INTERNATIONAL JOURNAL OF HEALTH & MEDICAL RESEARCH

ISSN(print): 2833-213X, ISSN(online): 2833-2148

Volume 03 Issue 12 December 2024

DOI : 10.58806/ijhmr.2024.v3i12n07

Page No. 873-877

The Role of Insulin Resistance and Pancreatic Beta -Cell Dysfunction in Type Two Diabetes: A Review Article

Maysm Barzan

Department of pharmaceutical science, College of Pharmacy, University of Thi-Qar, Thi-Qar, 64001, Iraq

ABSTRACT: Type 2 diabetes is a lifelong disease. It has to do with the way your body metabolizes blood sugar. It's known as being insulin-resistant – meaning the cells in your body don't respond well to insulin – and eventually as an insulin deficiency. Nobody knows exactly what causes it, but factors include genetics, obesity, no physical activity, and a junk food diet. symptoms are: increased thirst; frequent urination; extreme fatigue; blurred vision; slow healing of wounds. Most people who have type 2 diabetes find out when they have this blood test done or when they have a test that uses their blood. There is no cure for diabetes but you can control it by changing your lifestyle – eating healthy foods, exercising, and keeping a healthy weight. Oftentimes, though, medicines or insulin injections are needed to help with the disease. Prevention: Maintaining a healthy weight, eating a balanced diet rich in whole foods, engaging in regular physical activity, Avoiding smoking and excessive alcohol consumption. Type 2 diabetes is a manageable condition, and early intervention can significantly improve outcomes and quality of life.

KEYWORDS: Type 2 Diabetes, insulin, Beta -cells.

INTRODUCTION

Diabetes is a long-term illness that impairs the body's capacity to efficiently use glucose, or sugar. Type 1 and Type 2 diabetes are the two primary categories into which it is often divided. The hallmarks of type 2 diabetes are insulin resistance in target organs and relative insulin insufficiency brought on by pancreatic β-cell malfunction. The incidence and prevalence of type 2 diabetes have doubled between 1980 and 2004 due to an aging population, sedentary lifestyles, and an increase in obesity worldwide (1). Diabetes was the sixth leading cause of disability in 2015. This places significant socioeconomic strain on the individual and leads to enormous expenditures for global health economies. It has been estimated at US$825 billion to reduce the risk of complications and disease progression and effectively control cardiovascular diseases the very factors that account for most morbidity and mortality related to type 2 diabetes strict control of blood pressure, glucose, and lipid levels. Most evidence has come from numerous large randomized controlled trials VADT, ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) and UKPDS (United Kingdom Prospective Diabetes Study) regarding microvascular benefits of advanced glucose management that would be retinopathy, nephropathy and neuropathy (6-8). The evidence is rather weak, with improvements in microvascular outcomes, though not macrovascular outcomes such as cardiovascular disease and stroke rates. (9-12) An optimal glucose-lowering therapy barrier is hypoglycemia, and results from an observational study (13) demonstrated an association between severe hypoglycemia, even in non-insulin-receiving individuals, with increased mortality rates at 1 year. Patient outcomes quality includes early diagnosis of type 2 diabetes through screening and well-focused and intensified management of the patient. Disease management should also come with structured education programs and self-management programs supported by the latest protocols calling for psychological support by a multi-disciplinary team (14). Patient education must also be supported by recent advances in pathophysiology and the knowledge of disease processes, treatment should then be 'personalized,' that is adequately individualized to the patient. Those aged <25 years when they develop type 2 diabetes present a particular challenge because the phenotypes are so complicated that it may take decades of vigorous therapy to minimize the onset and progression of microvascular and macrovascular problems. In patients 65 years of age or older, intensive treatment of type 2 diabetes must be weighed against the risk of hypoglycemia, cognitive decline, and other comorbidities. The current management strategies are reviewed, new developments in diagnosis, therapy, and cardiovascular benefits (14).

