REVIEW ARTICLE

Metformin in Prevention of Type 2 Diabetes

Chamukuttan Snehalatha[1], Susairaj Priscilla[1], Arun Nanditha[1], Raghavan Arun[1], Krishnamoorthy Satheesh[1], Ambady Ramachandran[1]

Abstract

Identification and treatment of individuals with prediabetes is crucial. Effective interventional strategies are key to reducing the diabetes risk at the population level. Lifestyle intervention is found to be more effective but more expensive. Evidence of potential benefits from pharmacotherapy is accumulating. The choice of a pharmacologic intervention to reduce the progression of type 2 diabetes (T2DM) in high risk individuals must consider the balance between the benefit to risk ratio. A meta-analysis of the results of the three important studies has shown that metformin used for up to three years decrease the likelihood of progression to diabetes. Metformin showed greater beneficial effect in people with higher baseline Body Mass Index (BMI) and higher Fasting Plasma Glucose (FPG) than in leaner prediabetic counterparts with low FPG concentrations. Besides diabetes risk reduction, the drug has also proved to be cancer and cardio-protective. The National Institute for Clinical Excellence, UK has recommended the use of metformin in prevention of T2DM in adults at high risk on failure to adhere to lifestyle changes. In view of the long standing safety and tolerability, metformin could be prescribed to people who are unable to comply with lifestyle advice.

Introduction

The increasing prevalence of type 2 diabetes (T2DM) constitutes a leading global public health concern. It is estimated that there are more than 318 million people with prediabetes worldwide.[1] According to the American Diabetes Association (ADA) expert panel; up to 70% of individuals with prediabetes will eventually develop diabetes. An interaction of genetic and environmental risk factors causes T2DM and dysglycaemia. Insulin resistance and β-cell dysfunction are genetically determined, and weight gain and physical inactivity aggravate these inherited metabolic abnormalities. Current evidence explains a two-step development of T2DM.[2] Primarily in normal glucose tolerant (NGT) individuals, development of insulin resistance causes impaired glucose tolerance (IGT). At this stage, plasma insulin levels are elevated but β -cell compensatory hyperinsulinemia occurs due to β-cell insufficiency. Consequently, IGT advances to T2DM because of a progressive decline in β-cell function and insulin resistance increases further (Figure 1). The progressive decline in insulin sensitivity and β-cell function in prediabetes should be arrested or reversed. Persons with prediabetes are also at a high risk of damage to the micro and macrovasculature.

Persons with IGT characterized by postprandial (2hr plasma glucose 140mg to ≤199mg/dl) and fasting (110mg/dl to ≤125mg/dl) hyperglycaemia are at increased risk for the development of diabetes and are the target population for interventions which prevent or delay the onset of T2DM. Lifestyle modifications involving healthy dietary habits, regular physical activity have been shown to aid in prevention of diabetes. But the long-term adherence is often difficult, limiting their effectiveness. Pharmacotherapy has also shown the benefit with respect to diabetes prevention.

A few pharmacological agents such as metformin, thiazolidenediones, acarbose, drugs for weight loss and basal insulin have also proven to be effective in preventing the progression to diabetes in high risk subjects. They are likely to act through a number of mechanisms, in addition to weight control or reduction. [3]

This review revisits the utility of metformin in diabetes risk reduction and metabolic disorders and the safety profile of the drug.

Metformin is a biguanide that has been in use for decades to treat diabetes. Efficacy and safety of metformin in the management of T2DM is well established.[3] It has the advantage that it is rarely associated with hypoglycaemia unless used in conjunction with insulin secretagogues such as sulphonylureas or insulin. Metformin has beneficial effects on body mass index (BMI) and lipid concentrations and has been proven to be safe showing no serious adverse effects.[4] Besides acting as an oral hypoglycaemic agent, it has been used with diet and physical activity to prevent diabetes in people at high risk. It is also used in treating polycystic ovarian syndrome and gestational diabetes in women.

Metformin reduces plasma glucose level by several different mechanisms, in particular through non-pancreatic mechanisms without increasing insulin secretion. It sensitizes the effects of insulin; hence, termed "insulin sensitizer". Metformin also suppresses the endogenous glucose production by the liver, which is mainly due to a reduction in the rate of gluconeogenesis and a small effect on glycogenolysis.

