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REVIEW

# Treatment of prediabetes

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## Abstract

Progression of normal glucose tolerance (NGT) to overt diabetes is mediated by a transition state called impaired glucose tolerance (IGT). Beta cell dysfunction and insulin resistance are the main defects in type 2 diabetes mellitus (type 2 DM) and even normoglycemic IGT patients manifest these defects. Beta cell dysfunction and insulin resistance also contribute to the progression of IGT to type 2 DM. Improving insulin sensitivity and/or preserving functions of beta-cells can be a rational way to normalize the GT and to control transition of IGT to type 2 DM. Loosing weight, for example, improves whole body insulin sensitivity and preserves beta-cell function and its inhibitory effect on progression of IGT to type 2 DM had been proven. But interventions aiming weight loss usually not applicable in real life. Pharmacotherapy is another option to gain better insulin sensitivity and to maintain beta-cell function. In this review, two potential treatment options (lifestyle modification and pharmacologic agents) that limits the IGT-type 2 DM conversion in prediabetic subjects are discussed.

**Key words:** Prediabetes; Impaired fasting glucose; Impared glucose tolerance; Diabetes prevention; Type 2 diabetes mellitus



**Core tip:** Behavioral changes (dieting plus exercising) are effective in preventing impaired glucose tolerance (GT)-type 2 diabetes mellitus (type 2 DM) conversion as well as impaired fasting glucose (FG) - type 2 DM conversion but loosing weight is hard and also difficult to maintain. Pharmacological interventions (plus dieting and exercising) improving and preserving beta-cell function and enhancing insulin sensitivity may be suitable choices for high-risk IGT patients. Troglitazone in Prevention of Diabetes Study, Pioglitazone in Prevention of Diabetes Study, Diabetes Reduction Assessment with ramipril and rosiglitazone Medication Trial, Actos Now for the prevention of diabetes study and Diabetes Prevention Program have proven that thiazolidinediones obviously prevent the development of type 2 DM in IGT subjects as well as IFG subjects. In Diabetes Prevention Program and Indian Diabetes Prevention Program, metformin slowed down the

progression of IGT to type 2 DM, and eventually American Diabetes Association Consensus Conference Statement proposed metformin usage in high-risk IGT individuals. However, the efficacy of pioglitazone and rosiglitazone efficacy in preventing IGT progression to type 2 DM nearly doubles metformin's efficacy (31% *vs* 72% and 62%, respectively). Rosiglitazone (low dose = 2 mg/d) together with metformin (850 mg/d) was proven to slow down IGT progression to type 2 DM as well as being more tolerable.

Kanat M, DeFronzo RA, Abdul-Ghani MA. Treatment of prediabetes. *World J Diabetes* 2015; 6(12): 1207-1222 Available from: URL: http://www.wjgnet.com/1948-9358/full/v6/i12/1207.htm DOI: http://dx.doi.org/10.4239/wjd.v6.i12.1207

## INTRODUCTION

Impaired glucose tolerance (IGT) (second hour plasma glucose level 140-199 mg/dL) was first described in 1979 as "an intermediate stage in the transition from normal glucose tolerance (NGT) to overt type 2 diabetes mellitus (type 2 DM)"[1]. Individuals with IGT possess higher risk for type 2 DM later in life[2]. ADA-revised type 2 DM diagnostic criteria declared a new term called impaired fasting glucose (IFG) (glucose level 100-125 mg/dL) in 1997[3]. IFG is an intermediate stage that GT changes from NGT to type 2 DM gradually and defined by fasting plasma glucose level. Subjects who have IFG are also candidates for developing type 2 DM later. But clinical and epidemiologic studies showed that IFG and IGT are different sorts of glucose intolerance[4]. Both IGT and IFG are called "prediabetes" because of gradual progression to type 2 DM. Nearly 70 million prediabetics (IGT and/or IFG) live in America. Since prediabetes is so prevalent[5], increase mortality, morbidity and healthcare costs (annually $245 billion in 2012) it is accepted as an important public health problem. Thus, alleviating the progression of IGT and/or IFG to type 2 DM is a reasonable way to combat with diabetes epidemic and to lessen healthcare costs.

The Diabetes Control and Complications Trial[6], the United Kingdom Prospective Diabetes Study (UKPDS)[7,8] and the Kumamoto Study[9] showed hyperglycemia is a risk factor for macrovascular and especially for microvascular complications[10,11]. Latest evidence illuminated that strict glycemic control is more effective in controlling diabetic vascular complications in new-onset diabetes patients than in long-standing, poorly-controlled type 2 DM patients[12,13]. Therefore, in new-onset type 2 DM, main target must be to achieve normoglycemic control[14]. Early detection and effective intervention of type 2 DM diminishes long-term complications leading morbidity and mortality and eventually expected to provide social, medical, and economic benefits. Treatment should be initiated in IGT period in order to reverse the main pathophysiological defects in prediabetes[4,15-18] because this is a hopeful way of intervention to prevent hyperglycemia-related vascular complication development[15-18].

## TYPE 2 DM PATHOGENESIS

Recent proof favors dual-level emergence of type 2 DM[19-24] (Figure 1). In individuals tended to progress type 2 DM, earliest metabolic abnormality is the insulin resistance. When insulin resistance appears, beta-cells increase their insulin secretion to maintain normoglycemia. Thus, hyperinsulinemia is the main sign of insulin resistance. If beta-cells can not overcome insulin resistance, GT aggrevates. Eventually, IGT appears and followed by overt type 2 DM[22-25].

Thus, IGT individuals' plasma insulin levels are high but their beta-cell function are extremely diminished[22,23,25]. Therefore, noticing the difference between insulin secretion and beta-cell function is important.

### *Insulin resistance*

The common defect in prediabetes and type 2 DM is insulin resistance[26-29] and involves liver[22,23,30], muscle[22,23,28,31,32], and adipose tissue[23]. Insulin resistance antecedents the glucose intolerance and type 2 DM[22,23,33]. NGT offspring of two diabetic parents[34,35] and people with IGT[36] are markedly insulin resistant and develop hyperinsulinemia in order to compensate the pathologic state[14,34,35]. Evience supports that insulin resistance may have a genetic component that worsens by environmental factors such as sedantary lifestyle and gaining weight. Hence, interventions that ameliorate insulin resistance and limits the insulin secretory demand on beta-cells shown to stop or postpone IGT conversion to type 2 DM[37-40].

### *Impairment of beta-cell function*

Insulin resistance is the basic characteristics of IGT while deficiency of beta-cell function is the reason of IGT and its conversion to type 2 DM[22,23,41]. Thus, interventions preserving beta-cell function may be a good idea to prevent the generation of type 2 DM. In order to estimate IGT progression to type 2 DM oral glucose tolerance test (OGTT) can be used and a low plasma insulin response is a clue for progression. Especially, reduction of insulin secretion in the first phase (0-10 min later following intravenous glucose challenge) is a good indicator for conversion to diabetes[33,36,42,43]. The first phase insulin secretion deteriorates gradually when the fasting plasma glucose (PG) exceeds 90 mg/dL and is almost completely lost when the fasting PG reaches over 110 mg/dL[22,23,44,45]. As previously described, it is crucial to discriminate insulin secretion from beta-cell function. Beta-cells respond unit glucose increase (ΔG) with unit insulin increase (ΔI), and this response is modulated by severity of insulin resistance[46]. Pure plasma insulin response measurement can lead to confusing about the health of beta-cells. The gold standard for the estimation of beta-cell function is to calculate insulin secretion/insulin resistance (disposition) index (ΔI/ΔG/IR). Both genetic

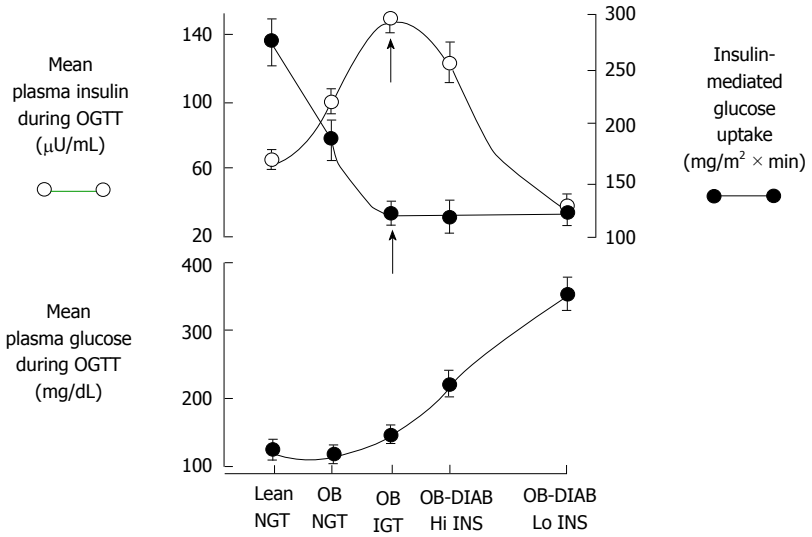



**Figure 1 Natural history of type 2 diabetes mellitus.** The plasma insulin response (open circles) depicts the classic Starling's curve of the pancreas. Closed circles = insulin-mediated glucose uptake (top panel). DIAB: Diabetes; Hi INS: High insulin secretion; IGT: Impaired glucose tolerance; Lo INS: Low insulin secretion; NGT: Normal glucose tolerance; OB: Obese; OGTT: Oral glucose tolerance test.

and acquired factors (glucotoxicity[47] lipotoxicity[48], incretin deficiency/resistance[49-51]) effect loss of beta-cell function. Compared to normal glucose tolerant individuals, impaired glucose tolerant individuals have a 4-6 fold increment in type 2 DM risk[52]. Prospective epidemiologic studies reveal that nearly 40% of subjects developing type 2 DM at follow-up had normal glucose tolerant initially. Beta-cell dysfunction is an optimal predictor for 2-h plasma glucose during OGTT in normal glucose tolerant individuals[43,52]. Beta-cell dysfunction is also an optimal predictor for NGT conversion to IGT and thereby to type 2 DM[23,24,52]. Individuals in the upper tertile of NGT have lost 50% of their beta-cell function, wheras subjects in the upper tertile of IGT 70%-80% (Figure 2). Individuals in the upper tertile of IGT are maximally insulin resistant and decline in beta-cell function is about 70%-80%. At this point, minimal extra reduction in insulin secretion causes a prominent increase in fasting and postprandial blood glucose levels. Once overt type 2 DM emerges, beta-cell function diminishes progressively[53] despite therapies with metformin, sulfonylureas, and insulin to control glycemia. Genetics, insulin resistance leading insulin secretory demand increment, glucotoxicity, lipotoxicity, impaired incretin release/action, amylin accumulation, and decreased beta-cell mass are causitive factors in the progression of beta-cell dysfunction. Interventions in order to postpone or preclude beta-cell failure are valuable tools in combatting with the conversion of IGT to type 2 DM.

## BETA-CELL FUNCTION AND INSULIN RESISTANCE IN IFG AND IGT

IGT or IFG patients, and particularly people possessing both IGT and IFG[54,55] carry high risk for type 2 DM[56-58]. IGT and IFG are eventually end up with type 2 DM but they exhibit different physiological and pathological processes and have distinct reflections on atherosclerotic cardiovascular disease emergence. In people with IFG hepatic insulin resistance is moderate and OGTT-early insulin response (0-30 min) is diminished[59]. When hyperglycemic clamp and IVGTT techniques were used in OGTT, first phase insulin secretion is found to be blunted in IFG[60,61] (Figure 3). But, late (60-120 min) plasma insulin response is unspoilt and muscle insulin sensitivity is near-normal in IFG patients; therefore two-hour plasma glucose levels returns to its initial fasting PG levels[62-64]. Adversely, people with IGT have moderate to severe muscle insulin resistance and impaired plasma insulin responses (both early and late responses) during oral GT test[63,64]. Even if fasting PG is relatively stable, it rises progressively during OGTT and not come back to normal levels for a long time while two-hour plasma glucose remains well above the fasting plasma glucose level. On the other hand, IGT and IFG share a characteristic impaired insulin secretion pattern in the first phase. However, insulin secretion in second-phase is intact in IFG states. Whereas, muscle insulin resistance is the dominant factor in IGT, in IFG tissue responsible for insulin resistance is that of liver. Also, IGT and IFG exhibit distinct characteristics for atherosclerotic cardiovascular disease. IGT seems to be related with metabolic syndrome and a good indicator of cardiovascular disease, while IFG predicts these events to a lesser extent[65].

## DETECTION OF HIGH RISK INDIVIDUAL BY HBA1C

ADA recommends considering HbA1c = 5.7%-6.4% level as an instrument to detect future diabetes risk. However, no previous study has adopted HbA1c level as a screening tool to identify subjects at high risk

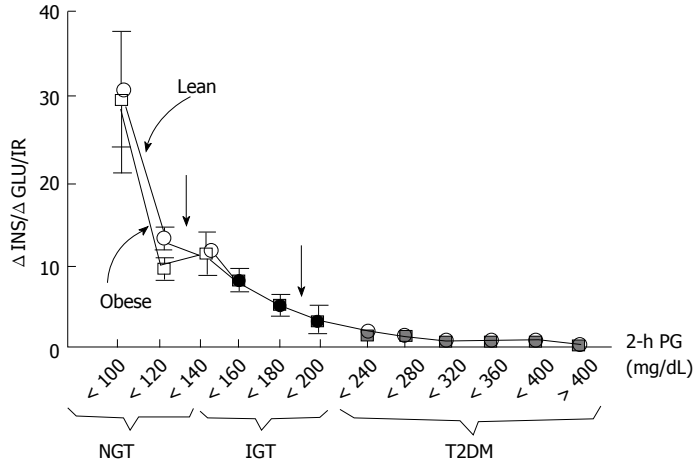



**Figure 2 Insulin secretion/insulin resistance (disposition) index (defined as change in insulin/change in glucose/insulin resistance) in individuals with normal glucose tolerance, impaired glucose tolerance, and type 2 diabetes mellitus as a function of the 2-h plasma glucose concentration in lean (closed circles) and obese (open circles) subjects.** IGT: Impaired glucose tolerance; NGT: Normal glucose tolerance; T2DM: Type 2 diabetes mellitus; PG: Plasma glucose; ΔINS/ΔGLU/IR: Change in insulin/change in glucose ÷ insulin resistance.