PREVENTIVE MEASURES FOR TYPE 2 DM

The benefits of not getting type 2 diabetes for patients are huge, especially when considering complications and many years of medication. Many controls obesity and poor glucose regulation through diet and activity changes, and to a lesser extent pharmaceutical therapy with metformin and thiazolidinedione, from studies so probably not to contract type 2 diabetes. The US

Diabetes Prevention Program (DPP) recently conducted research. On rigid lifestyle changes such as exercise, low-fat dieting to lose weight reduced the risk of contracting type 2 diabetes by 3234 for all<100.

Treatment of the overweight or obesity impaired glucose tolerance with Metformin in a mean follow-up of 2·8 years in overweight or obese subjects proved to be much more effective in terms of relative risk reduction, 58% compared with 31% for metformin alone or placebo in overweight or obese subjects with impaired glucose tolerance. There was no interaction by sex, race, or genetics on the action of the drug since all these patient groups benefited from the treatment. Most responding females where that gestational diabetes had before in their history; however, the most cost-effective mode of lifestyle intervention for people over 60 years of age. The lifestyle group assignment decreased the cumulative incidence of diabetes by 27% and by 18% among those assigned metformin at the 15-year follow-up from DPP (DPPOS) (16).

DPPOS confirmation of returned glucose tolerance at the 5-7 year follow-up after the year intervention reduced the estimated Framingham cardiovascular disease risk score by 2.7%($p < 0.01$) after 10 years in patients initially presenting with pre-diabetes(17).Even so, through these favorable findings, successive meta-analyses of intervention by lifestyle illuminated the failure of reproducing trial outcomes in reality, as any other writer predominantly declared because of low participation rates, poor insurance schemes' coverage, and failed issue cost-effectiveness. However, national programs are now rolling out in the UK in a cost-effective manner to tackle this epidemic as with the UK Diabetes Prevention Programme (18-20).

TREATMENT OF TYPE 2 DIABETES

Metformin is considered the first-line oral hypoglycemic drug in the management of type 2 diabetes mellitus, except in the presence of a specific contraindication like in renal impaired patients. Metformin works by decreasing the hepatic glucose overproduction and enhances peripheral tissue sensitivity while also increasing GLP-1 secretion. Additionally, it reduces HbA1c levels by 1-2%, is weight neutral, and non-hypoglycemic, with minor effects on blood pressure and lipid profiles (21). Gastrointestinal side effects can usually be avoided by a gradual increase in dose, and lactic acidosis with Metformin is extremely rare (less than 1 per 100,000 population) (84). Metformin causes vitamin B12 deficiency and cannot be used in severe chronic renal impairment eGFR <30mL/min/1·73m²). This also can be cautiously used in mild to moderate chronic kidney impairment, dose adjustment being required (21). The use of metformin as monotherapy has been associated with the reduction of cardiovascular risk versus placebo or sulfonylurea therapy. It has been five years since the American Diabetes Association and the European Association for the Study of Diabetes modified their treatment algorithm. As per the guidelines, all glucose-lowering therapies could be considered as possible second-line agents for addition to metformin when glycemic targets cannot be reached. Such action would provide more individualized treatment plans, although the multiplicity of therapeutic options makes it rather vague as to the 'right' combination; therefore, it should be better based on knowledge of existing evidence base and specific features of each drug class (21). The choice of sulfonylureas like gliclazide, and glimepiride for dual oral therapy is based on the mode of action which is through stimulation of insulin secretion by β cells. These first line anti diabetic drugs are, therefore, the preferred dual therapies by virtue of their proven efficacy and low cost. However, their adverse effects are hypoglycemia, with a 3-6-fold higher risk than that of metformin88 and weight gain. The unresolved controversies they provoke relate to adverse cardiovascular outcomes (22). Unlike thiazolidinediones, these first-line medications have little in the way of lasting control when used on their own other than metformin. DPP-IV inhibitors, GLP-1 receptor agonists and SGLT-2 inhibitors are challenging the preference for them as second line therapy (23). The most effective and safe drug combination must be identified by the results of an ongoing comparative effectiveness study of the major oral glucose-lowering therapies (excluding SGLT-2 inhibitors) when added to metformin. Meglitinides have similar actions to sulfonylureas but are weak and have a short duration of action. Less hypoglycemic risk suggests that they could be used as an alternative anti-hyperglycemic agent in patients who need meal-related short-acting insulin but do not secrete any endogenous insulin at other times of the day shift workers, fasting patients moderate to severe renal failure, thiazolidinediones also known as PPAR-g agonists (rosiglitazone, pioglitazone) increase insulin sensitivity in target organs. The use of these drugs has been quite controversial, with the first-in-class drug troglitazone having been withdrawn because of liver toxicity. Currently, rosiglitazone is rarely prescribed because of adverse cardiovascular outcomes (although these have been discredited). These agents give a sustainable control90 and reduce HbA1c by almost 1%. They usually do not cause hypoglycemia unless concomitantly given with sulfonylureas or insulin and generally cause weight gain, up to 6 kg, but most of this is fluid weight. Pioglitazone can be used at full dose throughout chronic kidney disease but it should not be used in heart failure (NYHA class III or IV) (24). Pioglitazone: warnings concerning bone fractures98, and potential signals for prostate and pancreatic cancers; the evidence regarding bladder cancer risks with pioglitazone is inconclusive. Basically, incretin therapies are injectable GLP-1 receptor agonists and oral DPP-IV inhibitors. GLP-1 Agonists induced effects similar to GLP-1: enhanced secretion of insulin, inhibition of glucagon secretion, decreased production of glucose by the liver, slowed gastric emptying, and increase in satiety (22). GLP-1 Agonists are either long or short acting exenatide or liraglutide once a week or twice a day. They lower the HbA1c by 1% on average and the weight of the patient by 4 kg. The only possible complication is hypoglycemia but only in combination with sulfonylureas or insulin. The major adverse effect is initiation of nausea and vomiting, though mostly attenuated by gradual dosage titration. the most efficacious glp-1 receptor agonists, in general, appear to be exenatide and liraglutide. Treatments with GLP-1 RA were uniformly efficacious in terms of

