Clinical Evidence Handbook

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Glycemic Control in Type 2 Diabetes (Drug Treatments)

KEES J. GORTER, *University Medical Centre, Utrecht, The Netherlands*

FLORIS ALEXANDER VAN DE LAAR, *Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands*

PAUL G.H. JANSSEN, *Dutch College of General Practitioners, Utrecht, The Netherlands*

SEBASTIAN T. HOUWELING, *Langerhans Research Group, Sleeuwijk, The Netherlands*

GUY E.H.M. RUTTEN, *University Medical Centre, Utrecht, The Netherlands*

Diabetes mellitus affects about 6.5% of persons 20 to 79 years of age worldwide. In 2010, an estimated 285 million persons had diabetes, more than 85% of whom had type 2 diabetes.

Type 2 diabetes is often associated with obesity, hypertension, and dyslipidemia, which are all powerful predictors of cardiovascular disease. For that reason, the treatment of type 2 diabetes requires a multifactorial approach, including lifestyle advice, treatment of hypertension, and lowering of lipid levels.

Without adequate blood glucose–lowering treatment, blood glucose levels may rise progressively over time in persons with type 2 diabetes. Microvascular and macrovascular complications may develop.

Metformin reduces A1C levels effectively compared with placebo.

• The UK Prospective Diabetes Study (UKPDS), a randomized controlled trial, found that metformin may be moderately protective against mortality and cardiovascular morbidity, but further high-quality studies are needed.

• We found no evidence to suggest that metformin increases the risk of lactic acidosis.

Sulfonylureas reduce A1C levels by 1% compared with placebo, and they may reduce microvascular complications compared with diet alone. They can cause weight gain and hypoglycemia. One review found that the risk of hypoglycemia was highest with glibenclamide compared with other second-generation sulfonylureas.

The effectiveness of the combination of metformin and a sulfonylurea on mortality and morbidity is unknown.

Meglitinides reduce A1C levels by about 0.4% to 0.9% compared with placebo, but robust data are sparse.

Alpha-glucosidase inhibitors reduce A1C levels by about 0.8% compared with placebo. We found no reports of dangerous adverse effects.

Thiazolidinediones reduce A1C levels by 1.0% compared with placebo but may increase the risk of congestive heart failure and bone fractures. Rosiglitazone increases the risk of myocardial infarction.

• *Drug alert*: Rosiglitazone has been withdrawn from the market in many countries because the benefits of treatment are no longer thought to outweigh the risks.

Dipeptidyl-peptidase-4 inhibitors reduce A1C levels by about 0.6% to 0.7% compared with placebo. We found no long-term data on effectiveness and safety.

Glucagon-like peptide-1 analogues reduce A1C levels compared with placebo and result in weight loss. We found no long-term data on effectiveness and safety.

Combined oral drug treatment may reduce A1C levels more than monotherapy, but it increases the risk of hypoglycemia.

Insulin improves glycemic control in persons with inadequate control of A1C who are taking oral drug treatment, but it is associated with weight gain and an increased risk of hypoglycemia.

Adding metformin to insulin may reduce A1C levels compared with insulin alone, with less weight gain.

Insulin analogues, short-acting, long-acting, and combined in various regimens, seem no more effective than conventional (human)

Clinical Questions

What are the effects of blood glucose–lowering medications in adults with type 2 diabetes?

Beneficial	Metformin (may be moderately protective against mortality and cardiovascular morbidity; reduces A1C levels more effectively than placebo and is comparably effective to sulfonylureas, alpha-glucosidase inhibitors, meglitinides, and insulin)
	Sulfonylureas (lower the occurrence of microvascular disease; reduce A1C levels more effectively than placebo, may be marginally more effective than alpha-glucosidase inhibitors, and comparably effective to metformin, meglitinides, TZDs, and dipeptidyl-peptidase-4 inhibitors)
Likely to be beneficial	Alpha-glucosidase inhibitors (acarbose, miglitol only; alpha-glucosidase inhibitors) (reduction of A1C: more effective than placebo, may be comparably effective to metformin, meglitinides, and dipeptidyl-peptidase-4 inhibitors, and may be slightly less effective than sulfonylureas; no evidence for an effect on disease-related mortality or morbidity)
	Dipeptidyl-peptidase-4 inhibitors (reduction of A1C: more effective than placebo, may be comparably effective to sulfonylureas and alpha-glucosidase inhibitors, but may be less effective than metformin and TZDs; evidence on long-term effects is lacking)
	Glucagon-like peptide-1 analogues (reduction of A1C: more effective than placebo, may be comparably effective to insulin; evidence on long-term effects is lacking)
	Insulin long-acting analogues vs. each other (both effective; however, unclear whether one long-acting analogue is consistently more effective than the other)
	Insulin plus metformin (more beneficial than insulin alone)
	Meglitinides (reduction of A1C: more effective than placebo, and comparably or a little less effective than metformin, sulfonylureas, and alpha-glucosidase inhibitors; however, robust data are sparse)
Trade-off between benefits and harms	TZDs (reduce A1C levels but increase the risk of congestive heart failure and bone fractures; *important note:* this categorization does not include rosiglitazone; rosiglitazone has been associated with an increased risk of myocardial infarction, has been withdrawn from the market in many countries, and is likely to be ineffective or harmful)
Unknown effectiveness	Continuation of insulin vs. switching to metformin or gliclazide in persons with severe hyperglycemia who were hospitalized and treated with insulin as first-line treatment
	Metformin plus a sulfonylurea (unclear effects on mortality and morbidity)
	One insulin analogue treatment regimen vs. another insulin analogue treatment regimen (excluding long-acting analogue vs. long-acting analogue)
Unlikely to be beneficial	Various insulin analogue regimens compared with various conventional (human) insulin regimens

TZD = thiazolidinedione.

insulin in reducing A1C levels. However, in persons presenting with recurrent hypoglycemic episodes, long-acting insulin analogues may be preferred over human insulin.

