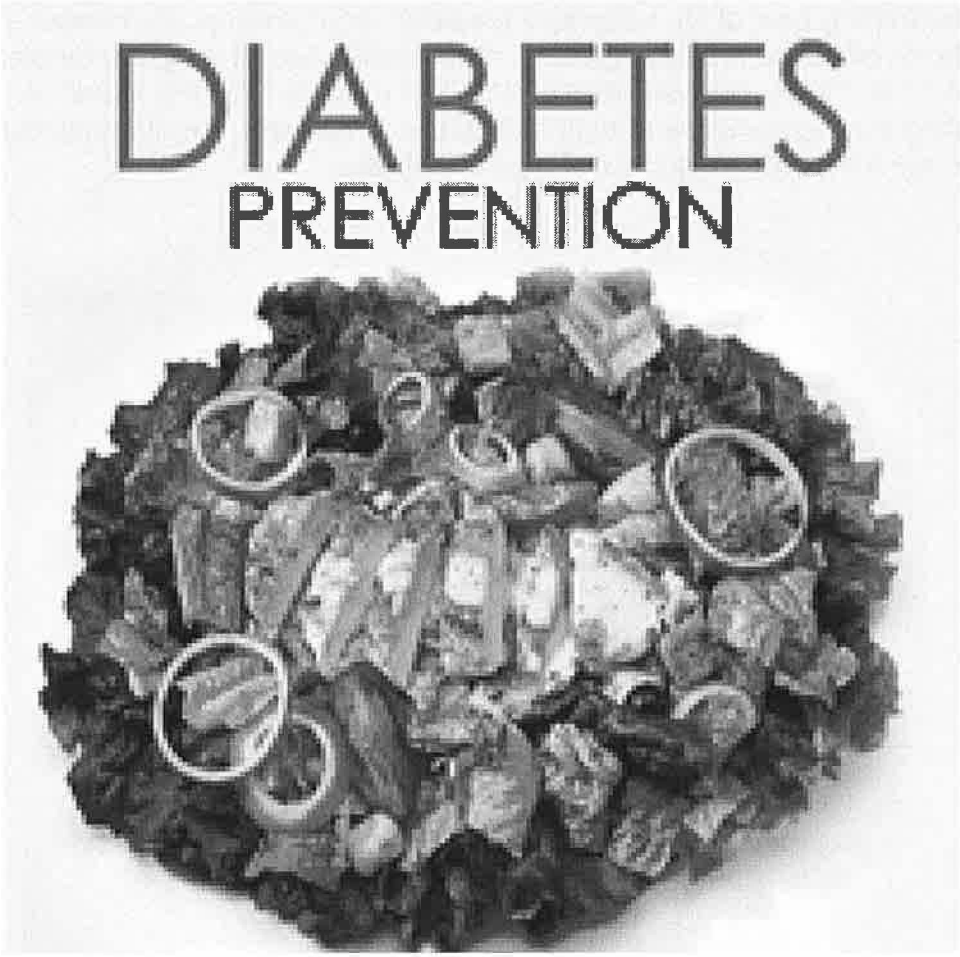

MORE THAN A DREAM?

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Internal Medicine Grand Rounds
June 20th, 2008

The overarching goal of Dr. Lingvay's research is to develop, implement, and promote an effective, multidisciplinary, mechanistic-based program for diabetes prevention and early disease intervention. Her research studies focus on unraveling the mechanisms of beta-cell failure in humans, a main pathogenic mechanism for the development of type 2 diabetes.

This is to acknowledge that Ildiko Lingvay, M.D., M.P.H., M. Clinical Sciences, has not disclosed any financial interests or other relationships with commercial concerns related directly or indirectly to this program. Dr. Lingvay will be discussing off-label uses in the presentation. Note: For the purpose of this presentation, type 2 diabetes will be referred to as "diabetes".

1. Why are diabetes prevention and early disease intervention important?

a. The prevalence of diabetes has tripled over the previous 2 decades.

In the US alone, it is estimated that 20.8 million adults and children (or 7% of the population) have diabetes. In addition, 54 million people are estimated to have pre-diabetes [1]. The prevalence of diabetes over the previous 2 decades has more than tripled [2] and future predictions are even more worrisome. According to the World Health Organization, the prevalence of diabetes worldwide will rise from 171 million in 2000 to 366 million in 2030 [3]. Such an unprecedented epidemic of a chronic disease will severely impact our health system and society; therefore prevention of diabetes and its associated complications is a very high national and global health priority [4, 5].

b. Microvascular complications are already present at the time of diabetes diagnosis and in subjects with pre-diabetes.

Microvascular complications associated with diabetes, including neuropathy, retinopathy, and nephropathy, are the leading cause of decreased quality of life, morbidity, and severe disability in this population. Once believed that such complications only occur after years of uncontrolled hyperglycemia, recent evidence suggests otherwise. Retinopathy, one of the complications most closely associated with diabetes and the leading cause of blindness in the US, was present in 7.9% of subjects with impaired glucose tolerance (IGT) and 12.6% of subjects with newly identified diabetes in the Diabetes Prevention Program (DPP) cohort [6]. In the DREAM study, 15.7% of the subjects had a renal abnormality associated with hyperglycemia [7]. These findings suggest that hyperglycemia-associated complications occur early in the course of disease and are often present at the time of diagnosis of diabetes or prior to diagnosis. Thus, early detection of dysglycemia and intensive intervention might be warranted.

c. Heart disease and stroke account for 65% of deaths in people with diabetes.

Diabetes is the fifth-deadliest disease in the United States. Since 1987 the death rate due to diabetes has increased by 45 percent, while the death rates due to heart disease, stroke, and cancer overall have declined. People with diabetes are 2-4 times more likely to develop cardiovascular disease, and are 2-4 times more likely to die in the event of a stroke or heart attack [8]. Though not yet proven scientifically, it is believed that preventing diabetes will result in a decreased burden of cardiovascular disease and associated mortality.

d. The diabetes-related cost is enormous.

The total annual economic cost of diabetes in 2007 was estimated to be $174 billion. Medical expenditures totaled $116 billion and were comprised of $27 billion for diabetes care, $58 billion for chronic diabetes-related complications, and $31 billion for excess general medical costs. Indirect costs resulting from increased absenteeism, reduced productivity, disease-related unemployment disability, and loss of productive capacity due to early mortality totaled $58 billion. This is an increase of $42 billion since 2002 (or 32%) [9]. These estimates omit the social cost of intangibles such as pain and suffering, care provided by non-paid caregivers, excess medical costs associated with undiagnosed diabetes, and diabetes-attributed costs for health care expenditure categories not studied.

Therefore the actual cost of diabetes is much higher. Diabetes represents an enormous economic burden to society, and if the current trends in diabetes prevalence and health care cost continue, we can anticipate a major strain on economy.

In conclusion, there is a strong rationale for early disease intervention and diabetes prevention. This manuscript will review updated results of pharmacological and lifestyle intervention diabetes prevention trials.

2. The pathophysiology of diabetes: two main players in the ring.

The main pathogenic determinants of diabetes are insulin sensitivity and beta-cell function. A fine balance between these 2 elements exists in order for normoglycemia to be maintained. Subjects with normoglycemia have varying degrees of insulin sensitivity (as much a 6-7 fold range), which is accommodated by an increase in insulin secretion [10]. When beta-cell function is no longer able to compensate for the change in insulin sensitivity, hyperglycemia ensues. **Therefore beta-cell dysfunction is mandatory for the occurrence of diabetes.** Interestingly, it was noted that insulin sensitivity decreases significantly very early in the pathogenesis of the disease, but plateaus before significant hyperglycemia occurs and diabetes is diagnosed (Figure 1).

