, the decline in body mass index (BMI) and body weight was greater in the combined intervention group than in the control group at the end of the active intervention in 1992 (0.69 kg/m² versus 0.34 kg/m² and 1.88 kg versus 0.89 kg). Although beta-cell function was not measured, this outcome

correlates with maintenance in glucose homeostasis as a probable result of beta-cell preservation.

The Finnish Diabetes Prevention Program and FIN-D2D

The Finnish Diabetes Prevention Program (DPP) was a large-scale prevention program, drawing participants across five hospital districts in Finland during 2003-2008, and FIN-D2D was a

one-year follow-up of the Finnish DPP [11]. The study was designed to include 3 major strategies: high risk, early treatment, and population. The "high risk" strategy, which was the primary, was aimed at the prevention of T2D and the reduction of cardiovascular risk factors in individuals at high risk of developing T2D according to the modified Finnish Diabetes Risk Score (FINDRISC), or a history of IFG, IGT, an ischemic cardiovascular disease event, or gestational diabetes. The "early treatment" strategy moved towards the care of early T2D in individuals who were found to have T2D on oral glucose tolerance test (OGTT). The "population" strategy worked towards raising awareness of diabetes and its associated risk factors in the overall population. A stepwise relationship between weight loss and the incidence of T2D was observed. Those who lost more than 5% of their body weight had a 69% reduction in the risk of developing T2D. The group with only 2.5-4.9% weight loss had 29% decreased risk, while the group with 2.5% weight gain had 10% increased risk. Overall, during the 4 year active intervention, the incidence of T2D was reduced by 58%. This study demonstrates that even modest weight loss can significantly reduce the risk of diabetes.

Table 1. Features and outcomes of studies analyzing weight loss in relation to diabetes prevention

Study	Length of study	Number of subjects	Outcome	Reference
CDQDPS	6 years active, 20 year follow-up	>570 Chinese persons with IGT	Incidence of T2D decreased by 23% with intervention at 6 years and 13% at 20 years	10
Finnish DPP	3 years	10,149 high-risk adults	Risk of T2D decreased by 58% with lifestyle intervention	11
FIN-D2D	1 year follow-up	2,798 adults from Finnish DPP	Weight loss of >5% of body weight produced 69% risk reduction	11
DPP	2.8 years	3,234 high-risk adults	Incidence of T2D decreased by 58% with lifestyle intervention and by 31% with metformin	9
DPPOS	5.7 year follow-up	2,766 adults from DPP	Weight loss delayed T2D by 4 years in lifestyle group and 2 years in metformin group	12, 13
DREAM	2 years	982 persons with prediabetes	Treatment with rosiglitazone resulted in significant improvements of beta-cell function	14
NAVIGATOR	5 years	9,306 person with IGT and CVD or CVD risk	Treatment with nateglinide did not reduce incidence of T2D or CV outcomes	15
ACT NOW	2.4 years	602 adults with IGT	Treatment with pioglitazone decreased conversion to T2D by 72%	18
TRIPOD	5 years	266 women with history of GDM	Treatment with troglitazone decreased T2D incidence by 18% and showed improvements in markers of beta-cell function	19
PIPOD	3 years	89 women who completed TRIPOD	Treatment with pioglitazone maintained beta-cell function; incidence of T2D was lowest in women who gained less weight	20
XENDOS	4 years	3,305 obese, non-diabetic patients	Treatment with orlistat and lifestyle interventions resulted in weight loss of 3.0 kg and reduced incidence of T2D by 52% in persons with IGT	21

Legend: ACT NOW - Actos Now for the Prevention of Diabetes, CDQDPS - China Da Qing Diabetes Prevention Study, CVD - cardiovascular disease, DREAM - Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication, DPP - Diabetes Prevention Program, DPPOS - Diabetes Prevention Program Outcomes Study, GDM - gestational diabetes mellitus, IGT - impaired glucose tolerance, NAVIGATOR - Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research, PIPOD - Pioglitazone in the Prevention of Diabetes, T2D - type 2 diabetes, TRIPOD - Troglitazone in the Prevention of Diabetes, XENDOS - XENical in Prevention of Diabetes in Obese Subjects.