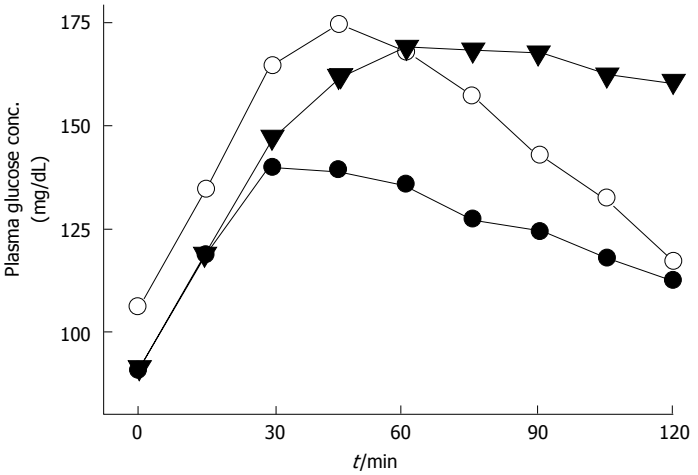



**Figure 3 Plasma glucose concentration during the oral glucose tolerance test in normal glucose tolerant (close circles) individuals and in subjects with impaired glucose tolerance (closed triangles) and impaired fasting glucose (open circles).**

(HbA1c = 5.7%-6.5%) and has examined the efficacy of interventions to reduce the risk of transition to type 2 DM. Kanat *et al*[66] and Færch *et al*[67] previously have demonstrated the concordance of HbA1c *vs* OGTT in high risk individuals and found only little overlap between them. Moreover, Kanat *et al*[66] have shown that HbA1c was a poor predictor of impaired beta cell function which is the principle factor mediating the process in which high risk individuals become overt diabetes. Discussion below is about how we should prevent diabetes among high risk individuals, namely individuals with IFG/IGT identified by OGTT results.

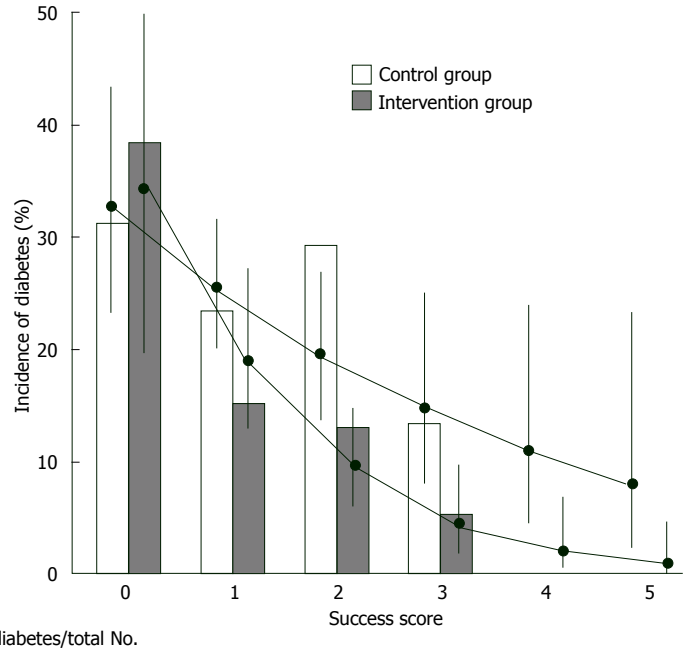
## INTERVENTION TO PREVENT THE PROGRESSION OF IGT TO TYPE 2 DM

First step in the progression of NGT to type 2 DM is IGT and IFG[22-24,33]. The IGT and IFG shares 2 features in common: Beta-cell function impairment and insulin resistance. Thereby, it seems logical to assume that efforts to preserve or increase functions of beta-cells and/or decrease insulin resistance may be a potent way to delay the conversion of IGT to DM.

### *Amelioration of insulin resistance: Loosing weight*

The basic risk factor in the progression of IGT to diabetes is obesity[34,68]. The main reason of type 2 DM epidemic confronted during the last two decades may be the obesity epidemic itself. Sedantary lifestyle and eventually gaining weight triggers insulin resistance and force the capacity of beta-cell insulin secretion. On the other hand, loosing weight by means of lifestyle interventions, pharmacologic therapies or bariatric surgery augments insulin sensitivity, decreases beta-cell work overload, and gets GT better in IGT states[69-71]. Four studies have shown that loosing weight through dieting and/or exercising improves insulin sensitivity and ameliorates beta-cell function, thus is a good way to limit IGT progression to type 2 DM[72-74]. When individuals loose the 5% of their body weight, total body insulin sensitivity improves by 30%[73] and decrease in their IGT to type 2 DM progression nearly by 58%[37].

Finnish Diabetes Prevention Study, intervention individuals were given special advice to loose weight (> 5% of total body weight), to decrease total fat consumption (< 30% of total calories) as well as saturated fat consumption (< 10% of total fat), to increase fiber consumption (15 g for each 1000 kilo-calories) and to increase physical activity (30 min/d). These individuals were followed up 3.2 years. Cumulative diabetes incidence was 58% lower in the intervention individuals compared to controls (HR = 0.4, $P < 0.001$). Individuals in the study were categorized




| No. with diabetes/total No. | | | | | | |
|---|---|---|---|---|---|---|
| Intervention group | 5/13 | 10/66 | 9/69 | 2/38 | 0/25 | 0/24 |
| Control group | 15/48 | 25/107 | 14/48 | 2/15 | 0/11 | 0/4 |

**Figure 4 Incidence of diabetes during follow-up, according to the success score.** At the one-year visit, each subject received grade of 0 for each intervention goal that had not been achieved and a grade 1 for each goal that had been achieved; the success score was computed as the sum of the grades (reproduced from J Tuomilehto and J Lindström).

considering whether they succeeded their initial targets at one year of assessment (Figure 4). Reciprocal relationship was determined between achievement score and new diabetes cases. If an individual succeeded 4-5 goals, diabetes did not develop[72]. Another landmark clinical trial [Dipeptidyl peptidase (DPP)] assigned 3234 prediabetic patients (IFG + IGT) to placebo, metfomin (2 × 850 mg per day), or a lifestyle modification program. In this program targets are loosing 7% of body weight, taking 150 min-physical exercise every week and reducing (25% of total calories) total intake of fat. Individuals were followed up to 2.8 years. Lifestyle modifications (compared to placebo) decreased the new diabetes cases by 58%. Hovewer, in subjects who lost weight and who met physical exercise/dieting targets, risk of diabetes decreased > 90%. These results are consistent with the Finnish Diabetes Prevention Study in which participants met four or five of their goals. In post-hoc analyses of both studies, weight loss was the most important contributor to type 2 DM prevention. In the DPP trial, a 5-kg weight loss over time could account for the 55% reduction in the risk of diabetes over the mean of 3.2 years of follow-up in this high-risk population[37].

Isolated IFG and isolated IGT individuals carry nearly the same risk about the progression of IFG to type 2 DM, but there is no major clinical trial assessing the lifestyle intervention efficacy on preventing IFG - type 2 DM conversion. A small study[75] in Japanese subjects with IFG has reported that an intensive weight loss program is more effective in reducing the conversion rate from IFG to type 2 DM compared to less intensive intervention (HR = 0.56, 95%CI: 0.36-0.87). Subgroup analysis revealed that subjects who had IFG + IGT at baseline manifested greater reduction in the conversion to type 2 DM (HR = 0.41, 95%CI: 0.24-0.69) while it was not statistically significant in subjects with isolated IFG (HR = 1.17, 95%CI: 0.50-2.74). A significant difference achieved by lifestyle intervention on diabetes conversion between two groups ($P$ = 0.03).

Lifestyle intervention is the most effective approach to combat with progression of IGT to type 2 DM, but preserving the final weight and exercising is unsustainable[76]; for example, when DPP trial ended, people gained weight again[77] (Figure 5). Weight loss achieved by drugs is also a good way to diminish conversion of IGT to type 2 DM. Orlistat brings 5.8 kg loss while lifestyle changes brings 3.0 kg loss, while IGT - type 2 DM conversion limited by orlistat was about a 37% in XENDOS study[78]. But, when placebo was given instead of the drug, individuals gained weight again although they continued their diets so weight loss provided by pharmacologic interventions is also unsustainable[79]. Typically, most weight loss programs resulted in weight regain no matter what intervention type (lifestyle or pharmacologic) was used and when loosing weight programme stopped, IGT - type 2 DM progression rate mimics control individuals[80]. Thus, we can conclude that "legacy" effect *via* weight loss is not much in terms of slowing down the IGT - type 2 DM progression. In real-life, even maintaining 5% weight loss is unrealistic. In a study performed in Finland community[81] a diabetes prevention program aiming 5%-7% weight loss applied 10149 registered subjects and 1/3 of these subjects lost more than 2.5% of their body weight. Moreover, in case of achievement of sustainable weight loss, diabetes incidence decrease was about 50%-60%. In other words, IGT - type 2 DM progression continued in 40% to 50% of subjects although they lost weight successfully. Therefore, changes in lifestyle are insufficient in preventing

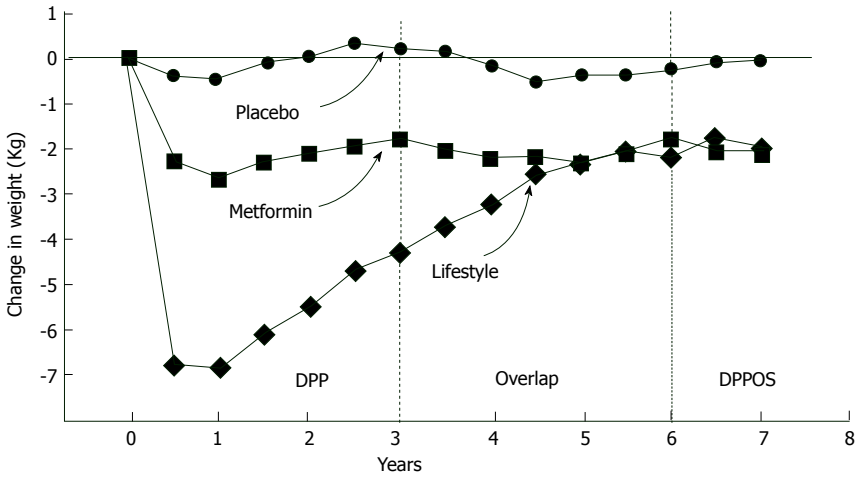



**Figure 5 Change in body weight during the dipeptidyl peptidase, during the overlap period, and during the Dipeptidyl peptidase Outcomes Study (reproduced from Eriksson and Lindgärde).** DPP: Dipeptidyl peptidase; DPPOS: Dipeptidyl peptidase Outcomes Study.

diabetes in prediabetic people. But opposite to behavioral interventions such as dieting and exercising, pharmacological interventions always limits IGT or IFG progression to type 2 DM.

### *Correction of insulin resistance: Pharmacotherapies*

Lifestyle intervention is impractical and not satisfactory for insulin sensitivity improvement, pharmacologic agents used as an alternative way of enhancing insulin impact and limiting IGT - type 2 DM progression. In some clinical studies, pharmacotherapy getting insulin sensitivity better in adipocytes, in muscle-cells or liver-cells have found to diminish conversion of IGT - type 2 DM.

**Metformin:** Fasting PG concentration and hemoglobin A1c can be decreased by metformin in type 2 DM through inhibition of liver glucose production[82-84] or through preserving beta-cell function[85]. However, in some studies including UKPDS and ADOPT, it is shown that hemoglobin A1c decreases first and then rises again gradually[7,8,85,86]. In DPP study, IGT conversion to type 2 DM by 31% when metformin was given at the dose of 1700 mg/d; also this therapy corrected insulin sensitivity and diminishes new metabolic syndrome cases. Again, metformin in Indian Diabetes Prevention Program limits the IGT - type 2 DM progression[87]. Other minor studies[88-90] show that metformin lowers the plasma glucose concentration in obese adolescents. However, there is no study investigating the efficacy of metformin on diminishing the conversion rate of IFG to type 2 DM. It is proven that metformin and weight loss has similar effectiveness on decreasing the progression of IGT to type 2 DM in younger than 65-year-old subjects, subjects with body mass index over 35 and subjects whose fasting plasma glucose exceeding 110 mg/dL[37]. Thus, it is not unusual to claim that metformin would significantly lower the conversion rate from IFG to type 2 DM. A prospective randomized clinical trial illuminated the answer. Eventually, American Diabetes Association advices metformin useage in high-risk individuals (younger than 60-year-old, body mass index over 30 kg/m$^2$ and HbA1c over 6.0%) with IGT or IFG, taking into account that metformin has been known as a safe generic drug[91]. However, similar to sulfonylureas, metformin cannot stop beta-cell failure which is crucial for type 2 DM. While metformin response initially seems good, HbA1c begins to rise eventually.

**Thiazolidinediones:** Thiazolidinediones act on "peroxisome proliferator activator receptor gamma" (PPAR-γ) and eventually improve two main defects generated by IGT. Thiazolidinediones bring adipocytes as well as liver and muscle cells sensitivity to insulin[92-94] and also support and protect beta-cells function[95]. Hypothesis that defends "thiazolidinediones improve muscle insulin sensitivity by reducing plasma free fatty acid levels and intramyocellular lipid content, and redistributing fat from visceral to subcutaneous adipose depots" finds lots of evidence. Moreover, muscle and fat cell PPAR-γ receptors mediates insulin-sensitizing effect directly[92-94]. There is no significant difference between troglitazone[96], pioglitazone[97], and rosiglitazone[98] in controlling glycemia and increasing insulin sensitivity in type 2 DM. Troglitazone increase GT and insulin sensitivity as well as limits type 2 DM conversion in IGT individuals[38,99,100] and in women developing diabetes during their pregnancies[101]. In Diabetes Prevention Program, IGT - type 2 DM progression reduced by 23% by troglitazone within three years, even if the drug was stopped after 10 mo[38]. After 1.5 years of follow-up diabetes incidence was markedly reduced for every 100 person-treatment years in IGT subjects taking troglitazone compared with placebo (3.0 *vs* 12.0 cases; $P < 0.001$), compared with metformin (3.0 *vs* 6.7 cases; $P = 0.02$) and compared with lifestyle changing activities (3.0 *vs* 5.1, $P = 0.18$) (Figure 6). IGT - type 2 DM conversion decrease attributed to rosiglitazone was 62% in DREAM trial[39] and best indicator of diabetes prevention was recovery in insulin secretion/insulin resistance index. Pioglitazone and troglitazone slows down IGT progression to type 2 DM in women with gestational diabetes history[101-103]. In Actos Now for the prevention of diabetes study, IGT -

type 2 DM conversion rate fall attributed to pioglitazone was 72% ($P < 0.00001$)[40].