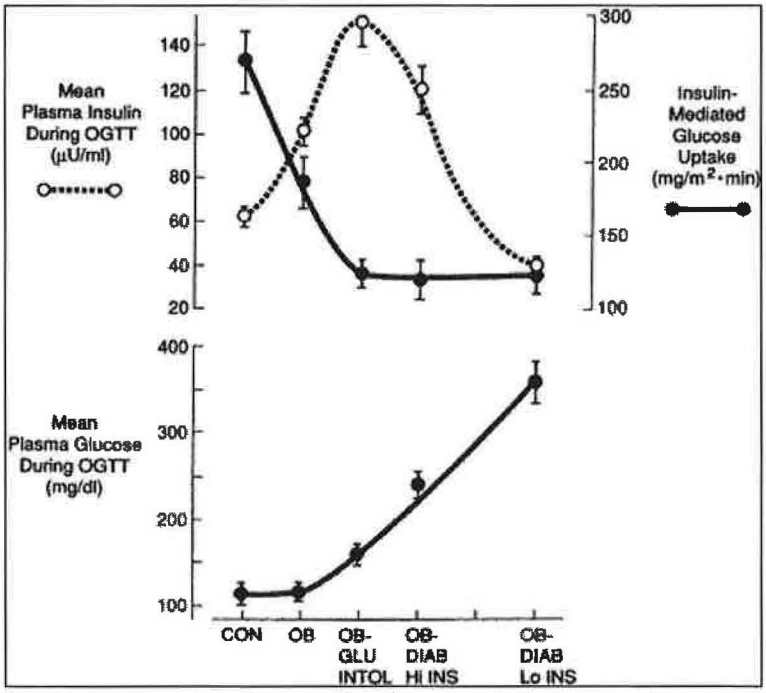

Figure 1 The relationship between insulin secretion (represented as mean plasma insulin during OGTT) and insulin sensitivity (represented as insulin-mediated glucose uptake) at varying degrees of hyperglycemia during an oral glucose tolerance test. CON – control group; OB – obese group with normal glucose tolerance; GLU INTOL – glucose intolerance; DIAB HI INS – diabetes with high insulin levels; Lo INS – low insulin levels. [11]

The dynamic of beta-cell function is different. In the initial phases of the disease, when insulin sensitivity decreases, insulin secretion rises to maintain normoglycemia. In fact, most subjects with insulin resistance are able to compensate appropriately and do not

develop diabetes. In individuals predisposed to diabetes, pancreatic beta-cells cannot compensate for insulin resistance. A relative insulin deficiency occurs, which leads initially to mild postprandial hyperglycemia (i.e. IGT). As the insulin secretion continues to decline, frank hyperglycemia occurs [12]. This pattern has been referred to as the Starling's curve of the pancreas for insulin secretion [13]. When followed longitudinally, normal subjects who progressed to IGT and diabetes and who had initially severe insulin resistance and a mild beta-cell dysfunction, showed a minimal deterioration of insulin sensitivity but a dramatic loss of beta-cell function [14]. Beta-cell dysfunction in subjects predisposed to the development of diabetes occurs long before diagnosis. Mathematical modeling of data from the UKPDS showed that at the time of diagnosis 50% of beta-cell function has been lost [15]. It also indicated that beta-cell function decline starts on average 10 years prior to the diagnosis of diabetes and that by 10-15 years after diagnosis insulin secretion is virtually lost (Figure 2).

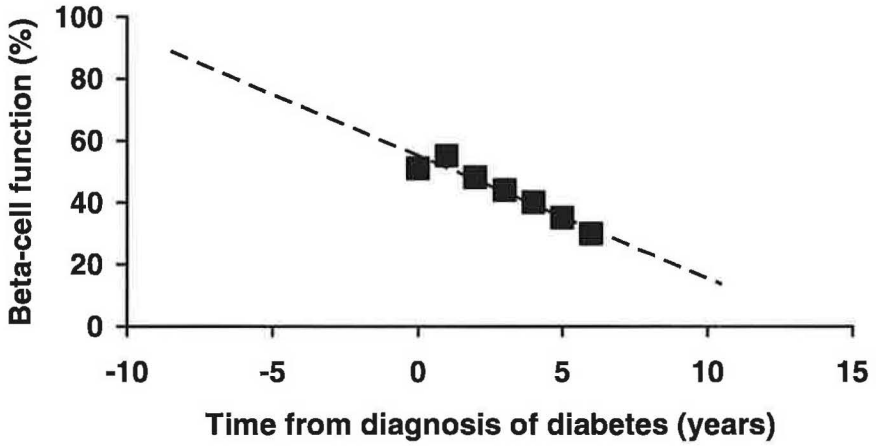

Figure 2: The progressive decline of beta-cell function starts approximately 10 years prior to diagnosis of diabetes. At the time of diagnosis, approximately 50% of the beta-cell function has been lost [15].

Multiple mechanisms contribute to the failure of beta-cell function. In addition to a genetic predisposition, acquired factors play a major role. These include: lipotoxicity, glucotoxicity, whole body insulin resistance increasing beta-cell demand, inflammation, oxidant stress, beta-cell insulin resistance and others.

Therefore, two main disorders contribute to the development of diabetes: insulin resistance and beta-cell dysfunction, and both of these abnormalities are present long before the actual diagnosis. Hence, the protection of pancreatic beta-cell function is essential to change the natural history of diabetes.

IGT, impaired fasting glucose (IFG), and diabetes are diagnosed empirically based only on fasting and/or post glucose load blood glucose levels (Table 1) [16]. It is important to note that even though categories with arbitrary cut-off points are used for diagnostic purposes, we are dealing with a continuous spectrum of abnormalities, were both insulin resistance and beta-cell dysfunction are present already at the "normal" glucose range in high risk individuals [17].

Table 1: Diagnosis criteria for Normal Glucose Tolerance (NGT), Impaired Fasting Glucose (IFG), Impaired Glucose Tolerance (IGT), and Diabetes. If only fasting serum glucose level is used for diagnosis of diabetes, a value of >125 mg/dl should be confirmed with a second measurement on a separate day.

	Serum glucose level (mg/dl)	
	Fasting	2 hrs after ingestion of 75 g of glucose solution
NGT	<100	<140
IFG	100-125	<140
IGT	100-125	140-199
Diabetes	>125	>199

The prevalence of IFG and/or IGT is difficult to estimate since screening is not done routinely in the population, and the Oral Glucose Tolerance Test (OGTT) is almost never used in clinical practice in the US. In the Diabetes Prevention Program, 27.2% of screened individuals had IFG and/or IGT, with an additional 13% who met the criteria for diabetes [18]. The natural history of IFG and/or IGT is variable, depending highly on the population studied, but it is thought that approximately 25% revert to normal glycemic status, 25% progress to fulfill criteria for diabetes, and 50% remain in their abnormal glycemic state over an observational period of approximately 3-5 years [19]. Older, overweight individuals with other classic diabetes-related risk factors are thought to be at a particular increased risk of progression to diabetes [18]. Also, individuals with a lower beta-cell reserve at baseline have the highest rate of progression to diabetes.

