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REVIEW ON DRUGS USED FOR MANAGEMENT OF PRE-DIABETES

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ABSTRACT

Pre-diabetes is the condition, which is used to classify patients with irregularly elevated blood glucose, but not asmuch as high to support the diagnosis of diabetes mellitus, but can progress to type 2 diabetes mellitus by life style changes. Lifestyle modifications, clinical advances and pharmacotherapy interventions in benefits have been observed in pre-diabetic individuals have shown the benefits in transformation back to normoglycemia and to diminish the incidence of diabetes. Metformin is the mostly recommended primary pharmacotherapy with lifestyle changes, unless it is contraindicated or not. It enhances the action of insulin bydeclining the amount of hepatic glucose production in the liver and mostly reduces the incidence of pre-diabetes.

KEYWORDS: Pre-diabetes, diabetes mellitus, metformin, lifestyle changes.

INTRODUCTION

Diabetes mellitus (DM), one of the utmost serious challenges for health care organizations all round the world. Around one third of the elderly have DM, more than 60% of those patients with DM die due to serious vascular diseases and a greater percentage of the very old population develops other geriatric illnesses related to DM.[1,2] In the elderly, DM is clinically diverse and its foremost high-risk state, pre-diabetes intermediate state of hyperglycemia, is increasing. Currently, 50% of US adults greater than 65 years have pre-diabetes and around 5-10% of them turn out to be diabetic every year.[3,4]It is posing a serious life threat to entire population of the world irrespective of stages of industrialization and development. The

increasing incidence of diabetes mellitus for South East Asian Region (SEAR) was assessed from the observed incidence in 1995.[5]

Worldwide, the total number of people affected with pre-diabetes is estimated to be 314 million and is expected to reach 418 million in 2025.[6] Clinical advances, lifestyle variations, and pharmacotherapy interferences in pre-diabetic individuals have revealed benefits for conversion back to normoglycemia and to weaken the prevalence of diabetes. This is particularly substantial in the older population above the age group of 80 years. Although diabetes-related complications begins in the pre-diabetic state, no clear guidelines have been established for the diagnosis and management of patients with pre-diabetes. There is no medication which has beenpermitted by the US Food and Drug Administration for treating IFG or IGT.[7, 8]

Types of diabetes

1.1. *Type 1 diabetes*

Type 1 diabetes, also known as insulin-dependent diabetes mellitus (IDDM) or juvenile-onset diabetes, may account 5 to 10 percent of all cases diagnosed with diabetes. In the Type1 diabetes (T1D) where the cause of hyperglycemia arises as an absolute deficiency of insulin secretion. The occurrence of this type of diabetes among the population is identified by the evidence of autoimmune pathologic process in pancreatic β-cells as a cause of the low insulin secretion.[9]

Risk factors are seen less for Type 1 diabetes than for Type 2 diabetes, but genetic, autoimmune and environmental factors are convoluted in the progression of this type of diabetes.

1.2. *Type 2 diabetes*

Type 2 diabetes comprises of older age, obesity, and family history of diabetes, previous history of gestational diabetes, impaired glucose tolerance, physical inactivity, and race/ethnicity.[10] The second category of diabetes mellitus named as Type 2 diabetes (T2DM) is the most predominant form that develops due to the combined action of both insulin resistance and insufficient insulin secretion.[9]

Pre-diabetes

Pre-diabetes was defined as HbA1c within the range of 5.7% to 6.4%. It is used when there is at risk for type 2 diabetes that is, the blood sugar is higher than the normal, but not sufficient to be considered as diabetes. Lengthy pre-diabetic duration usually persists prior to the development of type 2 diabetes.[11]

Pre-diabetes rises when the body doesn't use insulin proficiently (insulin resistance) or doesn't produce enough insulin. Many people having pre-diabetes will go on to advance diabetes, but some will stay as having pre-diabetes and some people will return to having standard glucose levels. Most people who get type 2 diabetes have pre-diabetes first. Effective treatments are now available to retard the progression of pre-diabetes to diabetes.[7,12] Lifestyle modifications may help to get the blood sugar levels back to normal and avoid or delay diabetes.[13]

The early symptoms of pre-diabetes shows

- Impaired glucose tolerance/postprandial glucose but normal plasma fasting glucose.
- Impaired fasting glucose/ chronic elevation of fasting plasma glucose.