The DPP and the DPPOS

The US DPP was a multicenter randomized clinical trial evaluating adults at high risk for the development of T2D defined by increased fasting plasma glucose (5.3-6.9 mmol/l) or IGT (2-hour OGTT 7.8- 11.0 mmol/l) with a BMI of 24 kg/m² or higher [12]. The primary outcome was the development of T2D. The incidence of T2D in these high-risk individuals was decreased by 58% with intensive lifestyle intervention and by 31% with metformin treatment compared to placebo at 2.8 years. Weight loss was the most important determinant of diabetes risk reduction (Figure 2).
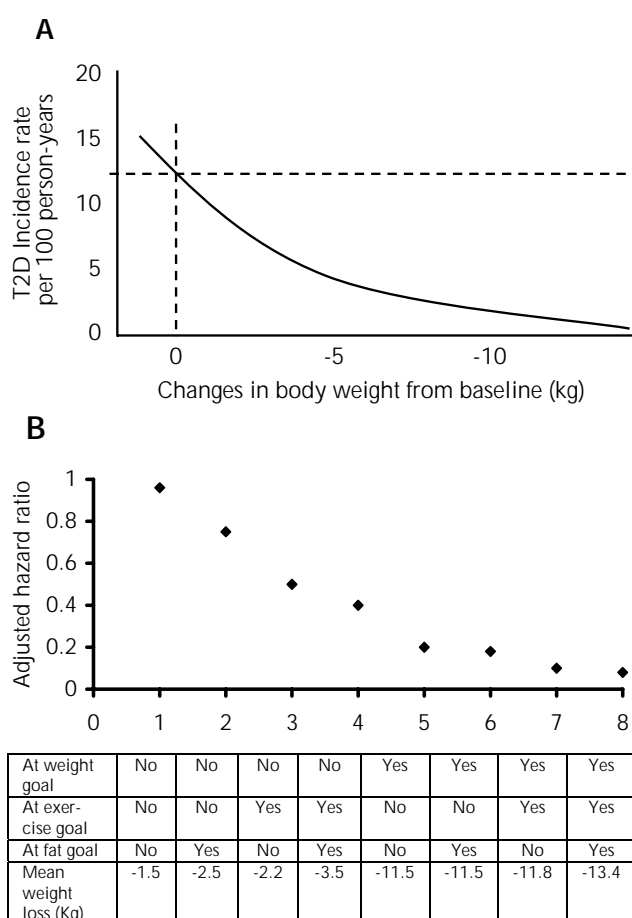
Figure 2. **A**: Diabetes incidence (per 100 person-years) by changes in weight after baseline among DPP intensive lifestyle (ILS) participants. **B**: Adjusted hazard ratios for diabetes onset over 3.2 years of follow-up in DPP ILS subgroups defined by meeting goals at 1 year compared with those not meeting goals.

The Diabetes Prevention Program Outcomes Study (DPPOS), the long-term follow-up of the DPP, evaluated whether the prevention of T2D was maintained, and also assessed long-term effects of lifestyle intervention versus metformin versus placebo [13]. Over 3000 DPP participants were eligible including the original lifestyle group with an average follow-up of 10 years. The members of the lifestyle group initially lost the most weight, about 7 kg, but did have some regain. The metformin group lost less, about 2.5 kg, but maintained the reduced weight. More importantly, this modest weight loss delayed the development of T2D by 4 years in the lifestyle group and 2 years in the metformin group. Both lifestyle and metformin were successful in long-term weight loss, and was associated with diabetes prevention. Weight loss was regarded as an important factor in the prevention of diabetes, but it may also be that the physical activity itself provokes the beneficial effect independent of weight loss, or in combination with weight loss.

The DREAM trial and the ACT NOW study

The Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) trial was a large, international, multicenter, double-blind randomized control study with 3366 persons at study end [14]. The study was designed to determine whether ramipril and/or rosiglitazone could prevent or delay the development of T2D in people with IFG or IGT. As part of a substudy, 892 DREAM trial participants attending Canadian research centers had OGTTs at baseline, again at 2 years and at study end. The primary outcome variable in the substudy was a change in beta-cell function over the course of follow-up. Beta-cell function was measured by the insulinogenic index (IGI) and proinsulin (PI) concentration. To account for a compensatory response of insulin secretion in relation to background insulin resistance, the IGI was divided by the homeostasis model assessment of insulin resistance index (HOMA-IR). The goal was to evaluate if ramipril and/or rosiglitazone could prevent or delay T2D in high-risk persons. The primary outcome was a change in beta-cell function utilizing the IGI, proinsulin concentrations, and HOMA-IR calculations.