Long-acting insulin analogues seem equally effective at reducing A1C levels.

There is lack of evidence about the effectiveness of various insulin analogue regimens after once-daily, long-acting insulin has failed.

The effectiveness of insulin basal bolus regimens is not well established.

Definition

The term diabetes mellitus encompasses a group of disorders characterized by chronic hyperglycemia, with disturbances of carbohydrate, fat, and protein metabolism resulting from defects of insulin secretion, insulin action, or both. Type 2 diabetes is the most common form of diabetes, and defects of both insulin action and insulin secretion are usually present by the time of diagnosis. The World Health Organization (WHO) recognizes diabetes as a progressive disorder of glucose metabolism in which individuals may proceed from normoglycemia (fasting plasma venous glucose less than 5.5 mmol per L) to impaired glucose tolerance (fasting plasma venous glucose less than 7.0 mmol per L and plasma glucose between 7.8 mmol per L and 11.1 mmol per L two hours after a 75-g oral glucose load, the oral glucose tolerance test), impaired fasting glycemia (fasting plasma venous glucose between 5.6 mmol per L and 7.0 mmol per L),

and diabetes. As a consequence of the inability of the body to use glucose as an energy source, blood glucose levels rise and symptoms such as thirst, polyuria, blurring of vision, or weight loss may develop.

Since 1965, WHO has published guidelines for the diagnosis and classification of diabetes. In 2006, WHO decided that the diagnostic criteria should be maintained. In the presence of symptoms, diabetes may be diagnosed on the basis of a single random elevated plasma glucose level (11.1 mmol per L or more). In the absence of symptoms, the diagnosis should be based on blood glucose results in the diabetes range taken at different time points, either from a random sample, or fasting (plasma blood glucose 7.0 mmol per L or more), or from the oral glucose tolerance test (plasma blood glucose 11.1 mmol per L or more two hours after a 75-g glucose load).

For the purpose of this review, we have excluded pregnant women and acutely unwell adults (e.g., after surgery or myocardial infarction), and persons with secondary diabetes (e.g., those with hyperglycemia based on temporal use of corticosteroids).

Incidence and Prevalence

It is estimated that about 285 million persons between 20 and 79 years of age had diabetes worldwide in 2010, or 5% of the adult population. This number will increase to about 438 million in 2030, an estimated prevalence of 7.7%, in the previously mentioned age category. By 2025, the region with the greatest number of persons with diabetes is expected to be Southeast Asia, with about 82 million persons with type 2 diabetes. Incidence and prevalence figures for children and adolescents are unreliable, but there is some evidence that type 2 diabetes is becoming more common in adolescents and young adults, especially in resource-poor countries. The overall estimated prevalence of 6.5% for type 2 diabetes conceals considerable variation in prevalence, which ranges from less than 2% in some African countries to more than 14% in some populations.

Etiology and Risk Factors

By definition, the specific reasons for the development of the defects of insulin secretion and action that characterize type 2 diabetes are unknown. The risk of type 2 diabetes increases with age and lack of physical activity, and it occurs more often in persons with obesity, hypertension, and dyslipidemia (the metabolic syndrome). Type 2 diabetes also occurs more often in women with previous gestational diabetes and in certain ethnic groups. There is also evidence of a familial, probably genetic, predisposition.

Prognosis

Persons with type 2 diabetes have blood glucose levels that have been shown to rise progressively from the time of diagnosis. During the UKPDS, A1C levels rose in persons with newly diagnosed type 2 diabetes, irrespective of the type of treatment given. In 2011, primary care physicians in Denmark, the United Kingdom, and the Netherlands succeeded in lowering A1C levels in patients with screen-detected type 2 diabetes for more than five years after diagnosis. Blood glucose levels above the normal range have been shown to be associated not only with the presence of symptoms, but also with an increased risk of long-term microvascular and macrovascular complications.

Early treatment of hyperglycemia in the UKPDS over nine years resulted in a significant decrease in microvascular complications and a continued reduction in microvascular risk and emergent risk reductions for myocardial infarction and death from any cause during 10 years of post-trial follow-up. However, in persons with long-standing type 2 diabetes, the effects of treating hyperglycemia are less positive or even absent. Data from the General Practice Research Database show that low and high mean A1C values are associated with increased all-cause mortality and cardiac events. Both intensive insulin treatment and the risk of hypoglycemia have been linked to an increased death rate.

EDITOR'S NOTE: Glibenclamide is called glyburide in the United States. Gliclazide is not available in the United States.

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Adapted with permission from Gorter KJ, Alexander van de Laar FA, Janssen PG, Houweling ST, Rutten GE. Diabetes: glycaemic control in type 2 (drug treatments). *Clin Evid Handbook.* December 2013:150-151. Please visit http://www.clinicalevidence.bmj.com for full text and references. ∎