AASD NEWSLETTER

Arabic Association for the Study of Diabetes & metabolism

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Management of Hypertension in Diabetic Patients

By

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Hypertension & Diabetes:

The prevalence of hypertension among patients with type 2 diabetes is as twice as high among persons without diabetes. Hypertension further contributes to the higher rate of cardiovascular mortality and renal failure that occurs in patients with diabetes. Threat at which glomerular filtration decreases in patients with diabetic nephropathy is directly related to diastolic and to a lesser extent, systolic blood pressure.

Effective treatment of hypertension in patients with diabetes may reduce the cerebrovascular and cardiovascular complications more than tight control of hyperglycemia does.

Most patients with diabetes and hypertension require two or more medications to control the blood pressure. An emerging consensus suggests that one of the two medications should be an ACE inhibitor or an ARB, because the benefits of ACE inhibition extend those of blood pressure control alone in preventing cardiovascular disease and because both ACE inhibitors and ARBs prevent the progression of renal disease.

Diabetes and Cardiovascular Disease:

Diabetes is a major risk factor for cardio-vascular disease (CVD). Approximately two thirds of people die from CVD. Nearly half of middle-aged people with diabetes have evidence of coronary artery disease (CAD) compared with only one-fourth of people without diabetes in similar populations.

Patients with diabetes are prone to a number of cardiovascular risk factors beyond hyperglycemia. These risk factors, including hypertension, dyslipidemia and a sedentary life style, are particularly prevalent among patients with diabetes. To reduce the mortality and morbidity from CVD among patients with diabetes, aggressive treatment of glycemia as well as other cardiovascular risk factors must be initiated.

Clinical trials have convincingly demonstrated the importance of intensive treatment of hypertension among patients with diabetes. Among Elderly hypertensive patients receiving placebo whom enrolled in studies such as the Systolic Hypertension in the Elderly Program (SHEP) and the Systolic Hypertension in Europe study (Syst – Eur), those with coexisting diabetes approximately had a double cardiovascular morbidity & mortality.

The Hypertension Optimal Treatment (HOT) study and the UK prospective Diabetes study (UKPDS) have shown the benefits of achieving tight blood pressure control. The UKPDS, which followed patients with diabetes for an average of 8.5 years, found that patients with tight BP control (< 150/85) versus less tight control (< 180/105 mm hg) had lower rates of myocardial infarction (MI), stroke and peripheral vascular events. In the UKPDS, each 10 mmHg decrease in the mean systolic BP was associated with a 12% reduction in the risk of any diabetes related complications, 15% reduction for diabetes related deaths & 11% reduction for MI.

The HOT trial has shown that patients assigned to lower BP targets have better outcomes. Patients who achieved a diastolic BP of < 80 mmHg benefited the most in terms of 50% reduction of cardiovascular events compared to those with a diastolic blood pressure of 90 mmHg or less.

Moreover benefits of tight blood pressure control in patients with diabetes exceed the benefits of tight glycaemia control and extend not only to the prevention of macrovascular diseases, but also to the prevention of microvascular complications.

The American Diabetes Association (ADA) has long advocated that hypertension should be treated aggressively to achieve & maintain BP in the normal range.
ADA has recommended a target BP goal of < 130/80 mmHg.

Therapeutic Management:

Many classes of drugs have been used in numerous trials to treat patients with hypertension. All classes of drugs have been shown to be superior to placebo in terms of reducing morbidity and mortality. Often, numerous agents (three or more) are needed to achieve specific target Levels of BP. Use of almost any drug therapy to reduce BP in patients with diabetes has been shown to be effective in decreasing CVD risk. Keeping in mind that numerous agents are often required to achieve the target level of BP control, recommending specific agents becomes a "not – so – simple" task. Both ACE inhibitors and angiotensin II receptor blockers (ARBs) have been shown to slow the development and progression of diabetic nephropathy.