Thiazolidinedione (TZD) improved beta-cell function significantly. This was in contrast to nateglinide, a short-acting insulin secretagogue that did not decrease the incidence of T2D in the Nateglinide and Valsartan in Impaired Glucose

Tolerance Outcomes Research (NAVIGATOR) trial [15]. The DREAM trial suggests that rosiglitazone may prevent or delay the development of T2D through effects on beta-cell function. However, it must be noted that some studies with TZD have found that, even in the presence of (modest) weight gain, the incidence of diabetes was decreased because of improved insulin sensitivity and possibly associated beta-cell function improvement [16, 17].

More recently, the Actos Now for the Prevention of Diabetes (ACT NOW) study, a randomized, double-blind, placebo-controlled study, examining the effects of a different TZD, pioglitazone, on the prevention or delay of conversion to T2D [18]. 602 patients with IGT were randomized to placebo or pioglitazone. The primary outcome was the development of diabetes (defined as a fasting plasma glucose ≥ 126 mg/dl or a 2-hour glucose level of ≥ 200 mg/dl. The participants were asked to fast overnight before undergoing an OGTT with 15 minutes serial collection for glucose, insulin, and C-peptide amongst other baseline measurements. The participants were randomized to receive pioglitazone with a titration of 30 mg to 45 mg, or alternatively, to receive placebo. Insulin sensitivity was determined from plasma glucose and insulin measurement obtained during the OGTT by way of the Matsuda index and from the results of an intravenous glucose tolerance test with frequent sampling. Beta-cell function was calculated as the index of insulin secretion factored by insulin resistance ($\Delta I_{0-120}/\Delta G_{0-120}$) x Matsuda index), where $\Delta I_{0-120}/\Delta G_{0-120}$ represents the mean incremental concentrations of plasma insulin and glucose during the 10 minute OGTT. Beta-cell function was also calculated as the product of insulin secretion and insulin sensitivity (ΔI_{0-10} x S_I). Pioglitazone reduced the risk of conversion to T2D by 72%. Insulin sensitivity, as measured with the Matsuda index, increased more with pioglitazone than with placebo (4.31 ± 0.24 to 7.65 ± 0.34 vs. 5.23 ± 0.31, p < 0.005). The index of insulin secretion factored by insulin resistance, calculated on the basis of the OGTT ($\Delta I_{0-120}/\Delta G_{0-120}$) x Matsuda index), increased more with pioglitazone than with placebo (3.43 ± 0.12 to 5.44 ± 0.31 vs. 3.81 ± 0.30 to 4.20 ± 0.20, p < 0.005).

These findings support the role of the beta-cell in glucose homeostasis, and shows TZD therapy improves beta-cell function. Further studies support that both rosiglitazone and pioglitazone decrease adipose inflammation, improve the insulin sensitivity of adipose tissue, and increase the "fat" cell hormone, adiponectin. All of these aspects are features of weight loss.

The TRIPOD study and the PIPOD study

The Troglitazone in the Prevention of Diabetes (TRIPOD) study evaluated a specific population at increased risk for the development of T2D, namely Hispanic women with a history of gestational diabetes mellitus (GDM) [19]. Insulin resistance and poor beta-cell compensation are strong predictors of post-pregnancy development of T2D. 230 women with a history of GDM were randomized to troglitazone, another member of the TZD class, 400 mg/day or placebo. Using the Bergman minimal model, whole body insulin sensitivity (SI) was calculated from intravenous glucose tolerance test (IVGTT). Overall SI was higher and IVGTT fasting insulin and total insulin areas were lower in the women randomized to study drug. During treatment, the average annual diabetes incidence rates were 12.1% in the placebo group versus 5.4% in the study group (HRR 0.45; 95% CI). More than 50 months after discontinuation of therapy, the group treated with troglitazone maintained their increased insulin sensitivity with an average annual diabetes incidence rate of 3.1% versus the placebo group which had a rate of 21.2% (HRR 0.13; 95% CI).

The Pioglitazone in the Prevention of Diabetes (PIPOD) study was a follow-up study of TRIPOD [20]. Participation was offered to women who completed the TRIPOD study. Treatment was initiated for 3 years after a 6 month post-treatment washout period. Eighty-nine women enrolled in the study, 86 of whom completed at least 1 year, and 65 completed the whole study. There was a halt in the decline of beta-cell function throughout the treatment period, but it returned to baseline when treatment was stopped. Of note, after 1 year of treatment both groups gained weight, but those who remained diabetes-free gained less weight, further supporting a role of weight maintenance in beta-cell preservation.