Moreover, metformin activates the enzyme adenosine monophosphate kinase (AMPK) resulting in the inhibition of key enzymes involved in gluconeogenesis and glycogen synthesis in the liver while stimulating insulin signaling and glucose transport in muscles. AMPK regulates the cellular and organ metabolism and

[1]India Diabetes Research Foundation & Dr. A. Ramachandran's Diabetes Hospitals, Chennai, Tamil Nadu

Received: 05.04.2016; Accepted: 21.12.2017

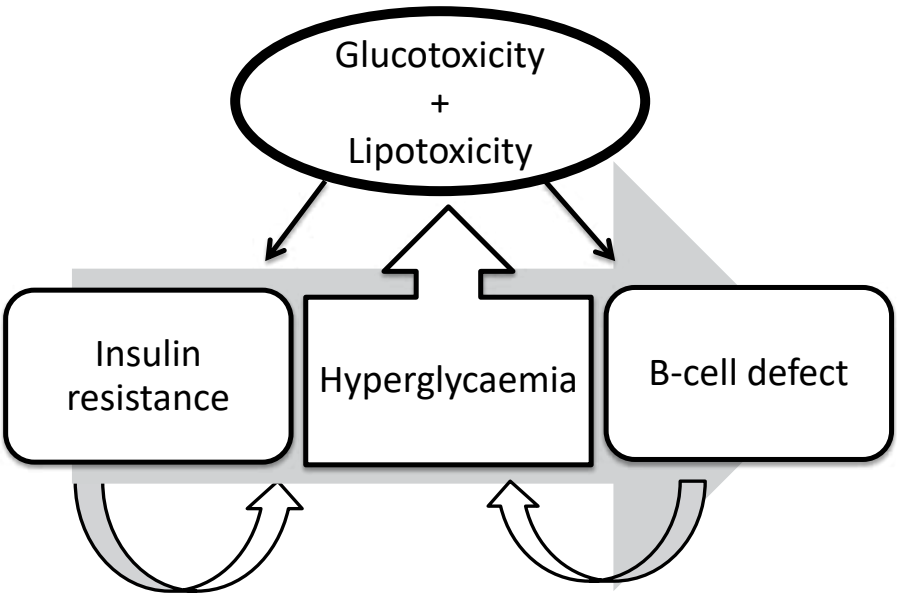

Fig. 1: Pathogenesis of type 2 diabetes

any decrease in hepatic energy, leads to the activation of AMPK. Furthermore, metformin increases the peripheral glucose disposal that arises largely through increased non-oxidative glucose disposal into skeletal muscle.[5-7]

The major side-effect of metformin is gastrointestinal irritations which can be minimized by smaller doses or by using prolonged–released formulations.[8] The risk of lactic acidosis is extremely rare. Vitamin B12 deficiency, if occurs can be reduced with supplementation of the vitamin.

Metformin is first line recommended therapy for T2DM according to the International Diabetes Federation Global Guidelines for type 2 Diabetes, in agreement with similar guidelines from the American Diabetes Association (ADA), as well as the European Association for the Study of Diabetes (EASD).[9,10] The ADA Consensus Conference also recommended that high-risk individuals (HbA1c ≥ 6.0%; body mass index ≥ 30 kg/ m^2; age ≤ 60 years) with IGT or Impaired Fasting Glucose (IFG) be treated with metformin.[11]

Studies in Primary Prevention using Metformin

Several drugs have been successfully used in the prevention of T2DM; among them metformin has been studied extensively in different populations for prevention of diabetes.

The BIGPRO (BIGuanides and the Prevention of the Risk of Obesity) study was one of the earlier studies designed to investigate whether metformin, used in combination with lifestyle modification, could modify the metabolic abnormalities associated with insulin resistance in persons without diabetes but with central adiposity (high waist-to-hip ratio).[12] Compared with placebo, this combination produced significant weight loss, better maintenance of fasting blood glucose, total and LDL cholesterol levels, and a greater decrease of fasting plasma insulin concentration. This was an early observation that suggested metformin would be a suitable candidate for long-term intervention treatment for the prevention of diabetes.