Therapeutic agents/classes with a potential beneficial effect on beta-cell function and possibly diabetes prevention are listed in Figure 3.

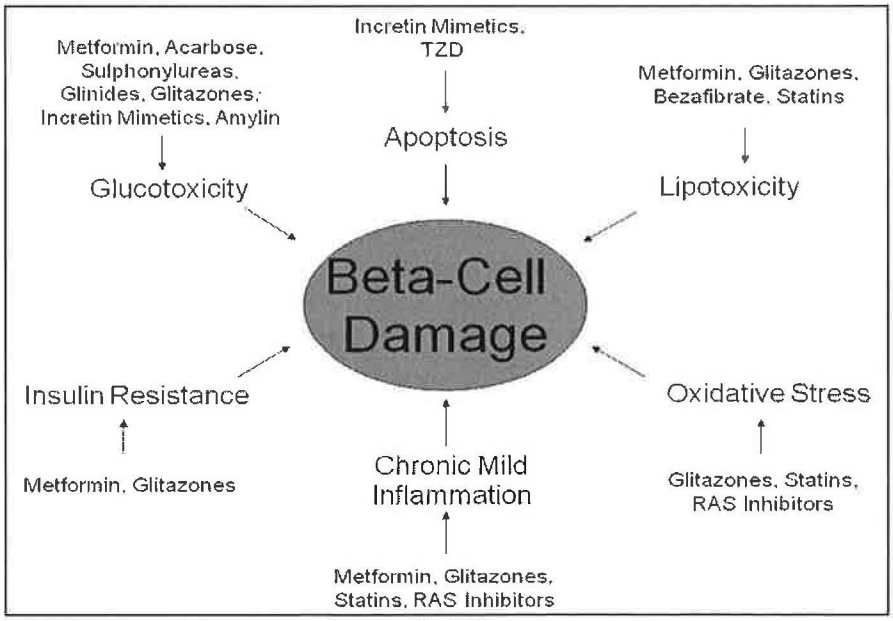

Figure 3: Drugs with potential to protect beta-cells [20].

In conclusion, an effective diabetes prevention intervention would have to significantly modify the main disease determinants, in addition to being practical, sustainable in the long-run, safe, and cost-effective.

3. Diabetes prevention studies

Several interventional studies evaluated the effect of lifestyle changes or various pharmacological agents on the rate of diagnosis of diabetes.

a. Lifestyle interventions:

Lifestyle interventions aimed at a weight loss of more than 5% of body weight through diet and/or increase in exercise level positively influence many of the risk factors associated with hyperglycemia. This kind of intervention was shown to improve whole body insulin resistance, and possibly improve beta-cell function by reducing excess demand and a reduction in lipotoxicity. The benefit of lifestyle intervention is that it will likely be sustained beyond the active intervention period, conferring a lasting effect on the beneficial effects noted.

The Diabetes Prevention Program (DPP) is the largest and most ethnically diverse study to date that evaluated the effect of an intensive lifestyle modification program on the rate of diagnosis of diabetes. More than 3,800 subjects with IGT were randomized into four treatment arms: intensive lifestyle intervention, placebo, metformin, or troglitazone [21]. This study was prematurely stopped by the sponsoring institution (NIDDK) because of an observed significant benefit in the intervention groups. Subjects randomized to the intensive lifestyle reached their goal of a mean 7% weight loss, which was maintained for 1 year, following which a small weight regain ensued. At the end of the study follow-up period, subjects had a mean weight loss of 4%. The placebo group maintained a constant weight through the study. The incidence of diabetes was 11% and 4.8% per year in the placebo and lifestyle groups, respectively, an overall 58% relative reduction (Figure 4) [22].

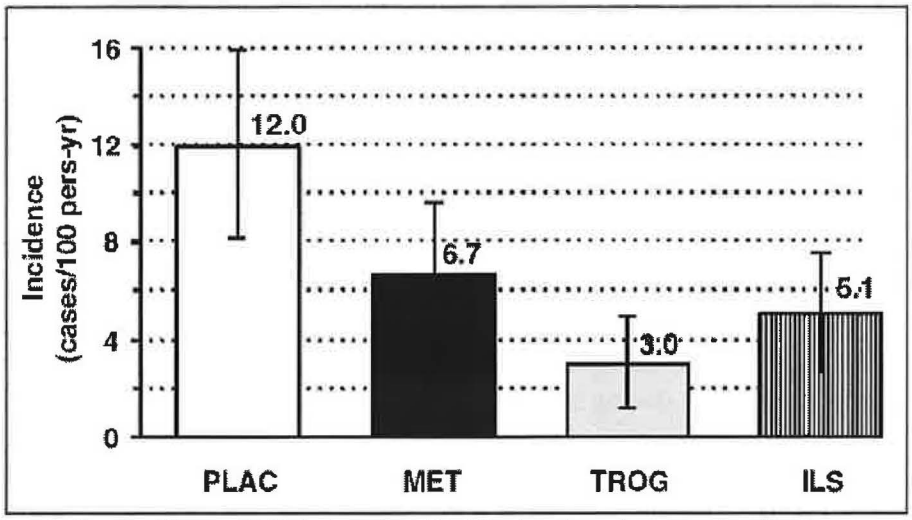

Figure 4: Cumulative incidence of diabetes, stratified by treatment group, for the four-arm Diabetes Prevention Program. TROG-troglitazone, ILS-intensive lifestyle, MET-metformin, PLAC-placebo [21].

In the Da Qing Study, 577 subjects were randomized to receive a diet intervention, exercise only, diet and exercise, or placebo. After a mean of 6 years of follow-up, there was a 31% relative risk reduction in the diet group, 46% in the exercise group, and 42% in the combined group (HRR 0.49 for the combined intervention group versus control) [23].

In the Finish Diabetes Prevention Study (DPS), 522 patients with IGT were randomized to intensive lifestyle intervention versus routine care. After a median of 3.2 years of follow-up, there was a 58% reduction in the incidence of diabetes in the intervention group [24].

In the Indian Diabetes Prevention Program (DPP), 531 subjects with IGT were randomized to 4 groups: control, lifestyle modification, metformin, lifestyle and metformin. The study aimed to evaluate if such interventions are also beneficial in a leaner population of asian-indian origin. Diabetes occurred in 55%, 39.3%, 40.5%, or 39.5% of the population in the 4 groups, respectively. Therefore, lifestyle interventions resulted in a 28.5% relative reduction in the occurrence of diabetes, and the combination of intensive lifestyle modifications with metformin did not confer any additional protection [25].

Table 2: Summary of lifestyle and metformin intervention trials. DPP – Diabetes Prevention Program; Da Qing – The Da Qing IGT and Diabetes Study; DPS – Diabetes Prevention Study; RRR – relative risk reduction.

Study	DPP	Da Qing	Indian DPP	Finish DPS
Reference	[22]	[23]	[25]	[24]
Total enrolled	3800	577	531	522
Follow-up (yrs)	3	6	2.5	3.2
Rate of diabetes in the control group (%)	33	66	55	23.6
RRR in the lifestyle group (%)	58	42	28.5	58
RRR in the metformin group (%)	31	n/a	26.4	n/a

b. **Metformin:**

Metformin is an oral hypoglycemic agent from the biguanide class, approved for the treatment of diabetes. Metformin reduces hepatic insulin resistance, and is also thought to improve whole-body insulin resistance. It might also modulate beta-cell function through improvement in glucotoxicity, lipotoxicity, decrease in demand, and possibly reduction in inflammation [26], all of which could contribute to the prevention or delay of diabetes. It is an attractive agent for chronic use as it has a weight neutral (or even weight loss) profile and a low occurrence of side-effects.