The XENDOS Study

The XENical in Prevention of Diabetes in Obese Subjects (XENDOS) study was a 4-year double-blind, randomized, placebo-controlled, prospective study performed at 22 Swedish medical centers from 1997-2002 [21]. Patients were randomized to orlistat, a gastrointestinal lipase inhibitor, 120 mg versus placebo with calorically reduced meals and lifestyle change recommendations. The primary objective was to determine the effect of orlistat in combination with a diet and lifestyle prescription on the delay of T2D and effects on body weight in

obese, non-diabetic patients with NGT or IGT. Assessments included a 75-g OGTT performed at baseline, and then at every 6 months in addition to standard clinical lab parameters and body weight and waist circumference measures. Weight loss was significantly greater in the orlistat group (6.9 kg versus 4.1 kg in the placebo group) at study completion. Over the 4-year study period, orlistat significantly decreased the progressive incidence of T2D by 37.3% compared to placebo. However, more specific measures of beta-cell function were not documented.

Conclusions

Together these pivotal studies suggest that weight loss prevents diabetes, and in turn preserves beta-cell function. At present, it is assumed that an increase in the intracellular deposition of triglycerides (TG) caused by visceral adipocytes flooding the portal circulation with free fatty acids leads to ectopic TG accumulation in muscles, liver, and pancreas. In subjects prone to diabetes, this event retards glucose metabolism by interfering with insulin signaling and insulin secretion, and finally leads to beta-cell dysfunction, IFG, and IGT [22]. A strategy to reduce the excessive fat outflow from the abdominal depots and to prevent ectopic fat deposition is to reduce the volume of visceral fat depots by weight loss.

Weight loss has positive effects on adipose tissue. It causes an increase in the beneficial fat cell hormone adiponectin, and a decrease in adipose tissue inflammation [23]. Also, it is associated with a reduction of insulin resistance and a resulting reduction in glucolipotoxicity, which can improve beta-cell function in itself. In summary, weight loss improves glycemic control and thereby mitigates diabetes symptoms and complications possibly through the preservation of beta-cell function. Based on these data, future efforts to prevent diabetes and preserve beta-cell function in patients with T2D should therefore more rigorously emphasize and target weight loss.

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■ References

1. **Garber AJ.** Obesity and type 2 diabetes: which patients are at risk? *Diabetes Obes Metab* 2012. 14(5):399-408.
2. **Perugini RA, Malkani S.** Remission of type 2 diabetes mellitus following bariatric surgery: review of mechanisms and presentation of the concept of 'reversibility'. *Curr Opin Endocrinol Diabetes Obes* 2011. 18(2):119-128.
3. **Lorenzo C, Wagenknecht LE, D'Agostino RB Jr, Rewers MJ, Karter AJ, Haffner SM.** Insulin resistance, beta-cell dysfunction, and conversion to type 2 diabetes in a multiethnic population: the Insulin Resistance Atherosclerosis Study. *Diabetes Care* 2010. 33(1):67-72.
4. **Guillausseau PJ, Meas T, Virally M, Laloi-Michelin M, Medeau V, Kevorkian JP.** Abnormalities in insulin secretion in type 2 diabetes mellitus. *Diabetes Metab* 2008. 34(Suppl 2):S43-S48.
5. **Bastard JP, Maachi M, Lagathu C, Kim MJ, Caron M, Vidal H, Capeau J, Feve B.** Recent advances in the relationship between obesity, inflammation, and insulin resistance. *Eur Cytokine Netw* 2006. 17(1):4-12.
6. **Bergman RN, Ader M, Huecking K, Van Citters G.** Accurate assessment of beta-cell function: the hyperbolic correction. *Diabetes* 2002. 51(Suppl 1):S212-S220.
7. **Villareal DT, Banks MR, Patterson BW, Polonsky KS, Klein S.** Weight loss therapy improves pancreatic endocrine function in obese older adults. *Obesity (Silver Spring)* 2008. 16(6):1349-1354.
8. **Borissova AM, Tankova TI, Koev DJ.** Insulin secretion, peripheral insulin sensitivity and insulin-receptor binding in subjects with different degrees of obesity. *Diabetes Metab* 2004. 30(5):425-431.
9. **Weyer C, Hanson K, Bogardus C, Pratley RE.** Long-term changes in insulin action and insulin secretion associated with gain, loss, regain and maintenance of body weight. *Diabetologia* 2000. 43:36-46.
10. **Li G, Zhang P, Wang J, Gregg EW, Yang W, Gong Q, Li H, Li H, Jiang Y, An Y, et al.** The long-term effect of lifestyle interventions to prevent diabetes in the China Da Qing Diabetes Prevention Study: a 20-year follow-up study. *Lancet* 2008. 371:1783-1789.
11. **Saaristo T, Moilanen L, Korpi-Hyovalti E, Vanhala M, Saltevo J, Niskanen L, Jokelainen J, Peltonene M, Oksa H, Tuomilehto J, Uusitupa M, Keinanen-Kiukaanniemi S.** Lifestyle intervention for prevention of type 2 diabetes in primary health care: one-year follow-up of the Finnish National Diabetes Prevention Program (FIN-D2D). *Diabetes Care* 2010. 33(1):2146-2151.
12. **Hamman RF, Wing, RR, Edelstein SL, Lachin JM, Bray GA, Delahanty L, Hoskin M, Kriska AM, Mayer-Davis EJ, Pi-Sunyer X, et al.** Effect of weight loss with lifestyle intervention on risk of diabetes. *Diabetes Care* 2006. 29:2102-2107.
13. **Diabetes Prevention Program Research Group, Knowler WC, Fowler SE, Hamman RF, Christophi CA, Hoffman HJ, Brenneman AT, Brown-Friday JO, Goldberg R, Venditti E, Nathan DM.** 10-year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009. 374(9702):1677-1686.
14. **Henly AJ, Zinman B, Sheridan P, Yusuf S, Gerstein HC.** Effect of rosiglitazone and ramipril on beta-cell function in people with impaired glucose tolerance on impaired fasting glucose - the DREAM trial. *Diabetes Care* 2010. 33:608-613.
15. **The NAVIGATOR Study Group, Holman RR, Haffner SM, McMurray JJ, Bethel MA, Holzhauer B, Hua TA, Belenkov Y, Boolell M, Buse JB, et al.** Effect of nateglinide on the incidence of diabetes and cardiovascular events. *N Engl J Med* 2010. 362(16):1463-1476.