In the US Diabetes Prevention Programme (DPP) use of metformin (1700 mg/day) resulted in a 31% relative risk reduction (RRR) in the incidence of T2DM in subjects with IGT during a median follow-up period of 2.8 years.[13] Its effectiveness was lower compared to that of intensive lifestyle modification (LSM) (58%). The effectiveness of intervention was largely attributable to weight reduction as subjects recruited were largely overweight or obese. In the LSM group nearly 5% developed diabetes per year compared to 7.8% metformin and 11% in the placebo group. During the extended follow-up; Diabetes Prevention Program Outcomes Study (DPPOS), both metformin and lifestyle intervention showed long-tem beneficial effects, but did not reduce microvascluar complications (Table 1).[14]

The Indian Diabetes Prevention Programme-1 (IDPP-1) conducted in subjects with IGT compared the effectiveness of moderate but consistent LSM and treatment with metformin in smaller does (500 mg/day) vs a control group.[15] A combination of LSM and metformin was also used. This study in comparatively non-obese, Asian Indian subjects showed that all the three modalities of intervention had approximately 28% RRR in relation to the control group in the incidence of diabetes in a period of 3 years. Thus, metformin was found to be equally effective as LSM in reducing the incidence of diabetes among subjects with IGT (Table 1).

The Chinese DPP, evaluated the effects of diet and exercise, acarbose and metformin on the incidence of T2DM in 321 subjects with IGT.[16] During the mean study period of 3 years, glycaemic level deteriorated in the control group. In the LSM group, the fasting plasma glucose increased slightly with beneficial changes in postprandial plasma glucose; and in the drug treated group, both the glycaemic indices showed significant reduction. Beneficial changes were seen with acarbose and metformin in reducing the risk of diabetes. The RRR with metformin (750 mg/day) was 77%, while it was 88% in the group treated with acarbose (Table 1).

A study in 63 subjects with IFG using acarbose and metformin compared to placebo showed that metformin was more effective at 3 years than acarbose in reducing the incidence of diabetes vs placebo (8%,37% RRR respectively).[17] At a 6 year followup of patients the RRR was significantly with acarbose (0.66) but not with metformin (1.09) for subjects with IGT at baseline. Probably, there could be difference in the effectiveness of therapy in subjects with IFG/IGT.

A meta-analysis of randomized trials of at least 8 weeks of metformin use compared with placebo or no treatment in non-diabetic persons was performed.[18] The analysis of 31 trials with 4570 participants followed for 8267person-years showed that incidence of diabetes was reduced by 40% with an absolute risk reduction of 6%. During mean trial duration of 1.8

Table 1: Randomized trials on primary prevention using metformin

Study (year) (Ref)	Population patients in each group (active: placebo)*	Medication (mg)	Duration (Years)	Cumulative incidence in control (%)	Relative Risk reduction % (95%CI)
DPP (2002)[13]	Multi ethnic (1073:1082)	Metformin: 850/ twice daily	2.8	28.9	31 (17-43)
DPPOS (2009)[14]	Multi ethnic (910:924)	Metformin: 850 mg/ twice a day	8	Metformin 4.9/100 person years (4.2-5.7)	18 (7-28)
IDPP-1 (2006)[15]	Asian Indian (133:136)	Metformin: 250/ twice daily	2.5	55	26 (19-5)
The Chinese Diabetes Prevention Trial (2001)[16]	Chinese (88:85)	Metformin: 250/ thrice daily	3	11.6	77 (NR)
CANOE (2011)[19]	Multi ethnic (103:104)	Rosiglitazone: 4 mg/ day and metformin: 1000 mg/day	3.9	39	66 (41-80)

NR: Not reported

years, significant improvement in body weight, lipid profile, insulin resistance and benefit on incidence of diabetes were noted.

Results of the Canadian Normoglycemic Outcomes Evaluation (CANOE) trial in 207 subjects with IGT, randomly assigned to receive a combination of 2 mg rosiglitazone and 500 mg metformin twice daily or matching placebo for a median of 3.9 years showed that the combination was highly effective in preventing type 2 diabetes (Table 1).[19]

Observational studies in insulin resistant adults have shown metformin use can reduce the incidence of diabetes with reduced fasting glucose and atherogenic lipid fractions.[20]

Prevention of T2DM in Women with Gestational Diabetes Mellitus (GDM)

Metformin has been found to be effective and safe for the treatment of GDM, particularly in overweight and in obese women. Recently, the Endocrine Society has confirmed the use of metformin during pregnancy and also recommended it as a first-line treatment of cutaneous manifestations, for prevention of pregnancy complications, and for the treatment of obesity.[21] In the DPPOS, women with a history of GDM assigned to the placebo group had a 48% higher risk of progressing to T2DM than women without a history of GDM. The study specifically examined 350 women with a history of GDM and 1416 women with previous live births but no GDM. Among those who had GDM, both intensive lifestyle intervention and metformin reduced progression to diabetes compared with placebo by 35% and 40% respectively. However, among women with no prior GDM, metformin had no impact while intensive lifestyle intervention reduced progression to diabetes by 30%.[22]