### *Beta-cell function sustainability*

Because IGT - type 2 DM conversion and appearance of hyperglycemia led by gradual beta-cell failure, improving beta-cell function in IGT individuals are expected to be useful in lowering the new cases of type 2 DM. Although thiazolidinediones strikingly increase insulin sensitivity in IGT individuals, the best indicator of type 2 DM prevention is reinforcing beta-cell function. In diabetic human trials[101,103] and animal studies[104] troglitazone[99-101], pioglitazone[95,97,102], and rosiglitazone[95,98] increased the function of beta-cells by: (1) unloading beta-cells *via* advancing insulin sensitivity; (2) decreasing plasma free fatty acid levels; (3) correcting lipotoxicity; in other words sending toxic lipid metabolites (diacylglycerol, ceramides and fatty acyl CoAs) away from beta-cells; and (4) exerting direct PPAR-γ receptor-mediated beta-cell effect[48,94,95]. Thiazolidinediones both advance insulin sensitivity and protect beta-cell function so that they blocks IGT - type 2 DM conversion and create a longstanding HbA1c decrement in type 2 DM[23]. Nevertheless, thiazolidinediones induce fluid retention plus fat weight gain and they have the disadvantage of being expensive[39,105]. For that reason, American Diabetes Association decleared metformin instead of thiazolidinediones for treatment of IGT or IFG[91] even if thiazolidinediones doubles the effect of metformin in preventing IGT - type 2 DM conversion[105,106] (Figure 6). In Actos Now for the prevention of diabetes study titrated pioglitazone dose was 45 mg per day. But, even 15 to 30 mg daily pioglitazone dose increased insulin secretion and sensitivity in type 2 DM[107] while causing lesser fluid retention and lesser fat gain[108]. Also, Canadian individuals with IGT were given 2 mg per day rosiglitazone plus 1000 mg per day metformin, and IGT - type 2 DM conversion reduction with this regimen was about 71% with no significant fluid retention and weight gain[109].

In all of the 8 studies continued over 1.5 years, thiazolidinediones reduced HbA1c levels and maintained this decrement in type 2 DM subjects. In ADOPT, 5-year rosiglitazone-associated HbA1c decrease was obtained[86]. Sustained reduction in HbA1c implicates that thiazolidinediones are long-acting drugs on beta-cell functionality. Parallely, in another study, insulin secretion/insulin resistance index which is the gold standart in the measurement of beta-cell function is calculated in 61 type 2 DM subjects and functions of beta-cells improved by rosiglitazone and pioglitazone in a similar way[95]. Consequently, thiazolidinediones protect and augment beta-cell function, sensitize insulin as well as preserve long standing HbA1c reduction and delay IGT- type 2 DM progression.

**Glucagon-like peptide-1 analogues:** Oral glucose consumption provides 2-3-fold greater plasma insulin response compared to same level of hyperglycemia enhanced by intravenous glucose and this is called "incretin effect"[110-112]. Ninety percent of incretin effect derived from L cell-associated glucagon-like peptide-1 (GLP-1) release and K cell-associted GIP release. GIP and GLP-1 are strong stimuli for insulin secretion. GLP-1 also blocks secretion of glucagon, postpones emptying of stomach, diminishes appetite, limits food consumption and potentiates loosing weight. Dipeptidyl peptidase-Ⅳ cleaves GLP-1 and GIP rapidly within one or two minutes, those peptides are not suitable for therapy of type 2 DM and/or IGT individuals. GLP-1 receptor agonists (namely liraglutide and exenatide) mimicing GLP-1 actions are resistant to degenarating effect of dipeptidyl peptidase-Ⅳ[113,114]. Like endogenous GLP-1, liraglutide and exenatide are powerful insulin secretagogues, and they decrease secretion of glucagon, potentiate loosing weight and effectively decrease plasma glucose levels in type 2 DM. A three-year prospective study showed exenatide reduced HbA1c for a long time, augmented functions of beta-cells and provided gradual weight loss[115]. One favorable aspect of GLP-1 analogues is that hypoglycemia is uncommon during therapy because GLP-1 analogues merely increase secretion of insulin whenever there is hyperglycemia. Glucose physiologically triggers release of insulin. Glucose increases the ATP generation, eventually generated ATPs close the potassium channels. Consequently, membrane of beta-cells are depolarized, calcium influx occurs and exocytosis begins in insulin-containing vesicles[116]. Eventually, glucose mediates insulin secretion. But effect of GIP and GLP-1 on beta-cells are totally independent from hyperglycemia. After they bind self receptors, adenylate cyclase is activated, ATP is converted to cAMP so they "amplifies" insulin secretion by means of hyperglycemia. If hyperglycemia does not exist, GLP-1 or GIP can not augment secretion of insulin[117].

The typical signs in subjects with IGT and type 2 DM are severe decrease in functions of beta-cells and obvious decrease in incretin effect after meal or after glucose consumption[110-112]. Studies have pointed out that in IGT and type 2 DM cases the main defect is the incapability of beta-cells to respond glucose. Incretin hormones partially overcome beta-cell "blindness" to glucose[118]. In IGT cases GLP-1 response after meal usually is not changed or slight impairment is observed[119-121] while GLP-1 response in the first 10 min is usually lessened (this implicates phasic defect in GLP-1 secretion) but GIP secretion is mildly elevated[122]. On the contrary, in type 2 DM beta-cells are resistant to GLP-1-mediated insulin secretion[123]. Also, beta-cells are resistant to GIP-mediated stimulation of insulin secretion. If insulin is given and glycemia reverted to normal, susceptibility of beta-cells to GIP can be improved, but this is not true for GLP-1[50].

If hyperglycemia exists, NGT individuals give powerful insulin secretion response against the GLP-1 increase. Inversely, in type 2 DM the same

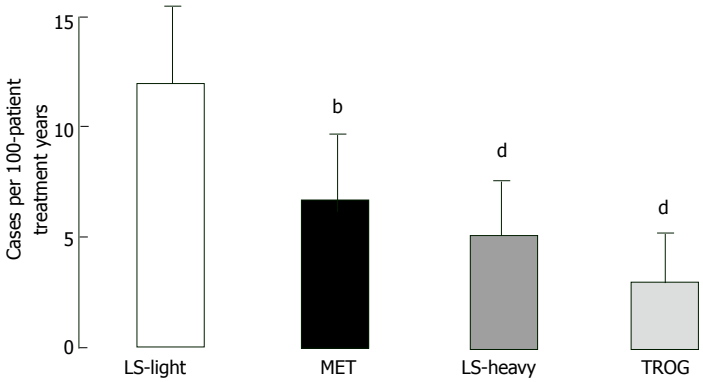



**Figure 6 Effect of lifestyle intervention, metformin, and troglitazone on the conversion rate of ımpaired glucose tolerance to type 2 diabetes in the first 1.5 years of the dipeptidyl peptidase (*i.e*, before the discontinuation of troglitazone from the dipeptidyl peptidase).** [b]*P* < 0.01 *vs* LS-light, [d]*P* < 0.01 *vs* LS-heavy. LS: Lifestyle; MET: Metformin; TROG: Troglitazone.

GLP-1 amount cannot increase insulin secretion even hyperglycemia exists[50,51]. But whenever plasma GLP-1 levels increased pharmacologically, insulin response becomes normal in hyperglycemic states (Figure 7). Hence, pharmacological plasma GLP-1 levels may restore "beta-cell glucose blindness" in IGT and type 2 DM. Although GLP-1-analogue-mediated beta cell stimulation is only sustainable during wash-out period, a novel trial declared that 3-year exenatide therapy partially recovered responsiveness of beta-cell to glucose[124].

Conversion of NGT to IGT and eventually to type 2 DM is mediated by nonstop failure of beta-cells (Figures 1 and 2). Exenatide: (1) increases responsiveness of beta cells to glucose and augments functions of beta-cells in type 2 DM; (2) facilitates loosing weight; (3) does not induce hypoglycemia; and (4) is applied once a week (Bydureon). For that reason, exenatide could be a good choice to decrease the conversion of IFG/IGT to type 2 DM and to a guarantee for NGT. There is no study investigating GLP-1 analogue effect on IGT - type 2 DM conversion. On the other hand liraglutide was investigated in obese but nondiabetic individuals (31% had IGT)[125]. In these IGT individuals, 84%-96% decrement was observed in type 2 DM progression. Five percent weight loss was achieved in 61% of individuals while ten percent weight loss achieved in 19% of individuals. New metabolic syndrome cases was decreased up to 60%. Therefore, long-acting GLP-1 analogues could be preferable drugs in order to prevent conversion of IGT to type 2 DM, because they carry additional effects such as weekly administration, beta cell function augmentation, and facilitation of loosing weight[126].

**DPP-Ⅳ inhibitors:** DPP-Ⅳ is the enzyme that cleaves GLP-1; DPP-Ⅳ inhibitors block this enzyme and therefore rise plasma GLP-1 concentrations. But, DPP-Ⅳ inhibitor-related increase in GLP-1 concentrations is uniquely dependent on endogenous GLP-1 secretion. Thus, DPP-Ⅳ inhibitor-related plasma GLP-1 rise usually is lower than GLP-1 analogue-related rise. DPP-Ⅳ inhibitors accomplish moderate increase in insulin secretion and have moderate inhibition on glucagon[110]. Vildagliptin administration in IGT individuals reveals little augmentation on functionality of beta-cells. However, vildagliptin effect totally disappeared after washout[116]. There is no study calculating DPP-Ⅳ inhibitor-mediated conversion rate of impiared GT - type 2 DM switch. In contrary to GLP-1 analogues, DPP-Ⅳ inhibitors cannot help loosing weight and they exert insufficient effect on beta-cells. Accordingly, GLP-1 analogues may be superior to DPP-Ⅳ inhibitors in IGT treatment.

**Alpha-glucosidase inhibitors:** IGT-type 2 DM conversion rate decreased about 25% by acarbose[127] and voglibose[128]. This effect was attributed to inhibition of carbohydrate absorption but increment in incretin secretion induced by alpha-glucosidase inhibitors may be the real reason of positive impact on glucose homeostasis[129]. Alpha-glucosidase inhibitors changes microbial flora of gut, thus they may help to heal glucose intolerance[130].

**Pharmacotherapy cessation and emergence of diabetes:** Pharmacological therapy applied to increase insulin sensitivity and beta-cell function have potent impact on prediabetes-diabetes conversion. But, we are not sure whether this effect is transient or sustained when the intervention is discontinued. Pharmacologic interventions prevents or delays diabetes onset by: (1) masking diabetes appearance by suppressing glucose; (2) preventing or delaying diabetes development only while it is being used; or (3) retaining their effects even after withdrawal.

Reassessing glycemic status after washing out the pharmacotherapy could clarify which possibility is relevant for the intervention[131]. Several studies investigating wash out effect are conducted in order to answer these questions. After 2.8 years of intervention in DPP trial, the incidence of diabetes in individuals with IGT was reduced by 58% with lifestyle modifications while the reduction is only 31% with metformin therapy compared with placebo. At the end of the trial 11-d washout period applied, participants who were taking metformin or placebo and had not developed diabetes were tested with a repeat OGTT in order to assess whether the observed metformin effect was sustained after cessation of the drug. Washout control reveals metformin participants had a significant increase in fasting glucose levels. It is concluded that one-quarter of the beneficial effect of metformin to prevent type 2

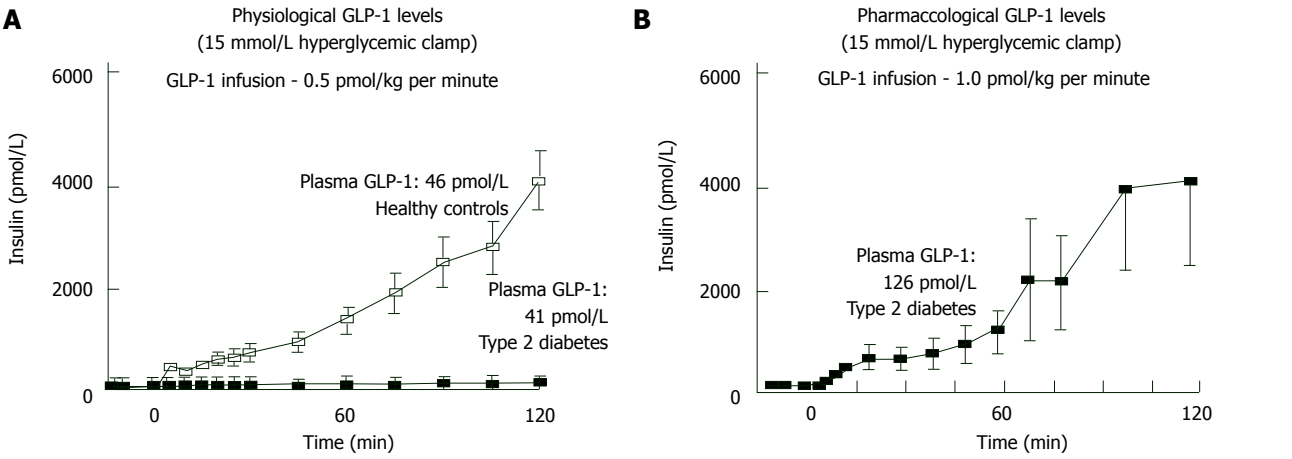



**Figure 7 Effect of physiologic (A) and pharmacologic (B) doses of glucagon-like peptide-1 on insulin secretion in normal glucose tolerance individuals and in subjects with type 2 diabetes mellitus.** GLP-1: Glucagon-like peptide-1.

DM was attributable to a pharmacological effect and this effect did not persist when the drug was withdrawn. However, the overall effect of metformin in preventing diabetes remained substantial at 25% after withdrawal of the intervention[132].

In DREAM trial rosiglitazone slows down the new-onset diabetes in people with IGT ± IFG significantly (HR = 0.40, $P < 0.0001$). After a median 71-d medication washout period, the incidence of diabetes is similar both in intervention and placebo groups. This evidence suggests rosiglitazone does not have a sustained effect on the underlying disease pathophysiology and effective as long as the therapy is being given[131].

In STOP-NIDDM trial acarbose given to IGT patients delayed progression to Type 2 DM. The risk of progression to diabetes over 3.3 years was reduced by 25%. In the last 3 mo of the study placebo was given to all subjects. During this placebo treatment period, the incidence of diabetes was higher in the group originally assigned to acarbose than in the group first randomized to placebo (HR = 0.45, $P < 0.005$). On the other hand, STOP-NIDDM trial demonstrated that beneficial effect of acarbose preventing type 2 DM was partially attributable to its pharmacological effect and similar to metformin, the effect is not sustainable when drug use is stopped.