16. **Miyazaki Y, Glass L, Triplitt C, Matsuda M, Cusi K, Mahankali A, Mahankali S, Mandarino LJ, DeFronzo RA.** Effect of rosiglitazone on glucose and non-esterified fatty acid metabolism in type II diabetic patients. *Diabetologia* 2001. 44(12):2210-2219.

17. **DeFronzo RA, Triplitt C, Qu Y, Lewis MS, Maggs D, Glass LC.** Effects of exenatide plus rosiglitazone on beta-cell function and insulin sensitivity in subjects with type 2 diabetes on metformin. *Diabetes Care* 2010. 33(5):951-957.

18. **DeFronzo RA, Tripathy D, Schwenke DC, Banerji M, Bray GA, Buchanan TA, Clement SC, Henry RR, Hodis HN, Kitabchi AE, et al.** Pioglitazone for diabetes prevention in impaired glucose tolerance. *N Engl J Med* 2011. 364:1104-1115.

19. **Buchanan TA, Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Tan S, Berkowitz K, Hodis HN, Azen SP.** Preservation of pancreatic beta-cell function and prevention of type 2 diabetes by pharmacological treatment of insulin resistance in high-risk Hispanic women. *Diabetes* 2002. 51:2796-2803.

20. **Xiang AH, Peters RK, Kjos SL, Marroquin A, Goico J, Ochoa C, Kawakubo M, Buchanan TA.** Effect of pioglitazone on pancreatic beta-cell function and diabetes risk in Hispanic women with prior gestational diabetes. *Diabetes* 2006. 55:517-522.

21. **Togerson JS, Hauptman J, Boldrin MN, Sjostrom L.** XENical in the prevention of diabetes in obese subjects (XENDOS) study. *Diabetes Care* 2004. 27:155-161.

22. **Raz I, Eldor R, Cernea S, Shafrir E.** Diabetes: insulin resistance and derangements in lipid metabolism. Cure through intervention in fat transport and storage. *Diabetes Metab Res Rev* 2005. 21(1):3-14.

23. **Kopp HP, Krzyzanowska K, Möhlig M, Spranger J, Pfeiffer AF, Schernthaner G.** Effects of marked weight loss on plasma levels of adiponectin, markers of chronic subclinical inflammation and insulin resistance in morbidly obese women. *Int J Obes (Lond)* 2005. 29(7):766-771.