The table 1 shows the accepted criteria for the diagnosis of pre-diabetes based on measurement of glycaemia. HaemoglobinA1C (HbA1c) is the recommended screening test for Type 2 diabetes and pre-diabetes. While stating that rising levels of HbA1c are allied with a constant gradient of risk of developing to diabetes, those with HbA1c levels ranges from 41–49 mmol/mol are considered to have prediabetes1, or else known as 'intermediate hyperglycaemia'.

Table 1: Classification of impaired glucose tolerance and impaired fasting glucose based on measurements of plasma glucose.

Criteria	FPG Level (mmol/L [mg/dl])	2-h plasma glucose (mmol/L [mg/dl])
NGT	<100 [<5.6]	<140 [<7.8]
IFG	100–125 [5.6–6.9]	140–199 [7.8–11.0]
IGT	<126 [<6.9]	140–199 [7.8–11.0]
Combined IFG/IGT	100–125 [5.6–6.9]	140–199 [7.8–11.0]
FPG- Fasting plasma glucose, *IFG*- Impaired fasting glucose, *IGT* -Impaired glucose tolerance, *NGT* -Normal glucose tolerance		

Pathophysiology

Multistage model development of diabetes that resembles to progression of diabetes, each stage manifest by changes in beta-cell mass, phenotype and function.[14] Diabetes development from standard glucose tolerance is a continuous process. The primarystep is

considered by insulin resistance, which is accompanied by increase in insulin release. Patients with both IFG and IGT have insulin resistance, but the site of their major insulin resistance varies.[10] Those with IFG have predominantly hepatic insulin resistance, whereas those with IGT have mostly muscle insulin resistance.

In the second stage, beta-cells fail to reimburse for increased insulin resistance and hyperglycemia develops, progressing from prediabetes to explicit diabetes as beta-cell failure get worse. This progressive loss of beta-cell secretion possibly has a combination of genetic, environmental, and biochemical elements.[15] in the next stage of diabetes development, the beta-cells become impotent to compensate for insulin resistance when glucose levels approximate to 7.3 mmol/l (130 mg/dl) and thereforeglucose levels start to increase quickly. This period almost certainly extends from prediabetes to diabetes during which the following two stages, stable and severe decompensation, occur.[16]

Multiple aspects including genetic predisposition, insulin resistance, increased insulin secretory demand, glucotoxicity, lipotoxicity, impaired incretin release/action, amylin build-up, and decreased beta-cell mass play a contributory role in the advanced beta-cell dysfunction characteristic of prediabetes.

Monitoring

Normal glucose levels are defined as a fasting blood glucose level of less than 100 mg/dL and a post challenge level of less than 140 mg/dL. Patients at high risk for diabetes are defined as having at least two out of these three conditions: IFG, IGT, and metabolic syndrome. Monitoring of patients with prevalence of prediabetes to estimate the deterioration of glycaemic status should include yearly measurement of fasting blood glucose level and HbA1c with a 2-hour post challenge glucose tolerance testing for those in which progression is suspected and a more subtle measure is needed. CVD risk factors (especially raised blood pressure and/or dyslipidaemia) and abnormal weight gain should be noticed and monitored at regular intervals. [17,18]

Micro albuminuria, fasting lipid concentrations, and blood pressure measures should have assessed at least annually in patients having prediabetes. In the future, biomarkers and genetic markers may be available for improved monitoring of prediabetic parameters.[19]

Management of pre-diabetes

Presently, there is no approved pharmacotherapy for pre-diabetes. However, some prevention studies have resulted that, early interventions with lifestyle modification or pharmacotherapies may slow down the advancement to diabetes by delaying the pathophysiology of the disease. Lifestyle intervention is avital treatment approach that can effectively delay or prevent the progression from pre-diabetes to diabetes, but can also reduce macrovascular and microvascular disease risks. The management principles for diabetes and pre-diabetes are henceconsidered similar.