HbA1c and FPG, but the discrepancy still exists between AEs such as nausea and effect on weight. Absolute contraindications are a past history of chronic pancreatitis or pancreatic cancer. There is no increase in adverse events related to pancreatic cancer. Fixed combinations of GLP-1 RA with long-acting insulins (insulin degludec and liraglutide, insulin glargine and lixisenatide) against insulin had lower hypoglycemia and lesser weight gain and total insulin (25-26). Direct head-to-head switch studies from basals to the GLP-1 RA combinations with patients on basal bolus insulin regimens show similar efficacy between the two interventions and likely reflect an GLP-1 RA effect on lowering postprandial glucose excursions. Sitagliptin, saxagliptin, linagliptin, vildagliptin, alogliptin and other DPP-IV inhibitors do enhance the effects of physiological GLP-1. 'Carded' once or twice a day orally, these inhibitors have a lowering of HbA1c of up to 0.7%, are weight neutral and do not cause hypoglycaemia unless in combination with sulphonylureas or insulin. DPP-IV inhibitors generally cause minimal side effects and are safe when used after doses adjustment (eg: sitagliptin) or even without dose adjustment (linagliptin) in moderate to severely impaired renal patients. Latest among the groups of anti-diabetic drugs are the SGLT-2 inhibitors- dapagliflozin, canagliflozin and empagliflozin. They reduce the blood glucose level by enhancing the renal proximal tubule's SGLT-2 inhibition and thereby increasing the urinary excretion of glucose. Exciting findings are those of meta-analyses of dapagliflozin and canagliflozin trials, which demonstrate an efficacy in terms of HbA1c reductions by around 0.7%. Modest weight reductions were observed in dapagliflozin versus glipizide and versus placebo (-3.2 kg vs 1.2 kg $p < 0.0001$; and 2.2 kg vs 0.7 kg $p < 0.01$ respectively). Empagliflozin, in the long term, showed 'weight reduction'. Placebos did not work (78 weeks: 2.2 kg vs 120 weeks: 2.2 kg vs 110878: 0.7 kg). They differ from other antihyperglycaemic agents in not causing hypoglycaemia unless used with sulphonylureas or insulin (27). Considerable side-effect profile of genital or urinary infections; incidence rate is higher for both with females. SGLT-2 inhibitors are nominally effective and dose reduction would be indicated among patients with moderate to severe renal impairment (eGFR 30-60 ml/min/1.73 m^2) but are contraindicated where eGFR is <30 ml/min/1.73 m^2. SGLT-2 inhibitors can cause euglycemic ketoacidosis, which will necessitate stopping during any intercurrent illness and admission Canagliflozin has been associated with bone fractures and peripheral vascular disease Insulin therapy boasts the highest efficacy in total glycaemic control, reducing HbA1c levels by 1.5–2%. However, it increases the risk of hypoglycaemia, especially in elderly patients, and an average weight gain of 4 kg. Insulin treatment algorithms should therefore be used for optimal insulin titration with rapid attainment of glycaemic targets. Concerns are primarily related to the risk and fear of hypoglycaemia or of gaining weight; practical issues with injecting oneself, or fear thereof (psychological insulin resistance); and lifestyle constraints. Basal insulin three times per day is the most effective oral and other subcutaneous agent addition in terms of both efficacy and safety; efficacy is highest with prandial insulins three times per day, but the highest safety due to the least hypoglycemia is not reached by these drugs. Fast insulin for short-term glucose control may help preserve β-cell function and reduce glucotoxicity. A direct comparison between basal human and analog insulins demonstrated equal efficacy without any clear differences. The only statistically significant benefit was lower rates of nocturnal and symptomatic hypoglycemia, which were found when all the insulins' analogs were combined compared with either basal insulins alone or human premix insulins. Detemir vs glargine. There is no difference in efficacy or safety, yet detemir correlates with lesser weight gain and higher insulin dose requirement. Ultra long-acting insulin analogs with a plasma half-life of 42 hours, such as insulin degludec, associate the least risk of nocturnal hypoglycemia since they are rather peakless. Higher strength insulin analogs-U300 glargine and U500 insulin are other good formulations in a patient with marked insulin resistance who requires such high insulin doses (28).