The Diabetes Prevention Program (DPP) study also evaluated the effect of metformin on the incidence of diabetes [27]. The rate incidence of diabetes in this group was 7.8%, representing a relative risk reduction of 31% compared with the placebo group (Figure 4) [22]. Patients randomized to this group lost 2.5 % of their body weight within the first year of treatment but regained it during the subsequent 2 years.

The Indian DPP showed a relative risk reduction for treatment with metformin over a median of 30 months of 26.4%, and in the combined metformin and lifestyle modification group of 28.2% [25].

c. Thiazolidinediones:

Thiazolidinediones (TZDs) are Peroxisome-Proliferator-Activated Receptor gamma (PPAR γ) agonists that have been approved for treatment of diabetes. TZDs improve insulin sensitivity and have a beneficial effect on beta-cell function through direct and indirect mechanisms [28]. Treatment with TZDs has been associated with significant weight gain through an increase in adipose-tissue mass, but a sparing of other insulin-sensitive tissues such as skeletal muscle and the liver, possibly even pancreatic beta-cells, from the harmful metabolic effects of high concentrations of free fatty acids. All these properties render this drug class a promising diabetes prevention agent.

The first TZD on the market was troglitazone, a very potent insulin sensitizer, but it was withdrawn from the market in 1998 due to an idiosyncratic reaction leading to liver failure. Two agents have been since used: pioglitazone and rosiglitazone. Though these agents are potent insulin sensitizers, their use has been hampered by the side-effect profile, mainly pedal edema (up to 20% of patients), congestive heart failure (up to 5% of patients), weight gain [29], and some bad publicity [30].

Troglitazone's effect on diabetes prevention was evaluated in 3 studies. The DPP had a troglitazone arm that was discontinued early when one patient suffered fatal liver failure. In this study, a total of 585 participants were treated with troglitazone for a mean of 0.9 years (range 0.5-1.5 years). The incidence of diabetes in this limited period of use was 3.0 cases/100 person-years, compared with 12.0, 6.7, and 5.1 cases/100 person-years in the placebo, metformin, and intensive lifestyle participants respectively (Figure 4) [31].

The TRIPOD study (TRoglitazone Prevention Of Diabetes) reported a reduction in the incidence of diabetes from 12.5% to 5.4% after a median follow-up of 30 months [32]. This study enrolled females with previous gestational diabetes mellitus who were randomized to receive troglitazone 400 mg/day or placebo. The authors analyzed the change in insulin resistance and insulin secretion and concluded that diabetes prevention with troglitazone was mediated mainly through an improvement of the beta-cell function. There was a high attrition rate of nearly 33% during the follow-up (in both groups, but higher in the intervention group).

A smaller cohort study evaluated the effect of troglitazone 400 mg daily, followed by rosiglitazone 4 mg daily or pioglitazone 30 mg daily, and observed an 89% risk reduction in the incidence of diabetes in the active intervention group [33], results consistent with the larger, randomized trials described above.

Women who completed the TRIPOD study were offered treatment with pioglitazone (30 mg daily for 2 months, followed by 45 mg daily) for a total of 3 years – PIPOD Study (Pioglitazone In Prevention Of Diabetes). Diabetes occurred at a rate of 4.6% per year. A comparison of changes in beta-cell compensation for insulin resistance across the TRIPOD and PIPOD studies revealed that pioglitazone stopped the decline in beta-cell function that occurred during placebo treatment in the TRIPOD study and maintained the stability of beta-cell function that had occurred during troglitazone treatment in the TRIPOD study [34].

Results of the ACTos NOW for the Prevention of Diabetes (ACT NOW) Study were reported recently at the American Diabetes Association (ADA) Annual Scientific Session in San Francisco, June 6-10th, 2008. In this study, 602 subjects with IGT were randomized to receive pioglitazone (45 mg daily) or placebo and were followed for a mean of 2.6 years (range 2-4 years). Diabetes occurred in 6.8% of subjects in the placebo group and 1.5% in the pioglitazone group, a relative risk reduction of 81% [35].

Rosiglitazone treatment in patients with IGT and no previous CVD was studied along with ramipril in a large, multicenter study, using a 2x2 factorial design [36], in the DREAM study (Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication). These participants were followed for a median of 3 years, over which period 11.6% of individuals developed diabetes in the rosiglitazone group, versus 26% in the placebo group (HR 0.40) [37].

d. **Other hypoglycemic agents**

Other hypoglycemic agents, like acarbose and sulfonylurea agents have also been evaluated. None of the sulfonylurea studies showed any significant improvement in the rate of occurrence of diabetes, although they were very small and possibly underpowered studies [38-40]. Given the mechanism of action of these agents, they are potent hypoglycemic agents, but are thought to promote beta-cell exhaustion [20], therefore are not ideal candidates for diabetes prevention.

Acarbose, an alpha-glucosidase inhibitor, improves insulin resistance and lowers glucose level, both mechanisms presumably leading to the relief of stress on the beta-cell. The STOP NIDDM trial (Study to Prevent Non-Insulin Dependent Diabetes Mellitus) randomized 1429 patients with IGT to acarbose 100 mg three times a day or placebo. After a mean of 3.3 years of follow-up, diabetes occurred in 42% of the patients in the placebo group, and 32% in the acarbose group, a relative risk reduction of 25%. A high gastro-intestinal side effect rate led to a 31% discontinuation rate in the acarbose group (versus 19% in the placebo group) [41].

e. **AT1 receptor blockade**

Secondary analysis of large hypertension trials have shown that Angiotensin Converting Enzyme inhibitors (ACEI) and Angiotensin Receptor Blockers (ARB) may lower the incidence of diabetes (RRR 34% in the HOPE trial with ACEI and approximately 20% with ARB in the CHARM, SCOPE, and VALUE trials) [42, 43].

The mechanism of action of the renin-angiotensin-aldosterone system (RAAS) blockade and its role in diabetes prevention is probably mediated through modulation of the adipocyte function and the ability of mature adipocytes to store fat. Decreasing angiotensin II levels with an ACEI or blocking the angiotensin II receptor with an ARB may promote recruitment of preadipocytes, thereby increasing the number of small insulin-sensitive adipocytes. Redistribution of lipids from muscle and other tissues to adipose tissue would result in improved insulin sensitivity [44]. ARBs and ACE inhibitors may also favorably affect the pancreatic beta-cell by increasing perfusion of the islet cell [45, 46] and

preserving pancreatic beta-cell function [46]. Many other possible mechanisms for the potentially beneficial effect of these agents on the risk of diabetes have been postulated [20].