Weight Loss

Obesity is the most important causal factor for progression of IGT to diabetes and is primarily responsible for the rising trend in T2DM. Weight loss achieved via lifestyle modification or pharmacologic intervention enhances insulin sensitivity thereby improving glucose tolerance in IGT individuals. Metformin reduces insulin resistance which is the underlying cause of both obesity and PCOS in non-diabetic persons. Improving insulin sensitivity may account for weight reduction under metformin therapy. Effect of metformin on weight loss has been reported in several trials.[23,24] Results of the two large studies by the Diabetes Prevention Program Research Group found metformin most effective in obese participants (baseline BMI > 35 kg/m^2), with a 53% reduction in the incidence of diabetes, and in participants < 45 years of age, with a 44% reduction. Metformin had little benefit for older individuals who were 60–85 years of age at baseline. The effectiveness of metformin was attributed in part to weight loss, which averaged 1.7 kg and accounted for 64% of the beneficial effect of metformin. Importantly, after an average of 10 years of follow-up, the metformin group had maintained an average weight loss of 2.5 kg, and diabetes risk was reduced by 18% compared to the former placebo group. The mean weight change at 1 year was 22.7 kg in the metformin group and 20.4 kg in the placebo group. However, adherence to metformin did not impact the waist circumference during the first two years.[14]

Studies conducted in India and China reported similar reductions in diabetes risk.[15,16] In a study comparing metformin, exercise (about 190 minutes per week), and the combination of the two in persons with impaired glucose tolerance, metformin and metformin plus exercise decreased body weight more than exercise alone.[25]

Cost Effectiveness

T2DM causes increased mortality and morbidity at a younger age than in the normal population. Management of the disease is costly and being a chronic disorder it requires constant medical care. In 2012, the ADA estimated that the cost incurred due to diabetes was $306 billion as direct medical costs which is more than 1 of 5 dollars spent on medical care in the U.S.[26] Only a few studies such as the DPP and IDPP-1 examined the cost and cost effectiveness of the prevention programmes. A recent within - trial analysis of resource utilization and outcomes from the DPP and DPPOS confirmed that an intensive lifestyle intervention is extremely cost-effective and metformin treatment is possibly cost-saving over 10 years.[27] In the IDPP, an analysis of the cost-effectiveness of the interventions showed both LSM and metformin to be cost-effective in preventing diabetes in India which may be applied to other developing countries as well.[28]

Other Benefits: Cardiovascular Disease and Cancer

Metformin has been associated with reduced incidence of cardiovascular disease (CVD) and cancer prevention. It has been shown to have favorable effects on a number of cardiovascular risk factors, including lipids, body weight, blood pressure and platelet function. In the UK Prospective Diabetes Study, metfomin was found to produce decreased risk of myocardial infarction compared to other intensive therapy in overweight persons (hazard ratio (HR) 0.61, 95%-confidence interval (CI) 0.41–0.89; p = 0.01]. The risk reduction for myocardial infarction persisted in the metformin group during 10 years of

post-trial observational follow-up (HR 0.67, 95%-CI 0.51–0.89; p = 0.005), despite an early loss of glycated haemoglobin (HbA1c) differences between treatment groups, suggesting a legacy effect of early intensive glucose-lowering therapy with metformin for obese patients. However, a cardioprotective effect of metformin in excess of that conferred by its glucose-lowering ability have not been confirmed based on meta-analyses from large and small trials. To date, no such prospective cardiovascular outcome trials with metformin are sparse.[29]

Epidemiologic evidence from large cohort metformin studies suggests benefit for several types of cancers. A meta-analysis of 11 observational studies showed a 31% reduced risk of cancer in those taking metformin compared to other antidiabetic drugs. Preclinical studies have shown that metformin can inhibit the growth of cancer cells in vitro and in vivo and provide evidence for a direct, insulin-independent anti-tumour effect. Metformin has shown strong antiproliferative effects on colon, pancreatic, breast, ovarian, prostate and lung cancer cells. Preclinical studies have also shown reliable anti-tumoral effects in different animal models. A clinical trial has demonstrated beneficial effect in colon and breast cancers.[30]