## DETECTION OF HIGH RISK PERSONS FOR PHARMACOLOGICAL INTERVENTION

Prediabetics prone to develop type 2 DM plus atherosclerosis-induced cardiovascular complications are usually sub-maximally insulin resistant. In addition, these individuals have lost two thirds of their beta cell functions, their HbA1c levels usually are around 6% and at least 10% have diabetic retinopathy[133,134], nearly the same percentage of individuals have peripheral neuropathy[135]. Characteristic primers of diabetes are beta-cell dysfunction and insulin resistance. Gold standard measurement method for insulin sensitivity is euglycemic insulin clamp technique while the gold standart measurement method for insulin secretion is hyperglycemic clamp technique. These techniques are not much applicable for screening in clinical practice. Other predictive models studied IGT - type 2 DM conversion[136] and it is concluded that neither anthropometric criteria (waist-to-hip ratio or body mass index) nor metabolic syndrome components are superior to two-hour plasma glucose of OGTT. Another study illuminated two subgroups carrying high type 2 DM risk: First group consisted of IGT individuals whose total plasma glucose is in the upper fifth percentile during OGTT while the second group consisted of fasting plasma glucose over 95 mg/dL[137]. Best predictive criterion for future type 2 DM in IGT subjects is one-hour plasma glucose over 155 mg/dL, independent of their GT status in the Botnia[54] and San Antonio Heart[138] studies. Some biomarkers such as fasting PG, ferritin, insulin, adiponectin, HbA1c, IL-2 receptor A, high-sensitivity C-reactive protein predict diabetes development in later life[139]. Actos Now for the prevention of diabetes study and Diabetes Prevention Program gives inspiration to select IGT subjects carrying extra risks for type 2 DM, in order to discriminate people that take advantage from pharmacotherapy.

## PREDIABETIC PATIENT ALGORYTHYM

The optimal strategy is to prevent development of hyperglycemia intervening at the stage of IGT and also to revert GT back to normal. Individuals with IGT are insulin resistant and lost 50%-80% of their beta-cell function. Also, in order to prevent vascular complications resumption of normoglycemia is crucial in type 2 DM. This algorithm is also cheaper in long run. Diabetes Prevention Program Research Group wrote "Over 3 years, metformin was clinically effective (in preventing diabetes in IGT subjects) and cost-effective from the perspective of a health system and society, especially if implemented with generic medication pricing"[140,141].

When model simulations performed, similar results were reached[142,143]. IGT - type 2 DM conversion blockage by pioglitazone[40] is two fold that of metformin[37], so it is logical to assume that pioglitazone also could be cost-effective. But, monitoring and side effect treatment costs of those drugs should be remembered. Two aspects should be taken into account while performing cost analysis of pioglitazone. First one is edema management (if occurs) and the second is monitoring and treating osteoporosis. Possible long bone fracture in postmenopausal women should also be evaluated in cost analysis. Some studies implies bladder cancer risk in individuals who are given 45 mg pioglitazone over two-year time. But FDA mandated a prospective study in order to clear the pioglitazone safety (Kaiser Permanente study) as after eight-year observation, in comparison to those who never used pioglitazone, hazard risk ratio of bladder cancer was 0.98 in diabetics receiving pioglitazone.

GLP-1 analogues are expensive and they may not be put on market in near future. For that reason, cost analysis of GLP-1 analogue use in prediabetes states should be done cautiously. From community perspective, different criteria are considered in drug usage. But from patient perspective any solution to postpone or avert hyperglycemia probably decreases new onset microvascular complications such as nephropathy, neuropathy and/or retinopathy. When the main argument is reducing new cases of blindness, amputations and/or end-stage renal disease, "cost" cannot be top criterion for the individual for ethical reasons.

Another option is to prefer waiting till diabetes emerges and initiate therapy at this stage rather than treating individuals with prediabetes. But there is several limitations for this option. First, it brings handicaps on detecting exact timing of diabetes onset, namely, prediabetic individuals should be regularly controlled during this period. Secondly, UKPDS results make us to realize that in initial stages of diabetes tight glucose control cannot prevent microvascular complications. Besides, progression of euglycemia to dysglycemia is a silent but secular process. Thus, defining diabetes initiation in the basis of plasma glucose (namely fasting plasma glucose or two-hour plasma glucose) levels or in the basis of HbA1c is controversial. In reality, one tenth of prediabetics already have evidence of diabetic microvascular complications. Thirdly, upper tertile of IGT group is insulin resistant, their beta cell function loss is nearly 70%-80% whereas volume loss is about 30%-40%. Fourthly, a major diminution in beta-cell mass in prediabetes accelerates the conversion process to type 2 DM[144]. There is no remedy to increase human beta cell mass, today.

All pathophysiological events observed in type 2 DM also appears in prediabetic individuals and nearly 10% of prediabetics exhibit microvascular complications. Consequently, initiating lifestyle changes and pharmacotherapy in high-risk prediabetics instead of waiting till diabetes emerges seems reasonable. However there is no study comparing prediabetic stage therapy *vs* the diabetic stage therapy. Because these studies necessitate large sample sizes and very long study periods in order to demonstrate incidence differences in terms of microvascular complications. Therefore, response to the question "when should we institute pharmacological therapy?" is unclear, yet.

Lastly, prediabetics carry high risk for cardiovascular complications (myocardial infarction, stroke, cardiovascular death) besides their type 2 DM risk. IGT individuals are highly insulin resistant and thereby, exhibit some typical metabolic abnormalities observed in insulin resistance. For example they become dysglycemic, dyslipidemic, hypertensive, obese, insulin resistant, prone to coagulation, vulnerable to inflammation and endothelial dysfunction. Those abnormalities are also the main risk factors for cardiovascular disease. Moreover, insulin resistance is an independent atherosclerotic risk factor irrespective of other associated risk factors[94]. Thus cardiovascular disease risk of prediabetics is much more compared to normal individuals. Some measures diminishing diabetes risk also reduce cardiovascular risk. For instance, pioglitazone decreases triglyceride concentrations and increases HDL levels while loosing weight decreases blood pressure and heals lipid profile[37]. Eventually, in order to decrease cardiovascular disease risk of these individuals one should apply measures diminishing type 2 DM risk on one hand, while giving special attention on treating CVD risk factors (blood pressure and dyslipidemia) on the other hand.

### *"Diabetes prevention" or "reversal of prediabetes to normoglycemia"?*

Restoration of normoglycemia in prediabetics obviously lessens diabetes risk. Diabetes Prevention Program Outcome Study (DPPOS) compared the 894 people who had at least one normal OGTT with the 1096 people who never regressed to normoglycemia in Diabetes Prevention Program. In follow-up period of the study relative risk of diabetes emergence was 56% lower in the first group (OR = 0.44)[145]. Regression from prediabetes to normoglycemia not only reduces the risk of diabetes, but also the risk of cardiovascular disease. DPPOS has proven that if prediabetes can regress to normal glucose state, cardiovascular complications decrease[146]. Because, nearly one tenth of prediabetics possess microvascular complications, it is likely that restoration of normoglycemia improves microvascular complications[147].

## SUMMARY

Behavioral changes (dieting plus exercising) are effective in preventing IGT-type 2 DM conversion as well as IFG - type 2 DM conversion but loosing weight is hard and also difficult to maintain. Pharmacological interventions (plus dieting and exercising) improving and preserving beta-cell function and enhancing insulin sensitivity may be

**Table 1 Summary of pharmacologic intervention trials in individuals with impaired glucose tolerance**

| Study | *n* | Duration (yr) | Incidence of DM in control (%) | Relative risk reduction (%) |
|---|---|---|---|---|
| IDPP | 269 | 2.5 | 18.3 | 26 |
| USDPP | 2151 | 2.8 | 11 | 31 |
| USDPP | 1172 | 0.9 | 11 | 75 |
| TRIPOD | 236 | 2.5 | 13.1 | 55 |
| PIPOD | 89 | 3 | 13.1 | 55 |
| DREAM | 5269 | 3 | 6.5 | 60 |
| ACT NOW | 602 | 2.8 | 6 | 72 |
| CANOE | 207 | 3.9 | 10.1 | 66 |
| STOP NIDDM | 1368 | 3.2 | 8.1 | 36 |
| XENDOS | 3305 | 4 | 2.2 | 37 |

DM: Diabetes mellitus; IDPP: Indian Diabetes Prevention Programme; USDPP: United StatesDiabetes Prevention Programme; TRIPOD: Troglitazon in the prevention of Diabetes; PIPOD: The pioglitazone in prevention of diabetes; DREAM: Diabetes Reduction Assessment with ramipril and rosiglitazone Medication; ACT NOW: Actos Now for the prevention of diabetes; CANOE: Canadian normoglycaemia outcomes evaluation; STOP NIDDM: Study to Prevent Non-Insulin-Dependent Diabetes Mellitus; XENDOS: Xenical in the prevention of Diabetes in Obese Subjects.

suitable choices for high-risk IGT patients. Troglitazone in Prevention of Diabetes Study, Pioglitazone in Prevention of Diabetes Study, Diabetes Reduction Assessment with ramipril and rosiglitazone Medication Trial, Actos Now for the prevention of diabetes study and Diabetes Prevention Program proven that thiazolidinediones obviously prevent the development of type 2 DM in IGT subjects as well as IFG subjects (Table 1). In Diabetes Prevention Program and Indian Diabetes Prevention Program, metformin slowed down the progression of IGT to type 2 DM, eventually ADA Consensus Conference Statement proposed metformin usage in high-risk IGT individuals. However, pioglitazone and rosiglitazone efficacy in preventing IGT progression to type 2 DM nearly doubles metformin's efficacy (31% *vs* 72% and 62%, respectively). Rosiglitazone (low dose = 2 mg/d) together with metformin (850 mg/d) was proven to be slows down IGT progression to type 2 DM as well as to be more tolerable. GLP-1 analogues: (1) effectively treats type 2 DM; (2) blocks IGT - type 2 DM progression; (3) preserves and augments functions of beta-cells; (4) facilitates loosing weight; (5) combat with cardiovascular risks; (6) do not cause hypoglycemia; and (7) can be used once a day (liraglutide) or once a week (Bydureon). For these reasons we speculate that this drug group, especially long-acting preperations[127], be ideal for obese patients with IGT.

The benefits and disadvantages of pharmacotherapy must be evaluated simultaneously. Although rare, metformin can induce lactic acidosis. If serum creatinine levels exceeds 1.4 mg/dL in females and 1.5 mg/dL in males, metformin is contraindicated. Gastrointestinal side effects are often and one tenth of patients are metformin intolerable. On the other hand, pioglitazone users experience fluid retention, fat weight gain and congestive heart failure. Paradoxically, while fat weight gain increses, reduction in HbA1c becomes more prevalent and much more insulin sensitivity/beta-cell function improvement is achieved. Easily detected clinical sign of fluid retention is peripheral edema and can be controlled easily with distally acting diuretics such as amiloride or spironolactone. Because these side effects are dose-related, restricting pioglitazone to 30 mg daily dose may decrease side effects. Trauma-related fracture cases were increased in postmenopausal women treated with pioglitazone. For that reason pioglitazone should be used carefully in postmenopausal women. Nausea/vomiting are main handicaps of GLP-1 receptor agonist usage; nearly one third of subjects experience nausea/vomitting. Though adverse effects are generally mild or temporary, liraglutide/exenatide intolerance is about 5%. Pancreatitis is also pronounced, but when large national databases were analysed retrospectively, there was no such increment in pancreatitis in GLP-1 receptor agonist users.

## CONCLUSION

In conclusion, we recommend strict lifestyle modification for patients with IGT ± IFG. Another option is to initiate pharmacotherapy with metformin plus low-dose pioglitazone. In high risk IGT individuals long-acting GLP-1 analogue use as well as diet plus exercise may be another option. Each component of this approach is effective in type 2 DM prevention and turning IGT back to normal. Depending on evidence described earlier, we believe "combination therapy" would especially be preventive for microvascular complications and is associated with lower adverse effects. Also, pharmacotherapy with generic drugs may be cost effective.

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REVIEW

# Molecular and biochemical trajectories from diabetes to Alzheimer's disease: A critical appraisal

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## Abstract

Diabetes mellitus (DM), a metabolic disorder is a major orchestra influencing brain and behavioral responses *via* direct or indirect mechanisms. Many lines of evidence suggest that diabetic patients apparently face severe brain complications, but the story is far from being fully understood. Type 2 diabetes, an ever increasing epidemic and its chronic brain complications are implicated in the development of Alzheimer's disease (AD). Evidences from clinical and experimental studies suggest that insulin draws a clear trajectory from the peripheral system to the central nervous system. This review is a spot light on striking pathological, biochemical, molecular and behavioral commonalities of AD and DM. Incidence of cognitive decline in diabetic patients and diabetic symptoms in AD patients has brought the concept of brain diabetes to attention. Brain diabetes reflects insulin resistant brain state with oxidative stress, cognitive impairment, activation of various inflammatory cascade and mitochondrial vulnerability as a shared footprint of AD and DM. It has become extremely important for the investigators to understand the patho-physiology of brain complications in diabetes and put intensive pursuits for therapeutic interventions. Although, decades of research have yielded a range of molecules with potential beneficial effects, but they are yet to meet the expectations.

**Key words:** Diabetes mellitus; Alzheimer's disease; Insulin; Type 2 diabetes; Type 3 diabetes



**Core tip:** This review provides a synopsis in which a metabolic disturbance becomes indispensible for life and emerges as a molecular signal defect leading to a syndrome with multiple complications. Insulin is a spotlight player which draws a trajectory from diabetes to Alzheimer's disease with multiple divergence and convergence. We have discussed their interplay to speculate their shared molecular footprints. These biochemical and molecular commonalities provide a clue to the investigators to look inside a therapy with a common experimental and clinical platform and also provide an insight for new interventions as future perspective to find a potential stone to kill two birds together.

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## INTRODUCTION

Every human cell relies on a complex set of programs installed during ontogeny. These programs and commands over them are the two interfaces which need faultless execution for normal body physiology. Physiology, behavior and defense are three eventful networks, which are supposed to function in synchronicity. A defect in any of these three events alters rest of two without any delay. Diabetes is a complex disorder where a molecular compromise alters the physiology with significant changes in behavioral responses.

Diabetes is associated with the production of auto-antibodies against pancreatic β-cells, *i.e.*, type 1 diabetes (T1D) or with insulin resistance (IR), *i.e.*, T2D[1,2]. T1D is a chronic hyperglycemic condition which affects multiple systems like brain, heart, eyes and kidneys[3]. Diabetes is found to be one of the causes of brain atrophy, mild cognitive impairment and white matter abnormalities[4-6]. In T2D insulin fails to stimulate utilization of glucose which gives rise to a phenomenon called IR. Chronic IR leads to several other complications such as lack of cellular energy, increased plasma lipids, cardiovascular problems and hypertension[7-11]. Increased risk of developing dementia and Alzheimer's disease (AD) was suggested in T2D, which was further supported by clinical and epidemiological studies[12,13]. Diabetes patients have two fold higher risk of AD as compare to non-diabetic patients[12]. In central nervous system (CNS), presence and distribution of insulin, insulin receptors (IRs) and its substrate are region specific[14,15]. Insulin is found to play important role in learning and memory by regulating the release of neurotransmitters and synaptic plasticity[16]. It is inferred from the literature that defective insulin signaling in diabetic patients plays a crucial role in synaptic physiology[17-19]. Many other molecules participating in insulin signaling pathway have been reported to be crucial for normal physiology[20]. Remarkable presence of IRs in different brain areas has provided a clue of possible link between insulin signaling and synaptic plasticity. This fact is strongly supported by up-regulation of IRs in hippocampus after training for spatial memory task *via* Morris-Water Maze[21].