DIAGNOSIS OF TYPE 2 DIABETES

Fasting Plasma Glucose (FPG): Classic diabetic criteria for the diagnosis of diabetes is: any random blood glucose level ≥200 mg/dL (11.1 mmol/L) in a patient with classic symptoms of hyperglycemia or fasting plasma glucose ≥126 mg/dL (7.0 mmol/L) on two or more occasions. Oral Glucose Tolerance Test (OGTT): Type 2 diabetes is diagnosed if the 2-hour plasma glucose level after a 75 g oral glucose load is equal to or greater than 200 mg/dL (11.1 mmol/L). Glycated Hemoglobin (HbA1c): Diabetes is said to be present should HbA1c equal to or greater than 6.5 (29). Random Plasma Glucose: Diabetes is diagnosed at a random plasma glucose in excess of or equal to 200 mg/dL (11.1 mmol/L) along with presence of classic symptoms of hyperglycemia such as polyuria, polydipsia and unexplained weight loss does also confirm this diagnosis. The importance of early detection and adequate management of type 2 diabetes cannot be overemphasized in the prevention or postponement in the development of systemic complications like cardiovascular disease, neuropathy, nephropathy and retinopathy (29).

TYPE 2 DIABETES MANAGEMENT:

Control of type 2 diabetes is by managing the perfect weight, and this is done through a balanced low-calorie diet. Keeping up with regular physical exercises does help to cause them to become more insulin sensitive and control their sugar levels. Foods that work to reduce glycemic control while improving it and complication risk reduction are whole, low processed, carbohydrate foods.