Based on these preliminary results, a large confirmatory trial was designed to test the effect of ramipril (an ACEI) on the incidence of diabetes. In the DREAM, study 5269 participants at high risk of diabetes were randomized to receive ramipril 15 mg daily or placebo. After a median of 3 years of follow-up, the incidence of the primary outcome (development of diabetes or death) did not differ significantly between groups (18.1% versus 19.5% in the ramipril and placebo groups, respectively) [47], but the group treated with ramipril was more likely regress to normoglycemia and had a lower plasma glucose level 2 hours after an oral glucose load.

f. Anti-obesity agents

Anti-obesity agents are good candidates for early intervention in the pathogenic pathway of diabetes through weight loss induced improvement in risk factors. Orlistat was evaluated in the Xenical for the Prevention of Diabetes in Obese Subjects (XENDOS) against placebo in 3305 obese patients for 4 years. Orlistat led to a weight loss of 2.8 kg over placebo, and a relative risk reduction of diabetes of 37%. Unfortunately this study had a very high attrition rate as well (57%), mostly due to gastrointestinal side-effects [48]. A meta-analysis of 3 smaller weight loss studies using orlistat confirmed these results. The incidence of diabetes was 2% in the placebo group and 0.6% in the orlistat group (a RR of 75%). These trials had a very low incidence rate of diabetes and a high attrition rated that averaged more than 30% [49].

g. Other pharmacologic classes

Statins, fibrates, and estrogen replacement have all shown positive signal effect on diabetes prevention (as secondary or post-hoc analyses), but all of these lack definitive studies supporting their effectiveness [50].

4. Effective interventions: delay or prevention?

The distinction between delay and prevention of diabetes in clinical trials is highly debated. Considering the pathophysiology of diabetes, true disease prevention requires stabilization or improvement of beta-cell function (given a constant level of insulin demand). In clinical trials though, diabetes prevention is measured with a "surrogate" end-point, which is a dichotomous variable of whether the subject has met the empiric blood glucose criteria for diagnosis of diabetes (as described above). Therefore, in the context of a relatively short clinical trial (3-6 years is a short period compared with the natural history of diabetes development), there are two ways in which this endpoint can be avoided: (1) A real modification of the pathophysiology of diabetes that leads to true prevention/delay of disease. Slowing in the deterioration of beta-cell function will lead to a delay, while a halt or improvement in beta-cell function will lead to prevention of diabetes. In this case scenario, a lower incidence of diabetes is maintained even after discontinuation of the active intervention. (2) By lowering the blood glucose level during the intervention period. In this situation, fewer people will cross the threshold for diagnosis of diabetes, but in the

absence of any change in the underlying disease biology, therefore as soon as the intervention is stopped the cumulative rate of diabetes "catches-up" with that in the control group. This concept is depicted graphically in Figure 5.

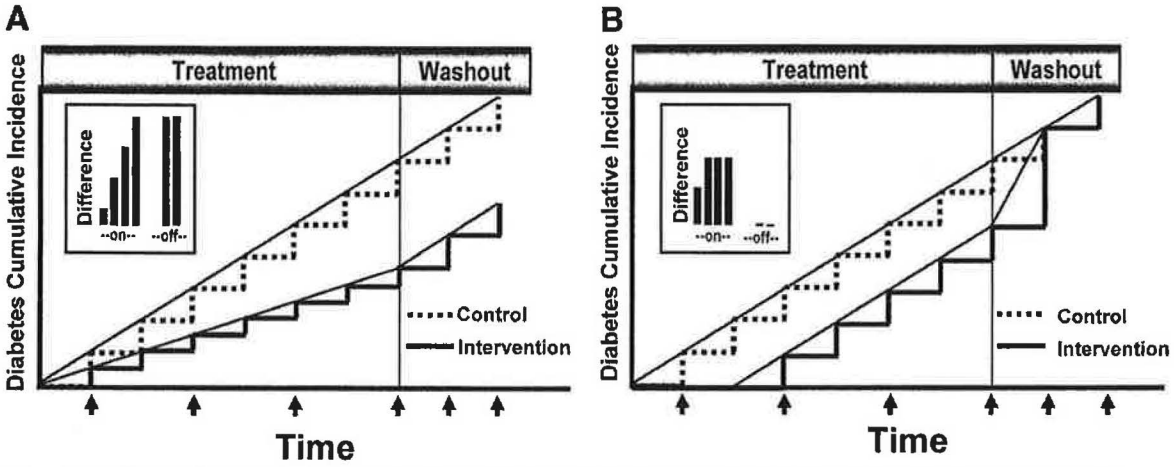

Figure 5: Schematic representation of two interventions in a clinical trial setting that would lead to diabetes prevention (A) or delay (B) [51].

Both scenarios result in lower glucose levels during the intervention, which can lead to health benefits, but only interventions that alter the biology of the disease will lead to true prevention. Therapies that do not alter the biology of progression can only delay it for a period of time proportional to the degree of the initial glucose lowering [51].

Monitoring study subjects following discontinuation of the active interventions in a clinical trial provides valuable data. For example, in the TRIPOD study, of the small number of participants (about half of the eligible subjects) whom were reassessed after 8 months of study drug discontinuation, one patient (2%) in the troglitazone arm and six patients (15%) in the placebo group developed diabetes, supporting a possible lasting effect of this intervention [51]. Similar results though were not found during follow-up in the DREAM study [52].

Supportive evidence that TZDs might have a disease modifying effect comes from the ADOPT (Diabetes Outcome Progression Trial). The study evaluated rosiglitazone, metformin, and glyburide as initial treatment in 4360 patients with recently diagnosed diabetes [53]. After a median follow-up of 4 years, failure of monotherapy to maintain normoglycemia occurred in 15% of patients treated with rosiglitazone, 21% with metformin, and 34% with glyburide (Figure 6). Therefore, intervention with an agent that modifies beta-cell function has a significant disease modifying effect, especially if used early, when beta-cell dysfunction is still reversible.

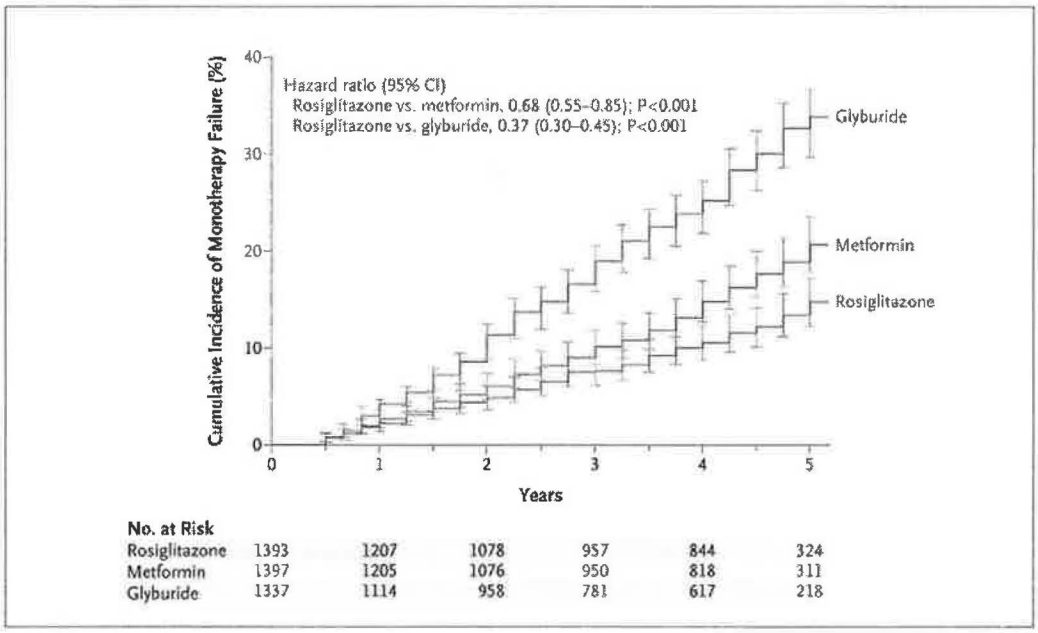

Figure 6: Cumulative monotherapy failure in ADOPT [53].