In 1998, a possible link between insulin dysfunction and AD was established[22,23]. The postmortem AD brains showed reduced insulin like growth factor (IGF) mRNA levels and its receptor as compared to controls[24]. Impaired peripheral glucose sensitivity[25] and elevated plasma and cerebro-spinal fluid (CSF) levels of insulin[26-28] were also reported in AD patients. Thus, there are consistent reports showing involvement of impaired insulin signaling in cognitive decline in AD patients. The role of insulin in enhancing memory performance in AD patients was confirmed by rescuing effect of intravenous and intranasal insulin administration[29,30].

Attempts are being made to unscramble the cellular and molecular mechanisms connects diabetes and AD. Present review critically examines impaired insulin signaling in diabetes as well as in AD patients with emphasis on critical molecular players such as fork head box O-1 (FOXO1), mammalian target of rapamaycin (mTOR) and glycogen synthase kinase 3 beta (GSK3β) which can be potential therapeutic targets.

## DIABETES MELLITUS

Diabetes mellitus (DM), a complex metabolic disorder is characterized by hyperglycemia with several macrovascular (coronary artery disease, peripheral arterial disease, and stroke) and microvascular complications (diabetic nephropathy, neuropathy, and retinopathy)[31]. Risk of developing any of microvascular complications of diabetes depends upon both the duration and the severity of hyperglycemia. Aldose reductase, initial enzyme in the intracellular polyol pathway is a key player involved in the development of diabetic complications. Polyol pathway converts glucose into sorbitol (glucose alcohol). Hyperglycemic condition increases the flux of glucose into this pathway and results in sorbitol accumulation which further leads to osmotic stress. Osmotic stress is reported to be most common underlying mechanism in the development of microvascular complications of diabetes[31]. American Diabetes Association has categorized diabetes as T1D and T2D. T1D is characterized by autoimmune destruction of pancreatic beta cells resulting in absolute absence of insulin whereas T2D is identified by peripheral IR. According to WHO reports 2012, 90% cases of diabetes are from T2D. Clinical and experimental studies suggested strong association between diabetes and cognitive impairment[32-35]. T2D is at the edge of several risk factors such as life style, obesity, physical inactivity, gestational diabetes history as well as genetic predispositions[36,37]. The hallmark symptoms of the disease are polyurea, polydipsia, polyphagia and weight loss[38]. Mechanisms of T2D involves lipid breakdown within fat cells, elevated plasma glucagon levels as well as an increase in electrolyte retention[39].

## AD

AD is an age dependent neurodegenerative disorder associated with deposits of plaques and tangles in brain[40]. Only 1%-5% of the AD cases are found to have genetic differences and out of these cases, only 0.1% cases follow familial autosomal non-sex linked inheritance pattern[41]. AD was for the first time reported in 1906 by Alois Alzheimer, a German psychiatrist and pathologist as a progressive neurodegenerative disorder of memory loss and confusion[42]. Postmortem AD brains revealed intracellular accumulation of neurofibrillary tangles (NFTs) and extracellular deposition of amyloid

beta (Aβ) plaques as two major hallmarks of AD. NFTs are hyperphosphorylated form of tau protein, which are involved in microtubule dynamics while Aβ plaques are the cleavage product of amyloid precursor protein (APP) which is a transmembrane glycoprotein of unknown function. Mutation in three genes encoding APP, presenilin 1 (PSEN1) and presenilin 2 (PSEN2) contributes to genetic cases of AD[43]. These loci are responsible for the familial type of disease while environmental factors influence sporadic form of AD with unclear etiology. Mutated form of these genes increase production of Aβ-42 protein product, a major component of senile plaques. ε4 allele of the apolipoprotein E (APOEε4) is another risk factor for AD[44,45] which is thought to contribute in neuronal lipid homeostasis, repairs injured neurons, maintains synapto-dendritic connections and scavenges neurotoxins. Loss of cholinergic system is a major cause of cognitive deficit in AD patients and the current therapies are targeted at improving cholinergic functions[46].

## TWIN MYSTERY OF AD AND DM: THE STORY SO FAR

In 1980, first line of evidence appeared when Adolfsson *et al*[47] performed glucose tolerance test on AD type dementia patients and hypothesized that hypoglycemic condition can ameliorate brain status. In 1994, Razay *et al*[48] spotted light on disturbed glucose metabolism and hyper-insulinemia in female AD patients and tried to establish a link between insulin dysfunction and dementia. In 1996, Messier *et al*[23] strengthened the evidences by uncovering the potential effects of glucose on memory and cognition of AD patients. In 2003, Messier[49] further established a clear association between non-insulin dependent diabetes mellitus with neuropathy which is an incidence of vascular disease and retinopathy, he further suggested that DM is a probable risk factor for AD. Many more groups stepped ahead to address the fundamental question of whether the basic premise about the disease is true or not.

In 2005, Susanne de la Monte's group at Brown University introduced the concept of brain diabetes or type 3 diabetes (T3D) and observed that after blocking brain insulin supply, neurons get disoriented and develops AD pathology in rats. This provided a promising platform to investigators to touch insight into T3D or brain diabetes[50]. In 2007, Li *et al*[50] published a review dedicated to common pathological process in AD and T2D which shared molecular degenerative cascades like dysfunction in insulin signaling pathway. In 2008, de la Monte *et al*[51] reappeared with some more set of explanations which were unclear in 2005. Diabetic brain was found to be compromised for acetylcholine homeostasis and cognitive impairment, whereas insulin sensitizers rescued these effects[52]. In 2009, Gotz *et al*[52] described the molecular commonalities between T2D and AD with hallmark feature of amylin deposition in pancreatic islets of T2D patients, whereas Aβ and NFTs deposition in AD brain which are characteristic fibrillar proteins leading to cell loss. In 2010, Saini *et al*[53] contributed a relevant publication to World Journal of Diabetes, establishing a molecular mechanism of IR in T2D. Crucial molecular players in these pathways came into the picture and provided new therapeutic targets. Streptozotocin induced diabetic rat model showed co-appearance of tau hyperphosphorylation and cognitive decline as an interesting evidence[55]. On the basis of clinical and biochemical evidences, it was further suggested that both of these diseases promote each other's progression[56]. It has recently been found that proinflammatory signals in the brain impair insulin signaling, mitochondrial dysfunction, synaptic crosstalk as well as cognitive impairment[57].

Since 1980, many reports appeared in literature to describe the correlation between these two distinct problems with common molecular and cellular interface. Glucose metabolism and insulin signaling are major elements bridging AD and diabetes. Some relevant reports, unraveling the twin mystery of AD and DM are listed in Table 1.

## THE CHICKEN OR EGG QUESTION

In spite of so many striking evidences, due to common interface of homeostatic mechanisms of AD and DM, the chicken or the egg question has remained unresolved. Citing all relevant findings, in 2005, first time Suzanne de la Monte has introduced insulin signaling dysfunction as a core of AD. To untangle this mystery, evidence of crosstalk between AD and DM, were put forward as crucial milestones. Patients with T2D were found to be at high risk of developing mild cognitive impairment (MCI), dementia and AD[60,61]. Similar type of evidence for MCI, dementia and AD were found in experimental models of diabetes[56,62-65]. AD brains have similar pathogenesis as observed during insulin deficiency[24,66-68]. Studies with AD patients and animal model of AD showed that intranasal insulin therapy significantly improved cognitive performance[69-71]. These clinical and experimental studies suggested that both of these disorders share common biochemical and molecular cascades[60,72,73]. Some of these common bridging elements have been schematically represented in Figure 1. Interestingly, insulin has been found to regulate Aβ and tau metabolism, which are major hallmarks of AD[74,75]. It is also evident that in T2D patients insulin signaling dysfunction accelerates AβPP (amyloid beta precursor proten)/Aβ trafficking from trans-Golgi network, a major site for Aβ generation and alters dynamicity of a Aβ synthesis[75]. Some studies report the presence of some downstream regulators of insulin signaling pathway which are involved in cleavage of AβPP at γ-secretase site, a determining site for Aβ amyloidogenicity[76]. Although, investigators found many evidences of common features in both of these disorders, the chicken or the egg question is still valid

**Table 1 Relevant reports bridging Alzheimer's disease and diabetes mellitus**

| Ref. | Key findings |
|---|---|
| Adolfsson *et al*[47] | Hypoglycemic condition can ameliorate brain status in AD |
| Razay *et al*[48] | Disturbances in glucose metabolism and hyper-insulinemia in female AD patients are responsible for cognitive decline |
| Ruigómez *et al*[58] | Documented a relationship between non-insulin dependent diabetes and neuropathy |
| Li *et al*[50] | Defective insulin signaling is a shared degenerative cascade in disease pathology of both AD and DM |
| Ke *et al*[59] | Amylin deposition in pancreatic islets of T2D patients whereas, Aβ and NFTs deposition in AD brain are common hallmarks feature of diabetes and Alzheimer's in terms of protein deposition |
| Saini[53] | Elucidated cellular and molecular mechanisms of insulin resistance and provided understanding for the molecular therapeutic targets |
| Park[54] | T2D and AD have some common pathogenic alterations like defects in insulin signaling, Aβ clearance, glucose metabolism, O-GlcNAcylation, Aβ aggregation by AGEs, inflammation, oxidative stress and circulating cortisol levels |
| Correia *et al*[55] | Amyloidogenesis and mitochondrial dysfunction are common denominators potentiating brain dysfunctions |
| Talbot *et al*[57] | Brain insulin signaling pathway including IGF-1R → IRs-2 → PI3K signaling is directly involved in AD and thus one of a causal factor in disease pathogenesis |

AD: Alzheimer's disease; DM: Diabetes mellitus; T2D: Type 2 diabetes; NFTs: Neurofibrillary tangles; Aβ: Amyloid beta; AGEs: Advanced glycation end products; IGF-1: Insulin like growth factor-1; IRs: Insulin receptors; PI3K: Phosphatidylinositide 3-kinases.

**Table 2 Symptoms of Alzheimer's disease symptoms in diabetes mellitus patients and symptoms of diabetes mellitus in Alzheimer's disease patients**

| Ref. | Key findings |
|---|---|
| Gasparini *et al*[75] | In T2D patients insulin metabolism dysfunction accelerates AβPP/Aβ trafficking from trans-Golgi network, a major site for a Aβ generation |
| Phiel *et al*[76] | Some studies claim for the presence of downstream regulators of insulin signaling pathway which are involved in cleavage of AβPP at gamma-secretase site, a determining site for Aβ amyloidogenicity |
| Steen *et al*[24] | Extensive dysfunction of IGF-I and IGF II signaling mechanisms reported in AD brain |
| Rivera *et al*[66] | Insulin and *IGF* gene expression altered with abnormal receptor binding in AD brain |

AD: Alzheimer's disease; T2D: Type 2 diabetes; Aβ: Amyloid beta; IGF: Insulin like growth factor.

and needs parsimonious explanations. Key reports supporting AD like symptoms in DM patients and DM like symptoms in AD patients are listed in Table 2.

## AMYLOIDOGENESIS: A COMMON PATHOLOGY IN AD AND DM

Protein structure and function is crucial for maintenance of life, moreover its mishandling leads to diverse pathological conditions. Neurodegenerative disorders lie in a class of disorders associated with different types of abnormal fibrous, extracellular poteinaceous deposits which are referred as amyloid[77]. β-sheet structured insoluble moieties play an important role in the pathology of many protein misfolding diseases[77]. Globular proteins due to their tertiary structure constrain, undergo destabilization of their native structure and adopt partial folded and unfolded form while natively folded proteins are devoid of any ordered form so they passes through the stabilization process of fibrillogenesis and acquire a partially folded conformation[78]. In a crowded cellular milieu when functional protein erroneously interacts with other components and transforms itself into ordered stable form, the phenomenon is known as amyloidogenesis.

Interestingly AD and DM both involve amyloidogenesis. Extracellular deposition of Aβ plaques is a feature of AD while amyloidogenic peptide deposition in pancreatic islets of Langerhans is a characteristic feature of T2D[79,80]. Amyloid deposits in islets consist of 37 amino acid peptide referred to as islet amyloid polypeptide (IAPP) amylin[81,82]. Aβ and IAPP have same folding patterns and configuration[83]. IAPP is reported to generate islet β-cells toxicity in the same way as Aβ do in neurons. Although we are far to understand the exact mechanism of amyloid formation, it can be speculated from the emerging data that amyloid formation is a basic cause of AD, DM and other disorders related to protein deposition[84-86].

## IR AS COMMON METABOLIC COMPROMISE IN AD AND DM

Glucose is the only required source of energy for neurons and any disruption in glucose metabolism leads to compromised neuronal functions[39]. Presence of insulin is crucial for brain in terms of its peculiar CNS functions[87] but any disturbance in its physiological level leads to CNS dysfunction. IRs are reported with low binding affinity with insulin in postmortem AD brain[87,88]. Moreover many other insulin signaling markers were altered in AD brain[24]. Elevated insulin plasma level in AD patients indicates a closed association of AD and IR[26,28]. Animal model studies revealed that factors contributing to T2D also regulate Aβ dynamics[89]. With this set of data it is clearly understood that IR or impaired IRs not only typify T2D but also orchestrate AD. Figure 2 depicts that how IR bridges peripheral and

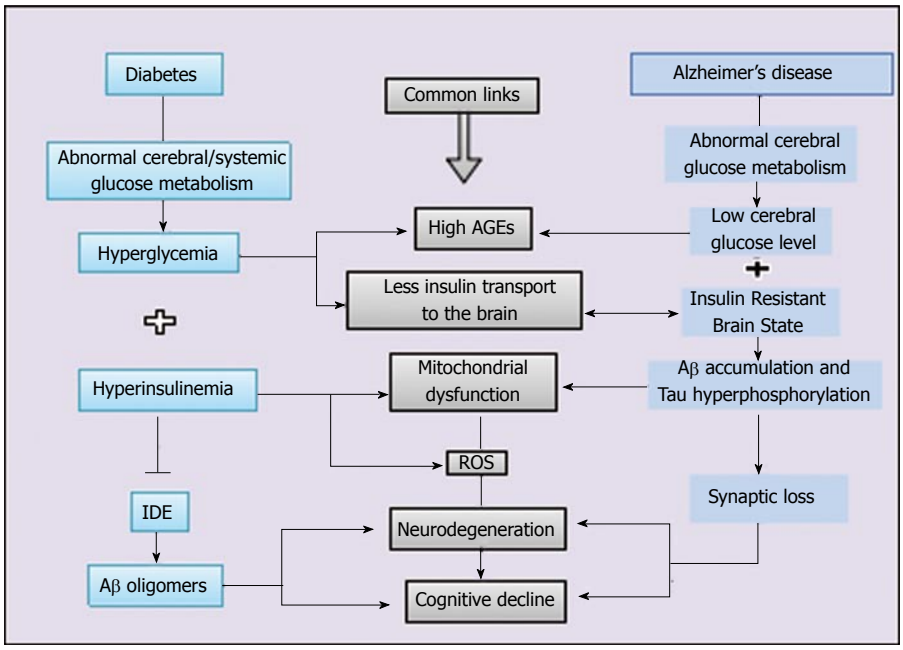


**Figure 1 Schematic representation of commonalities between diabetes and Alzheimer's disease.** Hyperglycemia and hyperinsulinemia are hallmark features of diabetes which leads to advanced glycation end product, reduced insulin supply to brain as well as mitochondrial dysfunction, which further leads to vicious cycle of oxidative stress. On the other side, any defect in glucose metabolism and insulin signaling in brain is one metabolic status of Alzheimer's disease brain which translates into insulin resistant brain status and converges to all common interfaces of mitochondrial dysfunction, oxidative stress and neurodegenrtaion. IDE: Insulin degrading enzyme; Aβ: Amyloid beta; AGEs: Advanced glycation end products; ROS: Reactive oxygen species.