Thepre-diabetes treatment will emphasis on intensive lifestyle interventions (losing weight of at least 7%, eating healthy foods, and getting involving in physical activities).The study conducted by Da Qing randomized communities to diet-only, exercise-only, or diet-plus-exercise, resulted inan associated risk reduction in new-onset diabetes of 31%, 46%, and 42%, respectively.[20]A diet that includes calorie restriction, increased fiber intake, and possible limitations in carbohydrate intake is advised. This is the chance to reverse pre-diabetes so it does not progress into type 2 diabetes. Lifestyle modification is suggested for all ages, although adjustments in the prescription may be necessary on an individual basis. Performing these events will also help to avoid other health problems, such as heart disease and stroke, which are associated to diabetes.

Pre-diabetes sugar levels can remain slightly above normal and can return back to normal, or can increase to a range that leads to a diabetes mellitus. The preventive measures include: maintaining an ideal body weight, BMI between 18.5 and 25, exercising regularly and having a balanced diet with enough calories to sustain a healthy weight. Choice of an antihyperglycemic drug should be guided by anticipated benefits in an individual patient, taking into consideration the genetic, physiological and environmental factors that caused the disease, concurrent medical condition like hypertension, CVD, renal impairment, adverse effects of drugs and cost.[21]

Nevertheless, as pre-diabetes progresses, pharmacotherapy may be needed. When it is detected, pre-diabetes should be managed with a treatment plan to prevent or slow the progression to diabetes. [17]Someantihyperglycemic agents, namely metformin, voglibose, and thiazolidinediones, can delay the transition from pre-diabetes to diabetes.[22]

α-glucosidase inhibitors, such as acarbose and voglibose, extend the whole carbohydrate digestion time, and diminishes the degree of glucose absorption, thus declines the increase in postprandial blood glucose.[23]

Metformin has been using for several decades for management of diabetes and also been noted to have supplementaryfavourable outcomes such as body mass index (BMI) reduction and better cholesterol profile.[24] In addition to metformin, orlistat, α-glucosidase inhibitors, exenatide, and combination rosiglitazone/metformin have shown to lessen the proportion of type 2 diabetes.[25,26–28]

Glucagon-like peptide-1 (glp-1) agonists

Exenatide and Liraglutide are GLP-1 receptor agoniststhatimitate the actions of GLP-1 and are resistant to dipeptidyl peptidase-IV degradation. In the body, GLP-1, together with glucose-dependent insulinotropic polypeptide (GIP), accounts for 90% of the incretin effect. Both these drug entities produce continued reduction in bodyweight in obese patients and have shown an increased decline from prediabetes to normoglycemia.[29]

Liraglutide has anextended duration of action of about 24 hours. They can cause 1.5% decline in A1C in individuals with type 2 diabetes, when used as monotherapy or in combination with one or more selected oral antidiabetic drugs. Liraglutide can decrease body weight, the greatest weight loss occured from treatment with liraglutide in combination with combined metformin/sulfonylurea.[12] Liraglutide treatment can increase glucose tolerance by improving glucose-stimulated insulin secretion rate.[30] A study conducted by Sun HK et al states that, liraglutide treatment was associated with a 0.5-mmol/L reductionin fasting glucose levels. In addition, when compared with 19% treated with placebo, 75% of those treated with liraglutide had normal fasting glucose.[31]

Major side-effectsresulted are nausea and vomiting, which occured in 20–30 % of individuals and are usuallyminor and temporary. While pancreatitis has been enumerated as a potential sideeffect, an increased prevalence of the latter has not been verified.[32]

Voglibose

Voglibose, an alpha-glucosidase inhibitor (AGI), are drugs that may be used in the treatment of patients with type 2 diabetes or impaired glucose tolerance.Voglibose (Volix®, Basen®) was the most preferred second line drugs for thetherapy of prediabetes, after metformin. The

other AGIs are miglitol (Glyset®) andAcarbose (Glucobay®).[33] These agents act by reducing the degree of polysaccharide digestion from the gut and have been shown to enhanceincretin secretion.

