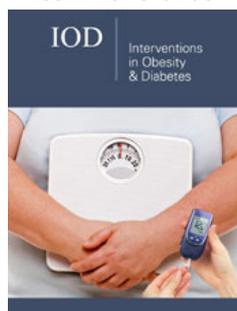


The Effect of Metformin in Treating Prediabetic Patients

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Abstract

Prediabetic is a state when the blood sugar level is high but not reaching the diagnostic status of diabetes mellitus. As defined by American Diabetic Association (ADA), it includes impaired fasting glucose (FBS 5.6-6.9mmol/L) and/or impaired glucose tolerance (glucose 7.8-11.0mmol/L, 2 hours after ingestion of a 75-g oral glucose load) and/or HbA1c 5.7-6.4%. The risk of progressing to diabetes is greater in patient with both IFG and IGT compared with isolated IFG or isolated IGT alone [1,2]. Although patients with prediabetes are asymptomatic, but they carry comparable macrovascular complication and retinopathy like diabetes mellitus. The progression to type 2 DM may vary from one individual to another depend on degree of insulin deficiency/resistance along with other risk factors. Several risk factors have been contributing to the development of prediabetes and it is almost like that factor related to development of type 2DM. These include increasing age, physical inactivity, obesity ($BMI \geq 30 \text{KG/M}^2$), family history of DM 2, High risk ethnic groups and past history of GDM and PCOS. Several approaches have been tried to manage prediabetic status to delay and/or prevent the progression to DM2 including pharmacological approach and lifestyle management. This article will give an overview about the use of metformin as a treatment of prediabetes.

Keywords: Prediabetes; Metformin; Sedentary lifestyle

Introduction

As per 2020 CDC report, more than 100 million U.S adult are living with diabetes or prediabetes. In Oman, 15.7% adult aged >18-year are diagnosed to have type 2 DM, and 17.4% are prediabetic. However, this figure might not represent the exact overall figure as some patients are not aware of their blood sugar status. Additionally, the prevalence of obesity ($BMI \geq 30 \text{KG/M}^2$) in Oman is almost 30.7% which is considered an important risk factor of developing prediabetes and diabetes. The average annual risk of developing diabetes is about about 5-10% per year in individuals with IFG or IGT [1]. Furthermore, the treatment of these conditions and its possible complication carry huge burden on the health care system which necessitate early preventive measures. Several studies looked at the effectiveness of pharmacological approaches (eg. metformin) versus lifestyle intervention in treatment of prediabetes. In the DPP study, there was a 58% reduction in the progression from IGT to diabetes with intensive lifestyle changes. On the other hand, metformin at 850mg twice daily resulted in a 31% reduction in progression to diabetes compared with standard lifestyle advice.

Mechanism of Action

Metformin is belonging to biguanide family which is antihyperglycemic agent. It is considered as insulin sensitizer which increase peripheral glucose uptake and utilization with multiple actions on tissues including the liver, skeletal muscle, endothelium, adipose tissue,

and the ovary. It also reduces intestinal glucose absorption and hepatic glucose production. Unlike sulfonylureas, metformin does not produce hypoglycemia except in patient who follow caloric restricted diet. Thus, it improves both basal and postprandial plasma glucose. It also possibly helps patients to lose weight. It is excreted unchanged in the urine and does not undergo hepatic metabolism. Metformin is contraindicated in patient with renal impairment, serum creatinine levels $\geq 1.5\text{mg/dL}$ [males], $\geq 1.4\text{mg/dL}$ [females] or $\text{eGFR} < 30\text{ml/min/1.73m}^2$, hypersensitivity reaction and acute/chronic metabolic acidosis.

Effect of Metformin in Prediabetic

Improve insulin sensitivity

Metformin acts primarily by enhancing the action of insulin in different organs. This include reduce the rate of hepatic glucose production (gluconeogenesis). Improvements in insulin action in skeletal muscle also contribute to the therapeutic actions of metformin. Together, these actions reduce blood glucose in the setting of hyperglycaemia, with very little potential for inducing hypoglycaemia.

Preserve beta cell function

Several studies have looked to the effect of metformin on preserving beta cell function. One study has shown that metformin can restore the intracellular abnormalities of glucose and FFA metabolism and to restore a normal secretory pattern in rat pancreatic islets especially for those whose secretory function has been impaired by chronic exposure to elevated FFA or glucose levels [3,4]. Another study of 390 insulin-treated patients with type 2 diabetes were randomized to either placebo or metformin found that Fasting C Peptide-to-Glucose Ratio (FCPGR) increased in the metformin group with 1.48 (95% CI, 1.09-1.87, $P < 0.00$) and thus improves long-term estimates of beta cell function in the fasting state [5]. These data might give hope that metformin has potential effect in preserving beta cell function in patients with prediabetic as well as diabetic mellitus.

Metformin effect on GIT

Metformin has an important role in gut. It increases glucose uptake within the intestine. This leads to cumulation of lactate within the enterocyte and thus lead to metformin intolerance. Secondly it increases plasma GLP1 concentration but mechanism still not clear. Thirdly it increases the bile acid pool within the intestine, and this may affect stool consistency, GLP1 secretion, cholesterol level and mycobiomes [6]. This effect in microbiome improves glucose tolerance but, on the other, have contribute to metformin intolerance.

When to use metformin in prediabetes patient

Several guidelines have been evolved to deal with treatment of prediabetics, but several trials emphasize on the important of lifestyle intervention as primary goal in treatment of prediabetes. According to ADA, metformin is recommended in patient with prediabetes especially in $\text{BMI} > 35\text{kg/m}^2$, age/60 years or prior GDM [4]. The ADEA Australian Diabetes Educators Association advice to consider 6-month trial of lifestyle intervention as first line management of prediabetic with possible pharmacologic intervention if lifestyle intervention doesn't improve glucose status [7]. European Expert Group (2013) Strong emphasis on lifestyle intervention. Metformin or acarbose second line (subject to tolerability) in people with IGT, or orlistat second line in obese subjects. Till now Metformin has not been approved for such use by the FDA.

Limitation of Use Metformin in Prediabetes

The main disadvantage of use of metformin as primary prevention of type 2 DM is troublesome GI side-effect. There is also possibility of vitamin B12 deficiency in long term run [7]. Furthermore, it might mask or delay the diagnosis of type 2 DM as it usually reduces blood glucose level. The long-term safety and outcome of using metformin it yet to be studied.

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