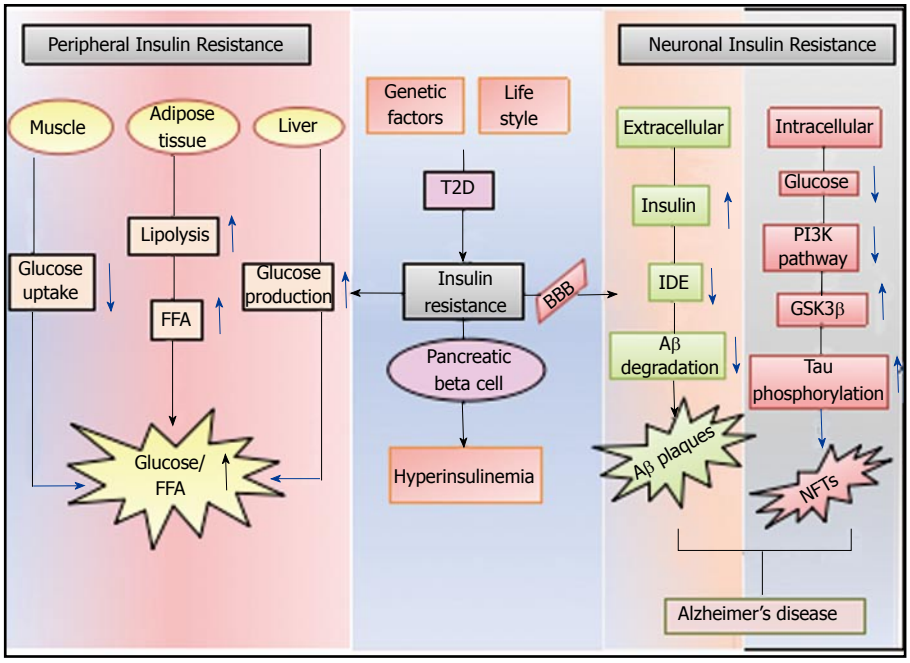


**Figure 2 Diagrammatic representation of peripheral and neuronal complications of insulin resistance in case of type 2 diabetes.** Insulin signaling dysfunction in peripheral system affect muscle, adipose tissue and liver (by decreasing glucose uptake, increasing free fatty acids) and by increasing glucose production respectively. When this dysfunction appears in CNS as a diabetes complication (by limited insulin supply to brain), it leads to deposition of Aβ plaques and NFTs in extracellular and intracellular milieu of neurons respectively and represents AD type brain status. AD: Alzheimer's disease; T2D: Type 2 diabetes; IDE: Insulin degrading enzyme; PI3K: Phosphoinositide 3-kinase; Aβ: Amyloid beta; NFTs: Neurofibrillary tangles; GSK3β: Glycogen synthase kinase 3 beta; FFA: Free fatty acids; BBB: Blood brain barrier.

neuronal IR and leads to AD.

### *How insulin modulates brain functions?*

Insulin expression in brain remained a debated topic for investigators and raised a question on its significance at ectopic site. Brain synthesizes insulin locally as well as receives through the blood brain barrier (BBB) mediated transfer[90]. With curious attempts, scientists

documented its role in feeding behavior and energy homeostasis which integrate whole body physiology[91]. The first article unpinning the relation between brain and insulin was reported in 1960, in which intracisternal injection of insulin in dogs reduced glucose levels, both in CSF and blood with its direct effects on the parasympathetic area of the brainstem[92]. Later, brain-centered glucoregulatory system (BCGS) that is involved in maintenance of blood glucose levels was found to act *via* insulin dependent as well as independent mechanisms[93]. The hypothesis of BCGS and its crosstalk with pancreatic islets gained experimental momentum by multiple supporting evidences that provided a clear understanding of BCGS[93]. BCGS is recognized as mechanistic node present in CNS which is channeled through peripheral hormone status[93]. Both of these regulatory nodes co-operate with each other and compensate the load of other's failure but when both are compromised, DM is an unavoidable issue.

### *Insulin as a synapto-dendritic player*

Insulin has drawn a wide trajectory in brain molecular milieu from cognitive function to orchestrate functions like development of neurite outgrowth, modulation of catecholamine release and uptake, regulation and trafficking of ligand-gated ion channels, expression and localization gamma-aminobutyric acid (GABA), N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors, synaptic plasticity regulation *via* NMDA, Phosphoinositide 3-kinase-Akt (PI3K-Akt)[94] and maintenance of excitatory synapses[95].

Presence of IRs at synapses rich in plasticity (hippocampus and cortex) reveals its involvement in cognition[90]. This fact was further strengthened in 1999 when Zhao *et al*[21] reported that rat hippocampus IRs expression is up-regulated when they are subjected to spatial memory task in Morris water maze. IRs are enriched in synaptosomes[96], co-localizes with axon terminal markers synaptophysin, synapsin, *etc*.[97], and dominates in post-synaptic density (PSD) fractions to interact with scaffolding protein shank and PSD-95. Insulin is also involved in various neuromodulatory functions such as electrophysiological properties of neurons[98,99], neurotransmitter receptors[100,101], trafficking of ion channels[102], neurotrophic effects[103,104] and the neuroprotective role against a wide range of insults such as apoptosis[105], oxidative stress[106], β-amyloid toxicity[107] and ischemia[108] in animal models as well as human studies.

Hyperinsulinemia is reported to reduce cholinergic activity in mice brain and resulted in impaired retention of an inhibitory avoidance[109]. It also alters membrane potential to affect the ion transport[110,111]. In streptozotocin induced rat model of DM, long term memory potentiation was found to be impaired and insulin treatment rescued the effects[112-114]. With these set of potential findings, it is evident that insulin is crucial synapto-dendritic player altering dendritic arbor morphology as well physiology.

## INSULIN RECEPTORS PLAYING DOWNSTREAM MOLECULAR ORCHESTRA: INSIGHT INTO THE MECHANISMS

Investigators unraveled the IRs downstream molecular orchestra and speculated that IRs activation further activates PI3K/protein kinase B (PI3K/PKB) pathway[115]. GSK3β is a major player of this pathway and involved in long term potentiation/long term depression (LTP/LTD) which is a sole mechanism of memory formation and synaptic plasticity[116]. Other than insulin, PI3K can be activated by multiple growth factor ligands including nerve growth factor, brain-derived neurotrophic factor (BDNF), glial cell-derived neurotrophic factor (GDNF), insulin like growth factor-1 (IGF-1)[117].

After investigating for over two decades, it is safe to accept that PI3K/Akt signaling pathway is a potential window through which various ON/OFF switches of cognitive decline get operated. Protein kinase B (PKB), also known as Akt is a main downstream hub of various other pathways and exists with its widely expressed isoforms such as PKB-α, PKB-β and PKB-γ (predominates in CNS)[118]. Akt pathway has its regulating arms over neuronal survival, glucose uptake, angiogenesis, metabolism and proliferation[119]. Moreover Akt has a negative feedback regulation over these *via* phosphatase and tensin homolog, protein phosphatase 2A, c-jun N-terminal kinases (JNK) and forkhead box O (FOXO)[119].

Loss of PI3K control is a central mechanism of neurodegeneration in DM patients[120]. Moreover, AD patients are reported with sustained PI3K/AKT signaling which is a primary response linking insulin, IGF resistance, tau pathogenesis and synaptic decline[121]. GSK3, mammalian target of rapamycin (mTOR) and FOXO are three main downstream targets playing this whole orchestra (represented in Figure 3).

### *Glycogen synthase kinase3β, a pivotal kinase in AD and diabetes*

Extensive reports supporting pivotal role of GSK3β proposed "GSK3β hypothesis of AD"[107], according to which GSK3β over-expression leads to impaired memory, amyloid β accumulation, tau hyperphosphorylation, neuronal defects and microglial mediated inflammation cascades. Genetic studies established that insulin signaling genes are also loci of AD[106]. Cholinergic system is one of the major regulating knob under GSK3β control with choline acetyltransferase and acetylcholinesterase as regulating keys[107,108]. GSK3β leads to reduction of acetylcholine synthesis, which is in accordance with the cholinergic deficit observed in AD brain[122]. GSK3β negatively affects axonal transport, microtubule dynamics and destabilizes microtubule by

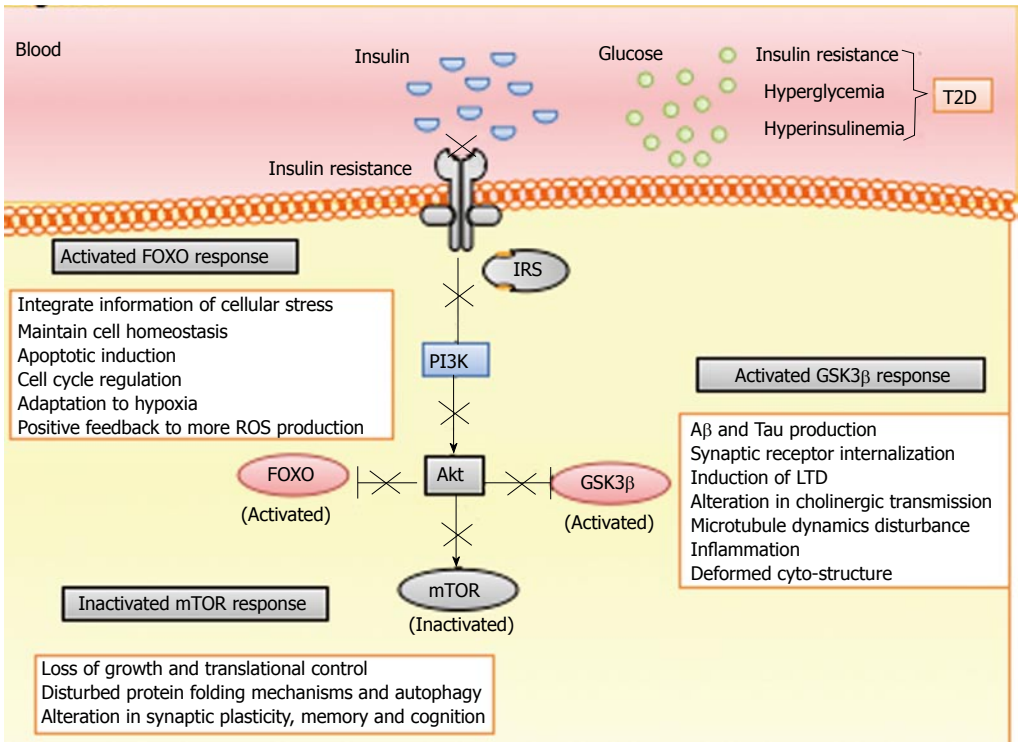


**Figure 3 Diagrammatic representation of molecular orchestra downstream of insulin receptor.** IRs activation leads to downstream PI3K signaling pathway with Akt as a central hub which diverges into three main branches including FOXO, GSK3β and mTOR. Akt inhibition leads to activated FOXO and GSK3β response while inactivated mTOR response. FOXO activation leads to cellular stress response, mTOR dysfunction leads to loss of translational control and altered cognition while GSK3β activation leads to Aβ and tau production. T2D: Type 2 diabetes; PI3K: Phosphatidylinositide 3-kinases; Aβ: Amyloid beta; GSK3β: Glycogen synthase kinase 3 beta; FOXO: Forkhead box O; mTOR: Mammalian target of rapamycin; LTD: Long term depression.

lowering its affinity with GSK3β phosphorylated tau[95-97] and contributes to AD pathology. Being a key mediator of apoptosis it may directly contribute to neuronal loss in AD[105,123]. GSK3β interestingly controls cell cycle in two way system by activating intrinsic pathway to trigger cell death and by inhibiting death receptors by extrinsic pathway[124]. In 2002, Sun *et al*[125] and in 2003, Phiel *et al*[76] reported that GSK3β increases Aβ production by regulating APP cleavage. On exposure of Aβ, neurons inhibit PI3K pathway and increase GSK3β activity[126]. GSK3α as well as GSK3β both are found to be an inducer of tau phosphorylation[127-132]. Drastic alteration in dendritic arbor and post synaptic density, a common morphological feature of AD brain has been observed in GSK3β deficient mice[132]. GSK3β is the only kinase involved in NMDAR-LTD[124]. It also maintains a threshold of LTP and LTD, *i.e.*, maintenance of metaplasticity[116,133,134]. Modulation in regulated/constituted expression of GSK3β orchestrates neuronal plasticity[84,116,134-140]. GSK3β dramatically induces the internalization of AMPA and NMDA receptors[141,142] and decreases the level of PSD proteins, a molecular marker of memory acquisition[77]. GSK3β phosphorylates CREB protein to inhibit its function which is a universal modulator of memory. It aids in cyto-architecture of cell by promoting actin and tubulin assembly for synaptic reorganization[143]. GSK3β is also a pivotal kinase involved in adult hippocampal neurogenesis which negatively regulates it by reducing the number of proliferating neurons in the dentate gyrus region[144,145]. GSK3β is directly involved in the production of pro-inflammatory cytokines such as interleukin (IL) 6, IL-1β, TNF-α which indicates its positive regulation towards inflammatory mechanisms[146,147].