In the Heart Outcomes Prevention Evaluation (HOPE) trial, ACE inhibitors was found to have a favourable effect in reducing cardiovascular morbidity and mortality, whereas recent trials have shown a renal protective benefit from both ACE inhibitors and ARB. ACE inhibitors and β-blockers seem to be better than di-hydro-pyridine calcium channel blockers to reduce MI and heart failure. However, recently the Antihypertensive and lipid – lowering treatment to prevent heart attack trial (ALLHAT) in high-risk hypertensive patients, including those with diabetes demonstrated that chlorthalidone "thiazide-type diuretic", was superior to an ACE inhibitor "Lisinopril" in preventing one or more forms of CVD.

Clinical Pearls:

- Hypertension is a risk factor for cardiovascular complications of diabetes.
- Clinical trials demonstrate that drug therapy versus placebo will reduce CVD events when treating hypertension and diabetes.
- A target BP goal of < 130/80 mmHg is recommended.
- Pharmacological therapy needs to be individualized to fit patients needs.
- ACE inhibitors, ARBs, diuretics and β -Blockers have all been demonstrated to be effective pharmacological treatment.
- Combinations of drugs are often necessary to achieve target BP levels.
- ACE inhibitors and ARBs are agents best suited to retard progression of nephropathy.

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Functional Disturbances in Islet Hormones In Type 2 DM

By

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Type 2 diabetes is characterized by:

1. Insulin deficiency.
2. Amylin deficiency.
3. Glucagon excess.

Pathophysiology of T2D:

Cellular resistance to the effect of insulin.

- Compensatory hyperinsulinemia.
- Abnormal glucagon secretion.
- Obesity.
- Defects in insulin secretion.
- Hyperinsulinemia may continue.
- Amyloid formation in pancreas.
- Fatty pancreas.
- Hepatic atrophy with fatty changes.
- Ischemia, pancreatic sclerosis.
- Decreased number and weight of beta cells.

Genetic-environmental interactions:

- Obesity-10X greater risk.
- Theories of development:

- Decreased number of insulin receptors in plasma membrane → decreased insulin binding.
- Post-receptor events in insulin-sensitive cells insulin resistance.
- Hyperinsulinemia is a compensatory adaptation to insulin resistance.
- Over eating leads to hyperinsulinemia development of peripheral insulin resistance to protect against hypoglycemia.

Normal reciprocal response of insulin and glucagon in persons without diabetes:

Reciprocal actions by insulin and glucagon lower blood glucose after a meal and prevent blood glucose from falling below normal range between meals (e.g. overnight).

Physiological role of early postprandial insulin secretion:

Rapidly and efficiently shifts metabolic processes from fasting state (glucose production) to prandial state (glucose disposal).

Suppressing hepatic glucose production.
- Inhibiting lipolysis.
- Direct effects on liver.

Limits postprandial glucose excursion.
Limits late hyperinsulinemia.

Kinetic defects in type 2 diabetes: Postprandial hyperglycemia:

- Loss of first phase insulin secretion.
- Delayed post-change insulin response: "too little, too late".
- Marked delay in insulin action (glucose disposal).
- Delayed suppression of hepatic glucose production.

Both Alpha & Beta - cell dysfunction contributes to hyperglycemia in T2DM:

How does glucagon affect blood glucose levels?

In the liver: (primary target):
- Stimulates glycogen breakdown: (↑) glycogen phosphorylase.
- Inhibits glycogen synthesis: (↓) glycogen synthase.
- Stimulates gluconeogenesis.

In adipose tissues:
- Stimulates fat mobilization: (↑) Triacylglycerol lipase.

Hyperglucagonemia through-out the day in people with type 2 diabetes.

Insufficient Insulin and Elevated Glucagon in T2 DM (↓ Insulin/ Glucagon Ratio).

Inappropriate hepatic glucose production in type 2 diabetes.

Glucagon from Alpha-cells is responsible for 75% of Hepatic Glucose Production (HGP) in Type 2 diabetes.

Suppression of Endogenous Glucose Production is Impaired in T2 DM In Patients with T2DM, Suppression of Glucagon Reduces Glycogenolysis and Plasma Glucose Levels.

Decreased Glucose Disposal and Increased HGP Contribute to Increased FPG in T2DM:

Amylin : The Second Beta-Cell Hormone:

Important regulator of glucose influx into bloodstream (similar to incretin mimetics = GLP-I).

Co-located and co-secreted with insulin {from pancreatic β-cells}.