A study conducted by Pavitra RD et al, also states that voglibose was the most chosen second line drug prescribed for prediabetes. When the physicians were asked regarding the order of choice of drug classes for the management of prediabetes, most of them chosen metformin (81%) as first line therapy, second line was alpha-glucosidaseinhibitors (56.7%), pioglitazone (43.4%) and DPP IV inhibitors (55.7%) as third and fourth, respectively. The result of prediabetesmanagement with either of these drug classes can lead to hypoglycaemia, which is not a complication which is seen commonly with therapy with either metformin or voglibose.[34]

Rosiglitazone

Thiazolidinediones are insulin sensitizers that are used as glucose-lowering agents in the therapy of diabetes. The glitazones are synthetic ligands for peroxisome proliferator-activated receptors-γ. TZD acts through the peroxisome proliferator activated receptors-γ by increasing hepatic and peripheral insulin sensitivity and preserving insulin secretion. These agents activate fat from muscle, liver, and beta-cell thereby improving lipotoxicity.[35]

The currently prescribed drugs include pioglitazone (15mg and 30mg) and rosiglitazone (4mg and 8mg). They increases the uptake of glucose, utilize it in the peripheral organs and declinesthe level of gluconeogenesis in the liver, and thereby reducing insulin resistance.[32] But they are not ideal for the keypreclusion due to multiple safety and tolerability concerns, in spite of their proven efficacy. The DREAM (Diabetes Reduction Assessment with ramipril and rosiglitazone Medication) trial evaluated the ability of rosiglitazone in preventing T2DM. Rosiglitazone (8 mg) showed a 60 % reduction in diabetes but was related with a significant increase in body weight (approximately 2 kg) and increased risk of heart failure. [36]

TZD had shown to successfully reduce and sustain a durable reduction in HbA1c in type 2 diabetes in long-term studies entailing preservation of beta-cell function. Rosiglitazone low dose (2 mg twice daily) in combination with metformin was studied to conclude if side-effects would be reduced.[37]

People with the following conditions are not recommended to take Rosiglitazone or Pioglitazone.

- Heart failure
- Active liver disease
- Type 1 diabetes
- Pregnancy

However, only an ADA consensus panel recommends metformin due to the side effects, issue of costs, and lack of persistent effect of the other medications. [38]

Sildenafil

Disposition Index (DI) is a complex measure that redirects both insulin secretion and insulin sensitivity. The finding that sildenafil have a tendency to increase DI in the variousstudies suggests that, this is a class effect of PDE5 inhibitors. PDE5 inhibition improves fibrinolytic balance, insulin sensitivity and albuminuria in subjects with prediabetes.[39] In the Otsuka Long-Evans Tokushima fatty rat model of type 2diabetes, sildenafil reduces albuminuria, glomerular hyper filtration, mesangial matrix expansion, and glomerulosclerosis.[40]

Metformin

Metformin,an oral antidiabetic agent which belongs to the class, biguanides. It is the recommended primary pharmacotherapy with lifestyle changes, unless it is contraindicated or not. It has shown 1.5% reduction in HbA1c with metformin monotherapy. It is an adjunct, not an alternative, and is less active alone than lifestyle change. Gastric side effects haveabided commonly in most of the patients, so that it should be titrated slowly. Beginning with a low-dose metformin (500 mg) once or twice a day with meals or 850 mg once a day will be more effective. If the gastric side effects didn't risen within 5-7 days, the dose can be increased to 1000 mg twice a day. [41,42,43]