### *FOXO1 signaling: A mechanistic node for a vicious cycle of IR and Aβ up-regulation*

FOXO1 signaling is a mechanistic node and regulates the fine balance of oxidative stress pathways (depicted in Figure 4). Before moving into the mechanism part, it has been briefly discussed about the dramatic story of its evolution in molecular series under discovery[148]. Many lines of evidence suggest its role in AD as well as IR with major involvement in cell proliferation, differentiation, cell survival, apoptosis and development of proliferative late onset diseases[148]. Short term activation of this player leads to protective mechanism of scavenging reactive oxygen species (ROS) which is a part of normal cell physiology but its persistent activation awakes the apoptosis pathway[148]. Cellular milieu tends to maintain a balance oxidant and antioxidants concentration to cope up any environmental stress, but whenever this balance acquires any plane of inclination, it comes to the cell survival[148].

Wnt and β catenin up-regulate FOXO signaling *via*

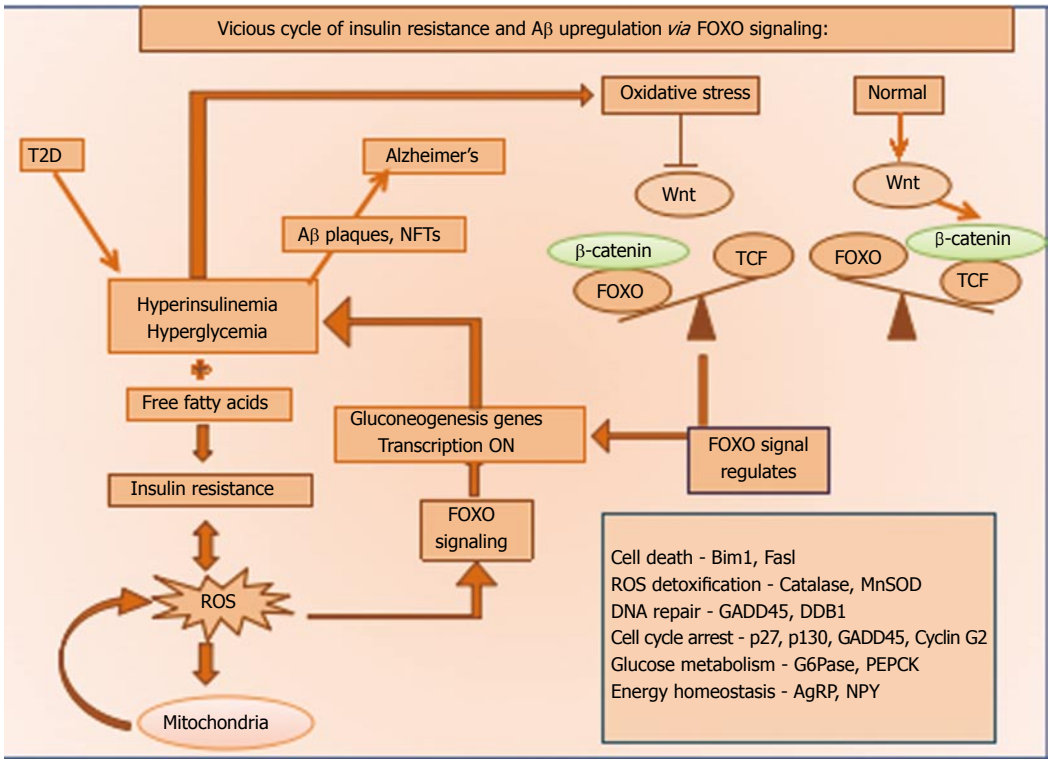


**Figure 4 Diagrammatic representation of vicious cycle of insulin resistance and amyloid beta up regulation *via* forkhead box O signaling.** FOXO signaling is a protective mechanism adopted by body to cope up with any cellular stress by ROS detoxification. In case of DM whenever there is any metabolic disturbance like hyperinsulinemia and hyperglycemia, it leads to further oxidative stress and ROS generation which promotes further trigger for FOXO signaling and promotes a vicious cycle of ROS generation leading the cell towards apoptosis. T2D: Type 2 diabetes; Aβ: Amyloid beta; FOXO: Forkhead box O; ROS: Reactive oxygen species; TCF: T cell factor; DM: Diabetes mellitus.

oxidative stress pathways[148]. Wnt signaling inhibits GSK3β expression and mediates β catenin transport into the nucleus and modulates transcription of T cell factor family gene, which has function opposite to FOXO1, this is known as the canonical pathway of Wnt signaling and involved in lipid and glucose metabolism[149]. ROS production inhibits canonical pathway of Wnt signaling and guides β catenin towards FOXO which acts as a cofactor of FOXO and enhance its transcription. Foxo signaling promotes gluconeogenesis and leads to hyperglycemia and hyperinsulinemia which further increases NFTs and Aβ accumulation to gear up ROS production and drives the vicious cycle of Oxidative stress[150].

When insulin is absent, FOXO1 is located in the nucleus and promotes transcription of respective enzymes for hepatic glucose production while in the presence of insulin; PKB is activated and leads to nuclear exclusion of FOXO 1 by phosphorylating it. State of IR in case of DM leads to impairment of PKB pathway and inhibition of FOXO activity resulting in hepatic glucose production triggering a vicious cycle of hyperglycemia and oxidative stress. FOXO, the downstream activator of PI3K/AKT controls energy homeostasis, locomotor behavior and leptin sensitivity[151,152].

### *mTOR pathway: A crucial intersection of AD and DM*

mTOR pathway has been evolved as environment sensor and growth promoter in unicellular organisms but as multi-cellularity emerged it acquired its role in central growth and homeostasis mechanisms. Metabolism and cell growth are two basic requirements and their proper functioning depends upon each other. Since mTOR pathway is centered for growth processes, it is activated by nutrition as well as insulin[136]. In evolutionary history from yeast to rodents, mTOR has evolved as key modulator of aging. Many investigators attempted to understand its basic role and decades of extensive pursuit revealed extensive network of mTOR. mTOR is found to accelerate growth but it has compromised some of metabolic signals by conflicting pathways and introduced a paradox or better to say insulin paradox[137].

This paradox appeared from the evidences of compromised insulin signaling with good health and IR leading to compromised health while both of the cases are of poor insulin signaling[138]. Parsimonious explanations are, compromised insulin signaling is unable to activate mTOR (good for health) while IR may be due to hyperactive mTOR which is bad. So in previous case compromised insulin signaling inhibits mTOR insurgence while active mTOR is promoting IR in the later case[138]. Mechanistic node of this story, S6 kinase (S6K) is activated by mTOR to phosphorylate and degrade insulin receptor substrate-1 (IRS-1) which ultimately leads to insulin desensitization[139,140].

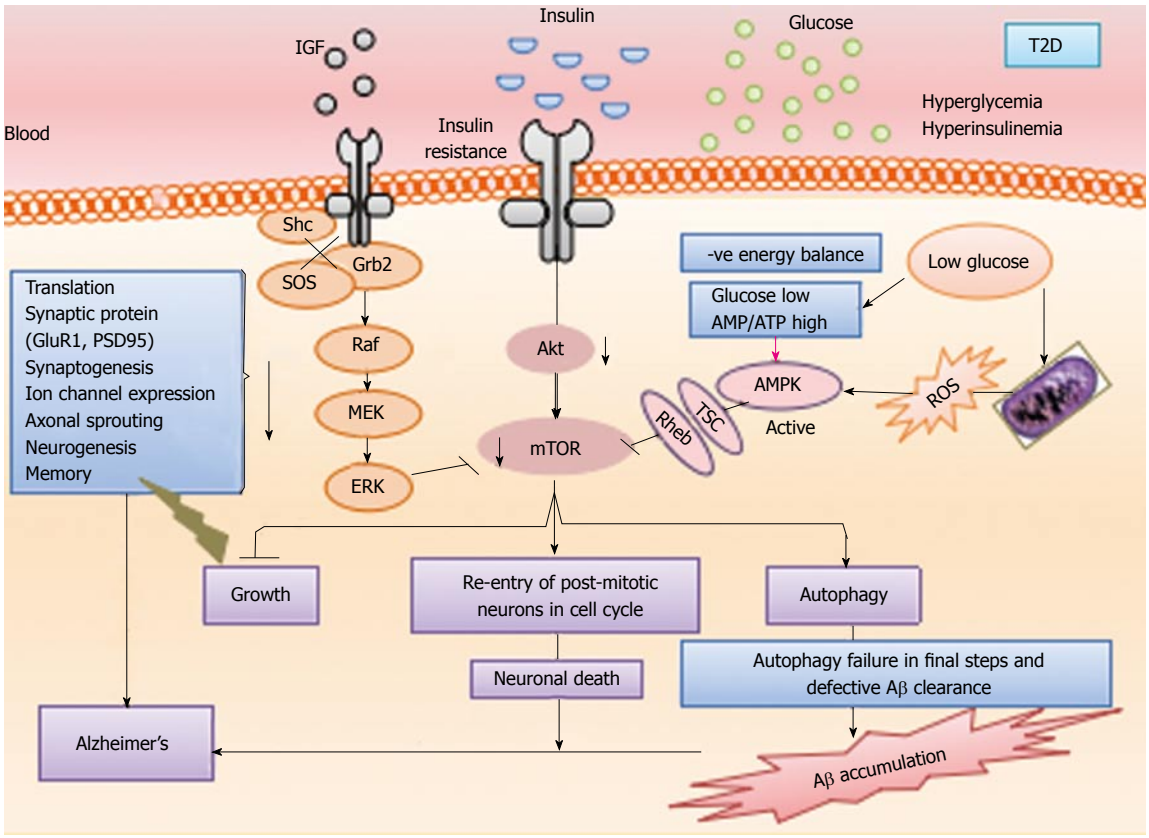


**Figure 5 Diagrammatic representation of mammalian target of rapamycin pathway: A crucial intersection of type 2 diabetes and Alzheimer's disease.** Diabetes results in dysfunctional insulin signaling which brings mTOR pathway down and ultimately results in autophagy failure to accumulate Aβ, inhibit re-entry of post mitotic neurons in cell cycle, stimulate aberrant growth pathways, lose of translational control and impaired neurogenesis, *etc*. T2D: Type 2 diabetes; IGF: Insulin like growth factor; mTOR: Mammalian target of rapamycin; Aβ: Amyloid beta; ROS: Reactive oxygen species.

mTOR signaling has a dramatic interplay with Aβ and tau proteins which are two hallmarks of AD in their aggregated forms. It was reported in 2012 that Aβ is an activator of PI3K/Akt pathway which further switches on mTOR cascade[153]. *In vitro* studies suggest that Aβ application elevates the level of p70S6K, a downstream target of mTOR which contributes in development of NFTs[154,155]. Consistent *in vitro* reports validated the fact that mTOR activity and activated p70S6K are either cause or consequence of the molecular cascade and hence are found with elevated levels in hippocampus and cortex of animal model of AD[156,157]. mTOR suppression leads to induction of autophagy which is a cell cleaning process. In AD brain it is evident that neuronal autophagy is induced to end up with impaired steps and leads to massive accumulation of Aβ plaques[158].

mTOR has characteristic property of maintenance of protein homeostasis, translational control and cellular maintenance, which plays an important role in the maintenance of synaptic plasticity. Figure 5 provides detailed information of mTOR domain. To execute these entire tasks mTOR pathway is operated under fine control of several surface receptors such as NMDA, dopaminergic and metabotropic glutamate receptors (mGluRs) and BDNF[159-163]. mTORC1 is one of the downstream targets of PI3K/AKT pathway which is very important for synaptic plasticity, neuronal repair, protein folding mechanism and autophagy[164,165].

## INFLAMMATION: A COMMON ALARM FOR AD AND DM

Inflammation is an exceedingly complex but equally fascinating and costly host defense system evolved with proximate set of mechanisms and exhibit phenotypic plasticity. It is crucial for life but once dysregulated, it can be detrimental. Emerging field of metabolic and aging syndromes spurred a renewed interest of scientists into inflammatory mechanisms. This is a compensatory mechanism for body to cope up with the hostile environment which involves many subtle factors and specialized cells to fight against any threat[166]. It has very critical progressive role with analogous mechanism in diabetic patients showing IR and defective neuronal signaling in AD patients[167]. Thus, DM and AD share inflammation as a common pathological feature.

Studies have reported elevated levels of proinflammatory cytokines such as TNF-α, IL-6, IL-1β, *etc.*, in AD patients[168]. In diabetes patients, elevated TNF-α triggers various stress kinases to phosphorylate IRS-1 (at inhibitory serine residues) and disrupts insulin signaling[169-171] (explained in Figure 6), while blocking TNF-α rescues its effects in obese mouse model[172,173]. JNK and double-stranded RNA-dependent protein kinase

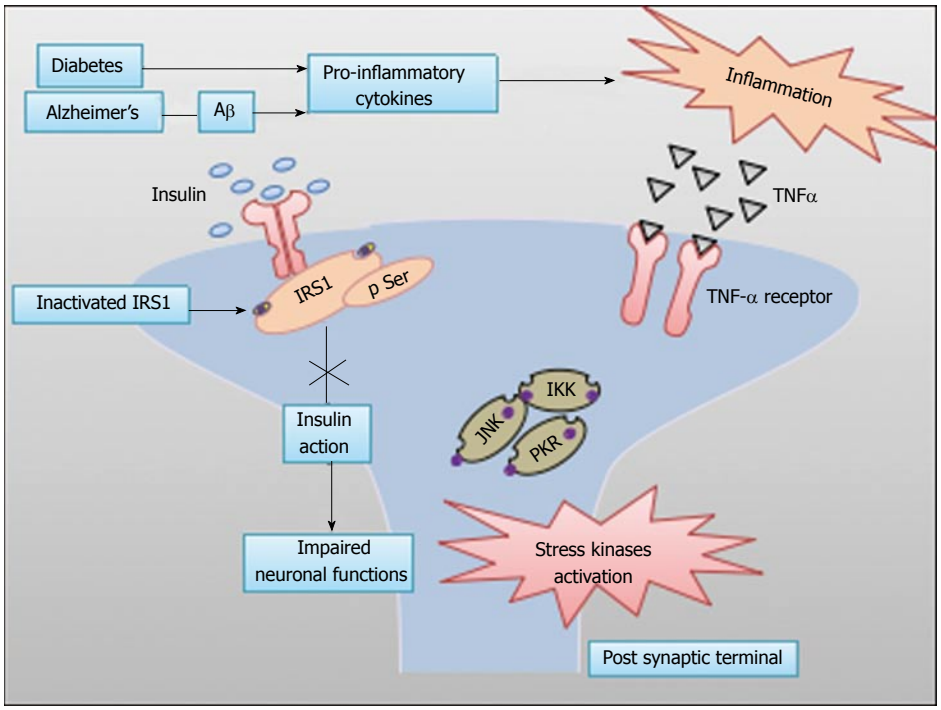


**Figure 6 Diagrammatic representation of insulin signal dysfunction in Alzheimer's disease and diabetes mellitus *via* common inflammatory cascade.** Diabetes and AD lead to production of pro-inflammatory cytokines in inflammatory response. These stress kinases inhibit IRs1, an adaptor protein for insulin receptor signaling and result into defective insulin signaling in brain. Aβ: Amyloid beta; IRs: Insulin receptors; JNK: c-Jun N-terminal kinases.

are major stress kinases which are common regulatory nodes between inflammation and metabolism[174,175]. Since insulin signaling contributes to normal functioning of neurons, any inflammation mediated alteration in these, results into defective neuronal function[95,176,177]. These evidences suggest that there is a common mechanistic pathway adopted by peripheral IR in T2D as well as impaired brain insulin signaling in AD.