Follow-up of the STOP NIDDM cohort after drug wash-out showed an increased occurrence of diabetes in the acarbose group [41].

The Da Qing study continued to follow their participants for 14 years after the conclusion of the intervention. They found that the intervention groups combined had a 43% lower incidence of diabetes (HRR 0.59) over the 20 year follow-up period, adjusted for age and clustering by clinic. The average annual incidence of diabetes was 7% for intervention participants versus 11% of control participants, with a 20-year cumulative incidence of 80% in the intervention groups and 93% in the control group [54].

The Finnish DPS also continued follow-up of the patients after cessation of the active intervention, for a total of 7 years of follow-up. During the total follow-up period, the incidence of diabetes was decreased in the intervention group from 7.4 to 4.3/100 person-years, indicating a 43% reduction in relative risk. The corresponding incidence rates for the post-intervention follow-up were 4.6 and 7.2 respectively, representing a 36% reduction in relative risk during this post-intervention period alone [55].

The risk reduction in the lifestyle intervention trials was related to the success in achieving the intervention goals of weight loss, diet modifications, and increase in physical activity. In all studies that evaluated lifestyle interventions, the follow-up data suggest that this intervention is truly protective. One explanation could be that the beneficial lifestyle changes achieved by participants in the intervention group were maintained after the discontinuation of the intervention. Nevertheless, lifestyle changes seem to have the biggest long term impact of all studied interventions to date.

Mathematical modeling represents a alternative way to evaluate the differential effect of an intervention on disease delay or prevention. According to Ratner, true prevention can only be assessed after the entire cohort has died and the differential development of diabetes is assessed before death [21], which is not attainable in the setting of a clinical trial. Mathematical modeling of the DPP data, with the assumption that the interventions are continued throughout the volunteer's lifespan, shows that: (1) in the placebo group more than 80% of the participants would develop diabetes, (2) intervention with metformin would decrease this by an absolute 7.9%, and (3) intensive lifestyle intervention has an absolute risk reduction of 20.2% (Figure 7) [56]. This data suggests that, given such intervention is continued over a lifetime, the DPP interventions would both delay and prevent diabetes.

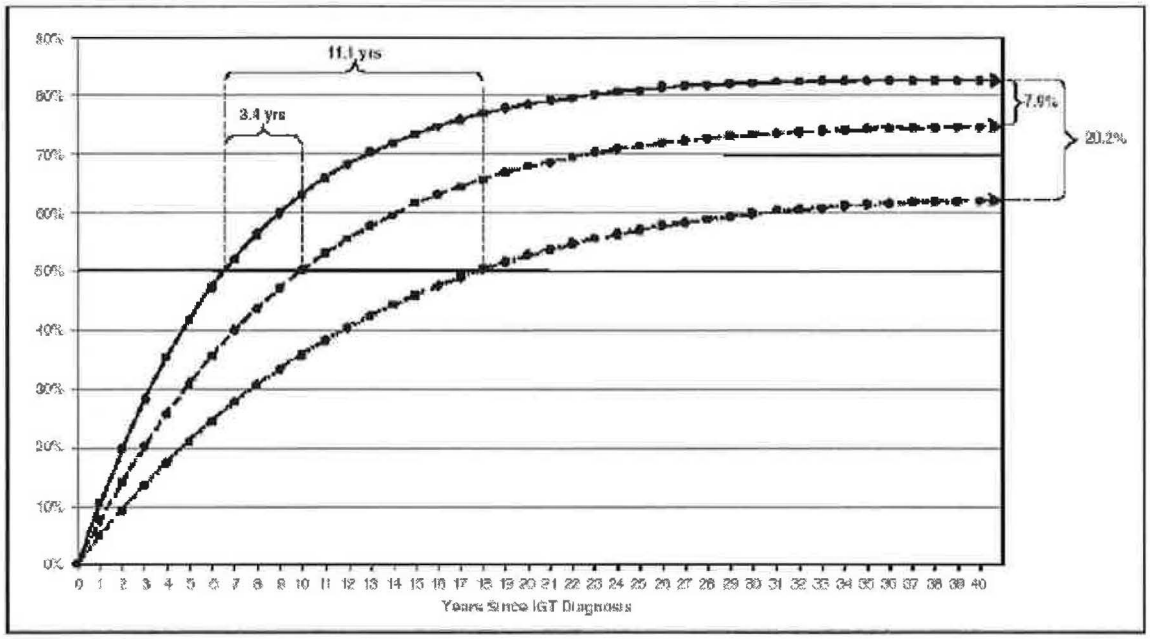

Figure 7: Computer modeling of Diabetes Prevention Program interventions and outcomes over a lifetime [21].

5. Does treatment of "pre-diabetes" or prevention of diabetes improve mortality and/or morbidity?

The ultimate goal of any disease prevention is to improve disease associated morbidity and mortality. In the case of diabetes prevention, it is important to evaluate the effect of any intervention on micro- and marcovascular complications that lead to significant morbidity and mortality. Direct data for either of these endpoints is not available. None of the studies to date has sufficient power to show a reduction in these hard outcomes.

The DPP evaluated, as a secondary outcome, the effect of the different treatment interventions on the development of cardiovascular disease (CVD) and CVD risk factors. This population had a very low rate of preexistent CVD (about 2%), but up to 50% had preexistent CVD risk factors (HTN or dyslipidemia). Due to the short duration of follow-

up (mean of 2.8 years), the relatively healthy cohort, and the very low incidence of any CVD events during the follow-up, no differences among treatment groups could be identified. CVD risk factors (HTN and dyslipidemia) progressively increased during follow-up in both the placebo and metformin treated groups, but intensive lifestyle intervention attenuated the increase in the cumulative prevalence of HTN during the 2.8 years of follow-up, and significantly reduced the prevalence of dyslipidemia. In fact, intensive lifestyle intervention resulted in a 17% reduction in the prevalence of pharmacologic therapy for HTN [57].

The DREAM trial evaluated the effect of ramipril and rosiglitazone on a cardiorenal composite outcome, but showed no significant benefit compared with placebo [7].

One of the aims of the Da Qing follow-up study was to evaluate the difference between groups in CVD, CVD mortality, and all cause mortality. They noted a non-significant reduction in the rate of first CVD events (HRR 0·98; 95% CI 0·71–1·37), CVD mortality (0·83; 0·48–1·40), and all-cause mortality (0·96; 0·65–1·41), yet the study had very limited statistical power to detect any differences for these outcomes [54].

A secondary analysis of the STOP NIDDM trial showed that acarbose reduced CVD events from 4.7% to 2.1% (HR 0.51) [58].

Obviously the answer to this important question is still up for debate and hopefully future studies, like the DPP-OS, NAVIGATOR, ORIGIN, and ONTARGET, will shed new light on this issue.

6. The balancing act: keeping it all in perspective

When the major diabetes prevention trials presented above are compared (Figure 8), it is noteworthy that interventions containing a thiazolidinedione agent were found most effective, at least in this indirect comparison. Unfortunately, this is also a class associated with clinically important side effects (weight gain, pedal edema, and congestive heart failure), significant attrition rates in clinical trials, and high cost. The lifestyle intervention trial results are significant as they were not only effective at reducing the risk of diabetes, but they also reduced other CVD risk factors, were cost-effective, and sustainable for at least 14 years even after the active trial intervention period.