Usually, metformin is the first-line medication for diabetes since it suppresses hepatic glucose release and enhances sensitivity to insulin. Patients might be prescribed other medications like sulfonylureas, DPP-4 inhibitors, GLP-1 agonists, and insulin sensitizers to control hyperglycemia. If lifestyle changes and OAMs fail, insulin may be required to control and normalize the glycaemic levels. Correcting treatment according to the level of the blood glucose and averting its complications through monitoring has made it

extremely vital for clients to frequently monitor blood glucose levels (30). Regular monitoring of blood glucose levels is a fundamental aspect of proper management for adjustment of therapy according to glycemic levels and to avert its complications (30). Prompt attention by the primary healthcare providers towards recognition of such issues is crucial, as many complications can be managed or stopped from worsening.

This must have an approach that includes lifestyle modifications, medication, and continued monitoring and self-care. Individuals with type II diabetes will then be able to achieve the desirable control of the disease process with reduced complications and good general health and quality of life (30).

CONCLUSION

The most common of all diabetic cases are Type 2. Generally, it is tied to conditions related to lifestyle such as obesity, inactivity, or improper diet that the body shows resistance to the insulin it produces or there is just not enough of the hormone to maintain normal function.

- Symptoms: The most usual symptoms are increased thirst, frequent urination, and increased fatigue blurred vision may also be a symptom, although some people may not show any symptoms initially.
- Complications: If the condition is not effectively managed, there are numerous associated complications, including cardiovascular disease, nerve damage, kidney failure, and loss of vision.
- Management: Good control involves dietary control with regular exercise and monitoring blood sugar levels, and if required, medication. The patient has to be intervened early so that he does not have a bad outcome and complications and to enhance his quality of life.

In summary, Type 2 diabetes is a condition that can be managed with the right lifestyle and medical intervention; it underscores the need for awareness and 'proactive health management.

REFERENCES

1) NCD Risk Factor Collaboration (NCD-RisC). Worldwide trends in diabetes since 1980: a pooled analysis of 751 population-based studies with 4·4 million participants. Lancet 2016; 387: 1513–30
2) GBD 2015 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 310 diseases and injuries, 1990– 2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016; 388: 1545–602.
3) Seuring T, Archangelidi O, Suhrcke M. The economic costs of type 2 diabetes: a global systematic review. Pharmacoeconomics 2015; 33: 811–31.
4) WHO. Non-communicable diseases country profi le 2014. July, 2014. http://www.who.int/nmh/publications/ncd-profi les-2014/en/ (accessed Oct 6, 2016)
5) Gaede P, Vedel P, Larsen N, Jensen GV, Parving HH, Pedersen O. Multifactorial intervention and cardiovascular disease in patients with type 2 diabetes. N Engl J Med 2003; 348: 383–93.
6) UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; 352: 837–53.
7) ADVANCE Collaborative Group, Patel A, MacMahon S, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008; 358: 2560–72.
8) Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009; 360: 129–39.
9) Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med 2008; 359: 1577–89.
10) Holman RR, Sourij H, Califf RM. Cardiovascular outcome trials of glucose-lowering drugs or strategies in type 2 diabetes. Lancet 2014; 383: 2008–17
11) Skyler JS, Bergenstal R, Bonow RO, et al. Intensive glycemic control and the prevention of cardiovascular events: implications of the ACCORD, ADVANCE, and VA diabetes trials: a position statement of the American Diabetes Association and a scientifi c statement of the American College of Cardiology Foundation and the American Heart Association. Diabetes Care 2009; 32: 187–92
12) Cefalu WT. Glycemic targets and cardiovascular disease. N Engl J Med 2008; 358: 2633–35.
13) Elwen FR, Huskinson A, Clapham L, et al. An observational study of patient characteristics and mortality following hypoglycemia in the community. BMJ Open Diabetes Res Care 2015; 3: e000094
14) Wilding JP. The role of the kidneys in glucose homeostasis in type 2 diabetes: clinical implications and therapeutic signifi cance through sodium glucose co-transporter 2 inhibitors. Metabolism 2014; 63: 1228–37