Controversies on the use of Metformin

Despite the several studies on the efficacy of metformin in reducing the incidence of diabetes there has been an active debate as to the rationale and benefit for using metformin as a pharmacological agent to delay or prevent diabetes progression. The American Diabetes Association in its "Standards for Medical Care in Diabetes" guidelines, 2013 has recommended metformin for use in diabetes prevention for those at very high risk, under the age of 60, are severely obese, or have a history of gestational diabetes. [31]

However, according to a study conducted between 2010 and 2012, metformin is still a rarely prescribed drug for prediabetes. Data obtained from a retrospective study conducted in a large private insuring company in the US found that among 17,352 adults aged 19 to 58 with pre-diabetes, metformin was prescribed for only 3.7% of individuals with prediabetes for over three years. Among those with a BMI ≥ 35 kg/m^2 or gestational diabetes the prevalence of metformin prescription was 7.8%.[32]

The major argument that drugs such as metformin could merely mask hyperglycaemia by reducing the blood glucose levels remains a matter for debate. More evidence on improved long-term outcomes in metformin – treated prediabetic persons is required.

Major international guidelines from expert groups in the US, Europe and the International Diabetes Federation favour the use of metformin as the second line intervention. The 2015 Position Statement from the American Diabetes Association recommends that metformin has the strongest evidence base of pharmacological agents for diabetes prevention.[33]

The reasons for the limitations in the use of metformin are still unclear. A possibility could be that the outcome of the evidence based trials is not fully realized in practicality by the caregivers. Also, metformin is not approved by the US Food and Drug Administration (FDA) for prediabetes, which may increase hesitancy to prescribe it "off label" in this context.

Conclusions

In the primary prevention of diabetes, use of metformin is proven to be effective and safe. Several long-term studies such as the DPPOS have shown the long-term effectiveness of the drug. The possible side-effects are minimal compared to other pharmacological agents used in prevention of diabetes. The major action of the drug is by improving insulin sensitivity and also partially by reduction in weight loss. On account of the relative safety and efficacy, expert groups such as the ADA, International Diabetes Foundation, EASD and the National Institute for Clinical Excellence, UK have recommended the use of metformin as the second-line intervention for individuals at high risk of developing diabetes.

References

1. International Diabetes Federation. *IDF Diabetes Atlas, 7 ed.* Brussels, Belgium: International Diabetes Federation, 2015.
2. Ralph A. DeFronzo and Muhammad A. Abdul-Ghani, Preservation of β-Cell Function: The Key to Diabetes Prevention. *J Clin Endocrinol Metab* 2011; 96:2354–2366.
3. DeFronzo RA. Pharmacologic therapy for type 2 diabetes mellitus. *Ann Intern Med* 1999; 131:281–303.
4. Tabák AG1, Herder C, Rathmann W, *et al*. Prediabetes: a high-risk state for diabetes development. *The Lancet* 2012; 16:379:2279-90.
5. Seo-Mayer PW, Thulin G, Zhang L, Alves DS, Ardito T, *et al*. Preactivation of AMPK by metformin may ameliorate the epithelial cell damage caused by renal ischemia. *Am J Physiol Renal Physiol* 2011; 301:1346–57.
6. Sung JY, Choi HC. Metformin-induced AMP-activated protein kinase activation regulates phenylephrine-mediated contraction of rat aorta. *Biochem Biophys Res Commun* 2012; 421:599–604.
7. Rosen P, Wiernsperger NF. Metformin delays the manifestation of diabetes and vascular dysfunction in Goto-Kakizaki rats by reduction of mitochondrial oxidative stress. *Diabetes Metab Res Rev* 2006; 22:323–30.
8. Scarpello JHB. Optimal dosing strategies for maximising the clinical response to metformin in type 2 diabetes. *Br J Diabetes Vasc Dis* 2001; 1:28–36.
9. Inzucchi SE, Bergenstal RM, Buse JB, *et al*. Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* 2012; 35:1364–1379.
10. Available from URL: http://apps.who.int/trialsearch/trial.aspx?TrialID=ISRCTN 34875079. Accessed 4 February 2016.
11. Nathan DM, Davidson MB, DeFronzo RA, *et al* American Diabetes Association. Impaired fasting glucose and impaired glucose tolerance: implications for care. *Diabetes Care* 2007; 30:753-9.
12. Fontbonne A, Charles MA, Juhan-Vague I, *et al*. The effect of metformin on the metabolic abnormalities associated with upper-body fat distribution: BIGPRO Study Group. *Diabetes Care* 1996; 19:920–926.
13. Knowler WC, Barrett-Conner E, Fowler SE, *et al*. The Diabetes Prevention Program Research Group. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002; 346:393–403.
14. Knowler WC, Fowler SE, Hamman RF, *et al*. 10-Year follow-up of diabetes incidence and weight loss in the Diabetes Prevention Program Outcomes Study. *Lancet* 2009; 374:1677–1686.
15. Ramachandran A, Snehalatha C, Mary S, *et al*. Indian Diabetes Prevention Programme (IDPP). The Indian Diabetes Prevention Pro-gramme shows that lifestyle modification and metformin prevent type 2 diabetes in Asian Indian subjects with impaired glucose tolerance (IDPP-1). *Diabetologia* 2006; 49:289-29.
16. Wenying Y, Lixiang L, Jinwu Q, *et al*. The preventive effect of acarbose and metformin on the progression to diabetes mellitus in the IGT population: A 3-year multicenter prospective study. *Chin J Endocrinol Metab* 2001; 17:131–6.
17. Holman RR, North BV, Tunbridge FK. Possible prevention of type 2 diabetes with acarbose or metformin. *Diabetes* 2000; 49Suppl:A111.
18. Shelley R Salpeter, Nicholas S.Buckley, Justin A Kahn, *et al*. Meta-Analysis: Metformin treatment in persons at risk for diabetes mellitus. *The American Journal of Medicine* 2008; 121:149-157.
19. Zinman B, Harris SB, Neuman J, *et al*. Low-dose combination therapy with rosiglitazone and metformin to prevent type 2 diabetes mellitus (CANOE trial): a double-blind randomized controlled study. *The Lancet* 2010; 376:103-111.
20. Andreadis EA, Katsanou PM, Georgiopoulos DX *et al*. The effect of metformin on the incidence of type 2 diabetes mellitus and cardiovascular disease risk factors in overweight and obese subjects–the Carmos study. *Exp Clin Endocrinol Diabetes* 2009; 117:175–80.
21. The Endocrine Society. Diagnosis and Treatment of Polycystic Ovary Syndrome: An Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab* 2013; 2013–350.
22. Aroda VR, Christophi CA, Edelstein SL, *et al*. The effect of lifestyle intervention and metformin on preventing or delaying diabetes among women with and without