Therefore, when interpreting such trial results it is important to critically evaluate not only the effectiveness of an intervention, but several additional aspects: safety, sustainability of the intervention over a life-time, cost-effectiveness, and the possibility for wide-scale population level implementation.

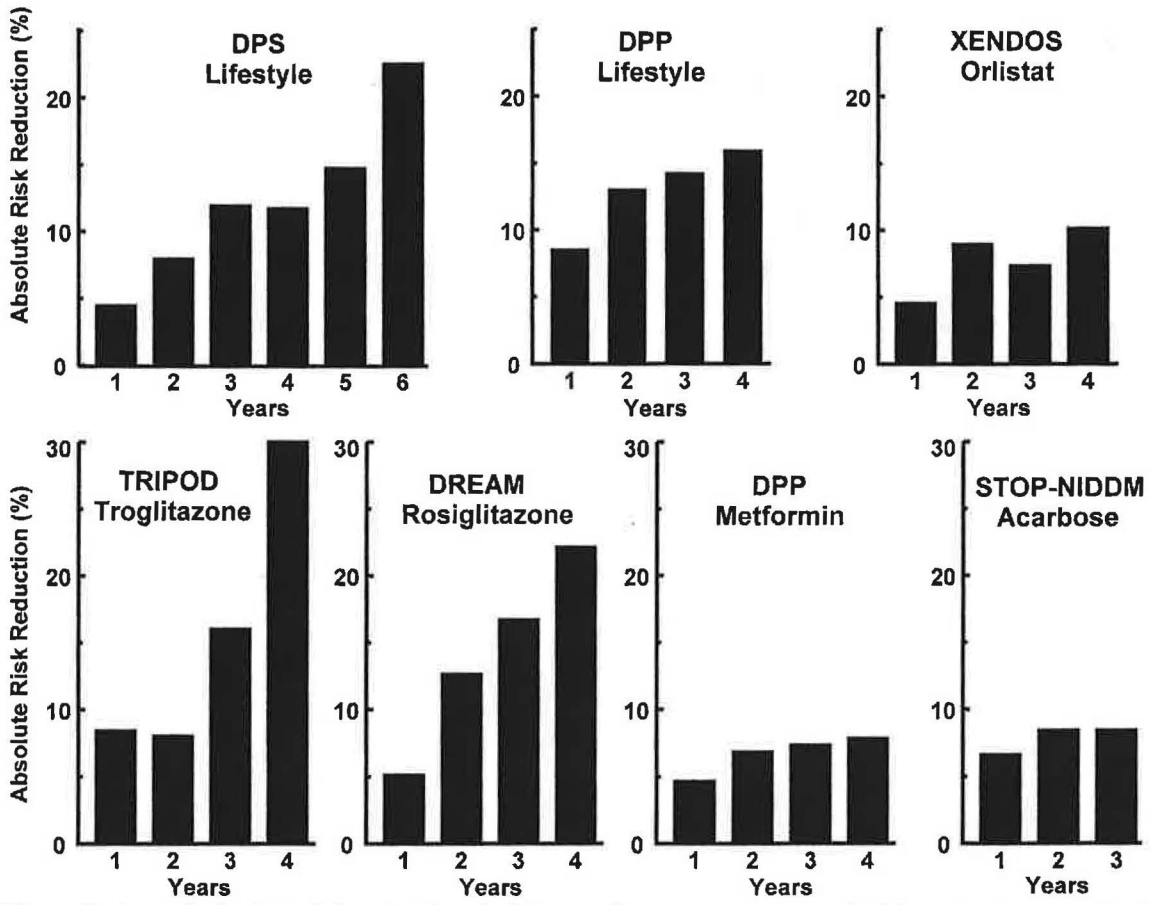

Figure 8: Annual absolute risk reductions in intervention groups compared with control groups during treatment in six studies using six different interventions for diabetes prevention in high-risk individuals [51].

a. **Safety**

Safety is of particular concern especially considering the characteristics of the population. These patients are considered to be healthy, represent a large percentage of the overall population (about 30-40% of the population could be considered at risk) and only about 25% of them will naturally transition to a diabetic state over 3-5 years of follow-up if left untreated. Also any intervention will likely have to be applied for a long period of time, if not for the entire remaining lifespan. Therefore, any intervention worth implementing on such a large scale has to be exceptionally safe. Lifestyle modifications are currently the only proven intervention that has an adequate safety profile. All pharmacologic interventions have side effects, ranging from gastro-intestinal (orlistat, acarbose, metformin), hypoglycemia (sulfonylureas), allergic reaction, renal insufficiency (RAAS blockade), pedal edema (TZDs), weight gain (TZDs), to life-threatening side effects like lactic acidosis (metformin) and congestive heart failure (TZD).

b. **Cost effectiveness**

From a societal perspective, cost-effectiveness of an intervention is an important consideration. Based on data from the DPP, in a real-life setting, it would cost $4,301 for the lifestyle intervention and $11,141 for metformin to prevent one case of diabetes over 3

years, both of which are considered acceptable from an economic stand-point [59]. From a health utility perspective, lifestyle intervention projected over a lifetime results in less than $3,000 per quality-adjusted life-years (QALY) gained in comparison with metformin at $33,000 per QALY, both amounts being considered an appropriate expenditure of health-care dollars from a societal perspective (obviously more so for lifestyle interventions than metformin) [59].

c. Large-scale population based implementation of effective measures

Based on the current state of knowledge, the only recommended large-scale intervention for diabetes prevention is lifestyle modifications. This is, however, a very challenging intervention to implement in the community. So far, several studies evaluated various methods of implementation of such measures at the community level [60-65]. Most of them have very encouraging results and hopefully very soon such measures can be incorporated into national programs for CVD and diabetes risk reduction.

Based on the evaluation of all of the above factors, the American Diabetes Association (ADA) now also recommends metformin in patients with IGT and/or IFG and one or more additional risk factors [16], especially if age is above 60 years and BMI is above 35 kg/m^2[66]. This intervention, currently off-label, has not yet been evaluated for its effectiveness in the primary care setting.

The key factor for balancing the risk-benefit ratio is the ability to accurately identify at risk individuals. The current guidelines [16], though proven to be reasonably accurate [18, 66], do not take into consideration the underlying disease biology. The best predictor of future progression to diabetes is the degree to which the beta-cell function is able to compensate for the prevailing insulin resistance. Such a screening tool, though potentially applicable in a small clinical trial, is currently too time-consuming and expensive to apply at a population level. Development of an accurate, reproducible, simple, and cost-effective prediction tool for development of diabetes is clearly needed. Low risk interventions, like lifestyle modifications, especially if delivered in a cost-effective manner, should be implemented in a large segment of the population. On the other hand, interventions that carry some risk of side-effects and are more costly should be geared only towards the highest risk segment of the population and highly customized based on the individual's risk factors.

7. Future directions

a. Ongoing studies

There are several ongoing trials that will help answer several diabetes prevention puzzles. First, the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study evaluates the effect of long-term therapy with valsartan or nateglinide on the incidence of diabetes in patients with IGT [67]. The ONTARGET (Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial) and TRANSCEND (Telmisartan Randomized Assessment Study in ACE

intolerant subjects with cardiovascular disease) studies, even though diabetes prevention is a secondary outcome, will also bring valuable information regarding prevention of diabetes by RAAS blockade [68].