15) Orozco LJ, Buchleitner AM, Gimenez-Perez G, Roque I Figuls M, Richter B, Mauricio D. Exercise or exercise and diet for preventing type 2 diabetes mellitus. Cochrane Database Syst Rev 2008; 3: CD003054
16) Merlotti C, Morabito A, Pontiroli AE. Prevention of type 2 diabetes; a systematic review and meta-analysis of diff erent intervention strategies. Diabetes Obes Metab 2014; 16: 719–27
17) Diabetes Prevention Program Research Group. Long-term eff ects of lifestyle intervention or metformin on diabetes development and microvascular complications over 15-year follow-up: the Diabetes Prevention Program Outcomes Study. Lancet Diabetes Endocrinol 2015; 3: 866–75.
18) Perreault L, Temprosa M, Mather KJ, et al. Regression from prediabetes to normal glucose regulation is associated with reduction in cardiovascular risk: results from the Diabetes Prevention Program outcomes study. Diabetes Care 2014; 37: 2622–31
19) Tuccori M, Filion KB, Yin H, Yu OH, Platt RW, Azoulay L. Pioglitazone use and risk of bladder cancer: population-based cohort study. BMJ 2016; 352: i1541.
20) Nauck MA, Meier JJ. The incretin effs ect in healthy individuals and those with type 2 diabetes: physiology, pathophysiology, and response to therapeutic interventions. Lancet Diabetes Endocrinol 2016; 4: 525–36
21) Garber A, Henry R, Ratner R, et al. Liraglutide versus glimepiride monotherapy for type 2 diabetes (LEAD-3 Mono): a randomised, 52-week, phase III, double-blind, parallel-treatment trial. Lancet 2009; 373: 473–81
22) Heine RJ, Van Gaal LF, Johns D, Mihm MJ, Widel MH, Brodows RG, GWAA Study Group. Exenatide versus insulin glargine in patients with suboptimally controlled type 2 diabetes: a randomized trial. Ann Intern Med 2005; 143: 559–69
23) Alberti G, Zimmet P, Shaw J, Bloomgarden Z, Kaufman F, Silink M; Consensus Workshop Group. Type 2 diabetes in the young: the evolving epidemic: the international diabetes federation consensus workshop. Diabetes Care. 2004; 27:1798–1811. doi: 10.2337/diacare.27.7.1798
24) Koopman RJ, Mainous AG 3rd, Diaz VA, Geesey ME. Changes in age at diagnosis of type 2 diabetes mellitus in the United States, 1988 to 2000. Ann Fam Med. 2005; 3:60–63. doi: 10.1370/afm.214
25) Grinstein G, Muzumdar R, Aponte L, Vuguin P, Saenger P, DiMartino-Nardi J. Presentation and 5-year follow-up of type 2 diabetes mellitus in AfricanAmerican and Caribbean-Hispanic adolescents. Horm Res. 2003; 60:121– 126. doi: 10.1159/000072523
26) JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). Heart. 2014;100(suppl 2): ii1– ii67. doi: 10.1136/heartjnl-2014-305693
27) U.S. Department of Health and Human Services. How tobacco smoke causes disease: the biology and behavioral basis for smoking-attributable disease. A report of the Surgeon General. Atlanta, Ga., Centers for Disease Control and Prevention, 2010
28) Ajala O, English P, Pinkney J. Systematic review and meta-analysis of different dietary approaches to the management of type 2 diabetes. Am J Clin Nutr 2013; 97:505–516
29) Stewart A, Kamberg CJ. Physical functioniong measures. In Measuring Functioning and Well-Being: The Medical Outcomes Study Approach. Stewart A, Ware JE, Eds. Durham, N.C., Duke University Press, 1992, p. 86–101
30) Krug LM, Haire-Joshu D, Heady SA. Exercise habits and exercise relapse in persons with non-insulin-dependent diabetes mellitus. Diabetes Educ 1991; 17:185–188