## OXIDATIVE STRESS: A COMMON BURDEN IN AD AND DM

Normal body physiology tends to maintain a balance between production of ROS and body's antioxidant defense system and any sort of imbalance altering this dynamic system leads to onset of metabolic disorder with cognitive dysfunction[178]. Hydrogen peroxide, hydroxyl radical, superoxide ion and singlet oxygen are such reactive species which are abundantly produced in cellular respiration cycles and have very short half life[179]. It is known that diabetic patients have more oxidative cellular environment as compared to healthy ones[180-182]. Hyperglycemic condition has proportionality with sorbitol production which reduces NADPH, a cofactor for GSH production and hence decreases antioxidant levels in the body[183-185]. One more prevalent mechanism of diabetes contributing towards ROS is insurgence of advanced glycation end products (AGEs) production[183,184,186], which binds to cell surface receptors, *i.e.*, receptor for advanced glycation end roducts (RAGEs). RAGEs-AGEs interaction leads to ROS production *via* NADPH oxidase system which in turn activates Ras-MAPK pathway and ultimately nuclear factor kappa-light-chain-enhancer of activated B cells (NFκB) activation[184,187]. Hyperglycemia also leads to flux of glucose or FFA into blood which turns hexosamine pathway on[188] for further ROS production[189]. Elevated levels of FFA have an adverse effect on mitochondrial functioning and uncouple oxidative phosphorylation to contribute in ROS production[190,191]. ROS production worsens the status of insulin signaling and stress pathways which lead to further ROS production to turn a vicious cycle on.

High polyunsaturated fatty acid proportion with GSH content leave neurons vulnerable and make them prone to free radical attack[192]. A noticeable increase in lipid peroxidation was observed in brain of AD patients[193-195]. Oxidative stress and Aβ aggregation has both way relationships controlling each other's turnover. Oxidative stress channels regulate Aβ dynamicity from non-aggregated form to aggregated form[196]. Aggregated Aβ acts like a source of free radical production and lipid peroxidation[197] to drive brain towards neurodegeneration.

## MITOCHONDRIAL VULNERABILITY IN CASE OF AD AND DM

Mitochondria, a result of 1.5 billion years of obligate endosymbiotic co-evolution is a sub-cellular niche to take care of cell survival as well as programmed cell death[198]. Several decades of research has establis-

hed that fission-fusion dynamicity of mitochondria is critical in neurodegeneration[198]. As the brain is offered with limited capacity of glycolysis, neuronal cells are highly dependent on aerobic oxidative phosphorylation for energy production which is an electron transfer event from lower redox potential to higher redox potential[199-202]. Although, this electron chain transfer process is very efficient, still some ROS are produced which leads to oxidation of mitochondrial DNA, lipids and proteins further contributing to mitochondrial dysfunction which is a prominent feature of AD[181,203].

Substantial data from diabetic patients and animal model systems revealed that brain faces several structural and functional deficits. Functional impairment of mitochondria leads to neurodegeneration and loss of control over neuronal metabolism. A study reflected that there is a significant decrease in coenzyme Q levels in diabetic animals which represents a marked deficit in antioxidant defense system[204]. There are reports which are directly linking impairment in glucose utilization with mitochondrial dysfunction and metabolic disturbances[205-208]. In 2003, clear evidence of oxidative phosphorylation uncoupling was found in rat model of T2D[209]. Mitochondrial capacity of $Ca^{2+}$ accumulation was also found to decrease in case of diabetes which is a favorable environment for mitochondrial permeability transition (MPT) opening and ultimately leads to cell death[210,211].

AD animal models as well as human studies suggested that AD pathology leads to mitochondrial dysfunction and ROS production. Some crucial molecules such as Aβ binding alcohol dehydrogenase are reported to aid to AD pathology by mediating Aβ induced cell death *via* mitochondrial channel[209,212]. In some reports it is mentioned that one of the insulin degrading enzymes isoform, a well established regulator of Aβ dynamicity targets mitochondria and interfere with its normal functioning[213]. Aβ is also found to be a good inhibitor of respiratory chain complex and thus leads to marked decrease in cellular ATP levels[214,215]. Importantly, Aβ 40 and Aβ 25-35 contribute in uncoupling of oxidative phosphorylation and impair respiratory chain as well as MPT opening[204,210,211]. Moreover Aβ induces $H_2O_2$ production which is rescued by CoQ10, a key enzyme of electron transport chain[216]. Various tri-carboxylic acid (TCA) cycle enzymes such as pyruvate dehydrogenase, α-ketoglutarate dehydrogenase and ATP citrate lyase were also found to be dysregulated in case of AD[217].

Mitochondrial morphology was found to be altered with some functional loss in neurodegenerative disorders such as AD[218-221]. In brief it can be mentioned that a small metabolic compromise is sufficient to trigger a cascade and disrupt normal mitochondrial function which plays a vital role in neuronal survival, growth and plasticity.

## THERAPEUTIC OPPORTUNITIES

Sedentary life style, dietary changes and genetic predisposition are conspired forces responsible for worldwide epidemic of metabolic and aging syndrome. Discovered molecular trajectories from T2D to T3D gained experimental momentum for new therapeutic interventions. Elucidating role of anti-diabetic drug for the treatment of AD translated the disease information and added new armaments to the arsenal of putative therapies. It is unquestionable issue that both of these disorders share common pathologies including glucose metabolism defects, mitochondrial dysfunction, oxidative stress and abnormal deposition of amyloidogenic proteins[55]. The reason why insulin got this recognition under frontier's of Alzheimer research is that its high level in CNS revealed its own crucial role in learning, memory, cognition and synaptic plasticity[222]. Although, brain has potential pyramidal neurons involved in synthesis and secretion of insulin, majority of brain insulin is replenished by peripheral source from pancreatic β cells transported through blood across BBB[223].

There are some well known potential oral drugs [such as biguanides, sulfonylureas (SUs), thiazolidinediones (TZDs), and dipeptidyl peptidase-Ⅳ (DPP-Ⅳ) inhibitors], injections (*e.g.*, insulin and GLP-1 analogs), and some other molecules like glucokinase activators, amylin analogs, D2-dopamine agonists, bile acid chelators, and sodium/glucose-linked transporter-2 inhibitors *etc.*, established for T2D. Most of the anti-diabetic drugs act through the mechanism of maintenance of plasma glucose level, regulation of inflammatory cascades and establishing the balance between ROS and antioxidants. We will briefly provide an overview of experimental and clinical trials of some anti-diabetic drugs which are being tested in patients with AD and with low to moderate mild cognitive impairment.

### *Metformin*

Metformin, a well known biguanide anti-diabetic drug is used to reduce IR. It sensitizes liver and skeletal muscle cell *via* AMP kinase cascade[224,225]. Brain is most vulnerable vital organ for oxidative stress, because of high oxidative metabolism rate and limited antioxidant level. Under oxidative stress mitochondrial permeability pores open up to release cytochrome c and trigger apoptotic cascade. Metformin is reported to inhibit opening of these permeability pores in ectoposide-induced cell death model to inhibit apoptotic cascade[226]. Metformin is also involved in neurogenesis by activation of protein kinase C-CREB binding pathway (PKC-CBP) pathway in neuronal cell culture study, in human and rodent model system[227]. In neuronal cell lines (neuro2A), metformin promotes insulin action and attenuates molecular and pathological features observed in AD. Metformin treatment was found to reduce the risk of dementia in human aged subjects[228]. AD patients taking calcium in diet supplemented with metformin were found to have better cognitive performance[229]. Thus these evidences support the fact that metformin is not only a known anti-diabetic agent

but also an effective neuroprotective molecule.

### Sulphonylurea

SUs is a class of anti-diabetic drugs which are used as mono or combined therapy to increase insulin secretion by enhancing pro-insulin level *via* voltage gated calcium channel but the actual mechanistic target is still under investigation[230]. SUs limits liver glucose production and decreases insulin clearance by liver. Glipizide and Glyburide (glibenclamide) are the main SUs compounds which are investigated for memory and cognition in diabetic patients.

### Experimental and clinical studies

In case of diabetes and AD, PI3K/mTOR is found to be aberrantly activated. Glyburide and glipizide are reported to have properties of mTOR antagonist[231] but their efficacy to recover AD patients is yet to be determined. Inflammosomes are involved in the secretion of proinflammatory cytokines that results in inflammation and associates it to AD. Along with inhibiting mTOR pathway, gliburide is found to inhibit inflammosome and thus brain inflammation[232]. Exalto *et al*[230] reported that SUs treated T2D patients shows improved AD type dementia symptoms but the precise mechanism is still unknown.

DM patients treated with glipizide are reported to have better learning efficiency[233]. Some recent studies show that there is no alteration in the development of AD in population using SUs in long term[234]. Metformin and SUs in combination are reported to reduce the risk of dementia upto 35% in a prospective cohort study[228].

### Intranasal insulin

Intranasal administration of insulin is reported to attenuate reduced insulin signaling in AD[235]. Importantly, intranasal insulin does not adversely affect blood insulin or glucose levels.

### Experimental and clinical studies

It is evident that AD patients have low insulin level and brain insulin resistant state which leads to impaired energy metabolism of neurons and make them vulnerable for survival. Insulin has been reported with its anti-amyloidogenic effect in human neuronal cell lines[236]. Some reports have shown that Aβ induced neuronal IR is attenuated by insulin treatment[237].

In a study it is found that 20 IU insulin twice a day over a period of 21 d in early AD or MCI subject's helps to retain verbal information more effectively[30]. In 2006 Reger *et al*[30] showed that 10 IU intranasal insulin improves cognition in APOE4 AD/MCI subjects.

### TZDs

TZDs (also represented as glitazones) are a potential class of drug used for T2D which includes rosiglitazone (avandia), pioglitazone (actos) and troglitazone (rezulin). Mechanism of this group lies in activation of peroxisome proliferator-activated receptors by mimicking as a potential agonist of it and involved in transcription of lipid and glucose metabolism genes[238,239]. Since TZDs are anti-amyloidogenic and anti-inflammatory compounds with insulin sensitizing role, these delay neurodegeneration[240]. It also improves glycemic control in diabetic patients by inhibiting hepatic gluconeogenesis. Moreover, TZDs (mainly Troglitazone) are supposed to have their involvement in rescuing memory loss and decreasing plasma Aβ 40 and Aβ 42 levels[241,242] but again it needs to be investigated further.

### Experimental and clinical studies

Rosiglitazone is reported to attenuate neuronal IR induced by Aβ oligomers[237]. Pioglitazone is found to improve cognitive performance in a rodent dementia model induced by intracerebroventricular (ICV) injection of streptozotocin[243].

In a randomized trial rosiglitazone (8 mg) is reported to improve cognitive function in mild to moderate AD patients (non APOE4 carrier[244]). In contrast, a recent phase III trial of the same drug has failed to show similar effects in AD subjects[245]. Moreover, long term use of TZDs, in general has no effect on risk of AD development[234].

### Glucagon like peptide 1

Glucagon like peptide 1 (GLP1) analogs are "incretin mimetics", used to treat T2D. Exenatide, a 39 amino acid long peptide is analogous to human GLP1 which stimulates insulin secretion in a glucose dependent fashion. In brain these analogues bind tor GLP receptors and mediate various functions like suppression of glucagon production, slow down gastric emptying, increase satiety and reduce food intake with lower risk of hypoglycemia.

### Experimental and clinical studies

In an animal study, GLP1 is reported to protect neurons from oxidative stress with reduced apoptosis, plaque formation and inflammatory response. Moreover, it strengthens synaptic plasticity in AD mouse brain l[246]. It is shown to improve spatial memory in transgenic AD mice model[247]. Liraglutide and lixisenatide are GLP1 receptor agonists which are reported to activate cAMP in the brain and induce neurogenesis[248]. In addition, liraglutide attenuates memory impairments in a mouse model of AD[249]. Subcutaneous administration of liraglutide is reported to restore both peripheral and brain insulin sensitivity and ameliorates tau hyperphosphorylation in rat model of T2D[250]. Clinical research on the effect of liraglutide on AD patients is still going to evaluate the changes in cognition using a neuropsychological test battery[251].

### DPP IV inhibitors: Oral hypoglyceimic

DPP-IV, pharmacological inhibitors are oral hypoglycemic. These compounds reduce blood glucose levels by increasing incretin (GLP-1 and GIP levels) and attenuating glucagon effects. Sitagliptin, Vildagliptin,

Saxagliptin, Linagliptin, Teneligliptin, Gemigliptin and Dutogliptin are major members of gliptins, out of which Dutogliptin is under Phase Ⅲ clinical trial[252]. Effect of sitagliptin administration is studied double transgenic mice model of AD and reported to significantly delay AD pathology including amyloid deposition and taupathies[253].

### *Insulin and oral anti-diabetics: A combined therapy*

Combination of insulin and other oral anti-diabetic drugs are reported to lower neuritic plaque density by 20% in AD brains[253]. Metformin in combination with rosiglitazone or glyburide is reported to improve working memory very significantly[253]. In a prospective cohort study, metformin and SUs are reported to reduce risk of dementia by 35%[228]. Although, a number of anti-diabetic drugs are reported to improve cognitive effect, it is still not well understood whether these effects are due to glucose lowering effects or adopt different pathways of neuroprotection. A broad range of anti diabetic therapies are undergoing clinical trials including those involving stimulation of the pancreatic beta-cell with the gut-derived insulinotropic hormones (incretins), GIP and GLP-1[254]. Some drugs have good glycemic control but have no history to improve cognitive functions[255]. In a study diabetes patients were maintained at normoglycemia over 3 mo but no significant improvement in cognitive performance was observed[256]. Other than glycemic control, anti-diabetic drugs improve cognitive function. Although various clinical trials are underway to evaluate the role of anti-diabetic drugs in treatment of neurodegenerative disorders such as dementia and AD but the search is still not over.

## CONCLUSION

This review provides a synopsis in which a metabolic disturbance becomes indispensible for life. This is a talk of a metabolic problem which emerges as a molecular signal defect and takes a form of syndrome with multiple complications. Spotlighted player, insulin draws a trajectory from diabetes to AD with multiple divergence and convergence.

AD and DM are two devastating syndromes with complex molecular interplay. Evidences of their shared molecular and biochemical footprints shed light on.

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