Second, the ORIGIN trial evaluates over 12,000 patients with IGT/IGF or newly diagnosed diabetes at high CVD risk after treatment with lantus insulin or standard care and omega-3 polyunsaturated fatty acids versus placebo (2x2 factorial design) [69]. The primary outcome variable is a composite CVD measure.

Finally, the DPP cohort will be followed in the DPP-OS (Outcomes Study) to examine the long-term effects of these interventions on incidence of diabetes and other CVD risk factors, as well as on mortality. A similar post-intervention follow-up has commenced for the ACT Now study. These trials will help answer the important question of: Do interventions that prevent or delay the onset of diabetes also prevent the development or worsening of CVD?

b. Incretin mimetics

Incretin mimetics are a newer class of hypoglycemic agents, comprised of Glucagon-like peptide 1 (GLP-1) agonists and dipeptidyl peptidase (DPP) IV inhibitors. Available preclinical trials suggest that these agents preserve beta-cell function and increase beta-cell mass [70, 71], in addition to a host of other beneficial effects, including weight-loss or weight neutrality (Figure 9). Given their mechanism of action and effect on beta-cell function and morphology, they are very promising agents to have a disease modifying effect, including diabetes prevention. Currently there are no clinical trials evaluating the effectiveness of such agents on diabetes prevention, but this is merely due to the fact that some of these agents were very recently approved for diabetes treatment, while others are still awaiting FDA approval.

c. Bariatric surgery

The effects of bariatric surgery induced weight loss on subjects with IGT/IFG have not been specifically studied, but we have ample indirect data supporting its benefits. The Swedish Obese Subjects (SOS) study was the largest to date to compare a conventional approach to bariatric surgery in a well matched obese population. In this study, the incidence of diabetes at 2 years was 8% in the conventionally treated group, versus 1% in the surgically treated group, and at 10 years it was 24% and 7% respectively [72].

A large meta-analysis of bariatric surgery outcome studies showed that diabetes was resolved in over 75% of cases, with only 0.7% of this population considered to be at very high risk of developing new onset diabetes [73]. Diabetes resolution was associated most strongly with disease duration, which again suggests the importance of early intervention while beta-cell function can still be reversed. All of this was achieved with a relatively low rate of side-effects, yet with a significant up-front cost.

To date, bariatric surgery is by far the most effective and durable diabetes prevention intervention. Significant weight loss leads to improvement in insulin sensitivity and has a

beneficial effect on beta-cell function. This intervention should be considered in more patients, especially those in the higher risk categories.

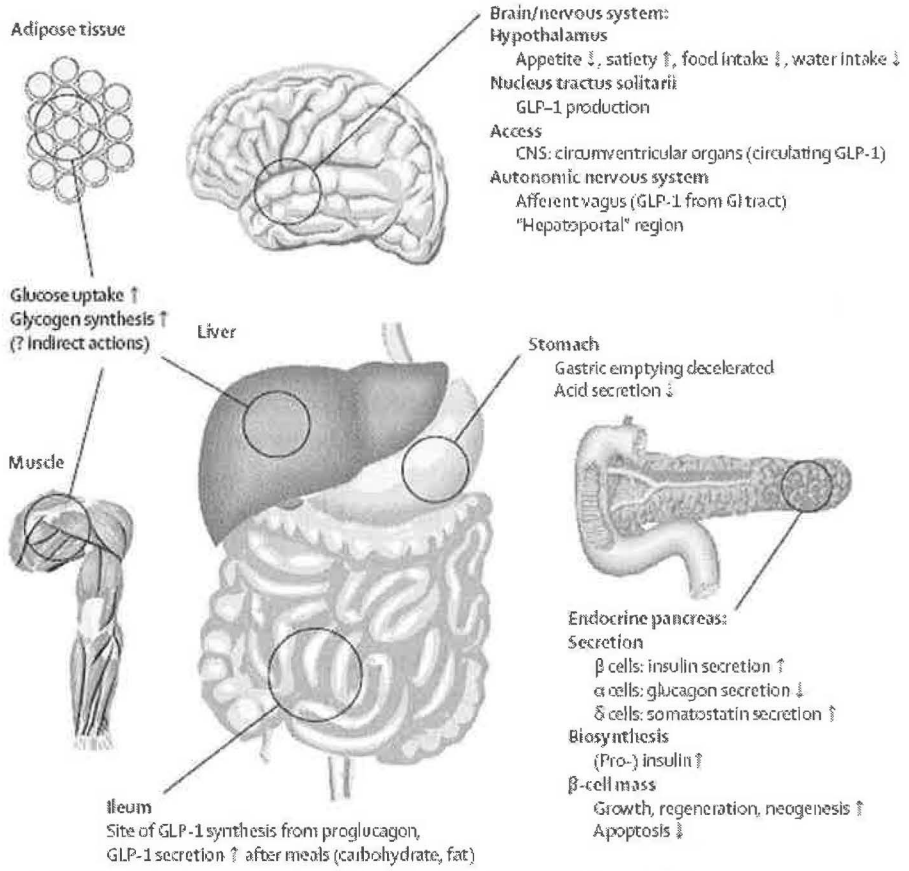

Figure 9: GLP-1 secretion and action in different organs and tissues [70].

d. Stem cell based treatment represent a hopeful distant future for diabetes prevention and treatment.

Stem cell derived therapy for prevention or treatment of diabetes is being investigated [74], but this hopeful approach is still far from the clinical arena [75]. Directed differentiation of stem cells with extensive proliferative ability to generate islet progenitor cells has been achieved; however, efficient and directed differentiation of these cells to an endocrine pancreatic lineage has been difficult to accomplish.

8. Conclusions

Screening and early intervention with the goal of diabetes prevention are highly debated areas. The opponents of such a strategy argue there is no evidence that delaying diabetes will translate to reduction in morbidity and mortality, and that screening and early treatment would impose an enormous economic burden. The supporters of diabetes prevention argue that if intervention is delayed until the diagnosis of diabetes (which is usually done when the patient develops symptomatic hyperglycemia) beta-cell function reserve is already very limited and the window of opportunity for a successful disease

modifying intervention has been lost. Recently presented results of the ACCORD, ADVANCE, and VA Diabetes Trial indirectly support this opinion (presented at the ADA Annual Scientific Sessions, San Francisco, June 6-10th, 2008). All of these trials attempted to prevent CVD and mortality through a very intensive treatment regimen, either focused at glycemia alone (VA Diabetes Trial), or all the major risk factors for CVD (ACCORD and ADVANCE). The results were disappointing, and one of the possible explanations is that all these studies enrolled patients with advanced disease (average 10 years duration), when there is little if any beta-cell reserve left and extensive atherosclerosis is already well established.

It is my opinion that early intervention, although it would increase burdens on patients and society in the short term, would pay large dividends in the long term.

Intensive lifestyle changes accompanied by weight loss are the most effective and durable interventions, but they are not easy to implement and maintain. Several pharmacologic agents have been shown to delay the diagnosis of diabetes and possibly decrease the incidence of micro- and macrovascular complications, but it is unclear if once the cost and side effects associated with such therapy are factored into the equation, these interventions are currently worthwhile.

Future efforts toward prevention of diabetes and its associated complications should focus on: (1) large scale population-based, ethnically-targeted education programs that support a healthy lifestyle and weight control, (2) development of sensitive and cost-effective screening methods to identify subjects at highest risk of progression to diabetes, (3) development of safe pharmacologic agents that address the leading pathogenic determinants of diabetes, and (4) last but not least, a better understanding of the underlying pathophysiology of diabetes.

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