Amylin plays a role in glycemic regulation:

Amylin suppresses postprandial glucagon secretion.
Amylin regulates gastric emptying.
Amylin has been shown to reduce food intake and exerts a positive effect on control of body weight.

Amylin has a role in reducing postprandial glucose excursions:

Amylin suppresses postprandial glucagon secretion:
- Glucagon is an important determinant of hepatic glucose production.
- Glucagon is abnormally elevated in diabetes.

Amylin regulates gastric emptying:
- Regulates rate of gastric emptying from stomach to small intestine.
- Rate of gastric emptying is an important determinant of early glucose excursion postprandially.

Rate of gastric emptying is important in postprandial glucose control:

Rate of gastric emptying:
- Is a key determinant of postprandial glucose excursions.
- Is often abnormal in people with diabetes.
- Is frequently accelerated in people with diabetes.

Amylin affects food intake:

Amylin dose dependently reduces food intake.
The effect appears to occur via central action on Amylin receptors.
Inhibition of food intake is independent of effect on gastric emptying.

Pramlintide – synthetic amylin (symlin):

Amylin secreted in the normal pancreas along with insulin to regulate blood glucose levels.

Enhancing postprandial control can produce significant hypoglycemia (Type1 diabetes). Used in Type1 and Type 2 patients.

Key statements:

1. Amylin is co-secreted with insulin and is deficient in DM patients.
2. Amylin suppresses pancreatic glucagon secretion, increases satiety and slows gastric emptying.
3. Pramlintide is an Amylin analog with the same functions as native Amylin.
4. Pramlintide is approved for DM1and DM2 patients uncontrolled on mealtime insulins.
5. Pramlintide can improve glycemic control and cause weight loss.

Diabetes Mellitus

By

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Diabetes Mellitus:

"A syndrome characterized by chronic hyperglycemia and relative insulin deficiency, resistance or both".

Glucose metabolism:

Blood glucose levels are closely regulated in health to be in the range between:

60-140 mg%

Liver is the main organ concerned with glucose homeostasis through 2 important processes, namely :

* **Glycogenesis**
* **Gluconeogenesis**

Glycogenesis:

The absorbed dietary glucose is stored in the liver in the form of glycogen:

Glucose → Glycogen

Between meals, Glycogen is broken into glucose then released into the circulation in a rate matching with peripheral glucose utilization:

Glycogen → Glucose

The formation of glucose from 3-carboon non-carbohydrate, structures (e.g.) glycerol, lactate, and alanine.
The blood glucose level is determined by the balance between glucose production and glucose utilization.

Glucose production:

The daily production is around:

200 gm

- 10% from the kidney "Gluconeogenesis "
- 90% from the liver
  - 3/4 "Glycogenolysis"
  - 1/4 "Gluconeogenesis"

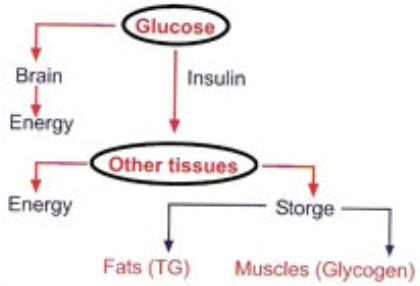
Glucose Utilization:

The main consumer of glucose is the brain

100 gm/day

Glucose utilization by the brain is obligatory *"insulin-independent"*.

Other tissues (e.g.) fat and muscle are *"Facultative consumers"* and "Insulin- dependent"



Hormonal regulation:

I) Insulin is the main regulator:

↓ Production
↑ Utilization

II) Counter-regulatory hormones: "Glucagon, Adrenaline, Cortisol & GH"

↑ Production
↓ Utilization

AASD *Events*






The Frist Annual Conference of the AASD
20-22 December 2006, Cairo Sheraton Hotel.

The Second CME
National Congress
on
Diabetes & Hypertension,
26 April 2007,
Ramsis Hilton Hotel.

CALENDAR

- The Third National AASD Congress on Diabetes & Hypertension,
  12 July 2007, Cairo Sheraton Hotel, Opening 9 am.
- Annual Conference of the AASD
  28-30 November 2007, Cairo Sheraton Hotel.