Metforminis theonly anti‑diabeticdrugthatiscapableofpreventingthecardiovascular complications of diabetes through reducing the blood concentration of low‑densitylipoprotein, cholesterol, andtriglycerides. Itiswell‑knownthat, metforminhadlesseffectonbodyweightcomparedtosulfonylureasandinsuli.[44]

The benefits

- Metformin doesn't cause weight gain anddefinitely help with decreasing weightby reducing appetite.
- Evidence oflipidlowering effect.
- Metformin does not allows theinsulin discharge and therefore doesn't results in hypoglycaemia.

The action of metformin

Metformin acts predominantly by improving the action of liverinsulins to decrease the frequency of hepatic glucose production (figure:1). Preventing or retreating the progress of insulin resistance and/or beta-cell dysfunction related to dysglycaemia has the vital role ininhibiting or slowing down the conversion of pre-diabetes to clinical type 2 diabetes.[45]Advances in the action of insulinin skeletal muscle also improve the therapeutic activities of metformin, mostly resulting in increased non-oxidative glucose clearance. Together, these actions thus decreasestheblood glucose levels in the progression tohyperglycaemia, with very less likely in inducing hypoglycaemia.[46]

Metformin may also enhance the up regulation of the expression of GLP-1 receptors on the surface of pancreatic beta cells.[47] As GLP-1 improves the glucose-dependent insulin discharge from the pancreas, provide the modestsupport for the roles and actionsof the betacell.[48,49] It decreases HbA1c and FPG levels by preventingthe production of hepatic glucose and improving insulin sensitivity and does not stimulate insulin emission or preserve beta-cell function.[50]

Metformin administration has shown to elevate circulating levels of glucagon-like peptide-1 (GLP-1) by improving the expulsion of GLP-1 itself and/or by diminishing the action of dipeptidyl peptidase-4 (DPP-4), the enzyme whichis primarilyin control for disabling GLP-1 in the tissues and circulation.[51,52]

In a meta-analysis of 4 randomized controlled trials in participants younger than 19 years, who were treated with metformin for at least 2 months, a statistically substantialdecrease in fasting insulin and BMI was seen with metformin (with and without lifestyle intervention) when compared with placebo.[53]

New approach to minimize the consequence the harmful effect by an attempt that reversesthemechanismofinsulin resistance, T2D and obesity have been appreciated through the use of pro and prebiotics, transplant of appropriate gut microbiota and intake ofsuitable antibiotictherapy.[54]