gestational diabetes: the Diabetes Prevention Program outcomes study 10-year follow-up. Diabetes Prevention Program Research Group. *J Clin Endocrinol Metab* 2015; 100:1646-53.

23. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *The Lancet* 1998; 352:854–865.
24. Bray GA, Greenway FL. Pharmacological treatment of the overweight patient. *Pharmacol Rev* 2007; 59:151–184.
25. Malin SK, Nightingale J, Choi SE, *et al.* Metformin modifies the exercise training effects on risk factors for cardiovascular disease in impaired glucose tolerant adults. *Obesity* 2013; 21:93-100.
26. American Diabetes Association. Economic costs of diabetes in the U.S. in 2012. *Diabetes Care* 2013; 36:1033–1046.
27. Within-Trial Cost-Effectiveness of Lifestyle Intervention or Metformin for the Primary Prevention of Type 2 Diabetes. The Diabetes Prevention Program Research Group* *Diabetes Care* 2003; 26:2518–2523.
28. Ramachandran A, Snehalatha C, Yamuna A et al. Cost-effectiveness of the interventions in the primary prevention of diabetes among Asian Indians: within-trial results of the Indian Diabetes Prevention Programme (IDPP). *Diabetes Care* 2007; 30:2548-52.
29. Bethel MA, Xu W, Theodorakis MJ. Pharmacological interventions for preventing or delaying onset of type 2 diabetes mellitus. *Diabetes, Obesity and Metabolism* 2015; 17:231–244.
30. Ben Sahra I, Le Marchand Brustel Y, Tanti JF, Bost F. Metformin in cancer therapy: A new perspective for an old antidiabetic drug? *Mol Cancer Ther* 2010; 9:1092–9.
31. Standards of medical care in diabetes--2013. American Diabetes Association. *Diabetes Care* 2013; 36Suppl1:S11-66.
32. Moin T, Li J, Duru OK, *et al.* Metformin prescription for insured adults with prediabetes from 2010 to 2012: a retrospective cohort study. *Ann Intern Med* 2015; 21:162:542-8.
33. American Diabetes Association. Standards of Medical Care in Diabetes 2015, *Diabetes Care* 2015; 38Supp1:S1-93.