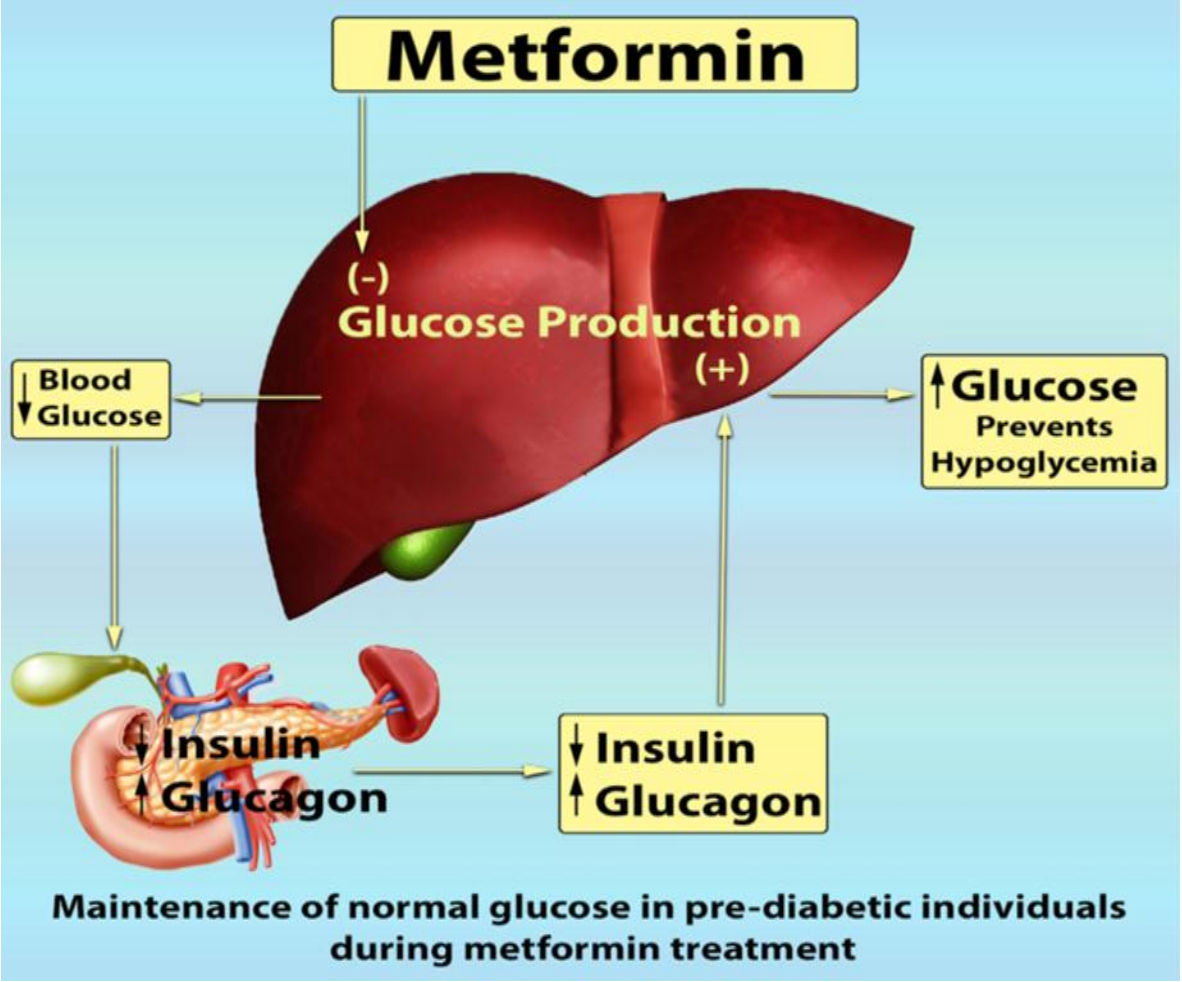

Figure 1: Maintenance of normal glucose in pre-diabetic individuals during metformin.

CONCLUSION

Studies had estimated that the people with prediabetesisexpected to be 418 million in 2025.A combination of lifestyle modification and pharmacologic intervention prevent or interrupt the onset of type 2 diabetes by precluding the pre-diabetic phase. Lifestyle modification is the keystone of treatment, and pharmacotherapy should be considered in high-risk patients provided the risk-benefit ratio is favourable. The use of metformin is sustained by its relative safety, cost effectiveness and long term data in several studies and they are considered as the first line drugs used inthe management of pre-diabetes. In low-risk patients, when lifestyle modification does not work precisely, medications such as metformin and/or voglibose are

recommended. Alpha glucosidase inhibitors like voglibose was the mostly chosen second line drugs for prediabetes, followed after metformin.The role of metformin in prevention of diabetes, combined with counselling, to attain a better lifestyle would be more likely than other antihyperglycemic agents.

AUTHOR CONTRIBUTIONS

All the authors were equally involved in the development of the manusript's framework and gathering of thenecessary information. All authors were discussed, drafted and wrote themanuscript.

CONFLICT OF INTEREST

The authors declare that the review was conducted in the absence of any commercial or financial relationships that could be construed as apotential conflict of interest.

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